Statistical Analysis Plan

A 12-Week, Randomized, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Fluticasone Propionate Multidose Dry Powder Inhaler Compared with Fluticasone Propionate/Salmeterol Multidose Dry Powder Inhaler in Patients Aged 4 through 11 Years with Persistent Asthma

Study Number FSS-AS-30003

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Statistical Analysis Plan Approval Date: 16 April 2019

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Phase 3

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Sponsor

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STATISTICAL ANALYSIS PLAN APPROVAL

Study No.: **FSS-AS-30003**

Study Title: **A 12-Week, Randomized, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Fluticasone Propionate Multidose Dry Powder Inhaler Compared with Fluticasone Propionate/Salmeterol Multidose Dry Powder Inhaler in Patients Aged 4 through 11 Years with Persistent Asthma**

Statistical Analysis Plan for:

- ☐ **Interim Analysis**
- ☐ **Integrated Summary of Efficacy**
- X **Final Analysis**
- ☐ **Integrated Summary of Safety**

Author: [redacted]

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ANCOVA	analysis of covariance
ANOVA	analysis of variance
BP	blood pressure
BMI	body mass index
BOCF	baseline observation carried forward
CI	confidence interval
CRF	case report form
CSR	clinical study report
ECG	electrocardiogram
ET	early termination (visit)
FAS	full analysis set
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
Fp MDPI	fluticasone propionate multidose dry powder inhaler
FS MDPI	fluticasone propionate/salmeterol multidose dry powder inhaler
ICH	International Conference on Harmonisation
ICS	inhaled corticosteroid
IMP	investigational medicinal product
IRT	interactive response technology
ITT	intent-to-treat
LABA	long acting β_2-agonist
LOCF	last observation carried forward
LS	least squares
max	maximum
MAR	missing at random
MDI	metered-dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
MDPI	multidose dry powder inhaler
min	minimum
MMRM	mixed model for repeated measures
MNAR	missing not at random
n	number

NCS	noncorticosteroid
PEF	peak expiratory flow
PFT	pulmonary function test(s)
PP	per-protocol
PT	preferred term
RV	randomization visit
SAS	statistical analysis system
SABA	short-acting β_2-agonist
SD	standard deviation
SDR	statistical data review
SE	standard error
SOC	system organ class
SV	screening visit
WHO Drug	World Health Organization dictionary of medical terms

INTRODUCTION

This Statistical Analysis Plan describes the planned analysis and reporting for Teva Pharmaceutical Global Respiratory Research and Development, Inc. Study FSS-AS-30003, (A 12-Week, Randomized, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Fluticasone Propionate Multidose Dry Powder Inhaler Compared with Fluticasone Propionate/Salmeterol Multidose Dry Powder Inhaler in Patients Aged 4 Through 11 Years with Persistent Asthma), and was written in accordance with SOP GBP_RD_702 (Statistical Analysis Plan).

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

The Statistical Analysis Plan is intended to be in agreement with the protocol, especially with regards to the primary and all secondary endpoints and their respective analyses. However, the Statistical Analysis Plan may contain more details regarding these particular points of interest, or other types of analyses (e.g. other endpoints). When differences exist in descriptions or explanations provided in the study protocol and this Statistical Analysis Plan, the Statistical Analysis Plan prevails; the differences will be explained in the Clinical Study Report.

1. STUDY OBJECTIVES AND ENDPOINTS

1.1. Primary and Secondary Study Objectives and Endpoints

The primary objective of this study is to evaluate the efficacy of Fp MDPI and FS MDPI when administered over 12 weeks in patients 4 through 11 years of age with persistent asthma.

The secondary objective of this study is to evaluate the safety and tolerability of Fp MDPI and FS MDPI.

The primary efficacy endpoints are as follows:

- For Fp MDPI versus placebo: the change from baseline in weekly average of the percent predicted trough morning forced expiratory volume in 1 second (FEV_1) at week 12
- For FS MDPI versus Fp MDPI: the change from baseline in 1-hour postdose percent predicted morning FEV_1 at week 12

The secondary efficacy endpoints are as follows:

- Change from baseline in the weekly average of daily trough morning (predose and pre-rescue bronchodilator) peak expiratory flow (PEF) over the 12-week treatment period
- Change from baseline in the weekly average of total daily (24-hour) use of albuterol/salbutamol inhalation aerosol (number of inhalations) over weeks 1 through 12
- Change from baseline in the weekly average of the total daily asthma symptom score (defined as the average of the daytime and nighttime scores) over weeks 1 through 12
- Change from baseline in asthma control (measured by Childhood Asthma Control Test [C-ACT]) score over the 12-week treatment period
- Time to first onset of effect defined as the first decrease from baseline in daily rescue medication use
- Proportion of patients discontinued from investigational medicinal product (IMP) for asthma exacerbation during the 12-week treatment period

The sequential order of the secondary endpoints for multiplicity will be described in Section 7.2.

1.2. Other Efficacy Endpoints

The other efficacy endpoints are as follows:

- Change from baseline in the weekly average of total daily (24-hour) use of albuterol/salbutamol inhalation aerosol (number of inhalations) at weeks 4, 8, and 12
- Change from baseline in the percentage of rescue-free days (defined as 24-hour periods with no rescue medication usage) during the 12-week treatment period

- Change from baseline in the percentage of symptom-free days (defined as 24-hour periods with asthma symptom score of 0) during the 12-week treatment period
- Change from baseline in the percentage of asthma-control days (defined as 24-hour periods with asthma symptom score of 0 and no rescue medication usage) during the 12-week treatment period
- Change from baseline in 1-hour postdose percent predicted morning FEV_1 at week 1
- Change from baseline in the weekly average of daily evening PEF over the 12-week treatment period
- Change from baseline in the weekly average of the percent predicted trough morning FEV_1 at weeks 1, 2, 4 and 8
- Proportion of patients who achieve at least a 15% increase in morning FEV_1 at 1 hour postdose at day 1 (randomization visit [RV]/treatment visit [TV] 1), week 1, and week 12
- Change from baseline in asthma control (measured by C-ACT) score at weeks 4, 8, and 12
- Time to consistent onset of effect defined as the decrease from baseline in daily rescue medication use on 3 consecutive days

2. STUDY DESIGN

2.1. General Design

This is a Phase 3, 12-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the safety and efficacy of Fp MDPI and FS MDPI administered twice daily at doses of Fp MDPI 25 mcg, Fp MDPI 50 mcg, and FS MDPI 50/12.5 mcg in pediatric patients with asthma. The total duration of patient participation in this study is approximately 15 to 17 weeks depending on the duration of the placebo run-in period.

Patients meeting all of the inclusion criteria and none of the exclusion criteria at the screening visit (SV) will begin a 14- to 30-day run-in period. An albuterol/salbutamol hydrofluoroalkane (HFA) metered-dose inhaler (MDI) (a SABA inhaler) will be provided to replace the patient's current rescue medication and is to be used as needed for relief of asthma symptoms during the run-in and treatment periods, with a maximum of 8 inhalations permitted per day. Starting day 1 of the run-in period, patients must discontinue all non-study asthma-related drugs and instead take a patient-blinded MDPI placebo device (1 inhalation twice daily).

The study consists of 3 periods as follows:

- Patient-blinded run-in period: SV to RV, up to 30 days
- Double-blind, randomized treatment period: RV through the TV6, approximately 12 weeks
- Follow-up period: TV6 through the follow-up visit (FV), approximately 7 days after TV6

At the prescreening or SV, the patient or parent/legal guardian must provide informed consent, and patients must give assent (as applicable) before any study procedures are performed. At the time of informed consent, the parent/legal guardian will be counseled that, once randomized to treatment, patients are to remain in the study and complete all study procedures unless the choice is made to withdraw consent. This includes patients who may require alternative asthma therapy, experience an adverse event, violate the protocol, or fail to comply with study procedures. Continued patient participation is important to contribute to the scientific investigation.

Patients will be provided with a handheld device at the SV, which will be used to measure lung function assessments (FEV_1 and PEF) and will serve as an electronic patient diary to collect asthma symptom scores, rescue medication use, and IMP use. The run-in period will not start until patients have met all inclusion criteria and none of the exclusion criteria.

Patients who qualify for entry into the placebo run-in period must discontinue all currently administered asthma medications until completion of the TV6 (week 12) visit or investigational medicinal product discontinuation visit (IMPDV) if, in the investigator's judgment, there would be no inherent harm in changing the patient's treatment and the patient or parent/legal guardian provides consent/assent (as applicable). Patients will be provided with albuterol/salbutamol HFA MDI or equivalent as rescue medication. During the run-in period (SV to RV), in addition to the

above rescue medication, patients will be provided with a patient-blinded placebo MDPI device for twice-daily use after appropriate training and demonstration of proper technique.

All patients who enter the placebo run-in period will perform daily morning and evening lung function assessments (FEV_1 and PEF) by handheld device at home and assess and record daytime and nighttime asthma symptom scores, rescue albuterol/salbutamol HFA MDI use, and morning and evening IMP dosing in the electronic patient diary built into the handheld device.

At the RV (end of run-in period, TV1), patients will be assessed for randomization. Patients who meet all randomization inclusion criteria and continue meeting all inclusion criteria and none of the exclusion criteria will be stratified by previous therapy (inhaled corticosteroid [ICS] or noncorticosteroid [NCS]) and randomly assigned into the double-blind treatment period of the study in a 1:1:1:1 ratio to Fp MDPI 25 mcg, Fp MDPI 50 mcg, FS MDPI 50/12.5 mcg, or placebo MDPI, twice daily (see Table 1). Patients will be instructed to take 1 inhalation from the assigned device twice daily approximately 12 hours apart.

Table 1: Treatment Group Description

Treatment group	Active devices	Total daily dose (mcg)	Blinding
A	Fp MDPI 25 mcg	50	Double-blind
B	Fp MDPI 50 mcg	100	Double-blind
C	FS MDPI 50/12.5 mcg	100/25	Double-blind
D	Placebo MDPI	0	Double-blind

Fp=fluticasone propionate; FS=fluticasone propionate/salmeterol; MDPI=multidose dry powder inhaler.

During the treatment period (RV through TV6 [week 12] or IMPDV), daily in the morning and evening at approximately the same time each day, patients will use the handheld device at home to record asthma symptom scores and rescue albuterol/salbutamol HFA MDI use, after which they will perform lung function assessments (FEV_1 and PEF) and then will take their dose of the IMP and record IMP dosing in the electronic patient diary built into the handheld device.

On the morning of each TV, patients will be instructed to record their asthma symptom score and rescue albuterol/salbutamol HFA MDI use and complete their morning lung function assessments (FEV_1 and PEF) by handheld device as usual, but to delay IMP dosing until they get to the investigational center. Patients are also to withhold their rescue SABA for a minimum of 6 hours prior to obtaining lung function assessments. If the patient inadvertently takes the morning IMP dose or rescue medication within 6 hours of the planned lung function assessments, the visit must be rescheduled. Similarly, patients who have been withdrawn from IMP but remain in the study should withhold their alternative asthma therapy dosing until after treatment visit assessments and avoid rescue medication for a minimum of 6 hours prior to clinic lung function assessments. The treatment visit should be rescheduled if either or both occur.

At the investigational center, after appropriate instruction and training (competent handheld device use and dosing technique using the training devices provided), patients will perform their lung function assessment (FEV_1 and PEF) under the supervision of the investigational center staff. They will then take their morning dose of the IMP unless IMP has been withdrawn. IMP administration at the investigational center should be timed so that lung function assessments will be approximately 12 hours following the doses taken the previous evening. Patients will

then perform 1-hour postdose FEV_1 measurements using the handheld device. Patients who have been withdrawn from IMP will be asked to perform 1-hour postdose lung function assessments; although the patients will not be taking a dose of IMP, the assessment should be approximately 1-hour after the predose lung function assessments were obtained.

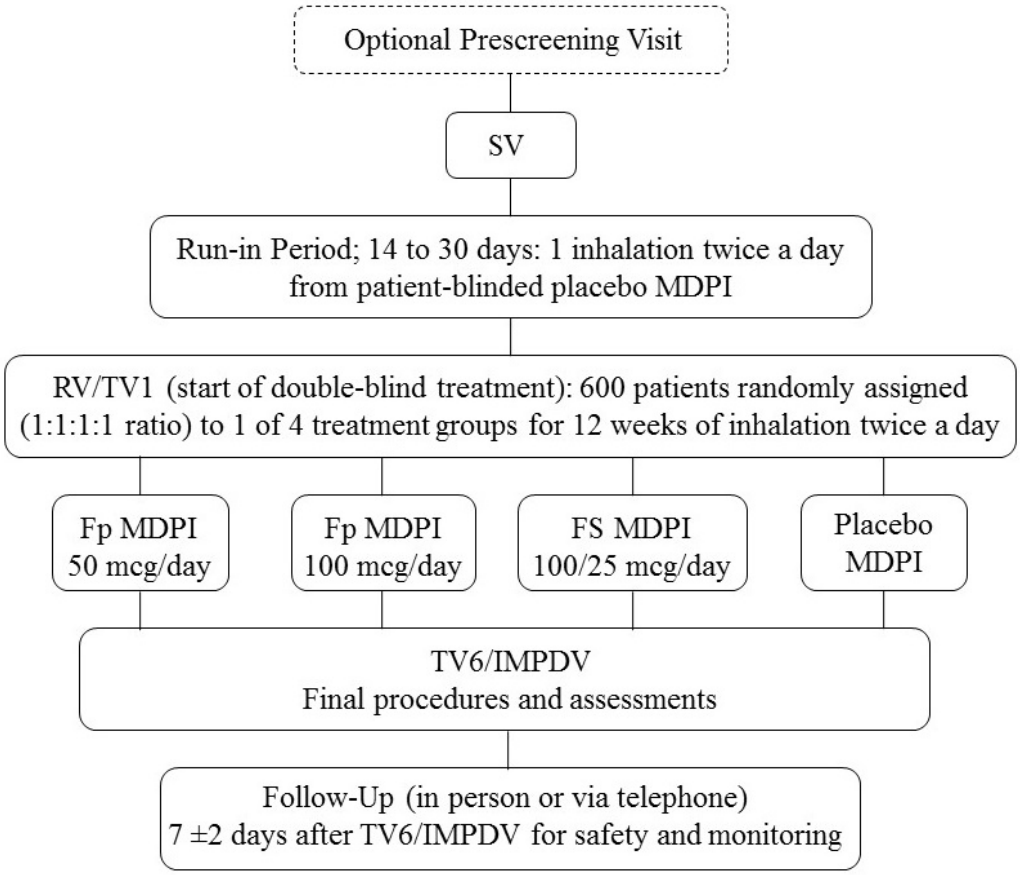
At each visit, the investigational center will determine if patients have experienced any adverse events, changes in medical history, changes in medication, or any difficulty following study procedures. The C-ACT will be completed by the patient and the patient's parent/legal guardian/caregiver (as applicable) at the investigational center, before any other assessments are performed, at specified visits. The same parent/legal guardian/caregiver should complete the assessments at each visit, if possible.

