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STATISTICAL ANALYSIS PLAN

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A Randomized, Single-Dose, Double-Blind, Double-Dummy, Four-Period, Four-Sequence, Four-Treatment, Placebo and Active Controlled, Comparative, Multiple-Center, Crossover-Design, Bronchoprovocation Study to Evaluate the Pharmacodynamic Equivalence of Albuterol Sulfate Inhalation Aerosol, eq 90 mcg base (Sun Pharmaceuticals Industries Limited) to PROAIR® HFA (albuterol sulfate) Inhalation Aerosol, eq 90 mcg base (Teva Respiratory, LLC) in Subjects With Stable, Mild Asthma

Protocol Number: CLR_17_08
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Sponsor:
Sun Pharmaceuticals Industries Limited
Formulation Development Department
Tandalja, Baroda
Gujarat, 390020, India

[redacted]

December 21, 2018

Final Version 1.0

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SAP FINAL VERSION APPROVALS

A Randomized, Single-Dose, Double-Blind, Double-Dummy, Four-Period, Four-Sequence, Four-Treatment, Placebo and Active Controlled, Comparative, Multiple-Center, Crossover-Design, Bronchoprovocation Study to Evaluate the Pharmacodynamic Equivalence of Albuterol Sulfate Inhalation Aerosol, eq 90 mcg base (Sun Pharmaceuticals Industries Limited) to PROAIR® HFA (albuterol sulfate) Inhalation Aerosol, eq 90 mcg base (Teva Respiratory, LLC) in Subjects With Stable, Mild Asthma

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STATISTICAL ANALYSIS PLAN

Albuterol Sulfate Inhalation Aerosol Protocol / Study No. CLR_17_08/ [redacted]

Revision History

VERSION	DATE	DESCRIPTION OF REVISIONS	REVISED BY
Draft 1.0	September 24, 2018	New Document	[redacted]
Final 1.0	December 21, 2018	Incorporate client's comments and finalize SAP	[redacted]

List of Abbreviations and Terms

Abbreviation	Term
AE	Adverse Event
ADaM	Analysis Data Model
ANDA	Abbreviated New Drug Application
ATS	American Thoracic Society
C	Celsius
CDISC	Clinical Data Standards Interchange Consortium
CRO	Clinical Research Organization
ECG	Electrocardiogram
eCRF	electronic Case Report Form
eCTD	Electronic Common Technical Document
°F	Fahrenheit
F	Relative bioavailability
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume (flow rate) in 1 second
FVC	Forced Volume Vital Capacity
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
kg	Kilograms
mcg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent-to-Treat
mL	Milliliter
NAEPP	National Asthma Education and Prevention Program
OGD	Office of Generic Drugs
PC_{20}	Concentration (mg/mL) of methacholine required to reduce FEV_1 by 20%
PD	Pharmacodynamic
PP	Per-Protocol
RR	Respiratory Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SDTM	Study Data Tabulation Model

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1. INTRODUCTION

This Statistical Analysis Plan (SAP) is based on the final Clinical Study Protocol CLR_17_08 [redacted] Study No. [redacted] Rev 5.0 dated 08/28/2018. The SAP provides details on the planned statistical methodology for the analysis of the study data. The SAP also outlines the statistical programming specifications for the tables, listings and figures.

This SAP describes the study endpoints, derived variables, anticipated data transformations and manipulations, and other details of the analyses not provided in the study protocol. This SAP therefore outlines in detail all other aspects pertaining to the planned analyses and presentations for this study.

The following documents were reviewed in preparation of this SAP:

- Final Clinical Study Protocol CLR_17_08 ([redacted] Study No. [redacted] Rev 5.0 dated 08/28/2018
- The final Electronic Case Report Form (eCRF) specification for [redacted] Study No. [redacted]

The reader of this SAP is encouraged to also read the clinical protocol for details on the conduct of this study, and the operational aspects of clinical assessments and timing for completing a patient in this study.

2. OBJECTIVES

The objectives of this study are to:

1. Demonstrate the pharmacodynamic equivalence of the Test formulation of albuterol sulfate inhalation aerosol, eq 90 mcg base (Sun Pharmaceuticals Industries Limited) to the marketed product PROAIR® HFA (albuterol sulfate) Inhalation Aerosol, eq 90 mcg base (Teva Respiratory, LLC) using methacholine bronchoprovocation in subjects with stable, mild asthma based on National Asthma Education and Prevention Program (NAEPP) guidelines.
2. Compare the safety of Test, low-dose Reference, high-dose Reference, and Placebo treatments in subjects with stable, mild asthma based on NAEPP guidelines.

3. OVERALL STUDY DESIGN

This randomized, single-dose, double-blind, double-dummy, four-period, four-sequence, four-treatment, Placebo and active controlled, comparative, multiple-center, crossover-design bronchoprovocation study has been designed to evaluate the pharmacodynamic equivalence of albuterol sulfate HFA inhalation aerosol, eq 90 mcg base per inhalation (Sun Pharmaceuticals

Industries Limited) to PROAIR® HFA (albuterol sulfate) Inhalation Aerosol, eq 90 mcg base per inhalation (Teva Respiratory, LLC) in subjects with stable, mild asthma.

Approximately 123 subjects with persistent bronchial asthma will be randomized. To qualify for inclusion in the study, subjects must be at least 18 years of age, with a documented diagnosis of mild asthma as defined by the NAEPP guidelines at least 6 months before Screening.

Randomized subjects who withdraw from the study will not be replaced.

Before any study-specific procedures are performed, all subjects will read and sign the IRB-approved informed consent form.

Eligible subjects will complete 5 clinic visits as follows:

- Visit 1: Screening (Day -14 to -1)
- Visit 2: Period 1
- Visit 3: Period 2
- Visit 4: Period 3
- Visit 5: Period 4

Clinical assessments will include FEV_1 taken at each visit. If reattempts are necessary, an acceptable FEV_1 is defined as the highest of three to four acceptable curves obtained at each time point. FVC and FEV_1/FVC ratio [(FEV_1/FVC) x 100] will also be recorded along with FEV_1 measurements at each visit.

Screening

Screening evaluations will be performed in accordance with the study calendar. Clinical assessments will include: vital sign measurement, height, weight, physical examination, urine pregnancy test (for all women of childbearing potential), 12-lead electrocardiogram (ECG), and pulse oximetry (during methacholine bronchoprovocation challenges). Chest x-ray may be performed at discretion of the Investigator. Qualifying FEV_1 at Screening must be $\geq$ 80% of predicted value. Once Qualifying FEV_1 is obtained, a sterile, saline control will be administered to the subject through a nebulizer. Spirometry will be performed following the saline administration. Post-saline FEV_1 should not drop more than 10% from pre-saline FEV_1 and should be $\geq$ 70% of predicted value. If the subject fails to meet any of these requirements, the procedures must be stopped, rescue albuterol administered, and the visit should be rescheduled. All clinical assessments except height and weight will be performed at each rescheduled visit. Subjects who fail three consecutive visits will not be eligible to participate in the study. Subjects meeting post-saline FEV_1 criteria will undergo methacholine bronchoprovocation challenge with

progressively increasing concentrations to determine the subject's baseline provocation concentration of inhaled methacholine required to reduce FEV_1 by 20% (PC_{20}) relative to the post-saline value. The maximum concentration of methacholine to be administered in this step will be 8 mg/mL. Subjects who do not respond to methacholine doses at or below 8 mg/mL will not be eligible for enrollment in the study.

Once the methacholine challenge test is completed, rescue albuterol will be administered and spirometry will be performed approximately 15 minutes later until the subject's FEV_1 returns to within 90% of the best post-saline FEV_1 or until the Principal Investigator determines that the FEV_1 has stabilized and it is safe to allow the subject to leave the site. Vital signs will also be repeated.

