[redacted]

STATISTICAL ANALYSIS PLAN

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A Randomized, Multiple-Dose, Blinded, Placebo-Controlled, Parallel-Design, Multiple-Center, Clinical Study to Evaluate the Therapeutic Equivalence of Fluticasone Propionate and Salmeterol Inhalation Powder, 100 mcg/50 mcg (Supplied by Teva Pharmaceuticals Ireland) to ADVAIR DISKUS® 100/50 (fluticasone propionate/salmeterol) Inhalation Powder, (GlaxoSmithKline) in Subjects With Asthma

Protocol Number: 71736001
[redacted]Study Number: 71736001

Sponsor:
Teva Pharmaceuticals USA, Inc.
400 Interpace Parkway
Parsippany NJ, 07054, US

Contract Research Organization:
[redacted]

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STATISTICAL ANALYSIS PLAN

Fluticasone Propionate and Salmeterol Inhalation Powder Protocol No. 71736001

SAP Final Version Approvals

A Randomized, Multiple-Dose, Blinded, Placebo-Controlled, Parallel-Design, Multiple-Center, Clinical Study to Evaluate the Therapeutic Equivalence of Fluticasone Propionate and Salmeterol Inhalation Powder, 100 mcg/50 mcg (Supplied by Teva Pharmaceuticals Ireland) to ADVAIR DISKUS® 100/50 (fluticasone propionate/salmeterol) Inhalation Powder, (GlaxoSmithKline) in Subjects With Asthma

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STATISTICAL ANALYSIS PLAN

Fluticasone Propionate and Salmeterol Inhalation Powder **Protocol No. 71736001**

Revision History

VERSION	DATE	DESCRIPTION OF REVISIONS	REVISED BY
[redacted]			

List of Abbreviations and Definition of Terms

ADaM	Analysis Dataset Model
AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
BE	Bioequivalence
C	Celsius
CDISC	Clinical Data Interchange Consortium
CRO	Clinical Research Organization
ECG	Electrocardiogram
eCRF	electronic Case Report Form
eCTD	electronic Common Technical Document
°F	Fahrenheit
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume (flow rate) in 1 second
FVC	Forced Volume Vital Capacity
g	Gram
ICF	Informed Consent Form
HR	Heart Rate
ICH	International Conference on Harmonization
IWRS	Interactive Web Response System
mcg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent-to-Treat
mL	Milliliter
PP	Per-Protocol
RR	Respiratory Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SPE	Safety Population Enrolled
SPR	Safety Population Randomized
US	United States