After the last TV (TV6, week 12), the patient will enter the follow-up period. One week (±2 days) after the last TV or the IMPDV, the patient will have a follow up visit (FV). This FV may be in person or over the telephone. The patient will be deemed to have completed the treatment period if they have completed all periods of the study, including screening, run-in, and all TVs. The patient will be deemed to have completed the study period if they have completed all periods of the study, including FV in additional to screening, run-in, and all TVs. Patients who stop IMP and return for safety evaluation at week 12 but who do not complete the FV will still be considered to have completed the treatment period for the purposes of primary analysis.

Study procedures and assessments with their time points are summarized in Table 3 of the study protocol.

The study schematic diagram is presented in Figure 1.

Figure 1: Overall Study Schematic Diagram



Fp=fluticasone propionate; FS=fluticasone propionate/salmeterol; IMPDV=investigational medicinal product discontinuation visit; MDPI=multidose dry powder inhaler; RV=randomization visit; SV=screening visit; TV=treatment visit.

2.2. Randomization and Blinding

This is a double-blind, parallel-group, placebo-controlled, randomized clinical study. Patients who meet all randomization criteria at the RV will be stratified by previous therapy (ICS or NCS) and randomly assigned into a 1:1:1:1 ratio to receive Fp MDPI 25 mcg, Fp MDPI 50 mcg, FS MDPI 50/12.5 mcg, or placebo MDPI, twice daily, for the entire treatment period. Randomization will be assigned via IRT. Patients being treated with a combination of ICS/NCS will be stratified as an ICS patient.

Approximately 206 patients will be randomized into each treatment group (approximately 824 patients in total). After the run-in period, patients and parents/legal guardians/caregivers will remain blinded to randomized treatment assignment during the study. In addition, the investigator and the sponsor's clinical personnel involved in the study will be blinded to the IMP identity after the run-in period until the database is locked for analysis and the treatment assignment is revealed.

No effort will be made to maintain a balance among treatment groups within an investigational center.

Patients will be randomly assigned to treatment groups by means of a computer-generated randomization list. The specifications for randomization will be under the responsibility and oversight of Teva Global Statistics. The output of the randomization process will be a patient randomization list.

The sponsor's clinical personnel involved in the study will be blinded to the identity of the treatment until the database is locked for analysis and the treatment assignment revealed.

2.3. Data Monitoring Committee

There will be no data monitoring committee in this study.

2.4. Sample Size and Power Considerations

Sample size and power calculations are driven by demonstrating superiority of FS MDPI 50/12.5 mcg twice daily over Fp MDPI 50 mcg twice daily in change from baseline in 1-hour postdose percent predicted morning FEV_1 at week 12 and the superiority of Fp MDPI 50 mcg twice daily over placebo in change from baseline in percent predicted trough morning FEV_1 at week 12.

For the superiority comparison of FS MDPI 50/12.5 mcg twice daily versus Fp MDPI 50 mcg twice daily, assuming that the change from baseline in 1-hour postdose percent predicted morning FEV_1 at week 12 is analyzed using an ANOVA model with only a single factor of treatment group, the following assumptions were made:

- The initial assumed common standard deviation (SD) was 9.3% and the true treatment difference was 4.5% between FS MDPI 50/12.5 mcg twice daily and Fp MDPI 50 mcg twice daily. This assumption was based on data collected in previous Teva studies with the same Fp MDPI and FS MDPI products in adult asthma patients who completed the 12-week treatment period and based on office-based spirometry.
- The initial power was 97% at a 2-sided significance level of 5%.

For the superiority comparison of Fp MDPI 50 mcg twice daily versus placebo, assuming that the change from baseline in percent predicted trough morning FEV_1 at week 12 is analyzed using an analysis of variance (ANOVA) model with only a single factor of treatment group, the following assumptions were made:

- The initial assumed common standard deviation (SD) was 13.25% and the true treatment difference was 5% between Fp MDPI 50 mcg twice daily and placebo. This assumption was based on data collected in previous Teva studies with the same Fp MDPI product in adult asthma patients and based on office-based spirometry
- The initial power was 85% at a 2-sided significance level of 5%.

Study FSS-AS-30003 is the very first study in which a handheld spirometry device is utilized 1) as the primary endpoint in a Phase 3 study and 2) in a pediatric asthma patient population for a pivotal study of this scale. This made it difficult to predict the actual variability of the data. A blinded sample size reassessment was not planned. Routine blinded data monitoring of this study FSS-AS-30003 revealed that the SD for the overall study population is indeed higher than the initial assumptions. In addition, FEV_1 stability has been monitored closely throughout this study

(see Clinical Study Protocol FSS-AS-30003 Section 6.1.3 for detail). A number of alerts were determined by the investigators as not related to worsening asthma but rather due to poor patients' effort, which has been challenging in this patient population as young as 4 years of age, despite the rigorous training and coaching provided by the investigators. To ensure the high quality of the FEV_1 data and integrity of the study, an unplanned blinded data quality evaluation and sample size reassessment was conducted. Some of the initial assumptions and the sample size described above were revised to the following:

- For the superiority comparison of FS MDPI 50/12.5 mcg twice daily versus Fp MDPI 50 mcg twice daily, the SD was revised to 22% and the overall mean change from baseline was revised to 6.5% (blinded SD observed after 427 patients completed week 12 of this study (excluding IMPD)) and the power down to 80%.
- With these assumptions, 181 patients per treatment group are required for the 2-sided test of FS MDPI 50/12.5 mcg twice daily and Fp MDPI 50 mcg twice daily.
- For the superiority comparison of Fp MDPI 50 mcg twice daily versus placebo, the SD was revised to 17% and overall mean change from baseline was 5% (blinded SD observed after 434 patients completed week 12 of this study (excluding IMPD) and the power was revised to 80%.
- With these assumptions, 181 patients per treatment group are required for the 2-sided test of Fp MDPI 50 mcg twice daily versus placebo.

Based on current blinded data and assuming a dropout rate of 12%, a total of 824 patients (206 patients per treatment group) will be randomized (initial assumption for dropout rate was 15%).

2.5. Sequence of Planned Analyses

2.5.1. Planned Interim Analyses

No formal interim analysis was initially planned for this study. However, this study is the very first study in which the handheld spirometry device is utilized as the primary endpoint and the study is conducted in a pediatric patient population across several age groups; Routine blinded data monitoring of this study revealed that the SD for the overall study population is higher than the initial assumptions based on the adult asthma patient population. Therefore, some of the initial assumptions and the sample size initially used were revised.

2.5.2. Final Analyses and Reporting

All analyses identified in this statistical analysis plan will be performed only after the last patient has completed the study as defined in the study protocol. The statistical analysis plan and any corresponding amendments will be approved before database lock, in accordance to SOP GBP_RD_702 (Statistical Analysis Plan). The randomization codes will not be unblinded until database lock.

Any exploratory analyses completed to support study analyses, which were not identified in this statistical analysis plan, will be documented and reported in the CSR.

3. ANALYSIS SETS

3.1. Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set will include all randomized patients.

In the ITT analysis set, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received.

The ITT analysis set will serve as the primary analysis set for the efficacy analyses.

3.2. Safety Analysis Set

The safety analysis set will include all randomized patients who receive at least 1 dose of IMP.

In the safety analysis set, treatment will be assigned based on the treatment patients actually received, regardless of the treatment to which they were randomized, unless otherwise specified.

The safety analysis set will be used for all analyses of safety data.

3.3. Per-Protocol Analysis Set

The per-protocol (PP) analysis set is a subset of the ITT analysis set including only patients without protocol violations that could have an effect on the primary outcome and who have greater than or equal to 80% compliance to the IMP over the entire treatment period. The compliance rate calculation is detailed in Section 8.3.

PP analysis set will be determined before unblinding at the Statistical Data Review (SDR) meeting and documented in the SDR meeting minutes. Note that since the use of incorrect IMP will be considered a protocol violation and will not be included in the PP analysis set, for treatment assignment in the PP analysis set, “as randomized” will coincide with “as treated”.

The PP analysis set will serve as the supportive population for the primary efficacy analysis only.

4. GENERAL ISSUES FOR DATA ANALYSIS

4.1. General

Descriptive statistics for continuous variables include n, mean, SD, standard error (SE), median, minimum, and maximum. Descriptive statistics for categorical variables include patient counts and percentages, missing category will be displayed as appropriate.

Inferential statistics for repeated measures and analysis of covariance (ANCOVA) analyses include least squares (LS) mean and SE of the LS mean, estimated treatment difference, 95% confidence interval (CI), and p-value.

For patients who prematurely discontinued study IMP participation for any reason but remain in the study for their scheduled weekly efficacy evaluation, data collected on other alternative therapies received after IMP discontinuation are defined as "retrieved dropout" data.

Data values which are deemed implausible from a clinical perspective (eg, post-randomization pre-bronchodilator percent predicted FEV_1 is ≥200% while the baseline FEV_1 was ≤85% as required by the protocol Inclusion/Exclusion criteria) will be identified and assessed at the SDR meeting and before unblinding of the database. Any percent predicted FEV_1 values that are ≥200% will be treated as missing and excluded from all data analyses. Exclusion of data values will be documented and justified in the clinical study report.

4.2. Specification of Baseline Values

In general, the baseline values for efficacy and safety variables are defined as the last observed data before the first dose of study drug, unless otherwise noted.

For data collected daily in electronic patient diaries (ie, daily FEV_1, PEF, asthma symptom scores, rescue medication use, etc.), baseline is defined as the average of daily data recorded in the 7 days before randomization. The prerandomization day consists of the electronic patient diary entries on the evening prior to the RV (TV1) or on the morning of the RV (TV1) for evening or morning FEV_1 and PEF values, respectively. The first postbaseline record is the data collected after the first dose on the evening of the RV (TV1). Patients have to record baseline values on at least 5 out of the last 7 days prior to the RV in order to be randomized, nonetheless, a few patients who were randomized with less than 5 nonmissing values. To eliminate number of missing baseline values, rules for handling missing electronic patient's diaries are specified below.

Weekly Average Percent Predicted Trough Morning FEV_1 and Trough Morning PEF:

The baseline percent predicted trough morning FEV_1 or trough morning PEF is defined as the average of recorded (nonmissing) percent predicted trough morning FEV_1 or trough morning PEF assessments over the 7 days prior to randomization. The first day before randomization consists of the electronic patient diary entry at **home** on the morning of the RV (TV1). A patient has to record trough morning FEV_1 and trough morning PEF values on at least 5 out of the last 7 days prior to the RV in order to be randomized. In case there are less than 5 non-missing values, the trough morning FEV_1 or trough morning PEF record will include days beyond 7 days prior to the randomization to ensure that the baseline value can be calculated. If a minimum of

5 nonmissing values cannot be satisfied during the entire run-in period (14-30 days), the patient's percent predicted trough morning FEV_1 or trough morning PEF baseline values will be replaced by the overall baseline value.

1-Hour Percent Predicted Trough Morning FEV_1:

The baseline 1-hour percent predicted trough morning FEV_1 is defined as the predose percent predicted trough morning FEV_1 measurement at the RV (TV1) at the **investigational center**. If the predose FEV_1 measurement is missing or the value is implausible, the baseline weekly at home average percent predicted trough morning FEV_1 will be used. If both, the baseline pre-dose FEV_1 measurement and the baseline weekly average percent predicted trough morning FEV_1 are missing, the baseline trough morning FEV_1 will be replaced by the overall baseline 1-hour value.

Trough Evening PEF:

The baseline trough evening PEF is defined as the average of recorded (nonmissing) trough evening PEF assessments over the 7 days prior to randomization. The first day before randomization consists of the electronic patient diary entry on the evening before the RV (TV1). Five out of the last 7 days nonmissing values are required for a patient to be randomized and to calculate the baseline value. In case the minimum of 5 nonmissing values cannot be satisfied during the entire run-in period (14-30 days), the patient's evening PEF baseline value will include days beyond 7 days prior to the randomization. If a minimum of 5 nonmissing values cannot meet, missing baseline value will be replaced by the overall trough evening PEF value.

Total Daily (24-Hour) Use of Albuterol/Salbutamol Inhalation Aerosol (Number of Inhalations):

Throughout the study albuterol/salbutamol inhalation aerosol will be provided to patients to be used as needed for the relief of asthma symptoms. Patients will record intake (number of inhalations) of rescue medication each morning and evening in the electronic patient diary. An entry of zero inhalations for both morning and evening will indicate a rescue-free 24-hour period.

