Statistical Analysis Plan

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A RANDOMIZED, BLINDED, PARALLEL GROUP, PLACEBO-CONTROLLED, MULTIPLE DOSE, MULTICENTER STUDY TO COMPARE THE THERAPEUTIC EQUIVALENCE OF FLUTICASONE PROPIONATE PRESSURIZED METERED DOSE INHALER, 110 MCG, TO FLOVENT® HFA 110 MCG, IN ADULT SUBJECTS WITH ASTHMA

Study Statistician [redacted]

Sponsor Representative [redacted]

TABLE OF CONTENTS PAGE

LIST OF ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse event
ANCOVA	Analysis of Covariance
ATC	Anatomical-Therapeutic-Chemical
ATS/ERS	American Thoracic Society/ European Respiratory Society
BDRM	Blinded Data Review Meeting
BMI	Body Mass Index
ECG	Electrocardiogram
eCRF	Electronic case report form
ENS	Enrolled Set
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in one second
FP	Fluticasone Propionate
FVC	Forced Vital Capacity
HFA	Hydrofluoroalkanes
IWRS	Interactive Web Response System
LOCF	Last Observation Carried Forward
LS	Least Squares
mcg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
mL	milliliter
NAEPP-EPR3	National Asthma Education and Prevention Program Expert Panel Report 3
NHANES III	National Health and Nutrition Examination Survey III
PEF	Peak expiratory flow
PEFR	Peak expiratory flow rate
pMDI	Pressurized metered dose inhaler
PPS	Per-protocol Set
PT	Preferred term
RiN	Run-in Set
RS	Reference Standard
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SOC	System organ class
TEAE	Treatment-emergent adverse event
USA	United States of America

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol "A Randomized, Blinded, Parallel Group, Placebo-Controlled, Multiple Dose, Multicenter Study to Compare the Therapeutic Equivalence of Fluticasone Propionate Pressurized Metered Dose Inhaler, 110 mcg, to Flovent® HFA 110 mcg, in Adult Subjects with Asthma", amendment 2, dated June 10, 2019.

Teva Pharmaceuticals USA, Inc. is developing a new generic formulation of fluticasone propionate pressurized metered dose inhaler, 110 mcg for which demonstration of bioequivalence to the reference product (i.e., Flovent®) is required. This study is designed to evaluate the bioequivalence between the administered test and reference products in accordance with the recommendations outlined in the US Food and Drug Administration (FDA) Draft Guidance on Fluticasone Propionate (Oct., 2017, Rev. July, 2018).

2. OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to confirm the therapeutic equivalence of FP pMDI 110 mcg and the RS, Flovent HFA 110 mcg, after a 4 week (28 day [redacted]) Treatment period in adult subjects with chronic but stable asthma as defined in the NAEPP-EPR3 guidelines at least 6 months prior to Enrollment at Screening Visit 1a.

2.2 Secondary Objective

The secondary objective of this study is to confirm the Test, FP pMDI 110 mcg, and RS, Flovent HFA 110 mcg, products are statistically superior to placebo ($p < 0.05$) on the primary study endpoint.

3. STUDY OVERVIEW

3.1 Study Design

This is a multicenter, blinded, parallel group, placebo-controlled, randomized, multiple dose clinical study designed to confirm therapeutic equivalence of FP pMDI 110 mcg per actuation and Flovent HFA 110 mcg in adult subjects with asthma.

The Screening and Run-in study periods and visit windows described in this section may be extended with Sponsor approval. The Treatment period may not be extended.

The study will be divided into 3 periods: a Screening period (up to 35 days), a minimum 14-day Run-in period, and a 28 day [redacted]) Treatment period. At the end of the Run-in period, eligible subjects will be randomly assigned in a [redacted] scheme to 1 of 3 treatment arms for a 28 day [redacted]) Treatment period. There will be up to 4 visits. All spirometry should be initiated in the morning, [redacted]

The Screening period will have up to 2 visits. Screening Visit 1a may be conducted up to 28 days prior to Visit 1b. At Visit 1a subjects will provide written informed consent, demographics, medical history, and concomitant medication information. Subjects will receive rescue medication for the duration of the study. Subjects' height and weight will be measured and BMI will be calculated. Subjects must withhold rescue medication for 6 hours prior to performing any spirometry. If all protocol-defined washout requirements are met, Visit 1a and 1b may be combined and conducted on the same day.