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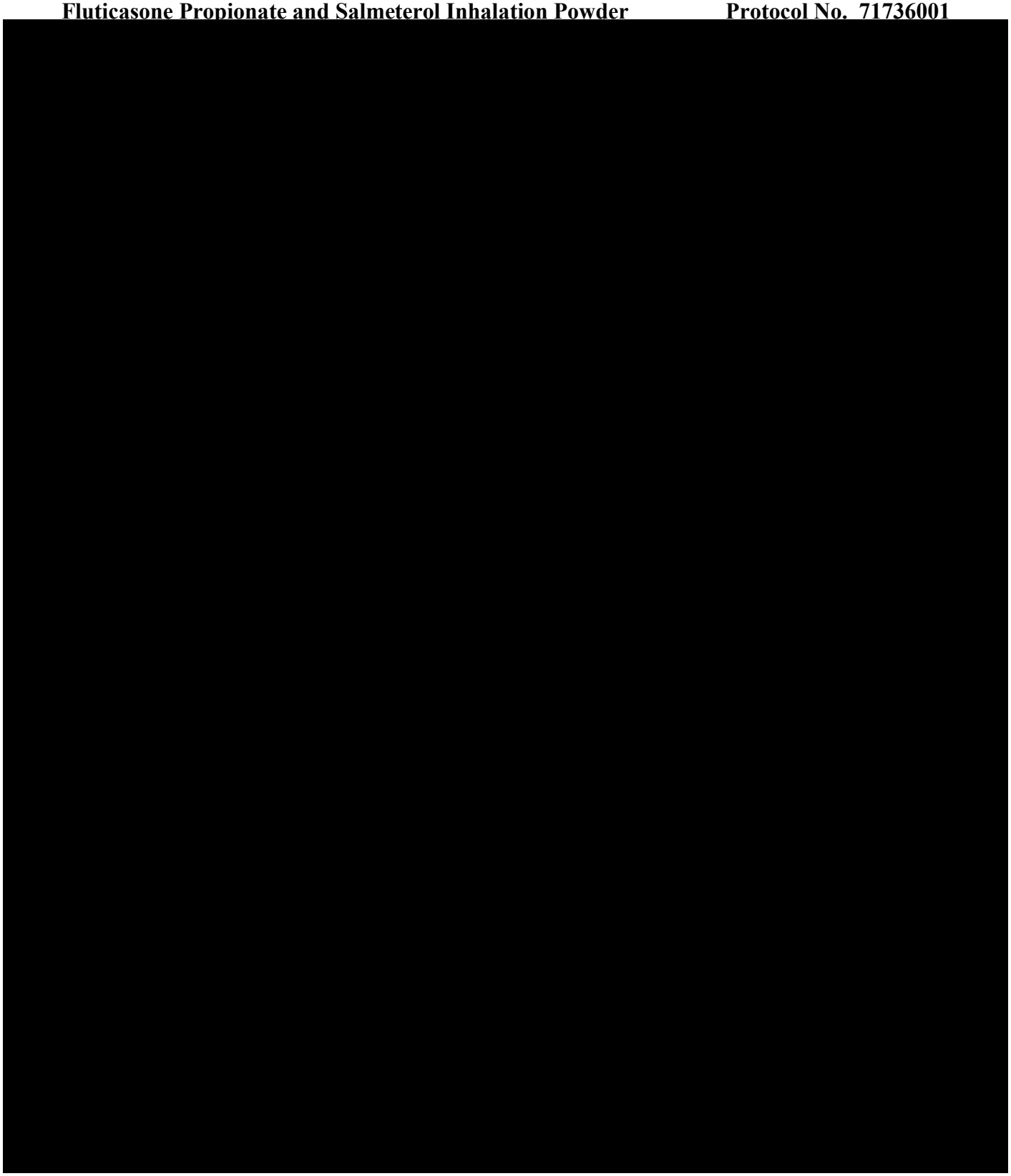

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STATISTICAL ANALYSIS PLAN

Fluticasone Propionate and Salmeterol Inhalation Powder Protocol No. 71736001

1. INTRODUCTION

This Statistical Analysis Plan (SAP) is based on the final Clinical Study Protocol 71736001 [redacted] 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:

[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 subject in this study.

2. OBJECTIVES

The objectives of this study are to:

1. Evaluate the therapeutic equivalence of a generic Fluticasone Propionate and Salmeterol Inhalation Powder, 100 mcg/50 mcg (Supplied by Teva Pharmaceuticals Ireland) to ADVAIR DISKUS® 100/50 (fluticasone propionate and salmeterol) Inhalation Powder, (GlaxoSmithKline) in subjects with asthma.
2. Demonstrate the superiority of the Test and Reference (active) treatments over Placebo treatment in subjects with asthma.

3. OVERALL STUDY DESIGN

This randomized, multiple-dose, blinded, placebo-controlled, parallel-design, multiple-center, clinical endpoint study has been designed to evaluate the clinical (therapeutic) effect of generic Fluticasone Propionate and Salmeterol Inhalation Powder, 100 mcg/50 mcg (Supplied by Teva Pharmaceuticals Ireland) to ADVAIR DISKUS® 100/50 (fluticasone propionate and salmeterol) Inhalation Powder, (GlaxoSmithKline) in subjects with asthma.