The baseline value is defined as the average number of inhalations over each 24-hour (day and night) period over the 7 days prior to the date of the first dose. Patients should withhold their rescue medication for at least 6 hours prior to the morning of the RV (TV1), and all other study visits. Five out of last 7 days nonmissing values are required for patient to be randomized. No missing data imputation rule will apply.

Percentage of Rescue-free Days (24-Hour Periods):

A rescue-free day is defined as a 24-hour period with no use of rescue medication recorded. The baseline percentage of rescue-free days is defined as the percentage of rescue-free days over the 7 days prior to the RV. An entry of zero inhalations for both morning and evening will indicate a rescue-free 24-hour period.

Total Daily (24-Hour) Asthma Symptom Score:

The total daily asthma symptom score is defined as the average of the daytime and nighttime scores. The baseline total daily asthma symptom score is defined as the average of recorded (nonmissing) total daily asthma symptom scores over the 7 days prior to randomization. Five out of the last 7 nonmissing values are required for a patient to be randomized. If a minimum of

5 nonmissing values cannot be satisfied during the entire run-in period (14-30 days), the patient's asthma symptom score will include days beyond 7 days prior to the randomization or replaced by the overall asthma symptom score. No missing data imputation rule will apply.

Percentage of Symptom-free Days (24-Hour Periods):

Symptom-free days are defined as 24-hour periods with asthma symptom scores of zero recorded on the asthma symptom score electronic patient diary for both morning and evening entries. The baseline is defined as the percentage of symptom-free days over the 7 days prior to randomization.

A 24-hour symptom-free period is associated with a score of zero on the asthma symptom score diary for both morning and evening entries. Should either the morning or evening entry be missing and the other value is equal to zero, the available value will be weighted by half, and similarly the denominator will be modified to reflect the missing value. If both, morning and evening values, are missing for a particular day, the value will not be used in the calculation of percentage. Table 2 illustrates a week of baseline symptom score and imputation rules as recorded in the electronic patient diary.

Table 2: An Example of Baseline Electronic Patient Diary Data for Symptom-free Days

Analysis Day	Morning score	Evening score	Value used for numerator of percentage calculation	Value used for denominator of percentage calculation
1	3	0	0	1
2	Missing	Missing	Not used in calculations	Not used in calculations
3	0	0	1	1
4	1	3	0	1
5	Missing	2	0	1/2
6	Missing	0	1/2	1/2
7	0	0	1	1
Week's total			2.5	5

The percent of symptom-free 24-hour periods for this example is derived as 2.5/5*100% = 50%. Similar rules apply to on-therapy interval.

Percentage of Asthma-control Days (24-Hour Periods):

Asthma-control days are defined as scores of zero recorded on the asthma symptom score diary during the 24-hour period and no rescue medication usage during the same 24-hour period. The baseline is defined as the percentage of asthma-control days over the 7 days prior to randomization. Detailed imputation rules are specified in Table 3.

Table 3: An Example of Baseline Electronic Patient Diary for Asthma-control days

Analysis Day	Total Daily Asthma Score / Rescue Medication Usage	Value used for numerator of percentage calculation	Value used for denominator of percentage calculation
-1	3 / 0	0	1
-2	Missing / 0	Not used in calculations	Not used in calculations
-3	0 / 0	1	1
-4	Missing / 3	0	1
-5	0 / 3	0	1
-6	3 / 3	0	1
-7	Missing / Missing	Not used in calculations	Not used in calculations
Week's total		1	5

The percent of asthma-control days for this example is derived as 1/5*100% = 20%. Note that if a patient's asthma score is missing, and there is no rescue medication usage during the same 24-hour period, the asthma-control days will not be used in calculations.

4.3. Handling Withdrawals and Missing Data

4.3.1. Missing Data Imputation for Efficacy Analysis

The primary analysis and sensitivity analyses for the primary endpoints include reference-base multiple imputations for missing data and tipping point approaches as detailed in Section 6 and Appendix A.

For endpoints analyzed using the mixed model for repeated measures (MMRM), there will be no imputation for missing data.

For all other variables, only the observed data from the patients will be used in the statistical analyses (ie, there is no plan to estimate missing data).

4.3.2. Study Days and Visit Windows

Study days are numbered relative to the first day of IMP administration. The start of treatment (Day 1) is defined as the date on which a patient takes the first dose of IMP. Days will be numbered relative to treatment start (ie, ..., –2, –1, 1, 2, ...; with day 1 being the first day of IMP administration and day –1 being the day before the first day of IMP drug administration).

For data collected at the investigational center visits, such as RV (TV1), TV2 toTV6/IMPDV, efficacy and safety data will be analyzed using the visit recorded in the case report forms (CRFs) unless otherwise stated for by-visit summaries. If there are multiple assessments at a postbaseline visit, then the last nonmissing assessment at that visit will be used for the summary. This includes assessments at scheduled and unscheduled visits (the reason for the unscheduled visit has to be included for that particular assessment). If there are both scheduled and unscheduled visits with nonmissing results at the specific visit, the last nonmissing assessment will be used for the summary. For the purpose of the efficacy analysis, assessments collected at the

unscheduled early termination visit will be assigned to the next scheduled visit and also used as the final assessment for the final assessment summaries.

For the analysis of electronic patient diary recorded data (ie, pulmonary function test [PFT], rescue medication usage and asthma symptom score, etc.), the day used for analysis consists of the evening assessment for the date of the first dose of IMP and the morning assessment for the following day as illustrated in Table 4.

Weekly average data will be generated using 7-day windows based on study days (before and after the first dose of double-blind IMP). For example, week 6 will start from day 36 to day 42. A summary will be provided using the derived week window.

Table 4: Analysis Day

Analysis day	Study day	Time point
-1	1 (predose)	AM
1	1	PM
	2	AM
2	2	PM
	3	AM
X	X	PM
	X + 1	AM
84	84	PM
	85	AM

5. STUDY POPULATION

5.1. General

The ITT analysis set will be used for all study population summaries unless otherwise specified. Summaries will be presented by treatment group and for all patients.

5.2. Patient Disposition

The following data will be summarized using descriptive statistics: patients screened; patients screened but not enrolled (and reason); patients enrolled in the run-in period; patients enrolled in the run-in period but not randomized (and reason); patients randomized; patients randomized but not treated; ITT analysis set, patients in the ITT with retrieved data, ITT without retrieved data, safety, and PP analysis sets; patients who complete the treatment, and patients who withdraw from the treatment (and reason); patients who complete the study, and patients who withdraw from the study (and reason) will be summarized using counts and percentages. The summary will include all patients screened. The denominator for calculation of percentages will be the number of randomized patients. All disposition information for screened patients will be provided in a listing by patient.

5.3. Demographics and Baseline Characteristics

Demographics variables (age, age group [4-6 years, 7-11 years], ethnicity, race, sex, weight, height, and body mass index [BMI]) will be summarized using descriptive statistics (refer to section 4.1). Baseline characteristics (baseline percent predicted FEV_1, baseline PEF, and previous asthma therapy [ICS or NCS], etc.) will also be summarized using descriptive statistics.

Patient demographics will be presented for both ITT and Safety analysis sets. The PP analysis set will be presented if the difference between ITT and PP is more than 5 patients in any of the treatment arm.

A listing for demographics and baseline characteristics in the ITT analysis set will be presented.

Patient demographic and baseline characteristics, including medical history, and prior medications and therapies will be examined to assess the comparability of the treatment groups and will be summarized using descriptive statistics (refer to section 4.1). Categories for missing data will be presented if necessary.

5.4. Medical and Asthma History

All medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of medical history abnormalities will be summarized using descriptive statistics by system organ class (SOC) and preferred term (PT). Patients are counted only once in each PT and SOC category. Patients who have a medical history assessment, with at least 1 abnormal finding and abnormal findings for each category will be summarized by treatment group and for all patients.

5.5. Prior Therapy and Medication

Any prior therapy and medication before study drug administration will be recorded on the CRF. Trade name or international nonproprietary name, indication, and dosage will be recorded. The sponsor will encode all therapy and medication according to the World Health Organization (WHO) drug dictionary (WHO Drug).

The incidence of prior therapies and medications will be summarized using descriptive statistics (count and percentages) by therapeutic class and PT. Patients are counted only once in each therapeutic class category, and only once in each preferred term category. Prior therapies and medications will include all medications taken and therapies administered before the first day of IMP administration.

5.6. Physical Examinations

Physical examinations, including height and weight, will be performed at the SV and at the final treatment visit (TV6/IMPDV). Patients with a physical examination, patients with at least 1 abnormal finding, and abnormal findings for each category will be summarized at baseline using descriptive statistics (counts and percentages). Abnormal values at or before screening will be reported as a part of medical history.

5.7. Childbearing Potential and Methods of Contraception

For all female patients, childbearing potential and premenarchal status will be listed.

5.8. Study Protocol Violations

Data from patients with any protocol violation (as recorded in protocol violation CRF) during the study will be summarized overall and for each category using descriptive statistics. Of note, medication errors, overdose, misuse, abuse, off-label use, and occupational exposure will be summarized in category "Non-Compliance to study medication”.

Patient with at least 1 protocol violation for each category will be summarized using count and percentages.

6. EFFICACY ANALYSIS

6.1. General

The ITT analysis set will serve as the primary analysis set for all efficacy analyses, the PP population will serve as a supportive population for the primary efficacy analyses, as detailed below. Summaries will be presented by treatment group, unless specified otherwise.

Descriptive statistics (n, mean, SD, SE, median, min, and max) for efficacy variables and change from baseline will be provided by visit or week window, as appropriate. Final assessments will compare between treatment groups.

6.2. Primary Estimands and Efficacy Analyses

The estimands selected for the 2 primary endpoints will assess the change from baseline due to the initially randomized treatment as actually taken. These estimands assess the effectiveness at week 12, focusing on the causal effects attributable to the initially randomized medication. The sponsor will make all efforts to avoid study withdrawal in this 12-week study. In instances where a patient decides to discontinue IMP or, more importantly, requires alternative therapy for worsening asthma or an asthma exacerbation, the investigators will be instructed to encourage the patient to continue in the study and return for planned visits until the study completion in order to collect data after IMP discontinuation.

The question of whether to use data collected after IMP discontinuation is an ongoing debate in statistical literature, in particular for studies with symptomatic endpoints and when it is common for patients who dropout to switch therapies (Mallinckrodt et al 2016, Mallinckrodt 2013, Little and Kang 2015, O'Neill and Temple 2012). This study is designed as a placebo-controlled study and it is expected that patients randomized to placebo would discontinue IMP due to worsening asthma at a higher rate than those randomized to active treatment, which is known to be an efficacious drug as established by multiple studies. After a patient discontinues IMP due to worsening asthma, the patient will be placed on alternative asthma therapies. The first choice will be ICS or a combination of ICS/LABA, exactly the classes of drugs being studied. Other therapeutic choices will include systemic corticosteroids, additional medications other than ICS, or both. All alternatives are proven to alter the spirometry collected after that point and therefore not be appropriate for assessment of IMP effectiveness. Improvement of asthma would be expected as rapidly and early as 1 week for FEV_1 for placebo patients placed on ICS (Szefler et al 1999). It has also been shown that patients placed on ICS with long acting beta-agonists can have significant improvement in serial FEV_1 measurements on the same day (Corren et al 2007, Pearlman et al 1999). Therefore, any patient who discontinued IMP and was placed on alternative therapies would be expected to have rapid and demonstrable improvements in lung function approximating the levels measured at screening.

The inclusion of patients who failed therapy and who were then treated with alternative medication would blunt the treatment effect, potentially causing the study to fail due to the analysis rather than the effectiveness of the treatment given during the study. These patients no longer represent a true placebo population and including them in the population for the primary outcome is not consistent with treatment by placebo. As a matter of fact, if retrieved drop outs

placed on the alternative therapy such as ICS or ICS/LABA treatments, the efficacy would be compared between two identical classes of drugs, making such comparison not appropriate for the clinical trial designed and powered as the placebo-controlled trial.

In a study recently completed by Teva under IND 114865, Study BDB-AS-30039, patients randomized to placebo had indeed higher IMP discontinuation rates than patients randomized to either of the 3 active treatment arms with beclomethasone dipropionate breath-actuated inhaler (BAI). Study BDB-AS-30039 was a randomized, double-blind, placebo-controlled, parallel-group trial that investigated the use of beclomethasone dipropionate BAI in patients 12 years of age and older with persistent asthma. Data from this study indicated that patients receiving placebo placed on alternative asthma therapies after IMP discontinuation had marked improvements in spirometry results collected after that IMP discontinuation (Table 5). Study BDB-AS-30039 had a shorter duration (6 weeks) than FSS-AS-30003 (12 weeks) and included adults, but patients were encouraged to attend study visits after discontinuation of IMP.

The study had 4 arms: placebo and 3 active treatment arms. IMP discontinuation rates were

11.2% in the placebo treatment arm compared to 3.1% in the pooled active treatment arm; 10 of the patients treated with placebo (9.3%) withdrew due to worsening asthma, while only 2 patients combined from all 3 active groups withdrew due to worsening asthma (0.6%). Table 5 shows the data collected for each individual patient after resumption of alternative therapy resulted in large increases from baseline for placebo.