At Screening Visit 1b, subjects will perform Screening spirometry with reversibility. Pre-bronchodilator FEV_1 must be ≥45% and ≤85% of predicted normal value at Screening Visit 1b using NHANES III predicted values. For Screening Visit 1b only, subjects who fail to meet FEV1 ≥45% and ≤85% of predicted normal value may repeat the visit one time within 1 week. Subjects must demonstrate reversibility of airway obstruction ≥12% and ≥200 mL of FEV_1 within 30 minutes of 360 mcg albuterol inhalation (4 puffs). Subjects who achieve ≥10% but <12% or achieve ≥12% but 175-199 mL reversibility at Screening Visit 1b may repeat the visit one time within 1 week. Subjects may have only one repeated visit during the Screening period.

Vital signs will be collected at all clinic visits after Screening Visit 1a (blood pressure and heart rate). Physical examination, urinalysis, drug/alcohol/cotinine screening, laboratory screening (blood: hematology, chemistry), and urine pregnancy test (women of childbearing potential only) will be conducted at Screening Visit 1b. A 12-lead ECG will be collected. Subjects must have no evidence or history of clinically significant disease such as congestive heart failure, myocardial infarction, or cardiac dysrhythmia.

Subjects who meet all Inclusion and no Exclusion Criteria at the end of Visit 1b will start a minimum 14 day placebo Run-in phase. Subjects will receive placebo Run-in medication with

instructions for home. Subjects will be instructed to take two oral inhalations twice daily, with a dosing interval of approximately 12 hours. Subjects will be provided with an eDiary and instructions for use at home, and will complete the first diary entries at the clinic under site staff supervision. Subjects will be instructed to record eDiary twice-daily (morning and evening) entries for study drug dosing and peak flows. Once-daily (morning) entries for rescue medication use, asthma symptoms, and reporting health and medication changes will also be recorded. A missed dose can be entered in the eDiary within 1 calendar day of a missed morning or evening diary. Subjects will be instructed to withhold their morning medication (last dose should be approximately 12 hours prior to lung function tests), as well as rescue medication for 6 hours, on the day of Visit 2 Randomization.

Subjects will return to the clinic for Visit 2 Randomization at the end of the minimum 14 day Run-in period. The subject's interim medical history (including AEs) and required medication washout will be reviewed. If washout for Run-in medication is not met, subjects will be allowed to continue with Visit 2 Randomization. Subjects must withhold rescue medication for 6 hours prior to spirometry on the day of Visit 2 Randomization. Urine pregnancy tests will be conducted for women if child-bearing potential. The subject's eDiary and medication compliance will be reviewed.

Subjects will perform serial spirometry. Starting at approximately 60 minutes pre-dose (where 0 minutes is the time of dosing), subjects will be required to perform three separate sessions of spirometry, allowing adequate time for subject recovery between sessions. Pre bronchodilator highest FEV_1 must be ≥45% and ≤85% of predicted normal value (using NHANES III values) on the first day of treatment prior to randomization. Spirometry must meet ATS/ERS guidelines for grades A or B ([redacted]). The average of the highest acceptable FEV_1 values from the 3 pre-dose sessions will be used as the baseline value (minimum of 2 acceptable sessions is required for continuation in the study). [redacted]

At the end of the Run-in period subjects will be randomized to treatment if they continue to meet all general Inclusion/Exclusion criteria. In addition, they must meet all randomization inclusion criteria and no randomization exclusion criteria specified in the protocol.

Eligible, randomized subjects will receive the first dose of study medication following serial spirometry at Visit 2 Randomization. Subjects will receive blinded study medication with instructions for home for the minimum 28 day [redacted]) Treatment period. Subjects will be instructed to take two oral inhalations twice daily, with a dosing interval of approximately 12 hours.

Subjects will review eDiary requirements and instructions for use of diary at home, and will complete the first diary entries at the clinic under site staff supervision. Subjects will be instructed to record eDiary twice-daily (morning and evening) entries for study drug dosing and peak flows. Once-daily (morning) entries for rescue medication use, asthma symptoms, and reporting health and medication changes will also be recorded. Subjects will be instructed to withhold their morning medication (last dose should be approximately 12 hours prior to lung function tests), as well as rescue medication for 6 hours, on the day of Visit 3 Day 29.

Medication and eDiary compliance will be monitored throughout the Run-in and Treatment period, beginning when the eDiary/PEF device is dispensed. Compliance monitoring will include alerts, edit checks, and data management review. Sites will contact subjects as needed to follow-up on diary and medication compliance alerts.