Dosing Visits

Eligible subjects will return for four treatment visits. The first dosing visit will occur no earlier than 24 hours and no more than 14 days after Screening procedures and the interval (washout period) between dosing visits should be at least 48 hours. At each treatment visit, the following will be performed before dosing:

- Vital sign measurement
- 12-lead electrocardiogram (ECG) as the discretion of the Investigator after the initial Screening visit
- Pulse oximetry (during methacholine bronchoprovocation challenges)
- Concomitant medication update (confirming washouts)
- Adverse Events (AE) review
- Urine pregnancy test for all women of childbearing potential

A pre-treatment evaluation will be performed. This will confirm that pre-challenge FEV_1 is $\geq$ 80% of predicted and within 88 and 112% of qualifying spirometry value at Screening visit. After the first inhalation of saline control is administered, the FEV_1 should not drop more than 10% compared to pre-challenge value and should be $\geq$ 70% of the predicted value. If the subject fails to meet any of these requirements, the procedures must be stopped, albuterol administered, and the visit should be rescheduled. Subjects who fail three consecutive visits should be dropped from the study.

Subsequently, review of inhaler dosing technique, priming and preparation of inhalers will be performed. The subject will receive one of the four randomized study treatments. The time of last actuation will be recorded, as well as the adequacy of inhaler technique. Approximately 15

minutes after the last inhalation of study treatment, a methacholine bronchoprovocation challenge will be given with progressive concentrations to determine the PC_{20}. The 20% reduction in FEV_1 will be determined relative to the post-saline FEV_1. After the procedures have been completed, albuterol will be administered to reverse airway obstruction and subjects will be followed until FEV_1 returns to within 90% of the best FEV_1 captured during the saline stage on that study day or until the Principal Investigator determines that the FEV_1 has stabilized and it is safe to allow the subject to leave the site.

Subjects who withdraw prematurely will be evaluated at a final visit, but spirometry, chest x-rays, and methacholine administration do not need to be performed.

The spirometry procedures and the methacholine bronchoprovocation challenges in this study are to be performed in accordance with the ATS Guidelines for Methacholine and Exercise Challenge Testing. The maximum methacholine dose administered will be 8 mg/mL at Screening and 128 mg/mL for treatment visits.

Figure 1: Study Schematic

Procedures	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	Screening	Period 1	Period 2	Period 3	Period 4 End of Study
Informed Consent	X				
Baseline Demographics	X				
Medical History	X				
Vital Signs*	X	X	X	X	X
Height and Weight	X				
Physical Exam	X				X
Urine Pregnancy Test**	X	X	X	X	X
12-Lead ECG	X	X†	X†	X†	X†
Chest X-Ray‡	X				
Concomitant Medication	X	X	X	X	X
Spirometry (FEV_1 and FVC)§	X	X	X	X	X
Saline Control Administration	X	X	X	X	X
Methacholine Challenge	X	X	X	X	X
Pulse Oximetry	X	X	X	X	X
Inclusion/Exclusion Criteria Review	X				
Prime, dispense study product and instructions		X	X	X	X
Dosing‖		X	X	X	X
Assessment of Compliance		X	X	X	X
Adverse Events	X	X	X	X	X
Provide Diary	X	X	X	X	
Collect /Review Diary		X	X	X	X
Schedule next visit	X	X	X	X	

* Vital signs will be measured before and after methacholine bronchoprovocation challenges at all visits.
** Female subjects of childbearing potential.
† 12-lead ECG to be performed at Screening may be repeated before methacholine bronchoprovocation challenges at discretion of Investigator.
‡ Chest X-ray is to be performed at discretion of Investigator.
§ FEV_1 and FVC measurements will be performed before saline control, after saline control, and after methacholine administration. If reattempts are necessary, an acceptable FEV_1 is defined as the highest of three to four acceptable curves obtained at each time point.
‖ Subjects will receive four puffs of study product from four different inhalers (each dose from a separate inhaler).

4. IDENTITY O F INVESTIGATIONAL PRODUCT

The following products will be used in the study:

Test (T active): Albuterol Sulfate Inhalation Aerosol, eq 90 mcg base per inhalation (Sun Pharmaceuticals Industries Limited)

Reference (R active): PROAIR® HFA (albuterol sulfate) Inhalation Aerosol, eq 90 mcg base per inhalation (Teva Respiratory, LLC)

Test Placebo (T Placebo): Placebo for Albuterol Sulfate Inhalation Aerosol (i.e., vehicle canister with T active actuator [Sun Pharmaceuticals Industries Limited])

Reference Placebo (R Placebo): Placebo for Albuterol Sulfate Inhalation Aerosol (i.e., vehicle canister with R active actuator [Sun Pharmaceuticals Industries Limited])

Treatments will be as follows:

Treatment A: Zero-dose Two different Reference Placebo inhalers and two different Test Placebo inhalers	1 puff Inhaler 1 1 puff Inhaler 2 1 puff Inhaler 3 1 puff Inhaler 4
Treatment B: 90 mcg of Reference One Reference inhaler, one Reference Placebo inhaler, and two different Test Placebo inhalers	1 puff Inhaler 1 1 puff Inhaler 2 1 puff Inhaler 3 1 puff Inhaler 4
Treatment C: 180 mcg of Reference Two different Reference inhalers and two different Test Placebo inhalers	1 puff Inhaler 1 1 puff Inhaler 2 1 puff Inhaler 3 1 puff Inhaler 4
Treatment D: 90 mcg of Test One Test inhaler, one Test Placebo inhaler, and two different Reference Placebo inhalers	1 puff Inhaler 1 1 puff Inhaler 2 1 puff Inhaler 3 1 puff Inhaler 4

5. RANDOMIZATION AND BLINDING

At Visit 1 eligible subjects will be enrolled in the study, and scheduled for Visit 2. At Visit 2, eligible subjects will be randomized to one of the four sequences as shown below. Treatments

will be administered according to a four-treatment, four-period, four-sequence design. The randomization will be generated in blocks of four with each sequence occurring once in each block.

Sequence	Period 1	Period 2	Period 3	Period 4
1	A	B	C	D
2	D	C	B	A
3	C	A	D	B
4	B	D	A	C

[redacted].

Subjects will be randomized to a treatment regimen in a blinded fashion by assigning randomization numbers in ascending sequential order starting with the lowest available randomization number at each site. All subjects randomized will be identified by initials, date of birth, and a unique seven-digit subject number. The first two-digits will identify the Investigator site where the subject was enrolled and the last five will correspond with the randomization number of study product 'Treatment Box' assigned to the subject. A perforated or two-part label will be attached to each of the small boxes containing individual inhalers. Both pieces of the label should include the following information: Protocol number, randomization number, space for subject's initials, statement that the study product is for Investigational Use only, space for dispensing date and the Sponsor's name. In addition all subjects will be provided with written instructions on how to use the study medication. One part of the label will remain attached to the box. The other part will be removed before dispensing and attached to the study product log.

The Investigator, staff at the study site, study monitors, and data analysis/management personnel will be blinded to the patient assignment.

6. SAMPLE SIZE

The sample size estimation for this study was based on data from the study by Newhouse et al. that reported the bronchoprotective effect of inhaled salbutamol (albuterol) on methacholine $PC_{20}FEV_1$.

The highest within-subject coefficient of variability (COV) value for ln-transformed PC_{20} was estimated as 0.846 from the mean ratio and SD values for the PC_{20} at the 200 and 100 mcg doses (Table 1 in reference 2). Based on this COV, 98 evaluable subjects would be required in the PD population to demonstrate pharmacodynamic equivalence (i.e., 90% confidence interval on relative bioavailability [F] is within the bioequivalence limits of 0.67 to 1.50) with 90% power for a crossover study, assuming a true ratio of F = 1.1. To allow for approximately 20% of subjects that may discontinue from the study or have major protocol violations, and therefore not qualify for the PD population, up to 123 subjects will be randomized in the study.

7. STUDY POPULATIONS

Per-Protocol (PP) Population

The PP population will include all subjects who:

- Completed all four randomized treatment periods with an evaluable $PC_{20}FEV_1$ in each period.
- Were compliant with study treatment dosing procedures.
- Did not use any restricted concomitant medications.
- Did not have any other significant protocol deviations.

Pharmacodynamic (PD) Population

The PD population used in the dose-scale analyses will include subjects who:

- Completed at least one of the four randomized treatment periods with an evaluable $PC_{20}FEV_1$.
- Were compliant with study treatment dosing procedures.
- Did not use any restricted concomitant medications.
- Did not have any other significant protocol deviations.

Safety Populations

The Safety population will include all subjects who administered at least one actuation of any of the four investigational products (Test, Reference, Test Placebo, Reference Placebo) in any of the four randomized treatment periods.