Table 5: Standardized Baseline-adjusted Trough Morning FEV_1 Area Under the Effect Curve from Time Zero to 6 Weeks for Individual Patient who Discontinued IMP with Retrieve Dropout Data

Treatment	Subject ID	Including data after IMP discontinuation	Excluding data after IMP discontinuation	Difference (Including – Excluding data after IMP	Treatment administered to patient after IMP discontinuation
BAI 320 mcg/day	[redacted]	-358.3	0.0	-358.3	Budesonide and formoterol with oral prednisone
BAI 320 mcg/day	[redacted]	-181.7	-125.0	-56.7	Oral prednisone
BAI 320 mcg/day	[redacted]	-136.7	-110.0	-26.7	Beclomethasone and montelukast
BAI 640 mcg/day	[redacted]	75.0	0.0	75.0	Oral methylprednisolone
MDI 320 mcg/day	[redacted]	-183.3	-100.0	-83.3	Budesonide and formoterol
Placebo	[redacted]	**-210.0**	**-200.0**	**-10.0**	**Beclomethasone**
Placebo	[redacted]	**-106.7**	**-285.0**	**178.3**	**Budesonide and montelukast**

Treatment	Subject ID	Including data after IMP discontinuation	Excluding data after IMP discontinuation	Difference (Including – Excluding data after IMP	Treatment administered to patient after IMP discontinuation
Placebo	[redacted]	-1.7	-150.0	148.3	Oral prednisone

Table 5: Standardized Baseline-adjusted Trough Morning FEV_1 Area Under the Effect Curve from Time Zero to 6 Weeks for Individual Patient who Discontinued IMP with Retrieve Dropout Data (Continued)

Treatment	Subject ID	Including data after IMP discontinuation	Excluding data after IMP discontinuation	Difference (Including – Excluding data after IMP	Treatment administered to patient after IMP discontinuation
Placebo	[redacted]	143.3	-155.0	298.3	Oral prednisone with budesonide and formoterol
Placebo	[redacted]	223.3	-32.5	255.8	Oral prednisone and montelukast
Placebo	[redacted]	396.7	0.0	396.7	Budesonide and formoterol
Placebo	[redacted]	976.7	-5.0	981.7	Fluticasone and salmeterol

Note: Data were not included for patients who withdrew from the study for worsening asthma for whom data post withdrawals was not available, since including and excluding data after IMP have the same value.

An imbalance in treatment discontinuation rates was also observed in another study conducted by Teva. Study BDB-AS-302 was a 12-week randomized, double-blind, double-dummy, placebo-controlled, parallel-group trial that investigated the use of beclomethasone dipropionate BAI in pediatric patients aged 4 through 11 years with persistent asthma. Patients randomized to placebo had a higher rate of discontinuation from IMP (14.2%) compared to patients randomized to active treatment (range from 7.9% to 10.4%).

Based upon the experiences with Study BDB-AS-30039 and Study BDB-AS-302, Teva is concerned that an imbalance in treatment discontinuation rates coupled with a markedly reduced treatment effect as a result of alternative asthma therapies for patients randomized to placebo will likely result in a study that fails to show a statistically significant effect of investigational therapy. In light of these issues, retrieved dropout data will be used only for sensitivity analyses. Missing data for patients who discontinue IMP will be imputed using reference-based multiple imputations representing a missing not at random (MNAR) mechanism. This approach is discussed Mallinckrodt et al 2016 (sections 3.2 and 3.4 for estimand 2 in the paper).

6.2.1. Variable Definition

A handheld device to measure FEV_1 will be provided to patients at the SV and used to determine the percent predicted trough morning FEV_1 throughout the course of the study.

Weekly Average Percent Predicted Trough Morning FEV_1:

Baseline percent predicted trough morning FEV_1 is defined as the average value of recorded (nonmissing) morning assessments 5 out of the last 7 days prior to randomization (Section 4.2 for details). The first day before randomization consists of the electronic patient diary entry at **home** on the morning of the RV (TV1) and the first day postrandomization consists of electronic patient diary entry at **home** on the morning of the day after the RV (TV1).

For postdose weekly average of percent predicted trough morning FEV_1 measurements, the values will be the averages based on the available data for that week. The averages will be calculated as the sum of morning FEV_1 values divided by the number of nonmissing assessments. There will be no imputation applied to postrandomization assessments.

1-hour Postdose Percent Predicted Morning FEV_1 at Week 12:

The baseline predose FEV_1 should be performed at the **investigational center** between the hours of 0530 and 1100 using the handheld device before administration of study drug or rescue medications (Section 4.2 for details).

The IMP dose should be administered right after the predose FEV_1 measurement (eg, within a 10-minute window). The patient will then perform 1-hour (+/-10 minutes) postdose lung function assessments on week 12 at the **investigational center**.

Electronic patient diary percent predicted FEV_1 time will be compared with IMP dose time. If a percent predicted FEV_1 measurement is performed after the IMP dose, a 10-minute window will be allowed and that measurement will be included in the analysis, otherwise the percent predicted FEV_1 measurement will be ignored.

Patients who have been withdrawn from IMP will be asked to perform 1-hour postdose lung function assessments; although the patients will not be taking a dose of IMP, the assessment should be performed approximately 1 hour after the predose lung function assessments were obtained.

6.2.2. Primary Efficacy Analysis

6.2.2.1. For Fp MDPI versus Placebo: Change from Baseline in Weekly Average of the Percent Predicted Trough Morning FEV_1 at Week 12

For the purpose of the efficacy analysis of weekly average of daily morning FEV1 measurements, the FEV1 value at week 12 will be the average based on the available data for that week. The averages will be calculated as the sum of the morning FEV1 values divided by the number of nonmissing assessments. There will be no imputation applied to postrandomization daily assessments.

The primary analysis of the change from baseline in weekly average of percent predicted morning FEV1 at week 12 due to the initially randomized treatment as actually taken will be analyzed using an ANCOVA model with effects due to baseline percent predicted trough

morning FEV1, sex, age, (pooled) investigational center, previous therapy (ICS or NCS), and IMP treatment group. Contrasts for pairwise treatment comparisons of interest will be constructed. The estimated treatment difference between each IMP treatment group and the placebo group will be presented together with the 2-sided 95% CI for the difference and the p-value.

In this analysis, missing data that are caused by early dropouts from the study or from IMP (regardless of availability of retrieved dropout data) will be imputed using reference-based multiple imputations which represents a missing not at random (MNAR) mechanism. The reference-based multiple imputation method multiply imputes the missing data in treatment group based on an imputation model built using data from the placebo group. This will yield a conservative treatment effect estimate as compared to the estimate obtained from multiple imputations (MI) under a missing at random (MAR) mechanism. The methodology and algorithm used for imputation is described in Appendix A.

6.2.2.2. For FS MDPI versus Fp MDPI: Change from Baseline in 1-hour Postdose Percent Predicted Morning FEV_1 at Week 12

The baseline predose percent predicted trough morning FEV_1 will be performed at the **investigational center** at the RV (TV1) (Section 4.2 for details). The postdose percent predicted morning FEV_1 (measured at the investigational center) at week 12 with the handheld device will be approximately 1-hour after the IMP administration.

The co-primary endpoint change from baseline in 1-hour postdose percent predicted morning FEV_1 at week 12 will be analyzed using an ANCOVA model with effects due to baseline trough morning percent predicted FEV_1, sex, age, (pooled) investigational center, previous therapy (ICS or NCS), and IMP treatment group. Contrasts for pairwise treatment comparisons of interest will be constructed. The estimated treatment comparisons of interest will be presented together with the 2-sided 95% CI for the difference and the p-value. Missing 1-hour postdose FEV_1 data at week 12 will be handled similarly to the above (see Appendix A for details).

For patients who completed the treatment period, but with clinically and physiologically implausible data (eg, percent predicted FEV_1 values post-randomization is ≥200%), imputation will be based on measurements observed at previous weeks and in the same treatment group (this represent a MAR mechanism).

6.2.2.3. Sensitivity Analyses

The following list of sensitivity analyses are prespecified for this study, to evaluate alternative estimands and assess the robustness of the primary efficacy results. Each sensitivity analysis will be conducted for the 2 primary efficacy endpoints, unless otherwise noted.

- Effectiveness with retrieved dropout data: to evaluate the estimand of the effect of the treatment regimens as actually taken (effectiveness), the analysis will be repeated including observed FEV_1 data over 12 weeks, for patients who completed the 12-week treatment period and for patients who discontinued from treatment earlier than week 12 but from whom the sponsor was able to collect efficacy data post discontinuation. Early withdrawal patients for whom the sponsor fails to retrieve data post discontinuation despite all attempts to contact the patient, a reference-based

imputation (RBI), which is an MNAR mechanism, will be utilized. The RBI method multiply imputes the missing data in every treatment group based on an imputation model built using data from the placebo group. This will yield a conservative treatment effect estimate as compared to the estimate obtained from multiple imputations (MI) under MAR (see Appendix A for details).

- Treatment completer analysis: In this completer analysis, the estimand is conditional on taking IMP. This estimand applies to all patients in the ITT analysis set who have completed the 12-week treatment period; patients who have taken their medication as directed without any major protocol violations. Note that since the use of incorrect IMP is considered a major treatment administration protocol violation, "as randomized" will coincide with "as treated" for the treatment assignment in this population. No imputation will be used since this is a completer analysis.
- "Tipping point" multiple imputations: similar to the primary estimand (change due to the initially randomized treatments as actually taken without retrieved dropout data), this sensitivity analysis will utilize multiple imputations under the MNAR assumption. For placebo patients, MAR will be assumed in all applications of multiple imputations. For the active arms, in the first application, MAR will be assumed and the imputations will be drawn from data in the corresponding active arms. In subsequent applications, shifts to the distribution of the active arms will be applied to represent different degrees of effect loss, ie, MNAR will be assumed. In this analysis, only data collected before IMP discontinuation will be utilized. If the sensitivity analysis reveals that the tipping point consists of unreasonable values, the robustness of the study results is supported. The methodology and algorithm used for imputations is provided in Appendix B.
- "2-dimensional tipping point" multiple imputations: similar to above, the shifts to the distribution will apply to both placebo and active arms, to represent different degrees of effect loss. In this analysis, only data collected before IMP discontinuation will be utilized. An example below shows that a specified amount from actives will be subtracted from its value and at the same time, another specified amount will be added to the placebo. The methodology and algorithm used for imputations is provided in Appendix C .

Table 6: An example of shift amount in percent predicted FEV_1

Placebo	Active
0	0
0	-5
0	-10
0	-15
2	-5
2	-10
2	-15

Placebo	Active
4	-5
4	-10
4	-15

Table 6: An example of shift amount in percent predicted FEV_1 (Continued)

Placebo	Active
6	-5
6	-10
6	-15

- Mixed approach of LOCF and baseline observation carried forward (BOCF): this sensitivity analysis will penalize discontinued patients who have a positive change from baseline score to zero by using (BOCF) method, thus these discontinued patients are treated as failures. While patients who discontinue IMP who have a negative change from baseline score will not have their results adjusted (LOCF) since their scores are already poor. In this imputation method, the imputed value is the lower between LOCF and BOCF for each patient. No adjustments will be made to the results for patients who complete the study. Retrieved dropout data will be included for this analysis. Details are provided in Appendix D.
- MMRM: similar to the primary estimand (change due to the initially randomized treatments as actually taken without retrieved dropout data), this sensitivity analysis will be performed using a MMRM model. This analysis represents a MAR assumption. The sensitivity analysis will be performed for the first primary endpoint, ie, change from baseline in the weekly average of percent predicted trough morning FEV_1 over the 12-week treatment period. Details are provided in Appendix E.

6.2.3. Sub-Group Analyses

The following subgroup analyses will be provided for the primary efficacy endpoints with ITT analysis set without retrieved dropout data:

- By sex (male and female)
- By age group (4-8 and 9-11 years)
- By race (white, black, and other)
- By region (US and non-US)
- By previous therapy (ICS and NCS)

The subgroup analyses will be summarized using descriptive statistics by each week/visit and by treatment.

6.3. Secondary Efficacy Endpoints and Analysis

Secondary efficacy endpoints are as follows:

- Change from baseline in the weekly average of daily trough morning (predose and pre-rescue bronchodilator) PEF over the 12-week treatment period
- Change from baseline in the weekly average of total daily (24-hour) use of albuterol/salbutamol inhalation aerosol (number of inhalations) over weeks 1 through 12
- Change from baseline in the weekly average of the total daily asthma symptom score (defined as the average of the daytime and nighttime scores) over weeks 1 through 12
- Change from baseline in asthma control (measured by C-ACT) score over the 12-week treatment period
- Time to first onset of effect defined as the first decrease from baseline in daily rescue medication use
- Proportion of patients who discontinued from IMP for asthma exacerbation during the 12-week treatment period.

The sequential order of the secondary endpoints for multiplicity will be described in Section 7.2.

6.3.1. Variable Definitions

6.3.1.1. Weekly Average of the Daily Trough Morning PEF

A handheld device will be provided to patients at the SV and used to determine the morning PEF throughout the course of the study.

Morning PEF will be determined in the morning, before administration of IMP or rescue medications. Daily PEF time will be compared with IMP dose time.

If a PEF measurement is performed after the IMP dose, a 10-minute window will be allowed and included in the analysis, otherwise the PEF measurement will be ignored.

The first day postrandomization consists of electronic patient diary entry on the morning of the day after the RV (TV1). For the purpose of the efficacy analyses of weekly average of daily morning PEF measurements, the values will be the averages based on the available data for that week. The averages will be calculated as the sum of morning PEF values divided by the number of nonmissing assessments. There will be no imputation applied to postrandomization assessments.

6.3.1.2. Weekly Average of Total Daily (24-Hour) Use of Albuterol/Salbutamol Inhalation Aerosol (Number of Inhalations)

Patients will record the number of inhalations of rescue medication (albuterol/salbutamol HFA MDI) each morning and evening in the electronic patient diary. An entry of zero inhalations indicates no rescue medication is needed.

To calculate the total daily use of albuterol/salbutamol inhalation aerosol (number of inhalations), the electronic patient diary entry on RV (TV1) is defined as the first day of analysis.

The weekly average of the total daily inhalations is the average based on the available data for that week. The average will be calculated as the sum of total daily inhalations over the 7 days for each analysis week divided by the number of nonmissing assessments.