Following a minimum 14-21 day placebo run-in period, subjects who continue to meet inclusion/exclusion criteria will be randomized in a [redacted] ratio (Test: Reference: Placebo) for 28 ± 2 days of treatment. Approximately [redacted] subjects will be screened to randomize

approximately [redacted] subjects to the active treatment period of the study. To qualify for inclusion in the study, subjects must be ≥ 12 years and ≤ 75 years of age, with a diagnosis of asthma as defined by the National Asthma Education and Prevention Program (NAEPP) guidelines at least 12 weeks before Screening.

Before any study-specific procedures are performed, all subjects will read and sign the IRB-approved informed consent form (ICF) or assent, as applicable.

Eligible subjects will complete the clinic visits as follows:

- Visit 1: Screening
  - Visit 1a: General Screening [redacted]
  - Visit 1b: Screening (Day -21 to -14). [redacted]

  Following completion of screening procedures, qualified subjects will enter into Placebo Run-in: (minimum 14-21 days prior to Day 1). [redacted]
- Visit 2: Randomization (Day 1)
- Visit 3: End of Study (Day 29 ± 2)/Early Termination

Screening

Screening evaluations will be performed in accordance with the study schematic. Safety assessments will include: vital sign measurement, height, weight, physical examination, serum pregnancy test (for all women of childbearing potential), drug, alcohol, and cotinine testing, 12-lead electrocardiogram (ECG), and clinical laboratory evaluations. Clinical assessments will include FEV_1 taken at each visit [redacted] Forced Volume Vital Capacity (FVC) and FEV_1/FVC ratio [(FEV_1/FVC) x 100] will be recorded with FEV_1 measurements at each visit. Pre-bronchodilator FEV1 at Screening must be 40%-85% (including these values) of predicted value. Once a qualifying FEV_1 is obtained, [redacted] puffs [redacted] mcg; 90 mcg per puff, pressurized metered-dose inhaler) of albuterol inhalation will be administered (at each inhalation, the breath is held for 5-10 second before the subject exhales; four separate doses are delivered at approximate 30 seconds intervals) and spirometry will be repeated starting approximately 15 minutes from the

last inhalation. The subject must demonstrate at least 15% reversibility of FEV_1 within 30 minutes [redacted] after albuterol administration to qualify for inclusion in the study. Post bronchodilator vital signs will be obtained.

[redacted]

Following completion of screening procedures, qualified subjects will enter into Placebo Run-in: (14-21 days prior to Day 1) [redacted]

Enrollment

Eligible subjects will be enrolled in a placebo run-in period for minimum 14-21 days to establish baseline FEV_1 values. Subjects will be dispensed an inhaler containing Placebo product to be administered twice daily. Subjects must administer at leas[redacted] of the required doses during the run-in period to be eligible for randomization. Subjects will also receive an albuterol inhaler to be used as a rescue medication throughout the study.

Compliance criteria for the placebo run-in period are as outlined in the table below:

Study Design			Compliance Criteria
Study Period	Treatment Duration	Scheduled Doses	[redacted]
Placebo Run-in	14-21 days	28-42	

Randomization

Subjects who meet all inclusion/exclusion and randomization criteria at Visit 2 will be randomized to study product in a [redacted] ratio (Test: Reference: Placebo). Serial pulmonary function tests will be performed over 12 hours at Visit 2. FEV_1 should be measured at approximately [redacted] the first dose of study product and approximately 30 minutes, 1, 2, 3, 4, 6, 8, 10, and 12 hours post-dose. The second dose of study product will be administered after the 12-hour FEV_1 is collected. At least two of the pre-dose time point FEV_1 measurements must meet ATS criteria for quality in

order to establish a baseline value. The average of the quality FEV_1 measurements will be used to determine the baseline FEV_1, which must be $\geq 40\%$ and $\leq 85\%$ of predicted normal value and may not vary by more **than** [redacted] from the qualifying Screening visit FEV_1 value at Visit 2 for the subject to be eligible for inclusion in the study.