Subjects will return to the clinic for Visit 3 Day 29 at the end of the minimum 28 day [redacted] Treatment period. The subject's interim medical history (including AEs) and required medication washout will be reviewed. Washout for Treatment medication must be observed for a minimum of 6 hours on Visit 3 Day 29. Subject must withhold rescue medication for 6 hours prior to spirometry on the day of Visit 3 Day 29. Laboratory screening (blood: hematology, chemistry) will be conducted. Urine pregnancy tests will be conducted for women of childbearing potential. The subject's Diary and medication compliance will be reviewed.

Subjects will perform serial spirometry over approximately 60 minutes, subjects will be required to perform three separate sessions of spirometry, allowing adequate time for subject

recovery between sessions. [redacted]. Sites will collect any remaining study medication and the eDiary device. Subjects will be discharged from the study after confirmation of stability by the Investigator.

If subjects decide to withdraw from the study prior to Visit 3 Day 29, an Early Termination visit will be scheduled, if possible. The subject's interim medical history (including AEs) and concomitant medications will be reviewed. Laboratory screening (blood: hematology, chemistry) will be conducted. Urine pregnancy tests will be conducted for women of childbearing potential. The subject's Diary and medication compliance will be reviewed. The remaining study medication and the eDiary device will be collected. A single spirometry session may be conducted if deemed necessary by the Investigator. Subjects will be discharged from the study after the Early Termination Visit upon confirmation of stability by the Investigator.

A detailed Schedule of Procedures is provided in Appendix 11.1.

3.2 Sample Size

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3.3 Randomization and Unblinding Procedures

Eligible subjects will be randomly assigned in a [redacted] scheme to 1 of 3 treatment arms by site. A sufficient number of randomization codes will be generated in order to ensure that an adequate number of codes are available to randomize up to approximately [redacted]. Randomization and kitting of study supplies will be handled by the IWRS vendor and the drug packager. The randomization programming will be provided by the IWRS provider, [redacted].

[redacted]. In case of an SAE, the Investigator may un-blind the subject's drug assignment when necessary to make treatment decisions for the subject. The Sponsor should be notified of the event prior to breaking the code, if possible. If this is not possible, the Sponsor should be notified immediately afterwards, and the subject's drug code assignment should not be revealed to the Sponsor. The circumstances leading to the breaking of the code should be fully documented in the Investigator's study files and in the subject's source documentation. The subject's treatment assignment should not be recorded in any study documents.

Unless emergency unblinding occurs, treatment group assignment will be kept blinding until the final database lock.

4. STUDY ENDPOINTS/OUTCOMES

This study's primary efficacy endpoint is mean change in morning pre-dose FEV_1 from the time of treatment randomization to Week 4 (Day 29 [redacted]).

5. HYPOTHESES TESTING

Hypothesis of Equivalence

A two-sided, 90% confidence interval on the test/reference ratio for the primary endpoint will be constructed using an Analysis of Covariance (ANCOVA) model of the Test and Reference results with [redacted]

Bioequivalence will be established if the 90% confidence interval for the ratio of test/reference means is contained within the interval [80.00%, 125.00%] for the Per-protocol Set.

Hypothesis of Superiority

In order to demonstrate adequate sensitivity, both test and reference treatments will be compared with placebo with respect to the primary endpoint using an ANCOVA model [redacted] Both treatments must be statistically superior to placebo for the Modified Intent-to-Treat Set in order to validate the assessment of clinical endpoint bioequivalence for the test/reference ratios for the primary endpoint.

6. ANALYSIS SUBSETS

6.1 Enrolled Set (ENS)

The Enrolled Set (ENS) will consist of all subjects who provided informed consent.

6.2 Run-in Set (RiN)

All patients who enter the Run-in Period and have a record of at least one study drug (placebo) administrationion the Run-in Period.

6.3 Run-in Failure Set (RIF)

The Run-in Failure Set will consists of all subjects in the Run-In set who did not receive any randomized study drug following randomization.

6.4 Randomized Set

The randomized set will consist of all subjects who were randomized.

6.5 Safety Analysis Set (SAF)

The Safety Analysis Set (SAF) will consist of all randomized subjects who received at least 1 dose of randomized study drug during the Treatment Period. Subjects will be classified by actual treatment received. The SAF will be the primary population for the safety analysis.

6.6 Modified Intent-to-Treat (mITT) Set

The Modified Intent-to-Treat (mITT) set will consist of all randomized subjects who received at least 1 dose of randomized study drug during the Treatment Period. [redacted]

Subjects will be classified by the treatment to which they were randomized. This population will be considered as definitive for testing superiority.