6.3.1.3. Asthma Symptom Score

Asthma symptom scores will be recorded in the patient's electronic patient diary each morning and each evening before determining PEF and before administration of IMP or rescue medications.

Daytime Symptom Score (determined in the evening):

0=No symptoms during the day
1=Symptoms for 1 short period during the day
2=Symptoms for 2 or more short periods during the day
3=Symptoms for most of the day which did not affect my normal daily activities
4=Symptoms for most of the day which did affect my normal daily activities
5=Symptoms so severe that I could not go to work or perform normal daily activities

Nighttime Symptom Score (determined in the morning):

0=No Symptoms during the night
1=Symptoms causing me to wake once (or wake early)
2=Symptoms causing me to wake twice or more (including waking early)
3=Symptoms causing me to be awake for most of the night
4=Symptoms so severe that I did not sleep at all

To calculate total daily asthma symptom score, analysis days are defined in Table 4. The total daily asthma symptom score is the average of the daytime and the nighttime scores. The total daily asthma symptom score will be considered missing if either the daytime or nighttime score is missing.

The weekly average will be calculated as the sum of total daily asthma symptom scores over the 7 days for each analysis week divided by the number of nonmissing assessments.

6.3.1.4. Childhood Asthma Control Test Score

The C-ACT is a simple, patient-completed tool used for the assessment of overall asthma control. The first 4 items of the test are completed by the patient, while the last 3 items are completed by the patient's parents/legal guardians/caregivers. The first 4 items are scored on a 3-point scale (0 to 3) and the last 3 items are scored on a 5-point scale (0 to 5), with summation of all items providing scores ranging from 0 to 27. In case of missing item score, the average value will be calculated for that particular item and treatment. For the first 4 items, a patient has to have a minimum of 2 items in order to replace the mean value and for the last 3 items, a minimum of 1 item is required to replace the mean value.

These scores span the continuum of poor control of asthma (score $\leq$5) to complete control of asthma (score $\geq$25), with a cutoff score of 19 indicating patients with poorly controlled asthma.

The C-ACT will be completed by the patient and the patient's parents/legal guardians/caregivers at the investigational center, before any other assessments are performed, at the RV (TV1), TV4,

TV5, and TV6/IMPDV. The same parent/legal guardian/caregiver should complete the assessments at each visit, if possible.

6.3.1.5. Time to First Onset of Effect

Patients will record the number of inhalations of rescue medication (albuterol/salbutamol HFA MDI [90 mcg ex-actuator] or equivalent) each morning and evening in the electronic patient diary. Total daily use will be calculated after the RV. The time to first onset of effect is defined as the first decrease from the weekly average baseline in daily rescue medication use.

6.3.1.6. Proportion of Patients Discontinued From IMP for Asthma Exacerbation During the 12-week Treatment Period

Once the investigator confirms that a case of asthma exacerbation requiring a significant alternative treatment has occurred, the event will be entered into the CRF as an asthma exacerbation event. Such patients will be discontinued from IMP. The proportion of patients discontinued from IMP for asthma exacerbation during the 12-week treatment period will be assessed.

6.3.2. Analysis Methods for Secondary Efficacy Variables

The analysis of the secondary efficacy variables will be performed on the ITT analysis set without retrieved dropout data.

6.3.2.1. Change from Baseline in the Weekly Average of Daily Trough Morning (Predose and Prerescue Bronchodilator) Peak Expiratory Flow (PEF) Over the 12-week Treatment Period

The analysis of change from baseline in the weekly average of daily morning (predose and pre-rescue bronchodilator) PEF over the 12-week treatment period will be performed using an MMRM with effects due to baseline weekly average of daily morning PEF, sex, age, (pooled) investigational center, previous therapy (ICS or NCS), week, treatment, and week-by-treatment interaction. No explicit structure will be assumed for the covariance among the repeated measures. However, if there is a convergence problem with unstructured covariance, then a compound symmetry covariance structure will be assumed.

6.3.2.2. Change from Baseline in the Weekly Average of Total Daily (24-hour) use of Albuterol/Salbutamol Inhalation Aerosol (Number of Inhalations) Over Weeks 1 Through 12

The change from baseline in the weekly average of total daily (24-hour) use of albuterol/salbutamol inhalation aerosol (number of inhalations) over weeks 1 through 12 will be analyzed using an MMRM with effects due to baseline value, sex, age, (pooled) investigational center, previous therapy (ICS or NCS), week, treatment, and week-by-treatment interaction. No explicit structure will be assumed for the covariance among the repeated measures. However, if there is a convergence problem with unstructured covariance, then a compound symmetry covariance structure will be assumed.

6.3.2.3. Change from Baseline in the Weekly Average of the Total Daily Asthma Symptom Score (Defined as the Average of the Daytime and Nighttime Scores) Over Weeks 1 Through 12

The change from baseline in the weekly average of the total daily asthma symptom scores over weeks 1 through 12 will be analyzed using an MMRM with effects due to baseline score, sex, age, (pooled) investigational center, previous therapy (ICS or NCS), week, treatment, and week-by-treatment interaction. No explicit structure will be assumed for the covariance among the repeated measures. However, if there is a convergence problem with unstructured covariance, then a compound symmetry covariance structure will be assumed.

6.3.2.4. Change from Baseline in Asthma Control (Measured by Childhood Asthma Control Test [C-ACT] Score Over the 12-week Treatment Period

The change from baseline in C-ACT score over the 12-week treatment period will be analyzed using an MMRM with effects due to baseline C-ACT score, sex, age, (pooled) investigational center, previous therapy (ICS or NCS), week, treatment, and week-by-treatment interaction. No explicit structure will be assumed for the covariance among the repeated measures. However, if there is a convergence program with unstructured covariance, then a compound symmetry covariance structure will be assumed.

6.3.2.5. Time to First Onset of Effect in Daily Rescue Medication Use

The time to first onset of effect, defined as the number of days elapsed from the date of randomization to the first date of decrease from baseline in daily rescue medication use. Patients who first have a decrease of effect will be counted as an event in the analysis; otherwise, patients will be right-censored at the date of last IMPDV assessments.

The analysis of time to first onset of effect will be performed using a log-rank test to compare the survival curves. Time to first onset of effect will be displayed graphically with a Kaplan-Meier figure, and median time to first onset of effect and associated 95% CIs will be provided.

Example SAS code for this analysis:

```
proc lifetest data=toasm method=KM outsurv=yyy;

      where treat in ("A", "D");

      time aval*cnsr(0);

      strata treat;

      ods output  CensoredSummary=count

                  Quartiles=qrt

                  productlimitestimates=kmest

                  HomTests = pvals(where=(upcase(test) = "LOG-RANK"));

run;
where: aval is days from the date of first double-blind study IMP
to the date of event or censoring. CNSR is the censoring flag (0=no
event [censored]; 1=event [meet criteria]). The code is executed for
each pair of treatment comparisons of interest.
```

6.3.2.6. Proportion of Patients Discontinued From IMP for Asthma Exacerbation During the 12-week Treatment Period

The proportion of patients discontinued from IMP for asthma exacerbation during the 12-week treatment period will be analyzed using a logistic regression model with effects due to previous therapy (ICS or NCS) and treatment. In case the algorithm does not converge, a stratified (based on previous therapy [ICS or NCS]) Cochran-Mantel-Haenszel (CMH) test will be used to analyze the proportion of patients discontinued from IMP for asthma exacerbation during the 12-week treatment period.

Example SAS code for this analysis:

```
proc logistic data=proasm descending;

      class treat therapy;

      model flag = treat therapy;

      output out=yyy predicted=pp;

      ods output  oddsratios=oddsratios
                  parameterestimates=parameterestimates

                  contrastTest=contrast
                  convergencestatus=convergencestatus;

run;
where: flag is either 1 (event) or 0 (no event)
```

6.4. Other Efficacy Endpoints Analysis

The other efficacy endpoints are as follows:

- Change from baseline in weekly average of the total daily (24-hour) use of albuterol/salbutamol inhalation aerosol (number of inhalations) at weeks 4, 8, and 12
- Change from baseline in percentage of rescue-free days (defined as 24-hour periods with no rescue medication usage) during the 12-week treatment period
- Change from baseline in percentage of symptom-free days (defined as 24-hour periods with asthma symptom score of 0) during the 12-week treatment period
- Change from baseline in percentage of asthma-control days (defined as 24-hour periods with asthma symptom score of 0 and no rescue medication usage) during the 12-week treatment period
- Change from baseline in 1-hour postdose percent predicted morning FEV_1 at week 1
- Change from baseline in weekly average of the daily evening PEF over the 12-week treatment period
- Change from baseline in weekly average of the percent predicted trough morning FEV_1 at weeks 1, 2, 4 and 8
- Proportion of patients who achieve at least a 15% increase in morning FEV_1 at 1-hour postdose at day 1 (the RV/TV1), week 1, and week 12

- Change from baseline in asthma control (measured by C-ACT) score at weeks 4, 8, and 12
- Time to consistent onset of effect defined as the decrease from baseline in daily rescue medication use on 3 consecutive days

6.4.1. Definition

6.4.1.1. Percentage of Rescue-free 24-Hour Periods

Rescue-free days are defined as 24-hour periods with no use of rescue medication. An entry in the electronic patient diary of zero inhalations will indicate a rescue-free 24-hour period. The percentage of rescue-free 24-hour periods is defined as the percentage of rescue-free days over the weekly analysis day during the treatment period. The entry on the day of the RV (TV1) excluding records prior to the first IMP dose is defined as day 1. A minimum of 60% of full days during the 12-week treatment period (or relative to the number of days that the patient participated in the study) cannot be missing in order for a patient to be included in this analysis.

6.4.1.2. Percentage of Symptom-free 24-Hour Periods

The asthma symptom scores are specified in Section 6.3.1.3. Scores of zero for both morning and evening indicate a 24-hour symptom-free period. The calculations of the percentage of symptom-free 24-hour periods will be based on the weekly analysis day data recorded during the treatment period. The missing data will be imputed according to the rules specified in Table 2. A minimum of 60% of full days during the 12-week treatment period (or relative to the number of days that the patient participated in the study) cannot be missing in order for a patient to be included in this analysis.

6.4.1.3. Percentage of Asthma-control 24-Hour Periods

An asthma-control 24-hour period is defined as a 24-hour period with asthma symptom scores of zero and no rescue medication use as recorded in the electronic patient diaries. The calculations of the percentage of asthma-control 24-hour periods will be based on the weekly analysis day data recorded during the treatment period. The missing data will be imputed according the rules specified in Table 3. A minimum of 60% of full days during the 12-week treatment period (or relative to the number of days that the patient participated in the study) cannot be missing in order for a patient to be included in this analysis.

6.4.1.4. Weekly Average of the Daily Trough Evening PEF

A handheld spirometry device measuring FEV_1 and PEF will be provided to patients at the SV and used to determine the evening PEF throughout the course of the study.

Trough evening PEF will be determined in the evening before administration of IMP. Daily PEF time will be compared with IMP dose time. If a PEF measurement is performed after the IMP dose, a 10-minute window will be allowed and included in the analysis, otherwise the PEF measurement will be ignored.

The first day postrandomization consists of the electronic patient diary entry on the evening of the day of the RV (TV1). For the purpose of the efficacy analyses of weekly average of daily

evening PEF measurements, the values will be the averages based on the available data for that week. The averages will be calculated as the sum of evening PEF values divided by the number of nonmissing assessments. There will be no imputation applied to postrandomization assessments.

6.4.1.5. Time to Consistent Onset of Effect

Patients will record the number of inhalations of rescue medication (albuterol/salbutamol HFA MDI [90 mcg ex-actuator] or equivalent) each morning and evening in the electronic patient diary. Total daily use will be calculated after the RV. The time to consistent onset of effect is defined as a decrease from baseline in daily rescue medication use on 3 consecutive days.

6.4.2. Analysis Methods for Other Efficacy Variables

The analysis of the other efficacy variables will be performed on the ITT analysis set without retrieved dropout data.

6.4.2.1. Change from Baseline in the Weekly Average of the Total Daily (24-hour) use of Albuterol/Salbutamol Inhalation Aerosol (Number of Inhalations) at Weeks 4, 8, and 12

The change from baseline in weekly average of total daily (24-hour) use of albuterol/salbutamol inhalation aerosol (number of inhalations) at weeks 4, 8, and 12 will be analyzed using an MMRM with effects due to baseline value, sex, age, (pooled) investigational center, previous therapy (ICS or NCS), week, treatment, and week-by-treatment interaction. No explicit structure will be assumed for the covariance among the repeated measures. However, if there is a convergence problem with unstructured covariance, then a compound symmetry covariance structure will be assumed.

6.4.2.2. Change from Baseline in the Percentage of Rescue-free Days (Defined as 24-hour Periods with no Rescue Medication Usage) During the 12-week Treatment Period

The change from baseline in the percentage of rescue-free days (defined as 24-hour periods with no use of rescue medication recorded in the morning and evening) as recorded in the patient diaries during the 12-week treatment period will be summarized and compared between treatment groups using the Wilcoxon-Mann-Whitney test.

Example SAS code for this analysis:

```
proc npar1way data=self wilcoxon;
where treat in ("A", "D");
class treat;
var change;
output out=yyy wilcoxon; run;
```

where: change is the change from baseline in percentage of rescue-free days. The code is executed for each pair of treatment comparisons of interest.

6.4.2.3. Change from Baseline in the Percentage of Symptom-free Days (Defined as 24-hour Periods with Asthma Symptom Score of 0) During the 12-week Treatment Period

The change from baseline in the percentage of symptom-free days (defined as 24-hour periods with asthma symptom scores of zero) as recorded in the patient diaries during the 12-week treatment period will be summarized and will be compared between treatment groups using the Wilcoxon-Mann-Whitney test.