End of Study

The final [redacted] time points FEV_1 measurements will be collected at Visit 3. The first FEV_1 should take place at the same time of day as the [redacted] pre-dose measurement, collected at Visit 2 (± 2 hours). The remaining FEV_1 measurements should be collected within [redacted] following the preceding measurement.

[redacted] The last dose of study product should be administered on the evening **before** Visit 3.

Subjects should not administer the rescue medication, or study product within 6 hours before any study visit.

Figure 1 Study Schematic

Procedures	[redacted]
Informed Consent	
Medical History and Baseline Demographics	
Vital Signs	
Height and Weight	
Physical Exam	
Drug, Cotinine, and Alcohol Testing	
Serum Pregnancy Test**	
Urine Pregnancy Test**	
12-Lead ECG	
Clinical Laboratory Testing	
Concomitant Medication	
Spirometry (FEV_1 and FVC) §	
Reversibility Test§	
Pulse Oximetry	
Inclusion/Exclusion Criteria Review	
Dispense Randomized Study Product and Instructions	
Dispense Run-In Product and Instructions	
Dispense Rescue Medication (as applicable)	
Dosing¶	
Adverse Events	
Provide Diaries	
Collect/Review Diaries	
Collect Placebo from Run-in Period	
Collect Rescue Medication	
Collect Study Product	
Schedule next visit	

*Vital signs will be measured before and after reversibility assessment.

**Female subjects of childbearing potential.

† Required for randomized subjects only. Subjects who fail randomization will be discharged from the study following completion of appropriate Visit 2 procedures.

[redacted]

¶Subjects will dose at the clinical site at Visit 1b and Visit 2.

[redacted]

4. RANDOMIZATION AND BLINDING

Enrollment

At Visit 1, using [redacted] (IWRS), all subjects who have read and signed the ICF will be assigned a Subject number. Eligible subjects will be dispensed a blinded Placebo inhaler for the placebo run-in period from the bulk supply provided to each site. Subject numbers will consist of a three-digit site number and a three-digit individual subject number. The three-digit subject numbers will be assigned automatically in ascending order beginning with 101 at each study site.

Randomization

The study product will be packaged and blinded by the Drug Depot. Randomization will be pre-planned according to a computer-generated randomization schedule using [redacted] (IWRS). The system will also assign study product kit numbers (based on the randomization schedule created by an independent biostatistician). The study product kit number is the identifying number listed on the study product dispensed to eligible subjects. The study product kit number is a [redacted]

At the end of the study, after all the clinical data have been entered and the study database has been locked, a copy of the randomization schedule will be sent to the statistician.

Blinding

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

5. SAMPLE SIZE

[redacted]

[redacted]

6. STUDY ENDPOINTS

The two co-primary efficacy endpoints are:

(1) the baseline-adjusted area under the serial FEV_1-time curve calculated from time zero to 12 hours ($AUC_{0\text{-}12h}$) on Day 1 of treatment (Visit 2), and
(2) the baseline-adjusted pre-dose FEV_1 measured in the morning of Day 29 ± 3 (Visit 3) after the last dose in the prior evening.

Baseline FEV_1 is defined as the average of at least two acceptable pre-dose FEV_1 values on Day

[redacted]

7. STUDY POPULATIONS

Per-Protocol (PP) Populations

[redacted]

[redacted]

Subjects who discontinue due to Lack of Efficacy will be included using LOCF, as described in Section 8.2.1.

[redacted]

Subjects taking fewer than [redacted] or more than [redacted] the required doses over the 28 ± [redacted] days treatment period will be considered non-compliant with dosing and excluded from the per-protocol (PP) population. Compliance with number of doses will be determined by Data Management from ERT data and verified by the use of the diaries. Compliance criteria for the active treatment period of the study are as outlined in the table below:

[redacted]

Protocol deviations will be derived algorithmically as well as reported by sites. Each protocol deviation will be classified as minor or major.

[redacted]

Specific deviation and their severity are defined in the separate Protocol Deviations List document.

Subjects with protocol deviations identifying them as participating in the study on more than one

occasion at two different sites will be tracked as "Double Dippers." All Double Dippers will be reviewed and evaluated for efficacy analysis prior to database lock.