PP and PD populations will be shortlisted upon a blinded review of the data by CRO and sponsor before database lock.

8. STATISTICAL ANALYSIS METHODS

According to standard statistical practice, the significance threshold is set to $p < 0.05$ (two-tailed). Data will be summarized with respect to demographic and baseline characteristics and safety variables.

For categorical variables and non-missing data, the number and percent of each category within a parameter will be calculated. For continuous variables, statistics will include n, mean, standard deviation, median, minimum and maximum values.

All statistical analyses will be conducted using Statistical Analysis System (SAS®, version 9.4 or higher). [redacted]

8.1 Baseline Characteristics

8.1.1 Patient Disposition

The patient disposition information will be summarized overall. The number of subjects randomized will be tabulated overall. In addition, completion status and primary reason for withdrawal will be summarized overall.

8.1.2 Demographic and Other Baseline Characteristics

The following subject demographic characteristics will be summarized separately in the PP, PD and Safety populations:

- Age (years)
- Sex (male/female)
- Ethnicity (Hispanic/non-Hispanic)
- Race (White, Black/African American, Native Hawaiian or Other Pacific Islander, Asian, American Indian or Alaska Native)
- Tobacco use (yes/no)
- Number of years patient suffered from symptoms caused by asthma
- Qualifying spirometry (Visit 1, Pre- and Post-saline)
- PC_{20} FEV_1 at Visit 1

Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, maximum); categorical variables will be described in frequencies and percentages. Summary tables will be included.

All data will be listed by patient.

8.1.3 Medical History

At Visit 1, subjects will be questioned about medical history, including acute and chronic medical history and medical history relevant to their asthma.

Medical history data will be listed by patient.

8.1.4 Concomitant Medications

On Visit 1, subjects will be asked to list their current and recent (≤ 6 months) medication use. During all subsequent visits, subjects will be asked about ongoing and new concomitant medications.

All prior and concomitant medications will be listed by patient.

8.2 Pharmacodynamic Equivalence Analyses

Pharmacodynamic (PD) equivalence between Test and Reference will be based on the dose-scale method of analysis of the post-dose PC_{20} (mg/mL) data using non-linear E_{max} modeling, as outlined in the FDA Draft Guidance on Orlistat capsule (3). Alternative models may be tested if warranted by the data, and these models as well as the specific criteria related to their use, are described in more detail in Section 8.2.7.

8.2.1 Primary Pharmacodynamic Endpoint

The primary pharmacodynamic endpoint is the post-dose $PC_{20,}$ which is the provocative concentration of methacholine challenge agent required to reduce the forced expiry volume in one second (FEV_1) by 20%, following the administration of different doses of albuterol (or placebo) by inhalation.

The 20% reduction in FEV_1 will be determined relative to the post-saline FEV_1 measure before placebo or albuterol administration. The methacholine PC_{20} will be calculated by linear interpolation from the observed data relating the % decrease in FEV_1 from the post-saline FEV_1 to the concentration of methacholine that provokes at least a 20% decrease in FEV_1. This interpolation will be based on log transformed methacholine concentrations. In the event that subjects receiving the maximum concentration of methacholine (128 mg/mL) at any dosing visit (Visits 2-5) do not achieve at least a 20% fall in FEV_1, then they will have their $PC_{20}FEV_1$ data recorded as > 128 mg/mL and the data from that visit will be excluded from the statistical analysis; the data from the other Visits for these subjects will be eligible for inclusion in the PD

population but will be excluded from the PP population.

8.2.2 Population

The primary dose-scale analysis will be performed using the PD population as NONMEM allows for the use of all available data, without biasing the F estimation. For information purposes only, an additional dose-scale analysis will be performed using the PP population.

8.2.3 PC_{20} Log Transformation

The FDA product-specific guidance for albuterol sulfate explains that "*log transformation of the PD data before fitting the Emax model is recommended for dose-scale analysis*" (4); however, this guidance does not specify which log transformation should be used. Therefore, the PC_{20} values will be transformed using the reported Log_2 method (5,6), prior to NONMEM® dataset construction.

[redacted]

The datasets will include individual albuterol dosing information and PC_{20} data. The actual dosing amount per treatment period will be used. Formulation will also be entered in the dataset. These will be entered as 0 for the reference product and 1 for the test product. The placebo dose will also be considered as the reference formulation. The dose amount for the placebo treatment will be set to 0. Data will be excluded from the analysis if insufficient or inaccurate dosing information are recorded.

8.2.5 Dose-Scale Approach

To assess bioequivalence using PD endpoints, the FDA albuterol-specific guidance (4) recommends using the dose-scale approach described in FDA's orlistat guidance (3). This approach involves fitting dose-response data using the following equation:

Equation 1 $$\text{Response} = E_0 + \frac{E\max \cdot Dose \cdot F_{rel}}{ED_{50} + Dose \cdot F_{rel}}$$

In Equation 1, the response is the measured PC_{20}, E_0 is the baseline response, Emax is the maximal response, ED_{50} is the dose associated with half of the maximal response and F_{rel} is the relative bioavailability of the test product compared to that of the reference product. This model is based on the assumption that E_0, ED_{50} and Emax are the same for the test and reference products.

The FDA orlistat guidance allows for the dose-scale Emax model to be fitted either to the mean or to the individual scores of dose response data. The analysis described in this plan will be

based on each individual score because this method is generally considered more robust in a bioequivalence (BE) crossover trial.

The PC_{20} data will be analyzed based on a two-step dose-scale analysis to estimate F_{rel}:

- Firstly, a dose-response relationship will be mathematically described by fitting the relevant Emax model to the individual dose-response data, and an estimate for F_{rel} will be obtained.
- Secondly, a 90% confidence interval for F_{rel} will be estimated by using Efron's (7) bias-corrected and accelerated (BCa) method.

8.2.6 Dose Response Emax Model

The analysis will use the FDA recommended Emax model using NONMEM®. The model will include the following:

- Etas will be included on PD parameters E_0, Emax and ED_{50}, coded as Theta(x)+Eta(x) for E_0 and Emax and as Theta(x)*exp(Eta(x)) for ED_{50}.
- The possibility of adding an eta on the F_{rel} parameter will be tested..
- A combination of proportional and additive residual error (Epsilons).

Additionally, the model may be simplified by removing certain parameters (Etas or Epsilons) if they are estimated to be close to the boundary (*e.g.,* 0).

Quality of fit and selection of an alternate model will be determined using the objective function. A lower objective function is preferred if a model has the same number of parameters. Otherwise, the model will be chosen according to the difference in the MOF based on a Chi-square distribution ($p < 0.01$ will be considered significant), taking the difference in the numbers of fitted parameters into account. Throughout the modeling process, the first-order conditional estimate (FOCE) option in NONMEM will be used.

8.2.7 Alternative Approach to the Dose Response Emax Model

The Emax model (as described in Sections 8.2.5 and 8.2.6) is the model described by the FDA in the Orlistat guidance (3) and is the preferred one. However, based on the results of this Emax model, further analysis may be required. More specifically, an alternate approach will be used to re-analyze the data if the following 2 criteria are met:

- If the predicted response of the low-dose and high-dose of albuterol fall within 20-80% of the maximum response.
- If the predicted response for the low-dose of albuterol is ≥ 75% of the predicted response for the high-dose albuterol.

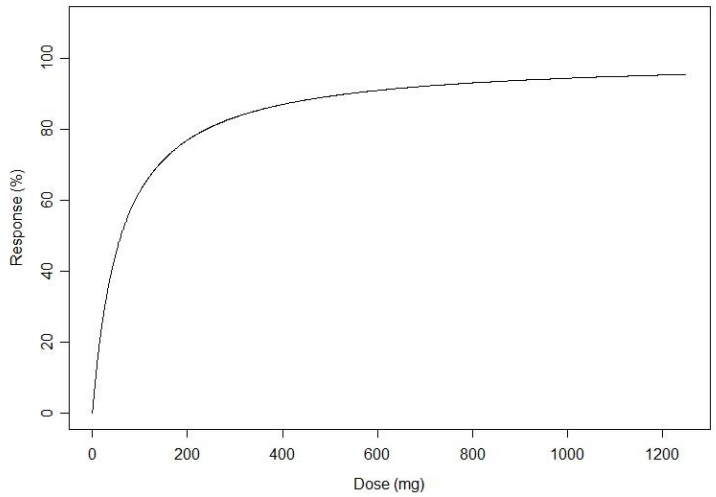
Therefore, if the Emax model previously described in this section is appropriate at describing the PC_{20} data, it will be used and will be considered final. However, if this Emax model is considered inappropriate (based on criteria listed above), the alternative modeling approach will be used as described below.