6.4.2.4. Change from Baseline in the Percentage of Asthma-control Days (Defined as 24-hour Periods with Asthma Symptom Score of 0 and no Rescue Medication usage) During the 12-week Treatment Period

The change from baseline in the percentage of asthma-control days (defined as 24-hour periods with asthma symptom scores of zero and no rescue medication use) during the 12-week treatment period will be summarized and compared between treatment groups using the Wilcoxon-Mann-Whitney test.

6.4.2.5. Change from Baseline in 1-Hour Postdose Percent Predicted Morning FEV_1 at Week 1

On the morning of the week 1 visit (TV2), patients will perform their predose FEV_1 assessment at the investigational center. They will take their morning dose of the IMP, and subsequently perform the 1-hour postdose FEV_1 measurements using the handheld device. Patients, who have been withdrawn from IMP but remain in the study, will be asked to perform the 1-hour postdose lung function assessments at the visit although patients will not be taking a dose of IMP. The assessment should be performed approximately 1 hour after the predose lung function assessments were obtained.

The change from baseline in 1-hour postdose percent predicted morning FEV_1 at week 1will be analyzed using an ANCOVA model with effects due to baseline percent predicted FEV_1, sex, age, (pooled) investigational center, previous therapy (ICS or NCS), and treatment. In cases where the 1-hour postdose value is missing at week 1, the 1-hour postdose at baseline (RV/TV1) will be used.

6.4.2.6. Change from Baseline in the Weekly Average of the Daily Evening PEF Over the 12-week Treatment Period

The analysis of change from baseline in weekly average of daily evening PEF over the 12-week treatment period will be performed using an MMRM with effects due to baseline weekly average of daily evening PEF, sex, age, (pooled) investigational center, previous therapy (ICS or NCS), week, treatment, and week-by-treatment interaction. No explicit structure will be assumed for the covariance among the repeated measures. However, if there is a convergence problem with unstructured covariance, a compound symmetry covariance structure will be assumed.

6.4.2.7. Change from Baseline in Weekly Average of the Percent Predicted Trough Morning FEV_1 at weeks 1, 2, 4 and 8

The change from baseline in weekly average of the percent predicted trough morning FEV_1 will be summarized descriptively by week and treatment.

6.4.2.8. Proportion of Patients who Achieve at Least a 15% increase in morning FEV_1 at 1-hour postdose at Day 1 (RV/TV1), Week 1, and Week 12

The proportion of patients who achieve at least a 15% increase in morning FEV_1 at 1-hour postdose at day 1 will be analyzed using a logistic regression model with effects due to previous therapy (ICS or NCS) and treatment. The proportion of patients who achieve at least a 12% increase in FEV_1 at 1-hour postdose at week 12 will be analyzed similarly.

6.4.2.9. Change from Baseline in Asthma Control (measure by C-ACT) score at Weeks 4, 8, and 12

The change from baseline in C-ACT score at weeks 4, 8 and12 will be summarized descriptively by visit and treatment.

6.4.2.10. Time to Consistent Onset of Effect in Daily Rescue Medication Use

The time to consistent onset of effect is defined as the number of days elapsed from the date of randomization to the first date of 3 consecutive days with a decrease from baseline in daily rescue medication use. Patients who have 3 consecutive days with a decrease in effect will be counted as an event in the analysis, otherwise, patients will be right-censored at the date of last IMPDV assessments.

The analysis of time to consistent onset of effect will be performed using a log-rank test to compare the survival curves. Time to first onset of effect will be graphically displayed with a Kaplan-Meier figure and the median time to first onset and associated 95% CIs will be provided.

7. MULTIPLE COMPARISONS AND MULTIPLICITY

7.1. Multiple Comparisons for the Primary Analysis

For the analysis of the co-primary endpoints, a fixed-sequence multiple testing procedure will be employed to control the overall Type I error rate at the 0.05 level, as described in Table 7. Specifically, treatment comparisons will begin with the first primary endpoint, [1] 1-hour postdose percent predicted morning FEV_1 at week 12 at the FS MDPI 50/12.5 versus Fp MDPI 50 mcg. If the resulting p-value is less than 0.05, then the next comparison of interest will be made, according to the direction of the arrow. This process will continue until the point where the p-value is greater than 0.05 at which no further comparisons will be interpreted inferentially.

Taking into consideration that this is the very first study that utilizes the handheld device in a large Phase 3 study in a pediatric asthma patient population (4 through 11 years of age), an unplanned blinded sample size re-assessment was conducted. Since the adjustment to sample size was based on blinded standard deviation, no adjustment to the multiplicity control is warranted.

No multiplicity adjustment will be made for sensitivity analyses of the primary endpoints or subgroups.

Table 7: Multiple Testing Procedures

Sequence	Primary Endpoint	Hypothesis Testing
1	**[1]** Change from baseline in1-hour postdose percent predicted morning FEV_1 at week 12	FS MDPI 50/12.5 mcg BID vs. Fp MDPI 50 mcg BID
		↓
2	**[2]** Change from baseline in weekly average of the percent predicted trough morning FEV_1 at week 12	Fp MDPI 50 mcg BID vs. Placebo
		↓
3	**[2]** Change from baseline in weekly average of the percent predicted trough morning FEV_1 at week 12	Fp MDPI 25 mcg BID vs. Placebo
FEV_1= forced expiratory volume in 1 second; FS MDPI = fluticasone propionate/salmeterol xinafoate multidose dry powder inhaler, Fp MDPI = fluticasone propionate multidose dry powder inhaler.		

7.2. Multiple Comparisons for the Secondary Analysis

If the p-value is less than 0.05 for the 3 inferential comparisons in the primary analysis, inferential testing will be extended to the secondary analysis.

Testing of secondary efficacy variables for the study drugs will be performed in the sequential manner described in Table 8 (Fp MDPI) and Table 9 (FS MDPI).

Treatment comparisons will begin with the change from baseline in weekly average of daily trough morning PEF (first secondary endpoint) with Fp MDPI 50 mcg versus placebo for

Fp MDPI, or FS MDPI 50/12.5 mcg versus placebo for FS MDPI. If the resulting p-value is less than 0.05, the next comparison(s) of interest will be made according to the direction of the arrows. To the right, this will be the same endpoint to compare Fp MDPI 25 mcg versus placebo (Fp MDPI), or FS MDPI 50/12.5 mcg versus Fp MPDI 25 mcg (FS MDPI). To the next endpoint, this will be the change from baseline in the weekly average of the total daily (24-hour) use of albuterol/salbutamol inhalation aerosol (second secondary endpoint) at the Fp MDPI 50 mcg versus placebo (Fp MDPI), or FS MDPI 50/12.5 mcg versus placebo (FS MDPI).

This process will continue testing sequentially through the next study drug/strength for each variable and at a given strength through the order presented in Table 8 and Table 9 until either all comparisons of interest are made, or until the point at which the resulting p-value for a comparison is greater than 0.05. At the point where the p-value is greater than 0.05, no further comparisons of either that strength or that measure can be made. This procedure allows for control of the Type I error for comparisons at a particular study drug/strength over the 6 secondary endpoints, as well as comparisons over study drugs/strengths within a particular endpoint. However, it does not control the overall Type I error, nominal p-value will be reported.

No multiplicity adjustment will be made for other efficacy analyses.

Table 8: Sequence of Testing Secondary Endpoints for Fp MDPI

Secondary Endpoint	Hypothesis Testing	
	Fp MDPI 50 mcg vs. Placebo	**Fp MDPI 25 mcg vs. Placebo**
[A] Change from baseline in weekly average of daily trough morning PEF over the 12-week treatment period	↓ →	↓
[B] Change from baseline in the weekly average of total daily (24-hour) use of albuterol /salbutomol inhalation aerosol (number of inhalations) over weeks 1 through 12	↓ →	↓
[C] Change from baseline in the weekly average of the total daily asthma symptom score over weeks 1 through 12	↓ →	↓
[D] Change from baseline in asthma control (measured by C-ACT) score over the 12-week treatment period	↓ →	↓
[E] Time to first onset of effect defined as the first decrease from baseline in daily rescue medication use	↓ →	↓
[F] Proportion of patients discontinued from IMP for asthma exacerbation during the 12-week treatment period	→	

Table 9: Sequence of Testing Secondary Endpoints for FS MDPI

Secondary Endpoint	Hypothesis Testing		
	FS MDPI 50/12.5 mcg vs. Placebo	**FS MDPI 50/12.5 mcg vs. Fp MDPI 25 mcg**	**FS MDPI 50/12.5 mcg vs. Fp MDPI 50 mcg**
[A] Change from baseline in weekly average of daily trough morning PEF over the 12-week treatment period	↓ →	↓ →	↓
[B] Change from baseline in the weekly average of total daily (24-hour) use of albuterol /salbutomol inhalation aerosol (number of inhalations) over weeks 1 through 12	↓ →	↓ →	↓
[C] Change from baseline in the weekly average of the total daily asthma symptom score over weeks 1 through 12	↓ →	↓ →	↓
[D] Change from baseline in asthma control (measured by C-ACT) score over the 12-week treatment period	↓ →	↓ →	↓
[E] Time to first onset of effect defined as the first decrease from baseline in daily rescue medication use	↓ →	↓ →	↓
[F] Proportion of patients discontinued from IMP for asthma exacerbation during the 12-week treatment period	→	→	

8. SAFETY ANALYSIS

8.1. General

The safety analysis set will be used for all safety analyses. Summaries will be presented by treatment group and will represent what treatment was actually received, unless specified otherwise. Summaries of clinically significant abnormal values will include all postbaseline values (including scheduled, unscheduled, and IMPDV).

8.2. Duration of Exposure to IMP

Duration of exposure to IMP (days) for the individual patient is the number of days patient received drug (last day of IMP – first day of IMP + 1). Duration of treatment (days) will be summarized using descriptive statistics.

The last day of the IMP is determined by the study drug exposure date on patient's electronic diary or the treatment completion/discontinuation date on the disposition page; whichever comes first. The reason is that in some cases, the question "*It is now time to take your study drug. Confirm that it was taken*" was continuing showing up on the AM3 device and it caused many confusions to patients who were on alternative medication, and should not need to answer this question after they were terminated from treatment.

8.3. IMP Compliance

IMP compliance during the study will be assessed based on data collected with the dose counter device. This will be the primary method to evaluate the patient's compliance rate. For patients who have a compliance rate of <80%, their handheld electronic diary will also be evaluated. A routine data monitoring report will be sent to a service provider to further investigate the issue (ie, diary data and IMP dose counter data are not consistent). Each of these individual patients will then be evaluated during the SDR meeting to determine whether the patient should be included in the PP analysis set.

The degree of IMP compliance will be determined by presenting the number of doses taken as a percentage of the number required by the protocol.

$$\text{Device: \% Compliance} = \frac{\text{Actual \# of actuations use per dose counter}}{\text{Expected \# of actuations to be used}} \; x\,100$$

$$\text{Diary: \% Compliance} = \frac{\text{Actual \# of actuations use per diary card}}{\text{Expected \# of actuations to be used}} \; x\,100$$

The denominator of "expected # of times study drug was to be taken" will be calculated based on patients' participation in the study (ie, last day of IMP – first day of IMP + 1). For patients who complete the study treatment period, the last day of IMP used in the denominator calculation will

be the last expected dosing day. For early termination patients, the last day of IMP used in the denominator calculation will be the last expected dosing day before termination day. See Section 8.2 for last IMP date definition.

Patients are supposed to return their devices with dose counters at each visit. However, if there is no date for the return of the device in the database or a dose counter error has been reported, the treatment duration for that patient will be prorated according to the number and day when the device was returned without dose counter error. Table 10 below illustrates as an example for patient who has an unreturned device and reported dose counter error.

Table 10: Example of Unreturned Device or Dose Counter Error

Dispense Date	Return Date	Report Dose Counter Error	# of Days	# of Doses (total count)
02 April 2018	09 April 2018	--	7	12
09 April 2018	Device not returned	--	N/A	N/A
16 April 2018	30 April 2018	Reported on 20-April-2019	N/A	N/A
30 April 2018	14 May 2018	--	14	12
Overall compliance rate: (12 + 12) / [(7 + 14+1)*2] = 57%				

If a patient has missing electronic patient diary pages, it is assumed that this patient did not take the IMP on the days as expected.

Compliance with IMP will be categorized as <60%, 60% to <80%, 80% to <100%, and ≥100% and summarized using descriptive statistics.

8.4. Adverse Events

All adverse events will be coded using the MedDRA version 19.0. The incidence of adverse events will be summarized using descriptive statistics (counts and percentages) by SOC and preferred term (PT). Patients are counted only once in each SOC category, and only once in each PT category. Treatment-related adverse event summaries will include adverse events with missing relationship to study drug. For the summaries by severity, patients are counted at the greatest severity. Summaries will be presented for all treatment-emergent adverse events (overall and by severity), treatment-emergent adverse events determined by the investigator to be related to IMP (see FSS-AS-30003 protocol Section 7.1.4) (defined as related or with missing relationship, overall and by severity), serious treatment-emergent adverse events, treatment-emergent adverse events causing withdrawal from the study, and nonserious adverse events. Summaries will be presented by treatment group and for all patients.

Any event occurring after the patient has signed the study informed consent/assent form should be recorded and reported as adverse event. Those events occurring prior to the first dose of IMP will be considered as non-treatment-emergent adverse events, and those occurring on or after the first dose of IMP drug through 7 days after the last dose of IMP will be considered as treatment-emergent adverse events. Any events that occurred beyond the 7 days after the last dose of IMP will be considered as non-treatment-emergent adverse events.