Modified Intent-to-Treat (mITT) Population

[redacted]

Safety Populations

[redacted]

8. STATISTICAL ANALYSIS METHODS

If not otherwise specified, statistical significance is defined as $p < 0.05$ and is two-tailed. Data will be summarized with respect to demographic and baseline characteristics and safety variables.

In general, all data will be listed by subject and visit/time point where appropriate. The summary tables will be stratified by, or have columns corresponding to, treatment groups. The total number of subjects in the treatment group (N) under the stated analysis set will be displayed in the header of summary tables. For categorical variables, the number and percentage of each category within a parameter will be calculated for non-missing data. In summary tables of categorical variables,

counts and percentages will be displayed. The count [n] indicates the actual number of subjects in a particular category, which should always be less than or equal to the total number of subjects in the respective study group with known (non-missing) category [M]. Percentage will be obtained by: % = n/M*100. Unless otherwise specified, all percentages will be expressed to one decimal place.

For continuous variables, statistics will include n, mean, standard deviation, median, minimum and maximum values. The minimum and maximum statistics should be presented to the same number of decimal places as the original data. The mean and median should be presented to one more decimal place than the original data. The standard deviation should be presented to two more decimal places than the original data.

All statistical analyses will be conducted using SAS®, Version 9.4 or higher. Datasets will be prepared using headings from Clinical Data Interchange Consortium (CDISC), Study Data Tabulation Model (SDTM) implementation for human clinical trials, and ADaM (Analysis Dataset Model).

8.1 Baseline Characteristics

8.1.1 Subject Disposition

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

8.1.2 Demographic and Other Baseline Characteristics

The following subject demographic characteristics will be summarized separately in the [redacted]

- Age (years) (Age will be derived from ICF date relative to birth date)
- Sex (Male/Female)
- Ethnicity (Hispanic/non-Hispanic)
- Race (White, Black/African American, Native Hawaiian or Other Pacific Islander, Asian, American Indian or Alaska Native)
- Number of years subject has suffered from symptoms caused by asthma
- Pre-dose Baseline FEV_1
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)

Summary tables by treatment group will be presented. Continuous variables will be summarized using descriptive statistics (number of observations, median, minimum, maximum, mean, and SD). Categorical variables will be summarized using frequencies and percentage. Baseline

treatment comparisons will be presented using Chi-Square or Cochran-Mantel-Haenszel tests for the categorical variables, and Analysis of Variance (ANOVA) for the continuous variables.

All data will be listed by treatment and subject.

8.1.3 Medical History

At Visit 1, subjects will be questioned about medical history, including smoking history, acute and chronic medical history, and medical history relevant to their asthma. Medical history data will be listed for asthma history and for non-asthma medical history by treatment and subject, respectively. These analyses will be done for the Safety Population Randomized.

8.1.4 Prior and Concomitant Medications

At Visit 1, subjects will be questioned about medication use over the previous 6 months. At all subsequent visits, subjects will be questioned about ongoing or new concomitant medication use.

Prior and concomitant medication will be coded according to the World Health Organization – Drug Reference List and the Anatomical Therapeutic Chemical classification system or similar. Prior medications are defined as those taken before the first dose of randomized study drug on Day 1 (i.e., start and end date before the first dose of randomized study drug). Concomitant medications are defined as those taken at the time of or after the first dose of randomized study drug. Any medications that were started before the first dose of randomized study drug on Day 1 but continued after dosing will be considered a concomitant medication.

Concomitant medications will be summarized by treatment group, ATC class (highest level available) and preferred name. This analysis will be done for the [redacted]

All prior and concomitant medications taken since screening until the end of the study will be listed by treatment group and subject.

8.2 Efficacy Analyses

8.2.1 Calculation of the Primary Endpoints

Acceptability Criteria.

[redacted] For the purpose of this study, ATS quality will be demonstrated by receiving a quality grade of [redacted] upon review and only these results will be used for analysis. Results with a quality grade of [redacted] will be treated as missing in all calculations.