The relationship between dose and response can often be described by a hyperbolic curve that is defined by the following equation, often called the "Emax model":

Equation 2 $$Response = \frac{Emax \cdot Dose}{Dose + D_{50}}$$

This relationship is depicted below, in Figure 1.

Figure 1. Example of Emax Dose-Response Relationship



In theory, a minimum of two observations are required to estimate the two model parameters (Emax and D_{50}). Ideally, these two data points should be as far apart as possible, and lie close to the inflection points on the curve, to properly characterize Emax and D_{50}. This ideal scenario is depicted in Figure 2; with the predicted Emax curve in black, observed data represented by red circles, and their associated error shown by vertical lines passing through the circle's center.

Figure 2. Example of Emax Relationship with Data Points that are Spread Out

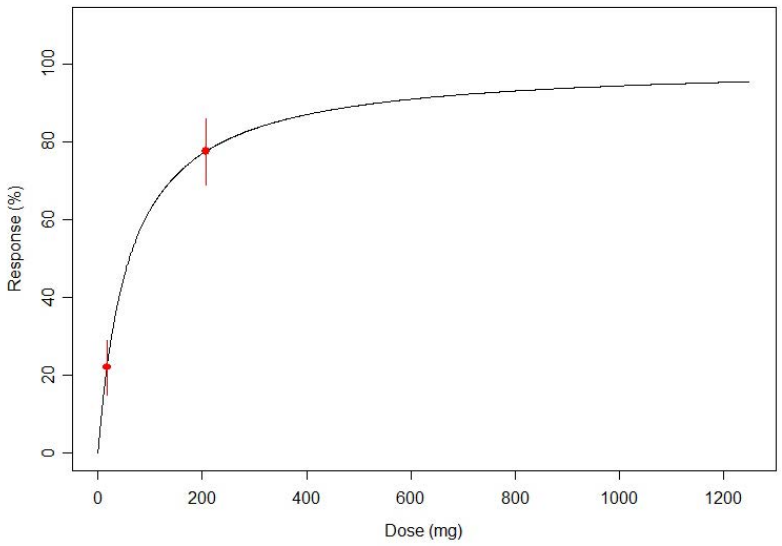
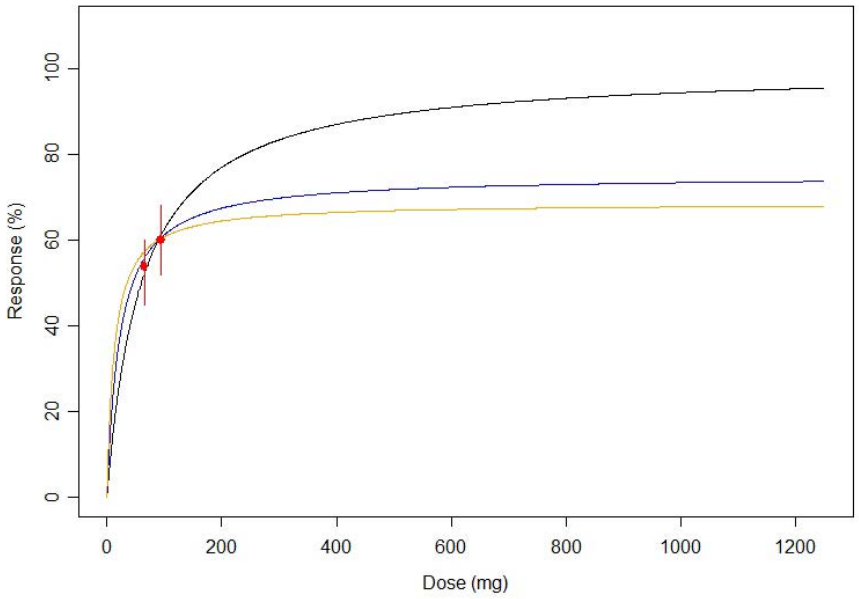


Figure 2 depicts the ideal scenario; however, in practice the data points may not always lie this far apart. If these two data points are too close to one and other, Emax and ED_{50} estimations can be more difficult and less certain.

In other words, different Emax relationships, or combinations of parameter estimates (Emax and ED_{50}), could explain the same data points; therefore, it becomes more difficult to know with certainty which relationship reflects reality. This problem is illustrated in Figure 3, where very different Emax curves (denoted by the black, blue and yellow lines) all pass through the same two observed data points (red points with vertical error bars).

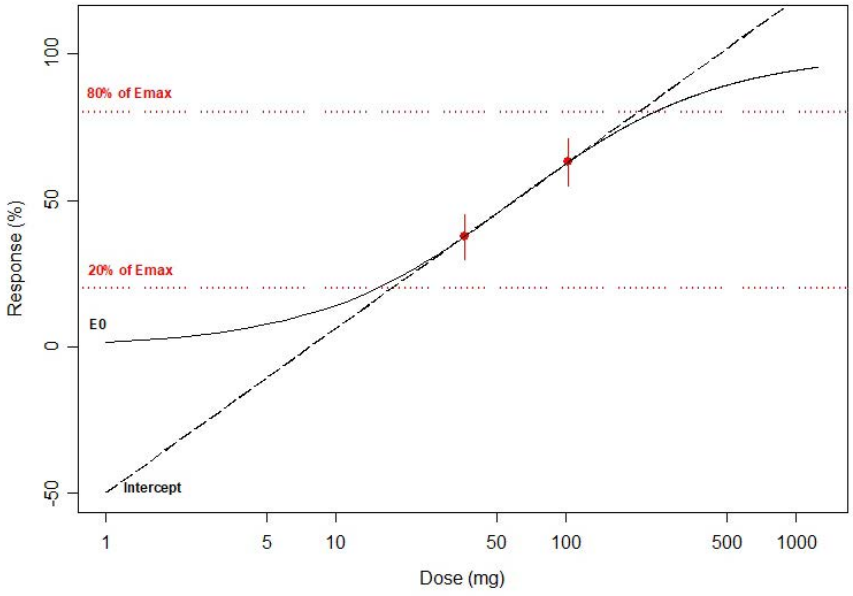
Figure 3. Example of Possible Emax Curves for the Same Data Points



If the response data associated with the two doses (90 mg and 180 mg) are close to one and other, which is analogous to the scenario depicted in Figure 3, this proximity of the data will make it difficult to properly estimate the parameters Emax and ED_{50}.

In such cases, log-transformation of the independent variable (dose) can be beneficial. The $\log_{10}$ transformation of dose is used in such analyses. Despite the hyperbolic nature of the Emax curve, it is recognized that when the data on the X-axis are log-transformed, the relationship becomes more linear, especially between doses that are associated with 20% and 80% of Emax. (8); this is illustrated in Figure 4.

Figure 4. Depiction of Log-Linear Dose-Response Relationship



When using a log-linear model, the relationship between log(dose) and response can be described by a straight-line between 20% and 80% of the maximum effect. Consequently, it is no longer necessary to estimate Emax and ED_{50} parameters, thereby removing the uncertainty associated with these parameter estimates. Instead, the relationship between log(dose) and response can be described by a simple slope and intercept.

It can also be appreciated from Figure 4 that when using the log-linear model, the intercept (the hypothetical response at dose zero based on a linear relationship) is not equivalent to the E_0 that is associated with the Emax model. Therefore, response data associated with the placebo should not be fitted by the log-linear model for two reasons:

1) Linearity only applies to doses that are associated with responses that are between 20% and 80% of the maximal response. By definition, this excludes a dose of zero that is not associated with a response.
2) Inclusion of placebo data would falsely bias the estimation of the intercept parameter, and the slope that would be fitted by the model would not reflect the true slope. Other parameter estimates (such as F_{rel}) will also be unreliable.