For all non-treatment-emergent adverse events that occurred during the run-in period, a summary and a patient listing will be presented separately. All non-treatment-emergent adverse events that occurred 7days after the last dose of IMP, prior to week 12 (mainly for patients who discontinued IMP but continued in the study) will be presented similarly. In addition, serious adverse events that were reported during the follow up period will be presented.

For all treatment-emergent adverse events that lead to discontinuation from IMP treatment through 7 days after the last dose of IMP will be summarized.

Patient listings of deaths, serious adverse events, adverse events leading to discontinuation, MedDRA dictionary terms for adverse event descriptions, and adverse event PT by patient number will be presented.

8.5. Deaths

If any patient dies during the study, all relevant information will be discussed in the patient's narrative included in the CSR.

8.6. Asthma Exacerbations

Asthma exacerbations that requires a change in medication or worsening of asthma that requires the patient to be treated with alternative therapy will be entered into the case report form (CRF), including the date at which any medication change was made and whether this medication change was implemented prior to or after the IMPDV lung function assessments (FEV_1 and PEF) were completed. Asthma worsening including asthma exacerbations with a change to alternative asthma therapy will not be considered an adverse event for this study since it is an expected outcome for this study in an asthmatic patient population. Asthma exacerbations that meet the criteria for a serious adverse event will be recorded as adverse events. For the purpose of this study, an asthma exacerbation is defined as worsening of asthma requiring any significant treatment other than IMP and study rescue medication.

The number and percentage (%) of patients experiencing an asthma exacerbation will be presented by treatment group.

A summary of the number and percentage of patients with asthma exacerbations resulting in hospitalization, leading to permanent withdrawal of study drug, and other actions will be presented by treatment group.

The number and percentage of patients with asthma exacerbations will be presented by maximum severity and treatment group. Severity will be classified as "mild", "moderate", or "severe". If a patient experiences more than 1 asthma exacerbations, only the asthma exacerbations with the greatest severity will be included in the summary table.

In all of the above summaries, each patient will be counted only once regardless of the number of asthma exacerbations experienced during the study.

8.7. Clinical Laboratory Tests

Clinical laboratory tests of chemistry, hematology, and urinalysis parameters are not collected for this study. However, optional clinical laboratory evaluation at the discretion of the investigator will be listed. All clinical laboratory tests will be listed (if any) to ensure the safety of the patients.

8.8. Physical Examinations

Physical examinations, including height (to be measured at the screening visit only) and weight, will be performed at the SV, RV and at the final treatment visit (TV6 or at the IMPDV). Patients with a physical examination, patients with at least 1 abnormal finding, and abnormal findings for each category will be summarized at baseline using descriptive statistics. Any physical examination finding that is judged by the investigator as a clinically significant change (worsening) compared with a baseline value will be considered an adverse event, recorded on the CRF, and monitored as described in Section 7.1.2 of the FSS-AS-30003 study protocol.

Shifts (normal and abnormal) from baseline to final treatment visit will be summarized by treatment for each physical examination category.

Descriptive statistics for weight and height will be provided and a listing of physical examinations by patient and all abnormal findings will be provided.

8.9. Vital Signs

Summary statistics for vital signs (blood pressure and pulse) will be presented at each visit throughout the study. Vital signs values and changes from baseline to each visit will be summarized using descriptive statistics. Height and weight will be recorded at SV and TV6/IMPDV.

Table 11 specifies the criteria for identifying vital signs as potentially clinically significant abnormal values. Note that in order to be identified as potentially clinically significant abnormal, a value needs to meet both criteria below: ie, have a value beyond the criterion value and a change of at least the magnitude specified in the change relative to baseline column. The potentially clinically significant abnormal vital signs values will include all post baseline values (including scheduled, unscheduled, and early termination visits) for the summaries.

Table 11: Criteria for Potentially Clinically Significant Vital Signs

	Criterion Value			Change relative to baseline		
Age (years)	**4-5**	**6-8**	**9-11**	**4-5**	**6-8**	**9-11**
Pulse (bpm)	>135	>130	>110	Increase of ≥25	Increase of ≥20	Increase of ≥20
	<65	<60	<60	Decrease of ≥ 25	Decrease of ≥20	Decrease of ≥20
SBP (mmHg)	>110	>120	>130	Increase of ≥20	Increase of ≥20	Increase of ≥20
	<80	<80	<80	Decrease of ≥20	Decrease of ≥20	Decrease of ≥20
DBP (mmHg)	>80	>80	>80	Increase of ≥15	Increase of ≥15	Increase of ≥15
	<50	<50	<50	Decrease of ≥15	Decrease of ≥15	Decrease of ≥15

Abbreviations: bpm=beats per minute; DBP=diastolic blood pressure; mmHg=mm of mercury; SBP=systolic blood pressure.
Note: All ranges are adapted from The Harriet Lane Handbook of Pediatrics, 20th ed, 2015. Pulse: Table 7-4. Blood pressure: Table 7-1.

8.10. Electrocardiography

Electrocardiography was not collected for this study.

8.11. Oropharyngeal Examinations

Oropharyngeal examinations for visual evidence of oral candidiasis will be conducted at the scheduled investigational center visits. This will be evaluated by obtaining an analyzing a swab of the suspect area. Any occurrence of oropharyngeal candidiasis that is confirmed by culture during the study will be reported as an adverse event.

The number and percentage of patients with clinical/visual evidence of oral candidiasis will be tabulated for each treatment group at each visit. In addition, the number and percentage of patients with a positive swab will be tabulated for each treatment group at each visit.

A listing of all visual evidence of oral candidiasis will be provided.

8.12. Concomitant Medications or Therapies

Concomitant therapies and medications, including medications that are taken on an as needed basis and occasional therapies, will be monitored during the study. Details of prohibited medications may be found in Section 5.7 and Appendix H of the FSS-AS-30003 study protocol. All concomitant medications will be coded using the WHO Drug.

The incidence of concomitant therapies and medications will be summarized using descriptive statistics by therapeutic class category and preferred term. Patients are counted only once in each therapeutic class, and only once in each preferred term category. Concomitant therapies and medications will include all medications taken while the patient is being treated with IMP as defined in the FSS-AS-30003 study protocol. In addition, a separate summary table will be provided for patients who discontinue IMP but stay in the study.

9. TOLERABILITY VARIABLES AND ANALYSIS

Tolerability will be assessed via other endpoints.

10. STATISTICAL SOFTWARE

All data listings, summaries, and statistical analyses will be generated using SAS® version 9.4 or later.

11. CHANGES TO ANALYSES SPECIFIED IN THE STUDY PROTOCOL

There is no change to the analyses specified in the FSS-AS-30003 clinical study protocol. Only one clarification to the PP analysis set has been made.

Table 12: Changes to the Statistical Analysis Plan

SAP Section	Protocol Description	SAP Change	Rationale
3.3	The per-protocol (PP) analysis set is a subset of the ITT analysis set including only patients without major protocol violations and who have >80% compliance to the IMP over the entire treatment period. Treatment compliance during the study will be assessed based on data collected in the IMP dose counter. In the event the IMP isn't returned by a patient or a dose counter is broken, treatment compliance will be assessed based on the patient's diary. Major protocol violations will be determined before unblinding. Note that since the use of incorrect IMP will be considered a major protocol violation, for treatment assignment in the PP analysis set, "as randomized" will coincide with "as treated."	The per-protocol (PP) analysis set is a subset of the ITT analysis set including only patients without protocol violations that could have an effect on the primary outcome and who have greater than or equal to 80% compliance to the IMP over the entire treatment period. The compliance rate calculation is detailed in section 8.3. PP analysis set will be determined before unblinding at the Statistical Data Review (SDR) meeting and documented in the SDR meeting minutes. Note that since the use of incorrect IMP will be considered a protocol violation and will not be included in the PP analysis set, for treatment assignment in the PP analysis set, "as randomized" will coincide with "as treated".	This change was made so that the language is consistent with SOP GBP-RD-312

12. REFERENCES

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APPENDIX A. MULTIPLE IMPUTATION STEPS FOR PRIMARY ENDPOINTS

The following represents an outline of the planned methodology for the multiple imputation (MI) procedure for the primary analyses. Minor deviations from this outline will be addressed in the CSR. In the situation that more significant updates are warranted, changes will be addressed in a SAP amendment to be finalized prior to database lock.

Change from Baseline in Weekly Average of the Percent Predicted Trough Morning FEV_1 at Week 12:

Multiple imputation (MI) method will be applied to impute the weekly missing data that are caused by early discontinuation from the study or from IMP (regardless of availability of retrieved dropout data). The data will be processed by the following steps:

1. For all patients who prematurely discontinue from IMP, regardless of assigned treatment arm, imputation will be based on data from the placebo-treated patients (eg, reference-based imputation).
2. For patients who completed the treatment period but with clinically and physiologically implausible data (eg, percent predicted FEV_1 values postrandomization are ≥200%), imputation will be based on data from patients treated with the same treatment.
3. Assume patients with arbitrary missing data patterns, the fully conditional specification statement will be used to impute by using regression with treatment arm and percent predicted FEV_1 measurements from previous weeks as explanatory variables.

```
proc mi data=outmi_mono seed=56789 nimpute=10 out=outmi;
      class sex therapy center trt;
      fcs nbiter=50 reg(wk1= &covlist / details);
      fcs nbiter=50 reg(wk2= &covlist wk1 / details);
      fcs nbiter=50 reg(wk3= &covlist wk1 wk2 / details);
      fcs nbiter=50 reg(wk4= &covlist wk1 wk2 wk3 / details);
      fcs nbiter=50 reg(wk5= &covlist wk1 wk2 wk3
                        wk4 / details);
      fcs nbiter=50 reg(wk6= &covlist wk1 wk2 wk3
                        wk4 wk5 / details);
      fcs nbiter=50 reg(wk7= &covlist wk1 wk2 wk3
                        wk4 wk5 wk6 / details);
      fcs nbiter=50 reg(wk8= &covlist wk1 wk2 wk3
                        wk4 wk5 wk6 wk7 / details);
      fcs nbiter=50 reg(wk9= &covlist wk1 wk2 wk3
                        wk4 wk5 wk6 wk7 wk8 / details);
```

```
        fcs nbiter=50 reg(wk10= &covlist wk1 wk2 wk3
                          wk4 wk5 wk6 wk7 wk8 wk9 / details);
        fcs nbiter=50 reg(wk11= &covlist wk1 wk2 wk3
                          wk4 wk5 wk6 wk7 wk8 wk9 wk10 / details);
        fcs nbiter=50 reg(wk12= &covlist wk1 wk2 wk3
                          wk4 wk5 wk6 wk7 wk8 wk9 wk10 wk11 /
                          details);
        var trt &covlist wk1 - wk12;
        mnar model( wk1 - wk12 / modelobs = (trt = "D"));
run;
where: the order of &covlist includes: sex, (pooled)
investigational center, previous therapy, base, and age
Note: wk1 - wk12 is the AVAL raw data, change from baseline
values should not be used in PROC MI procedure.
```

4. The ANCOVA model will be fitted to the above dataset using the model described in Section 6.2.2.1. The difference will be estimated in adjusted LS means and p-value will be output for each dataset. An example SAS code to the following will be used:

```
proc mixed data=fev_model;
      where week = "week 12";
      class sex center therapy trt;
      model chg= base sex age therapy trt;
      lsmeans trt/diff=CONTROL("Placebo") cl alpha=0.05;
      ods output Estimates=Est LSMeans=lsmeans Diffs=Diffs;
run;
where: chg is the change from baseline percent predicted FEV1
value at week 12.
```

5. The results from the ANCOVA model will be combined using the following code:

```
data diff2;
      set diff;
      comparison=trt||' vs '||left(_trt);
run;
proc sort data=diff2;
      by comparison;
```

```
run;
```

6. The SAS® procedure PROC MIANALYZE procedure will be used to generate the final LS means for the treatment groups, treatment difference as well as p-values associated with treatment differences. The 95% confidence intervals for the treatment differences will be also calculated. An example of the SAS code will be used:

```
proc mianalyze data=diff2;
      by comparison;
      modeleffects estimate;
      stderr stderr;
      ods output ParameterEstimates=mianalyzeparm;
run;
```

Change from Baseline in 1-hour Postdose Percent Predicted Morning FEV_1 at Week 12:

The 1-hour postdose percent predicted morning FEV_1 measurement will be performed at the investigational center at the RV, TV2 (week 1), TV3 (week 2), TV4 (week 4), TV5 (week 8) and TV6 (week 12). The MI method will be applied similarly to impute the 1-hour postdose missing data that are caused by early dropouts from IMP without including retrieve dropout data. Steps 1 to 6 will be repeated similarly.

Sensitivity Analysis: Effectiveness with retrieved dropout data:

In order to evaluate the estimand of the effect of the treatment regimens as actually taken (effectiveness), the above analysis will be repeated including observed FEV_1 data over 12 weeks, for patients who completed the 12-week treatment period, including clinically and physiologically implausible data at week 12, and for patients who discontinued from treatment earlier than 12 week but from whom the sponsor was able to collect data post discontinuation. The sensitivity analysis will be conducted for both primary efficacy endpoints.

APPENDIX B. SENSITIVITY ANALYSIS: TIPPING POINT ANALYSIS

The following represents an outline of the planned methodology for the "tipping point" multiple imputation sensitivity analysis of the change from baseline in weekly average of the percent predicted trough morning FEV_1 at week 12. Minor deviations from this outline will be addressed in the CSR. In the situation that more significant updates are warranted, changes will be addressed in a SAP amendment to be finalized prior to database lock.

The tipping point analysis evaluates several combinations of imputed missing data values until it reaches a "tipping point" or point at which a particular combination of imputed missing data changes the study conclusions, as summarized by its p-value. This is a sensitivity analysis utilizing MI under the missing not at random (MNAR) assumption, and will only be conducted if a significant result ($p \leq 0.05$) is observed as part of the primary analysis. If the sensitivity analysis reveals that the tipping point consists of unreasonable values, then the robustness of the study results is supported.