6.7 Per-protocol Set (PPS)

The Per-protocol Set (PS) will consist of all subjects in the mITT set who had between 75% and 125% compliance with the dosing schedule in the Treatment period, and had no major protocol deviations that are considered to have an impact on the analysis of the primary endpoint. The PPS will be defined before database lock and unblinding during the BDRM.

In the PPS subjects will be classified by randomized treatment. This population will be considered as definitive for testing bioequivalence.

7. STATISTICAL METHODS OF ANALYSIS

7.1 General Principles

The statistical analyses will be performed by [redacted], with approval of the Sponsor, using SAS Version 9.4 (or higher). All tables, figures and listings will be produced in landscape format.

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 specified analysis set will be displayed in the header of summary tables.

Data will be summarized using descriptive statistics for continuous variables. Unless otherwise specified, descriptive statistics will include number of subjects, mean, standard deviation, minimum, median and maximum. Number of subjects with missing values will also be displayed, but only if non-zero. The minimum and maximum statistics will be presented to the same number of decimal places as the original data. The mean and median will be presented to one more decimal place than the original data. The standard deviation will be presented to two more decimal places than the original 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.

All statistical tests will be two-sided at a significance level of $\alpha = 0.05$, unless otherwise indicated. No adjustment will be made for multiplicity.

Baseline will be defined as the last assessment, scheduled or not, prior to the first dose of the randomized study drug, unless otherwise specified.

In by-visit summaries, only data collected on scheduled visits/timepoints will be summarized. Data from unscheduled assessments will be included in listings and may be used in determination of baseline if applicable.

Relative days will be calculated relative to date of first dose of randomized study medication. Relative days will be calculated as follows only when the full assessment date is known (i.e., partial dates will have missing relative days).

For assessment on or after the day of first dose of the randomized study drug:

[redacted]

7.2 Subject Disposition

This analysis will be based on the ENS. The number of subjects enrolled in the study, randomized to treatment, included in the SAF, mITT, and PPS, prematurely discontinued from the study after randomization (along with the reasons for discontinuation) will be presented. The same analysis will be repeated by study site.

An overall summary of the number of subjects in each population by site will be created.

All disposition information will be listed. Additionally, a listing of subjects who discontinued from the study prematurely will be created, including date of discontinuation and primary reason. Also a listing of enrollment details will provide the date of informed consent/assent and inclusion/exclusion criteria not met, if any.

7.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics will include:

- age
- sex
- race
- ethnicity
- baseline height, weight and body mass index (BMI)
- time since asthma diagnosis (years)

Descriptive statistics will be presented for continuous variables. Frequency counts and percentage will be presented for categorical variables. Height will be reported in centimeters, weight in kilograms and BMI in kg/m^2.

Age will be derived from [redacted].

Demographic and baseline characteristics will be evaluated for comparability across treatment groups in the following manner. Continuous variables will be analyzed with an analysis of variance with factors of treatment and investigational site. Overall p-value for the global null hypothesis of all groups being equal will be displayed. [redacted].

These analyses will be performed for the SAF, mITT and PPS.

All demographic parameters and baseline characteristics will be presented in the by-subject listings.

7.4 Medical history

Medical history will be summarized by MedDRA (version 22.0) System Organ Class and Preferred Term. One subject will be counted once for each applicable Preferred Term and System Organ Class. This summary will be performed for the SAF. All medical history information will be listed.

7.5 Protocol Deviations

[redacted]

All major protocol deviations will be summarized by deviation category and treatment group. This analysis will be performed for the Randomized set.

7.6 Lung function testing

The results of the spirometry measurements (including reversibility testing) at Screening Visit 1b will be listed for each subject including the FEV_1, FVC (absolute values and percentage of

predicted values rounded to whole numbers). For the reversibility testing, both the absolute measurements and percentage change after inhaled bronchodilator will be presented. Spirometry data from the vendor may include several attempts for each subject/visit/time-point with the best attempt flagged. [redacted]

If Screening Visit 1b is repeated, only the data from the repeat visit will be used in analysis. The results will be summarized by treatment and parameter for the mITT set and PPS.