For the reasons above, the placebo data should not be fitted in the log-linear model. In such an analysis, only response data associated with the 90 mg and 180 mg should be fitted by this type of model. An additional analysis may be done for which the response data associated with the 90 mg and 180 mg may be placebo-corrected to account for the placebo effect.

Therefore, in this alternate model, PC_{20} would be fitted according to the following equation:

Equation 3 $$Response = Intercept + Slope * Dose * F_{rel}$$

In this relationship, both response and dose are log-transformed.

The analysis using the Emax model detailed in the previous section will be presented for information purposes only even if this alternative approach is used.

8.2.8 Bootstrap

In the FDA orlistat guidance (3), 90% CI are constructed using a nonparametric bootstrap technique. Essentially, subjects are repeatedly sampled at random with replacement, creating new datasets of the same size as the original dataset and new PD parameters are estimated using the same final model. Ten thousand (10 000) of these bootstrap samples will be constructed and NONMEM® analyses will be performed on all. A matrix of bootstrap mean population estimates (F_{rel}) will thus be obtained (9). Only the bootstrap for successful NONMEM® analyses will be used to build the 90% CI.

Bootstrapping analyses will be conducted using Wings for NONMEM® version WFN7.

8.2.9 Calculation of Confidence Intervals for Frel

The bias-corrected and accelerated (BCa) method for constructing the 90% CI for F_{rel} will be employed as described in the FDA guidance for orlistat (3), using the formulae described by Efron & Tibshirani (7).

The BCa interval of intended coverage 1-2α is given by Equation 4, where $\hat{\theta}^{*(\alpha_1)}$ and $\hat{\theta}^{*(\alpha_2)}$ are the $100 \cdot \alpha_1^{th}$ and $100 \cdot \alpha_2^{th}$ percentiles of the B bootstrap replications, respectively. The variables α_1 and α_2 are defined in Equations 5a and 5b.

Equation 4 $$BC_a : \left(\hat{\theta}^{*(\alpha_1)}, \hat{\theta}^{*(\alpha_2)}\right)$$

Equations 5a $$\alpha_1 = \Phi\left(\hat{z}_0 + \frac{\hat{z}_0 + z^{(\alpha)}}{1 - \hat{a} \cdot \left(\hat{z}_0 + z^{(\alpha)}\right)}\right)$$

Equation 5b $$\alpha_2 = \Phi\left(\hat{z}_0 + \frac{\hat{z}_0 + z^{(1-\alpha)}}{1 - \hat{a} \cdot \left(\hat{z}_0 + z^{(1-\alpha)}\right)}\right)$$

In Equations 5a and 5b, $\Phi(\cdot)$ represents the standard normal cumulative distribution function and $z^{(\alpha)}$ is the $100 \cdot \alpha^{th}$ percentile point of a standard normal distribution. The variables $\hat{a}$ and $\hat{z}_0$ represent acceleration and bias-correction, respectively. They are computed as described by Equations 6 and 7.

Equation 6

$$\hat{z}_0 = \Phi^{-1}\left(\frac{\#\left\{\hat{\theta}^*(b) < \hat{\theta}\right\}}{B}\right)$$

Equation 7

$$\hat{a} = \frac{\sum_{i=1}^{n}\left(\hat{\theta}_{(\cdot)} - \hat{\theta}_{(i)}\right)^3}{6\left\{\sum_{i=1}^{n}\left(\hat{\theta}_{(\cdot)} - \hat{\theta}_{(i)}\right)^2\right\}^{3/2}}$$

In Equation 6, $\Phi^{-1}(\cdot)$ indicates the inverse function of a standard normal cumulative distribution function. The numerator represents the number of bootstrap values $\hat{\theta}^*(b)$ that are less than the original estimate of $\hat{\theta}$. B is the number of bootstrap replicates.

Equation 7 uses $\hat{\theta}_{(\cdot)}$ and $\hat{\theta}_{(i)}$, which are the average values of all jackknife replications and the i^{th} jackknife replication of $\hat{\theta}$, respectively.

The calculation of the BCa interval will be performed with the code provided by Efron & Tibshirani (10), using S-Plus for Windows®.

8.2.10 Calculation of Confidence Intervals for F_{rel}

The test formulation will be declared bioequivalent to the reference formulation if the estimated F_{rel} and the 90% CI are completely contained within the range of 67.00 to 150.00%.

8.3 Safety Analysis

All study subjects who administered at least one actuation of any of the study products (Safety Population) will be included in the comparative safety analysis.

8.3.1 Adverse Events

All the adverse events (AEs) reported throughout the study will be coded and classified according to the MedDRA (Medical Dictionary for Regulatory Activities) coding dictionary

(Version 20.0 or higher). Each adverse event is to be evaluated for date of start and end, seriousness, severity, causal relationship with the study drugs, action taken and outcome.

A summary table of the number and percent of subjects with AEs by system organ class, preferred term, will be presented. Each patient will be counted only once within each preferred term. Other summaries may be added based on the data obtained.

A frequency summary table of the number of AEs by system organ class, preferred term, and severity will be presented. Severity will be classified as "Mild", "Moderate" or "Severe".

Similarly, a frequency summary table of the number of AEs by system organ class, preferred term, and relationship to a study drug will be presented. Relationship to a study drug will be classified as "Not Related" or "Related" where causality "Certain, Probable and Possible" will be assessed as "Related" while "Unlikely and Unrelated" will be assessed as "Not Related".

A frequency summary table of the number of SAEs by system organ class, preferred term will also be presented by treatment group.

If sufficient data exist, AEs frequencies will be compared among treatments using Fisher's exact test. If the overall Fisher's exact test is significant for comparisons across the 4 treatments, pair-wise testing between treatments will be conducted to determine which contrasts are significant.

All AEs will be listed by patient for the Safety Population.

8.3.2 Vital Signs

At each clinic visit, subjects' vital signs (pulse, BP, temperature, and respiration rate) will be recorded before and after methacholine procedures.

Descriptive summaries (number of observations, mean, standard deviation, minimum, median and maximum) will be provided by treatment and time point.

All data will be listed by patient.

8.3.3 Physical Exam

At Visits 1 and 5, the Investigator will perform a general physical exam for each qualified patient; any significant findings will be noted. At minimum, the physical exam must include a head, ear, eyes, nose, lungs and throat examination.

Any abnormal physical exam results will be listed by patient and visit.

8.3.4 12-lead ECG

Subjects will undergo a 12-lead ECG at Screening. An ECG may be performed at subsequent visits at the Investigator`s discretion. Any clinically significant findings will be noted.

12-lead ECG results will be listed by patient and visit.

8.3.5 Pregnancy Test

Urine pregnancy tests on women of childbearing potential will be performed at each clinic visit, including rescheduled visits.

Positive urine pregnancy test results will be listed by patient and visit.

8.3.6 Concentration of Methacholine Required to Reduce FEV_1 by 20% (PC_{20})

Descriptive summaries (number of observations, mean, standard deviation, minimum, median and maximum) will be provided separately for PC_{20} by treatment for the PP, PD and Safety Population.

8.3.7 Forced Expiratory Volume (flow rate) in 1 second (FEV_1)

Descriptive summaries (number of observations, mean, standard deviation, minimum, median and maximum) will be provided separately for pre-challenge FEV_1 by visit for the PP, PD and Safety Population.

8.3.8 Protocol Deviations

The total number of subjects with protocol deviation, the total number of protocol deviations as well as protocol deviation categories will be summarized.

Protocol deviations will be listed by patient.

8.4 Multiple Comparisons

No multiple comparison adjustment will be made in this study.

8.5 Methods for Handling Missing Data

Each demographic and baseline characteristic variable will be analyzed using all available data. Thus, subjects with missing data will only be excluded from analyses for which data are not available.

8.6 Interim Analyses

No interim analyses are planned for this study.

9. TABLE, LISTING AND FIGURE SHELLS

The following shells are included to provide a framework for displaying data in the final clinical study report. These shells are meant to provide a general layout for final Tables, Listings and Figures; therefore, they may not reflect every aspect of the current study.

Tables, Listings and Figures are numbered in accordance with the ICH structure. Following data

analyses, table headers, variables names and footnotes will be modified as needed.

Descriptive and inferential statistical (including bootstrap) analyses will be performed using SAS® statistical software version 9.4 or higher and NONMEM®, unless otherwise noted.