FEV_1 Baseline.

The FEV_1 baseline will be defined as the average of the pre-dose FEV_1 values obtained at Visit 2 Day 1. If some of these measurements are missing, the average will be calculated using the available measurements, however, a minimum of two pre-dose FEV_1 values is required; subjects who have only one or no pre-dose FEV_1 measurements on Day 1will have their FEV_1 baseline missing, and this the subject will be excluded from analysis.

Calculation of FEV_1 AUC_{0-12}.

The endpoint of Baseline-adjusted FEV_1 AUC_{0-12} on Day 1 will be calculated as follows:

1. Each FEV_1 assessment on Day 1 will be baseline-adjusted by subtracting the FEV_1 baseline value defined above.
2. FEV_1 AUC_{0-12} will be calculated from the baseline-adjusted values using the linear trapezoidal method. The calculation will assume that at time of dosing (time 0) the baseline-adjusted FEV_1 is also 0. The calculation will proceed over all available postdose FEV_1 assessments on Day 1 (including unscheduled timepoints, if any) using actual elapsed time from dosing.
3. FEV_1 AUC_{0-12} will be considered non-computable in a subject if one of the following occurs in that subject:

[redacted]

Calculation of Baseline-adjusted Pre-dose FEV_1 at End of Treatment.

The endpoint of Baseline-adjusted pre-dose FEV_1 at end of treatment will be calculated as [FEV_1 at end of treatment] – [Baseline FEV_1] where FEV_1 at end of treatment will be defined as the

[redacted]

If a subject has no pre-dose assessment at Visit 3, Day 29, in the mITT analysis Average FEV_1 at end of treatment will be imputed (following LOCF rule) as the average of available predose assessments on the last post-baseline day (Day 2 through 32) when at least one pre-dose FEV_1 assessment is available (e.g. the Early Termination visit). Only assessments occurring after start of the randomized treatment (Day 2) and up to day [redacted] will be considered for LOCF. In the PP

8.2.2 Therapeutic Equivalence

Therapeutic equivalence will be evaluated for the primary endpoint in each PP population. Under the assumptions of normally distributed data, the adjusted 90% confidence interval will be calculated for the Test/Reference ratio of the mean baseline-adjusted $AUC_{0\text{-}12h}$ on Day 1 [redacted] and for the Test/Reference ratio of the mean baseline-adjusted morning pre-dose FEV_1 on Day 29 ± [redacted] using an iterative procedure similar to Fieller's method outlined in Appendix A.

The analysis for calculating 90% confidence intervals will be conducted using mean baseline FEV_1. The mean baseline value for use in the iterative procedure will be determined from the Baseline FEV_1 of all subjects receiving active treatment in the Day 1 PP population, without regard to the treatment received. The value will be included as the initial baseline value in the ESTIMATE statement of the iterative procedures outlined in Appendix B.

The statistical analyses will involve Analysis of Covariance (ANCOVA) with terms for [redacted] and using [redacted] as a covariate in the model.

SAS PROC GLM procedure will be used in the analysis. The initial statements of a SAS PROC GLM analysis would be

[redacted]

If the adjusted 90% confidence intervals for the least-squares mean Test/Reference ratios are within 80.00-125.00% for both co-primary endpoints, then therapeutic equivalence of the Test to Reference product will be considered to have been demonstrated.

[redacted]

8.2.3 Superiority to Placebo

The superiority to Placebo will be evaluated for the co-primary endpoints in mITT population.

The superiority of the Test and Reference products over Placebo is concluded if the values for mean baseline-adjusted $AUC_{0\text{-}12h}$ and the mean baseline-adjusted morning pre-dose FEV_1 on Day 29 [redacted] for the active treatments are statistically superior to those respective values of the Placebo at the 5% significance level ($p < 0.05$, two-sided). The superiority of Test and Reference treatments over the Placebo will be evaluated in the same ANCOVA model for Test vs. Placebo and Reference vs. Placebo [redacted]

The LSMeans for each treatment, the LSMeans of the treatment difference together with the corresponding 95%-confidence interval and the p-value will be presented.