7.7 Efficacy Analyses

7.7.1 Analysis of Equivalence and Superiority

7.7.1.1 Calculation of the Primary Endpoints

Acceptability criteria. [redacted]

FEV_1 baseline. The FEV_1 baseline will be defined as the average of the acceptable pre-dose FEV_1 values obtained at Visit 2 Randomization. If some of these measurements are missing or are not acceptable, 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 Visit 2 Randomization will have their FEV_1 baseline missing, and thus the subject will be excluded from analysis.

Calculation of Change in Pre-Dose FEV_1 From Baseline to Week 4.

The endpoint of change in morning pre-dose FEV_1 from the time of treatment randomization to Week 4 will be calculated as [redacted]

[redacted]

If a subject has no pre-dose assessment at Visit 3 Day 29 (or Visit 3 occurred outside of the allowed window), in the mITT analysis FEV_1 at end of treatment will be imputed (following LOCF rule) as the average of available pre-dose assessments on the last post-baseline day when at least one acceptable pre-dose FEV_1 assessment are available (e.g. the Early Termination visit). [redacted]. In the PPS analysis, however, the endpoint will not be imputed and the subject will be thus excluded from the analysis, unless the subject missed Visit 3 Day 29 because he/she discontinued from the study due to lack of efficacy. In the latter case the endpoint will be imputed in the same way as for mITT analysis even in the PPS analysis.

7.7.1.2 Site pooling

[redacted]

- [redacted]
- [redacted]

[redacted]

7.7.1.3 Analysis of bioequivalence of test and reference treatments

To show the bioequivalence, the following steps will be taken:

1. [redacted].
2. Bioequivalence will be declared if the 90% confidence interval for the test/reference LS mean ratio is entirely contained within the interval from 80% to 125%.

Analysis of bioequivalence will be performed on the PPS.

7.7.1.4 Analysis of superiority to placebo

The analysis of superiority will be performed separately for the Test treatment versus the Placebo and for the Reference treatment versus the Placebo. Each of these analyses will be performed as follows:

1. [redacted]
2. Superiority will be declared if the Test and Reference LS means are each greater than the Placebo LS mean and the respective p-values are < 0.05.

Analysis of superiority will be performed on the mITT set.

7.8 Safety Analyses

All safety analyses will be performed on the SAF. Additionally some analysis of safety in the Run-in period will be performed on the Run-in Failure Set.

7.8.1 Adverse Events

Adverse Events will be coded using the Medical Dictionary of Regulatory Activities (MedDRA Version 22.0) AE coding system for purposes of summarization.

An AE will be considered as study-emergent if the date of onset is on or after the date of informed consent.

An AE will be considered as treatment-emergent if the time of onset is on or after the time of the first randomized study drug administration in the Treatment period. AEs with unknown start dates will be counted as treatment-emergent unless the AE resolution date is prior to the randomized drug start date. If the start date is partially missing, the AE will be considered treatment-emergent, unless the month and year (when available) rule out the possibility that the event occurred post start of randomized dosing.

A TEAE is defined as treatment-related if its relationship to study medication is recorded as "reasonable possibility" on the eCRF. In case the relatedness was not assessed, the most conservative result (related) will be chosen for the analysis.

In summaries of TEAEs a subject experiencing the same AE multiple times will only be counted once for that preferred term. Similarly, if a subject experiences multiple AEs within the same system organ class that subject will be counted only once in that system organ class. When summarizing AEs by severity, only the most severe occurrence within the preferred term or system organ class will be used. Similarly, when summarizing AEs by relationship to study drug, only the most related occurrence within the preferred term or system organ class will be selected for displays in summary tables.

An overall summary for the SAF will include, by treatment group and overall, the number and percentage of subjects reporting at least 1 TEAE in the following categories:

- Any TEAE
- Treatment-related TEAE

- Serious TEAE
- TEAE leading to discontinuation of the study medication
- TEAE leading to death.

The following TEAE frequency tables will be prepared summarizing the overall number of TEAEs, the number and percentage of subjects reporting at least one TEAE by MedDRA System Organ Class (SOC) and preferred term (PT), by treatment group for the SAF:

- All TEAEs
- Serious TEAEs
- Treatment-related TEAEs
- AEs leading to discontinuation of the study medication
- TEAEs by Severity
- TEAEs by Relationship to Study Medication.

Additionally, the following summaries of the study-emergent AEs that are not treatment-emergent (i.e. occurred in the Run-in period) will be presented for the Run-in Failure Set:

- Overall summary similar to the overall summary of TEAEs
- AEs by System Organ Class and Preferred Term

All information pertaining to adverse events noted during the study will be listed by subject, detailing verbatim, preferred term, system organ class, start date, stop date, intensity, outcome, action taken and causal relationship to the study drug. The adverse event onset will also be shown relative (in number of days) to the date of first administration of the study medication. In addition the adverse event duration (if AE Stop Date is available) will be evaluated as below and presented (in number of days).