T16.1.9.1 Summary of Patient Disposition

Subjects	Overall (n (%))
Subjects Screened	xx
Subjects Randomized	xx
Safety Population	xx
Completed Study	xx (xx.x)
Terminated Early	xx (xx.x)
Adverse Event	xx (xx.x)
Lack of Efficacy	xx (xx.x)
Lost to follow-up	xx (xx.x)
etc.	xx (xx.x)
	xx (xx.x)
Other	xx (xx.x)

% is based on total number of subjects in the safety population.

T16.1.9.2 Summary of Protocol Deviations
(Safety Population)

	Total N = xx
Total Subjects with Protocol Deviations	xx
Total Deviations	xx
Assessment conducted out of window	xx
Lost to Follow-up	xx
Missed Visit	xx
Non-compliance with study drug	xx
Non-compliance with study procedures	xx
Restricted Medication	xx
etc.	xx
	xx
Other	xx

T16.1.9.3 Summary of Patient's Treatments Included in the Pharmacodynamic Analysis

Patient Screen Number	Patient Randomization Number	Sequence	Treatment A	Treatment B	Treatment C	Treatment D
xx-xxxx	xx-xxxxx	1	Yes	Yes	Yes	No

Sequence: 1=ABCD, 2=DCBA, 3=CADB, 4=BDAC

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T16.1.9.4 Summary of Demographic Data and Baseline Characteristics (Safety Population)

		Total N = xx
Age (years)	n	xx
	Mean ± SD	xx.x ± x.x
	Median	xx.x
	Range	xx-xx
Race (n (%))	American Indian or Alaska Native	xx (xx.x)
	Asian	xx (xx.x)
	Black/African American	xx (xx.x)
	Native Hawaiian or other Pacific Islander	xx (xx.x)
	White	xx (xx.x)
	Other	xx (xx.x)
Ethnicity (n (%))	Hispanic or Latino	xx (xx.x)
	Not Hispanic or Latino	xx (xx.x)
Gender (n (%))	Female	xx (xx.x)
	Male	xx (xx.x)
Tobacco use (n (%))	Yes	xx (xx.x)
	No	xx (xx.x)
Number of years patient has suffered from symptoms caused by asthma	n	xx
	Mean ± SD	xx.x ± x.x
	Median	xx.x
	Range	xx-xx

		Total **N = xx**
FEV_1 (L) (Pre-saline)	n	xx
	Mean ± SD	xx.x ± x.x
	Median	xx.x
	Range	xx-xx
FEV_1 (L) (Post-saline)	n	xx
	Mean ± SD	xx.x ± x.x
	Median	xx.x
	Range	xx-xx
PC_{20} FEV_1 (mg/mL)	n	xx
	Mean ± SD	xx.x ± x.x
	Median	xx.x
	Range	xx-xx

N= number of subjects in the safety population; n= number of subjects with data available; % is based on N

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Similar table will be created for:

T16.1.9.5 Summary of Demographic Data and Baseline Characteristics
(Pharmacodynamic Population)

T16.1.9.6 Summary of Demographic Data and Baseline Characteristics
(Per-Protocol Population)

T16.1.9.7 Summary of Concentration (mg/mL) of Methacholine Required to Reduce FEV_1 by 20% (PC_{20}) (Safety Population)

Statistic	Treatment A N = xx	Treatment B N = xx	Treatment C N = xx	Treatment D N = xx
n	xx	xx	xx	xx
Mean ± SD	xxx.x ± xx.x	xxx.x ± xx.x	xxx.x ± xx.x	xxx.x ± xx.x
Median	xxx.x	xxx.x	xxx.x	xxx.x
Range	xxx.x – xxx.x	xxx.x – xxx.x	xxx.x – xxx.x	xxx.x – xxx.x

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T16.1.9.8 Summary of Concentration (mg/mL) of Methacholine Required to Reduce FEV_1 by 20% (PC_{20}) (Pharmacodynamic Population)

T16.1.9.9 Summary of Concentration (mg/mL) of Methacholine Required to Reduce FEV_1 by 20% (PC_{20}) (Per-Protocol Population)

T16.1.9.10 Summary of Pre-challenge Forced Expiratory Volume (flow rate) in 1 second (FEV_1) (Safety Population)

Visit	Statistic	Overall
Visit 1 (Pre-saline)	N	xx
	Mean ± SD	xxx.x ± xx.x
	Median	xxx.x
	Range	xxx.x – xxx.x
Visit 1 (Post-saline)	N	xx
	Mean ± SD	xxx.x ± xx.x
	Median	xxx.x
	Range	xxx.x – xxx.x
Visit 2 (Pre-saline)	N	xx
	Mean ± SD	xxx.x ± xx.x
	Median	xxx.x
	Range	xxx.x – xxx.x
Visit 2 (Post-saline)	N	xx
	Mean ± SD	xxx.x ± xx.x
	Median	xxx.x
	Range	xxx.x – xxx.x
Visit 3 (Pre-saline)		
Visit 3 (Post-saline)		
Visit 4 (Pre-saline)		
Visit 4 (Post-saline)		
Visit 5 (Pre-saline)		
Visit 5 (Post-saline)		

T16.1.9.11 Summary of Pre-challenge Forced Expiratory Volume (flow rate) in 1 second (FEV_1) (Pharmacodynamic Population)

T16.1.9.12 Summary of Pre-challenge Forced Expiratory Volume (flow rate) in 1 second (FEV_1) (Per-Protocol Population)

T16.1.9.13 Overall Summary of Adverse Events

(Safety Population)

Description	Treatment A N = xx n (%)	Treatment B N = xx n (%)	Treatment C N = xx n (%)	Treatment D N = xx n (%)	Total N = xx n (%)
Subjects in Safety Analysis Population	xx	xx	xx	xx	xx
Subjects with at least one AE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Discontinued study drug due to above AEs	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
AEs reported	xx	xx	xx	xx	xx
Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not Related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Death	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Serious AE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

"Certain, Probable and Possible" were assessed as "Related" while "Unlikely and Unrelated" were assessed as "Not Related".

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T16.1.9.14.1 Summary of Frequency of All Adverse Events by System Organ Class (Safety Population)

	Treatment A N = xx		Treatment B N = xx		Treatment C N = xx		Treatment D N = xx		
Body System/ MedDRA Term	**Events**	**Subjects n (%)**	**Events**	**Subjects n (%)**	**Events**	**Subjects n (%)**	**Events**	**Subjects n (%)**	**Fisher's P-value**
Patient with at least one AE	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	x.xxxx
Ear and labyrinth disorders/ Ear pain	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	x.xxxx

etc.

N= number of subjects in the safety population in that particular group; n= number of subjects with data available for that particular group;
% is based on N

Programming Note: Note that if the overall Fisher's exact test is significant for comparisons across the 4 treatments then pair-wise testing between treatments will be conducted to determine which contrasts are significant.

T16.1.9.14.2 Summary of Frequency of Serious Adverse Events by System Organ Class (Safety Population)

	Treatment A N = xx		Treatment B N = xx		Treatment C N = xx		Treatment D N = xx		
Body System/ MedDRA Term	**Events**	**Subjects n (%)**	**Events**	**Subjects n (%)**	**Events**	**Subjects n (%)**	**Events**	**Subjects n (%)**	**Fisher's P-value**
Patient with at least one AE	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	x.xxxx
Ear and labyrinth disorders/ Ear pain	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	x.xxxx

etc.

N= number of subjects in the safety population in that particular group; n= number of subjects with data available for that particular group;
% is based on N

Programming Note: Note that if the overall Fisher's exact test is significant for comparisons across the 4 treatments then pair-wise testing between treatments will be conducted to determine which contrasts are significant.

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T16.1.9.15.1 Summary of Frequency of All Adverse Events by Relationship to Study Drug (Safety Population)

	Treatment A N = xx		Treatment B N = xx		Treatment C N = xx		Treatment D N = xx	
Body System/ MedDRA Term	**Related n (%)**	**Not Related n (%)**	**Related n (%)**	**Not Related n (%)**	**Related n (%)**	**Not Related n (%)**	**Related n (%)**	**Not Related n (%)**
Patient with at least one AE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ear and labyrinth disorders/ Ear pain	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

N= number of subjects in the safety population in that particular group; n= number of subjects with data available for that particular group; % is based on N

"Certain, Probable and Possible" were assessed as "Related" while "Unlikely and Unrelated" were assessed as "Not Related".