[redacted]

Descriptive statistics (number of observations, mean, standard deviation, median, minimum and maximum) will be provided for baseline, post treatment and change from baseline by treatment group.

8.2.4 Pooling of Sites

[redacted]

8.2.5 Lung Function Testing

The results of the spirometry measurements (including reversibility testing) at Visit 1b Screening will be listed for each subject including the FEV_1, FVC, FEV_1 to FVC ratio, FEF_{25-75} (absolute values and percentage of predicted values rounded to whole numbers). For the reversibility testing, both the absolute measurements and percentage change after inhaled albuterol will be presented [redacted]

Definitions of the quality grades will also be summarized.

8.3 Safety Analysis

All study subjects who were randomized and used the study product on at least one occasion (Safety Population Randomized) will be included in the comparative safety analysis.

All subjects who signed the ICF for the study and were either not randomized or were randomized but did not use the study product (SPE) will be used in listing of L16.2.7.3 for AEs reported during Screening (Visit 1) for Safety Population Enrolled.

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 21.1 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 patients with AEs by system organ class, preferred term, will be presented by treatment. 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 by treatment. 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 by treatment. Relationship to a study drug will be classified as "Not Related" or "Related".

[redacted]

8.3.2 Vital Signs

The subject's vital signs will be recorded (heart rate, blood pressure, temperature and respiration rate) at each clinic visit.

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

All data will be listed by treatment and subject.

8.3.3 Pregnancy Test

A serum pregnancy test on women of childbearing potential will be performed at Screening (Visit 1). Urine pregnancy tests on women of childbearing potential will be performed the repeat screening visit, if applicable, and at Visits 2 and 3.

Positive pregnancy test results will be listed by treatment and subject.

8.3.4 Clinical Laboratory Testing

As part of the Screening procedures (Visit 1) and at Visit 3 (or early termination for randomized subjects only), subjects will have a blood sample taken for hematology and clinical chemistry testing and a urine sample for urinalysis.

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

All data will be listed by treatment and subject.

8.3.5 12-Lead ECG

Subjects will undergo a 12-lead ECG at Screening and End of Study. An ECG may be performed at Visit 2 at the discretion of the Investigator. Any clinically significant findings will be noted.

ECG results were collected as 'Normal', 'Abnormal – NCS', 'Abnormal – CS'.

ECG results will be listed by treatment and subject.

8.3.6 Physical Exam

At Visits 1 and 3, the Investigator will perform a general physical exam for each qualified subject and any significant findings will be noted. The physical exam at a minimum must include a head, ear, eyes, nose, lungs, and throat examination.

Abnormal physical exam results will be listed by treatment and subject.

8.4 Multiple Comparisons

No multiple comparison adjustment will be made in this study.

8.5 Methods for Handling Missing Data

For demographic and baseline characteristics, each variable will be analyzed using all available data. Subjects with missing data will be excluded only from analyses for which data are not available.

8.6 Interim Analyses

There is no interim analysis planned in this study.

8.7 Changes to the Protocol Defined Statistical Analysis Plan

The following changes from the protocol specified analysis have been made:

[redacted]

[redacted]

9. TABLE, LISTING AND FIGURE SHELLS

The shells presented in Appendix B are provided in order to provide a framework for the display of data from this study. These shells may not be reflective of every aspect of this study but are intended to show the general layout of the Tables, Listings and Figures that will be included in the final clinical study report. Tables, Listings and Figures are numbered following the ICH structure. Table headers, variables names and footnotes will be modified as needed following data analyses. All descriptive and inferential statistical analyses will be performed using SAS® statistical software Version 9.4 or higher, unless otherwise noted.

Appendix A: Outline of Statistical Analysis Method using SAS PROC GLM

[redacted]

[redacted]

Appendix B: TABLE AND LISTING SHELLS