[redacted]

AEs occurring in the Run-in period will be listed separately from the TEAEs.

7.8.2 Laboratory tests

Laboratory safety assessment (i.e., clinical chemistry, hematology, urinalysis) will be assessed by investigators for the presence of any findings that meet the description of an AE.
Laboratory test results will not be listed or summarized.

Pregnancy test results and results of the drug, alcohol and cotinine screen will be listed.

7.8.3 Vital signs

Vital signs include systolic and diastolic blood pressure and heart rate and will be measured at Screening Visit 1b, Visit 2, Visit 3 and early termination, as well as unscheduled visit if required.

Vital signs will be summarized descriptively by scheduled visit and treatment group. For Visit 3 the change from baseline will also be summarized.

All vital signs will be listed.

7.8.4 12-Lead ECG

ECG will be performed at Screening Visit 1b. Overall interpretation will be recorded as Normal, Abnormal not clinically significant or Abnormal clinically significant.

All ECG findings will be listed.

7.8.5 Physical Examination

Physical examination will be performed at Screening Visit 1b. Results will be listed by subject and body system.

7.8.6 Peak Expiratory Flow Rate

The PEFR entries from the subjects' diaries will be listed for each subject for both morning and evening measurements obtained during the Run-in Period and the Treatment Period.

PEFR values will be summarized graphically. A line plot will be created with X axis showing study day and Y axis showing mean PEFR. A separate line will be plotted for each treatment group.

7.8.7 Exposure to Product

The subjects will be instructed to use the diary to document all doses taken.

Study drug compliance will be determined separately for Run-In and Treatment period as [redacted]

- [redacted].
- Planned number of doses is determined as follows:
  - [redacted].
  - [redacted]

Note that if Screening Visit 1b is repeated for reversibility assessment, then the date of the repeat visit will be used in the calculation of the planned number of doses for the run-in period.

All doses in the diary recorded on or after the date of Visit 2 and dosing time as reported in the spirometry data will be considered as belonging to the Treatment period. All doses in the diary prior to that date and time will be considered as belonging to the Run-in period.

Compliance will be rounded to whole percentages. The compliance will be analyzed using the descriptive statistics by study period and treatment group. The proportion of subjects with at least 70% compliance in the Run-In period and 75% to 125% compliance in the Treatment period will be tabulated for each study period and treatment group.

Duration of exposure will be calculated by study period as [Date of last use of study medication in the period] – [Date of first use of study medication in the period] + 1. Duration of exposure will be summarized descriptively by study period and treatment group.

Compliance and duration of exposure will also be listed.

These analyses will be performed for the SAF for the Run-in and Treatment periods and also for the Run-in Failure Set for the Run-in period only.

7.8.8 Rescue medication use

Number of days with rescue medication uses in Run-in and Treatment periods will be counted in the diary, using the answers from "Morning Diary" ("Number of Puffs of Albuterol"). This number will be summarized descriptively by study period and treatment group. It will also be listed.

These analyses will be performed for the SAF for the Run-in and Treatment periods and also for the Run-in Failure Set for the Run-in period only.

7.8.9 Prior and Concomitant Medication

Prior and concomitant medication will be coded according to the World Health Organization – Drug Dictionary version March 2019 and the Anatomical Therapeutic Chemical classification system. 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.

All previous and concomitant medication will be listed by subject. Concomitant medications will be summarized by treatment group, ATC class (highest level available) and preferred name. This analysis will be done for the SAF.

8. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

There are no changes from the protocol-specified analyses.

9. LIST OF PLANNED TABLES, FIGURES, AND LISTINGS

See separate document with the table, figure and listing shells.

10. LITERATURE CITATIONS / REFERENCES

1. Study protocol: "A Randomized, Blinded, Parallel Group, Placebo-Controlled, Multiple Dose, Multicenter Study to Compare the Therapeutic Equivalence of Fluticasone Propionate Pressurized Metered Dose Inhaler, 110 mcg, to Flovent® HFA 110 mcg, in Adult Subjects with Asthma", amendment 2, dated June 10, 2019
2. US Food and Drug Administration (FDA) Draft Guidance on Fluticasone Propionate (Oct., 2017, Rev. July, 2018).