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T16.1.9.15.2 Summary of Frequency of Serious Adverse Events by Relationship to Study Drug (Safety Population)

	Treatment A N = xx		Treatment B N = xx		Treatment C N = xx		Treatment D N = xx	
Body System/ MedDRA Term	**Related n (%)**	**Not Related n (%)**	**Related n (%)**	**Not Related n (%)**	**Related n (%)**	**Not Related n (%)**	**Related n (%)**	**Not Related n (%)**
Patient with at least one AE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ear and labyrinth disorders/ Ear pain	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

N= number of subjects in the safety population in that particular group; n= number of subjects with data available for that particular group; % is based on N

"Certain, Probable and Possible" were assessed as "Related" while "Unlikely and Unrelated" were assessed as "Not Related".

T16.1.9.16.1 Summary of Frequency of All Adverse Events by Severity (Safety Population)

	Treatment A N = xx			Treatment B N = xx			Treatment C N = xx			Treatment D N = xx		
Body System/ MedDRA Term	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**
Patient with at least one AE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ear and labyrinth disorders/ Ear pain	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

N= number of subjects in the safety population in that particular group; n= number of subjects with data available for that particular group;
% is based on N

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T16.1.9.16.2 Summary of Frequency of Serious Adverse Events by Severity (Safety Population)

	Treatment A N = xx			Treatment B N = xx			Treatment C N = xx			Treatment D N = xx		
Body System/ MedDRA Term	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**
Patient with at least one AE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ear and labyrinth disorders/ Ear pain	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

N= number of subjects in the safety population in that particular group; n= number of subjects with data available for that particular group;
% is based on N

T16.1.9.17 Summary of Vital Signs
(Safety Population)

Vital Signs	Time Point	Statistic	Treatment A N = xx	Treatment B N = xx	Treatment C N = xx	Treatment D N = xx
Systolic Blood Pressure (mmHg)	Pre-Challenge	n	Xx	xx	xx	xx
		Mean ± SD	xxx.x ± xx.x	xxx.x ± xx.x	xxx.x ± xx.x	xxx.x ± xx.x
		Median	xxx.x	xxx.x	xxx.x	xxx.x
		Range	xxx.x – xxx.x	xxx.x – xxx.x	xxx.x – xxx.x	xxx.x – xxx.x
	Post-Challenge					
Diastolic Blood Pressure (mmHg)						
Pulse Rate (beats/min)						
Respiration Rate (breaths/min)						
Temperature (F)						

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L16.2.1 Listing of Discontinued Subjects

Patient Screen Number	Patient Randomization Number	Sequence	Date of Early Termination	Early Termination Reason
xx-xxxx	xx-xxxxx	1	yyyy-mm-dd	Lost to Follow-up

Sequence: 1=ABCD, 2=DCBA, 3=CADB, 4=BDAC

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L16.2.2 Listing of Protocol Deviations

Patient Screen Number	Patient Randomization Number	Sequence	Event Description
xx-xxxx	xx-xxxxx	1	Outside Visit Window (Visit 3)

Sequence: 1=ABCD, 2=DCBA, 3=CADB, 4=BDAC

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L16.2.3.1 Listing of Subjects Excluded from the Per-Protocol Population

Patient Screen Number	Patient Randomization Number	Sequence	Exclusion Reason
xx-xxxx	xx-xxxxx	1	Patient did not meet IE criterion

Sequence: 1=ABCD, 2=DCBA, 3=CADB, 4=BDAC

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L16.2.3.2 Listing of Subjects Excluded from the Pharmacodynamic Population

Patient Screen Number	Patient Randomization Number	Sequence	Exclusion Reason
xx-xxxx	xx-xxxxx	1	Patient did not meet IE criterion

Sequence: 1=ABCD, 2=DCBA, 3=CADB, 4=BDAC

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L16.2.4.1 Listing of Demographic Data

Patient Screen Number	Patient Randomization Number	Sequence	Age (yrs)	Gender	Ethnicity	Race
xx-xxxx	xx-xxxxx	1	21	Female	Not Hispanic or Latino	Black or African American

Sequence: 1=ABCD, 2=DCBA, 3=CADB, 4=BDAC

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L16.2.4.2 Listing of Medical History

Patient Screen Number	Patient Randomization Number	Sequence	System	Diagnosis or Surgical Procedure	Start Date	End Date	Ongoing
xx-xxxx	xx-xxxxx	1	xxxxxxxxxxxxxx	xxxxxxxxxxx	yyyy-mm-dd	yyyy-mm-dd	
xx-xxxx	xx-xxxxx	2	xxxxxxxxxxxxxxxx	Xxxxxxxxxxxx	yyyy-mm-dd		Ongoing

Sequence: 1=ABCD, 2=DCBA, 3=CADB, 4=BDAC

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L16.2.4.3 Listing of Concomitant Medication

Patient Screen Number	Patient Randomization Number	Sequence	Medication	Dosage	Frequency*	Route	Start/End Date	Indication
xx-xxxx	xx-xxxxx	1	Lisinopril	20 MG	QD	PO	yyyy-mm-dd / yyyy-mm-dd	Hypertension

Sequence: 1=ABCD, 2=DCBA, 3=CADB, 4=BDAC
*PRN - As needed; QD – Daily (once per day); Q4H - Every 4 hours; Q8H - Every 8 hours; Q12H - Every 12 hours; BID - Twice per day; TID - 3 times per day; QID - 4 times per day; QOD - Every other day; QS - Every week; QM - Every month; Q3M - Every 3 months

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L16.2.5 Listing of Dosing

Patient Screen Number	Patient Randomization Number	Sequence	Visit	Is the Patient Eligible for Dosing?	First Actuation Time	Last Actuation Time	Was the Study Product Primed?	Was the Patient Instructed on How to Properly Dose?	Dispenser Observe the Study Product Was Administered?	Was the Patient Compliant with the Dosing Instruction?
xx-xxxx	xx-xxxxx	1	Visit 2	Yes	hh:mm	hh:mm	Yes	Yes	Yes	Yes
			Visit 3	Yes	hh:mm	hh:mm	Yes	Yes	Yes	No (Spray mist was seen)
			Visit 4	Yes	hh:mm	hh:mm	Yes	Yes	Yes	Yes
			Visit 5	Yes	hh:mm	hh:mm	Yes	Yes	Yes	Yes

Sequence: 1=ABCD, 2=DCBA, 3=CADB, 4=BDAC

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L16.2.6.1 Listing of Methacholine Challenge and Pulse Oximetry

Patient Screen Number	Patient Randomi-zation Number	Sequence	Visit	Methacholine Bronchoprovocation Challenge Administration Time	Time FEV_1 Reduced by ≥ 20%	Treatment Dose (mcg)	PC_{20} (mg/mL)	Pulse Oximetry Time	Pulse Oximetry (%)	FEV_1 at Time of Discharge (L)
xx-xxxx	xx-xxxxx	1	Visit 1	hh:mm	hh:mm	NA	xxx.x	hh:mm	xx.x	xxx.x
			Visit 2	hh:mm	hh:mm	Placebo, 0	xxx.x	hh:mm	xx.x	xxx.x
			Visit 3	hh:mm	hh:mm	Test, 90	xxx.x	hh:mm	xx.x	xxx.x
			Visit 4	hh:mm	hh:mm	Reference, 90	xxx.x	hh:mm	xx.x	xxx.x
			Visit 5	hh:mm	hh:mm	Reference, 180	xxx.x	hh:mm	xx.x	xxx.x

Note: Methacholine Bronchoprovocation Challenge administration time refers to the time of the start of the first MC bronchoprovocation challenge administration.

Sequence: 1=ABCD, 2=DCBA, 3=CADB, 4=BDAC

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L16.2.6.2 Listing of Methacholine Challenge Stages

Patient Screen Number	Patient Randomi-zation Number	Sequence	Visit	StageN	Stage	FEV_1	FVC	FEV_1/FVC x 100
xx-xxxx	xx-xxxxx	1	Visit 1	-1	Pre-Saline	x.xxx	x.xxx	xx.xxxx
			Visit 1	0	Post-Saline	x.xxx	x.xxx	xx.xxxx
			Visit 1	1	0.0312	x.xxx	x.xxx	xx.xxxx
			Visit 1	2	0.0625	x.xxx	x.xxx	xx.xxxx
			Visit 1	3	0.1250	x.xxx	x.xxx	xx.xxxx
			Visit 1	4	0.2500	x.xxx	x.xxx	xx.xxxx
			Visit 1	5	0.5000	x.xxx	x.xxx	xx.xxxx
			Visit 1	6	1.0000	x.xxx	x.xxx	xx.xxxx
			Visit 1	7	2.0000	x.xxx	x.xxx	xx.xxxx
			Visit 1	8	4.0000	x.xxx	x.xxx	xx.xxxx
			Visit 1	9	8.0000	x.xxx	x.xxx	xx.xxxx
			Visit 1	10	Recovery	x.xxx	x.xxx	xx.xxxx
			Visit 2	-1	Pre-Saline	x.xxx	x.xxx	xx.xxxx
			Visit 2	0	Post-Saline	x.xxx	x.xxx	xx.xxxx
			Visit 2	1	0.0312	x.xxx	x.xxx	xx.xxxx
			Visit 2	2	0.0625	x.xxx	x.xxx	xx.xxxx
			Visit 2	3	0.1250	x.xxx	x.xxx	xx.xxxx
			Visit 2	4	0.2500	x.xxx	x.xxx	xx.xxxx
			Visit 2	5	0.5000	x.xxx	x.xxx	xx.xxxx
			Visit 2	6	1.0000	x.xxx	x.xxx	xx.xxxx
			Visit 2	7	2.0000	x.xxx	x.xxx	xx.xxxx
			Visit 2	8	4.0000	x.xxx	x.xxx	xx.xxxx
			Visit 2	9	8.0000	x.xxx	x.xxx	xx.xxxx
			Visit 2	10	16.0000	x.xxx	x.xxx	xx.xxxx

	Visit 2	11	32.0000	x.xxx	x.xxx	xx.xxxx
	Visit 2	12	64.0000	x.xxx	x.xxx	xx.xxxx
	Visit 2	13	128.0000	x.xxx	x.xxx	xx.xxxx
	Visit 2	14	Recovery	x.xxx	x.xxx	xx.xxxx
	Visit 3					
	Visit 4					
	Visit 5					

Sequence: 1=ABCD, 2=DCBA, 3=CADB, 4=BDAC

Visit 3-5 will be the same as Visit 2.

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L16.2.6.3 Listing of Spirometry Test

Patient Screen Number	Patient Randomization Number	Sequence	Visit	Is the Qualifying FEV_1 >= 80% Predicted Value? / and within 88-112% of Qualifying FEV_1 from the Screening Visit?	Was a 2-Minute Inhalation of a Normal Sterile Saline Control Administered?	Was the Post-saline FEV_1 <= a 10% Drop from the Qualifying FEV_1 and >=70% of Predicted Value?
xx-xxxx	xx-xxxxx	1	Visit 2	Yes	Yes	Yes
			Visit 3	Yes	Yes	Yes
			Visit 4	Yes	Yes	Yes
			Visit 5	Yes	Yes	Yes

Sequence: 1=ABCD, 2=DCBA, 3=CADB, 4=BDAC

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L16.2.7.1 Listing of Adverse Events (Safety Population Randomization Period)

Treatment	Patient Randomi-zation Number	System Organ Class / MedDRA Term / AE Term	Start /End Date	Severity	Relationship to Study Drug	Outcome	Action Taken	Other Action Taken	SAE?
Treatment A	xx-xxxxx	Nervous system disorders / Headache / Headache	yyyy-mm-dd / yyyy-mm-dd	Mild	Possible	Recovered	Dose Not Changed	None	No
Treatment B									
Treatment C									
Treatment D									

Sequence: 1=ABCD, 2=DCBA, 3=CADB, 4=BDAC

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L16.2.7.2 Listing of Adverse Events (Safety Population Screening Period)

Patient Screen Number	System Organ Class / MedDRA Term / AE Term	Start /End Date	Severity	Relationship to Study Drug	Outcome	Action Taken	Other Action Taken	SAE?
xx-xxxx	Nervous system disorders / Headache / Headache	yyyy-mm-dd / yyyy-mm-dd	Mild	Possible	Recovered	Dose Not Changed	None	No

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L16.2.7.3 Listing of Positive Pregnancy Test Results

Patient Screen Number	Patient Randomization Number	Sequence	Visit	Results
xx-xxxx	xx-xxxxx	1	Visit 3	Positive

Sequence: 1=ABCD, 2=DCBA, 3=CADB, 4=BDAC

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L16.2.7.4 Listing of Abnormal Physical Examinations

Patient Screen Number	Patient Randomization Number	Sequence	Visit	Body System	Result
xx-xxxx	xx-xxxxx	1	Visit 1	xxxxxxx	Abnormal (xxxxx)

Sequence: 1=ABCD, 2=DCBA, 3=CADB, 4=BDAC

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L16.2.8.1 Listing of Vital Signs

Patient Screen Number	Patient Randomization Number	Sequence	Visit	Time Point	Systolic BP (mmHg)	Diastolic BP (mmHg)	Pulse Rate (beats/min)	Respiration Rate (breaths/min)	Temperature (F)
xx-xxxx	xx-xxxxx	1	Visit 1	Pre-Challenge	120	70	84	18	98.6
				Post-Challenge	140	80	74	18	97.0
			Visit 2	Pre-Challenge	140	80	74	18	97.0
				Post-Challenge	140	80	74	18	97.0
			Visit 3	Pre-Challenge	140	80	74	18	97.0
				Post-Challenge	140	80	74	18	97.0
			Visit 4	Pre-Challenge	140	80	74	18	97.0
				Post-Challenge	140	80	74	18	97.0
			Visit 5	Pre-Challenge	140	80	74	18	97.0
				Post-Challenge	140	80	74	18	97.0

Sequence: 1=ABCD, 2=DCBA, 3=CADB, 4=BDAC

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L16.2.8.2 Listing of 12-Lead ECG

Patient Screen Number	Patient Randomization Number	Sequence	Visit	ECG Date	ECG Time	ECG Result	Comments
xx-xxxx	xx-xxxxx	1	Visit 1	yyyy-mm-dd	hh:mm	Abnormal (Not Clinically Significant)	xxxxxxxxxxxxxxxxxxx

Sequence: 1=ABCD, 2=DCBA, 3=CADB, 4=BDAC

Created on: ddmmmyy hh:mm

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NOTE TO FILE

STUDY TITLE: A Randomized, Single-Dose, Double-Blind, Double-Dummy, Four-Period, Four-Sequence, Four-Treatment, Placebo and Active Controlled, Comparative, Multiple-Center, Crossover-Design, Bronchoprovocation Study to Evaluate the Pharmacodynamic Equivalence of Albuterol Sulfate Inhalation Aerosol, eq 90 mcg base (Sun Pharmaceuticals Industries Limited) to PROAIR® HFA (albuterol sulfate) Inhalation Aerosol, eq 90 mcg base (Teva Respiratory, LLC) in Subjects With Stable, Mild Asthma

PROTOCOL NO.: CLR_17_08 (Revision 6.0)

[redacted]

This Note to File explains the changing of numbering as per ICH guidance E3 for Tables, Listings and Figures that are included in the final SAP dated December 21, 2018.

T14.1.1 Summary of Patient Disposition
T14.1.2 Summary of Protocol Deviations
T14.1.3 Summary of Patient's Treatments Included in the Pharmacodynamic Analysis
T14.1.4 Summary of Demographic Data and Baseline Characteristics
T14.1.5 Summary of Demographic Data and Baseline Characteristics
T14.1.6 Summary of Demographic Data and Baseline Characteristics
T14.2.1.1 Summary of Concentration (mg/mL) of Methacholine Required to Reduce FEV_1 by 20% (PC_{20}) (Safety Population)
T14.2.1.2 Summary of Concentration (mg/mL) of Methacholine Required to Reduce FEV_1 by 20% (PC_{20}) (Pharmacodynamic Population)
T14.2.1.3 Summary of Concentration (mg/mL) of Methacholine Required to Reduce FEV_1 by 20% (PC_{20}) (Per-Protocol Population)
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