Change from Baseline in Weekly Average of the Percent Predicted Trough Morning FEV_1 at Week 12:

In the tipping point analysis, missing percent predicted FEV_1 values will be imputed for patients who discontinued treatment before the week 12 visit for weekly average in which FEV_1 values are missing. MI and associated combining rules will be applied to propagate imputation uncertainty. In the placebo group, the missing percent predicted FEV_1 values will be imputed based on measurements observed at previous weeks and treatment group; that is, the missing data in the placebo group are assumed missing at random (MAR). For the active treatment groups, missing FEV_1 values will be imputed in the same manner, but then a constant (positive value) shift will be subtracted from the imputed FEV_1 values. The initial shift value will be zero (representing MAR) and it will then be increased and the process repeated until the treatment effect is no longer significant at the 5% level. The shift point at which the effect is no longer significant is the tipping point.

More specifically, the "tipping point" analysis will be performed using the following steps:

1. Assume patients with arbitrary missing data patterns, the fully conditional specification statement will be used to impute by using regression with treatment arm and percent predicted FEV_1 measurements from previous weeks as explanatory variables. For the 3 active treatment groups, MNAR will be assumed using specified shift parameters to adjust imputed values. For the placebo group, the imputed values will be generated using a zero shift parameter (namely, MAR is assumed for placebo). This will be done using code similar to the following:

```
proc mi data= outmi_mono seed=56789 nimpute=10 out=outmi;

    class trt sex therapy center;

    fcs nbiter=50 reg(wk1= &covlist trt / details);

    fcs nbiter=50 reg(wk2= &covlist trt wk1 / details);

    fcs nbiter=50 reg(wk3= &covlist trt wk1 wk2 / details);
```

```
fcs nbiter=50 reg(wk4= &covlist trt wk1 wk2 wk3 / details);
fcs nbiter=50 reg(wk5= &covlist trt wk1 wk2 wk3 wk4 / details);
fcs nbiter=50 reg(wk6= &covlist trt wk1 wk2 wk3
                  wk4 wk5 /details);
fcs nbiter=50 reg(wk7= &covlist trt wk1 wk2 wk3
                  wk4 wk5 wk6 / details);
fcs nbiter=50 reg(wk8= &covlist trt wk1 wk2 wk3
                  wk4 wk5 wk6 wk7 / details);
fcs nbiter=50 reg(wk9= &covlist trt wk1 wk2 wk3
                  wk4 wk5 wk6 wk7 wk8 / details);
fcs nbiter=50 reg(wk10= &covlist trt wk1 wk2 wk3
                  wk4 wk5 wk6 wk7 wk8 wk9 / details);
fcs nbiter=50 reg(wk11= &covlist trt wk1 wk2 wk3
                  wk4 wk5 wk6 wk7 wk8 wk9 wk10 / details);
fcs nbiter=50 reg(wk12= &covlist trt wk1 wk2 wk3
                  wk4 wk5 wk6 wk7 wk8 wk9 wk10 wk11 / details);

mnar adjust( wk1 / shift=&sj  adjustobs=(trt='A' ));
mnar adjust( wk2 / shift=&sj  adjustobs=(trt='A' ));
mnar adjust( wk3 / shift=&sj  adjustobs=(trt='A' ));
mnar adjust( wk4 / shift=&sj  adjustobs=(trt='A' ));
mnar adjust( wk5 / shift=&sj  adjustobs=(trt='A' ));
mnar adjust( wk6 / shift=&sj  adjustobs=(trt='A' ));
mnar adjust( wk7 / shift=&sj  adjustobs=(trt='A' ));
mnar adjust( wk8 / shift=&sj  adjustobs=(trt='A' ));
mnar adjust( wk9 / shift=&sj  adjustobs=(trt='A' ));
mnar adjust( wk10 / shift=&sj  adjustobs=(trt='A' ));
mnar adjust( wk11 / shift=&sj  adjustobs=(trt='A' ));
mnar adjust( wk12 / shift=&sj  adjustobs=(trt='A' ));

mnar adjust( wk1 / shift=&sj  adjustobs=(trt='B' ));
mnar adjust( wk2 / shift=&sj  adjustobs=(trt='B' ));
```

```
    mnar adjust( wk3 / shift=&sj  adjustobs=(trt='B' ));
    mnar adjust( wk4 / shift=&sj  adjustobs=(trt='B' ));
    mnar adjust( wk5 / shift=&sj  adjustobs=(trt='B' ));
    mnar adjust( wk6 / shift=&sj  adjustobs=(trt='B' ));
    mnar adjust( wk7 / shift=&sj  adjustobs=(trt='B' ));
    mnar adjust( wk8 / shift=&sj  adjustobs=(trt='B' ));
    mnar adjust( wk9 / shift=&sj  adjustobs=(trt='B' ));
    mnar adjust( wk10 / shift=&sj  adjustobs=(trt='B' ));
    mnar adjust( wk11 / shift=&sj  adjustobs=(trt='B' ));
    mnar adjust( wk12 / shift=&sj  adjustobs=(trt='B' ));

    mnar adjust( wk1 / shift=&sj  adjustobs=(trt='C' ));
    mnar adjust( wk2 / shift=&sj  adjustobs=(trt='C' ));
    mnar adjust( wk3 / shift=&sj  adjustobs=(trt='C' ));
    mnar adjust( wk4 / shift=&sj  adjustobs=(trt='C' ));
    mnar adjust( wk5 / shift=&sj  adjustobs=(trt='C' ));
    mnar adjust( wk6 / shift=&sj  adjustobs=(trt='C' ));
    mnar adjust( wk7 / shift=&sj  adjustobs=(trt='C' ));
    mnar adjust( wk8 / shift=&sj  adjustobs=(trt='C' ));
    mnar adjust( wk9 / shift=&sj  adjustobs=(trt='C' ));
    mnar adjust( wk10 / shift=&sj  adjustobs=(trt='C' ));
    mnar adjust( wk11 / shift=&sj  adjustobs=(trt='C' ));
    mnar adjust( wk12 / shift=&sj  adjustobs=(trt='C' ));

    var trt &covlist wk1 - wk12;
run;
where: the order of &covlist includes: sex, (pool) investigational
center, previous therapy, base, and age

Note: wk1 - wk12 is the AVAL raw data, change from baseline values
should not be used in PROC MI procedure.
```

The same shift will be assumed for all weekly average and all active treatments.

2. The MMRM model will be fitted to the completed datasets using the model that was used for analysis. The difference will be estimated in adjusted LS means and p-value. SAS code similar to the following will be used:

```
ods output diffs=middiffs;
proc mixed data=dateset;
     by shift;
     class usubjid sex center therapy visit trt;
     model chg=base sex age center therapy visit trt visit*trt /
               ddfm=KR alpha=0.05;
     repeated visit / type=un sub=usubjid(trt) r;
                ** repeated visit / type=cs sub=usubjid(trt) r;
                ** if type=un fails to converge;
     lsmeans trt / diff cl;
run;
```

3. The results from the MMRM models will be combined using the following code:

```
data diffdt;

      set midiffs;

      comparison=trt||' vs '||left(_trt);

run;

proc sort data=diffdt;

      by comparison shift;

run;

ods output parameterestimates=miparm1;

proc mianalyze data=diffdt alpha=0.05 theta0=0;

      by comparison shift;

      modeleffects estimate;

      stderr stderr;

run;
```

4. Steps 2 through 3 will be repeated using different values for the shift parameter. After this step, for each shift parameter, a treatment effect (difference in adjusted means from placebo) and associated p-value will be estimated.

Since the tipping point analysis is to find out how much of a change is required to "tip" the result from statistically significant to not statistically significant, it will not be performed for any comparison that is not statistically significant at the onset.

Change from Baseline in 1-hour Postdose Percent Predicted Morning FEV_1 at Week 12:

The 1-hour postdose percent predicted morning FEV_1 measurement will be performed at the investigational center at the RV, TV2 (week 1), TV3 (week 2), TV4 (week 4), TV5 (week 8) and TV6 (week 12). MI method will be applied similarly to impute the 1-hour postdose missing data that are caused by early dropouts, then tipping point analysis will be performed.

APPENDIX C. SENSITIVITY ANALYSIS: 2-DIMENSIONAL TIPPING POINT ANALYSIS

The following represents an outline of the planned methodology for the "2-dimensional tipping point" multiple imputation sensitivity analysis of the change from baseline in weekly average of the percent predicted trough morning FEV_1 at week 12. Minor deviations from this outline will be addressed in the CSR. In the situation that more significant updates are warranted, changes will be addressed in a SAP amendment to be finalized prior to database lock.

The 2-dimensional tipping point analysis evaluates several combinations of imputed missing data values until it reaches a "tipping point" or point at which a particular combination of imputed missing data changes the study conclusions, as summarized by its p-value. This is a sensitivity analysis utilizing MI under the missing not at random (MNAR) assumption, and will be only conducted if a significant result ($p \leq 0.05$) is observed as part of the primary analysis. If the sensitivity analysis reveals that the tipping point consists of unreasonable values, then the robustness of the study results is supported.

Change from Baseline in Weekly Average of the Percent Predicted Trough Morning FEV_1 at Week 12:

In the 2-dimensional tipping point analysis, missing percent predicted FEV_1 values will be imputed for patients who discontinued treatment before the week 12 visit for weekly average in which FEV_1 values are missing. MI and associated combining rules will be applied to propagate imputation uncertainty. In each treatment group, the missing percent predicted FEV_1 values will be imputed based on measurements observed at previous weeks and in the same treatment group. For the active groups, a constant (positive value) shift will be subtracted from the imputed FEV_1 values. For the placebo group, a constant (positive value) shift will be added to the imputed FEV_1 values. The initial shift values will be zero (representing MAR) and they will then be increased and the process repeated until the treatment effect is no longer significant at the 5% level. The shift point at which the effect is no longer significant is the tipping point.

More specifically, the "tipping point" analysis will be performed using the following steps:

1. Assume patients with arbitrary missing data patterns, the fully conditional specification statement will be used to impute by using regression with treatment arm and percent predicted FEV_1 measurements from previous weeks as explanatory variables. For the 3 active treatment groups, MNAR will be assumed using specified shift parameters to adjust imputed values. For the placebo group, first imputed values will be generated using a zero shift parameter (namely, MAR is assumed for placebo). This will be done using code similar to the following:

```
proc mi data= outmi_mono seed=56789 nimpute=10 out=outmi;

    class trt sex therapy center;

    fcs nbiter=50 reg(wk1= &covlist trt / details);

    fcs nbiter=50 reg(wk2= &covlist trt wk1 / details);

    fcs nbiter=50 reg(wk3= &covlist trt wk1 wk2 / details);
```

```
fcs nbiter=50 reg(wk4= &covlist trt wk1 wk2 wk3 / details);
fcs nbiter=50 reg(wk5= &covlist trt wk1 wk2 wk3 wk4 / details);
fcs nbiter=50 reg(wk6= &covlist trt wk1 wk2 wk3
                  wk4 wk5 /details);
fcs nbiter=50 reg(wk7= &covlist trt wk1 wk2 wk3
                  wk4 wk5 wk6 / details);
fcs nbiter=50 reg(wk8= &covlist trt wk1 wk2 wk3
                  wk4 wk5 wk6 wk7 / details);
fcs nbiter=50 reg(wk9= &covlist trt wk1 wk2 wk3
                  wk4 wk5 wk6 wk7 wk8 / details);
fcs nbiter=50 reg(wk10= &covlist trt wk1 wk2 wk3
                  wk4 wk5 wk6 wk7 wk8 wk9 / details);
fcs nbiter=50 reg(wk11= &covlist trt wk1 wk2 wk3
                  wk4 wk5 wk6 wk7 wk8 trt wk9 wk10 / details);
fcs nbiter=50 reg(wk12= &covlist trt wk1 wk2 wk3
                  wk4 wk5 wk6 wk7 wk8 wk9 wk10 wk11 / details);

mnar adjust( wk1 / shift=&sj  adjustobs=(trt='A' ));
mnar adjust( wk2 / shift=&sj  adjustobs=(trt='A' ));
mnar adjust( wk3 / shift=&sj  adjustobs=(trt='A' ));
mnar adjust( wk4 / shift=&sj  adjustobs=(trt='A' ));
mnar adjust( wk5 / shift=&sj  adjustobs=(trt='A' ));
mnar adjust( wk6 / shift=&sj  adjustobs=(trt='A' ));
mnar adjust( wk7 / shift=&sj  adjustobs=(trt='A' ));
mnar adjust( wk8 / shift=&sj  adjustobs=(trt='A' ));
mnar adjust( wk9 / shift=&sj  adjustobs=(trt='A' ));
mnar adjust( wk10 / shift=&sj  adjustobs=(trt='A' ));
mnar adjust( wk11 / shift=&sj  adjustobs=(trt='A' ));
mnar adjust( wk12 / shift=&sj  adjustobs=(trt='A' ));

mnar adjust( wk1 / shift=&sj  adjustobs=(trt='B' ));
mnar adjust( wk2 / shift=&sj  adjustobs=(trt='B' ));
```

```
mnar adjust( wk3 / shift=&sj  adjustobs=(trt='B' ));
mnar adjust( wk4 / shift=&sj  adjustobs=(trt='B' ));
mnar adjust( wk5 / shift=&sj  adjustobs=(trt='B' ));
mnar adjust( wk6 / shift=&sj  adjustobs=(trt='B' ));
mnar adjust( wk7 / shift=&sj  adjustobs=(trt='B' ));
mnar adjust( wk8 / shift=&sj  adjustobs=(trt='B' ));
mnar adjust( wk9 / shift=&sj  adjustobs=(trt='B' ));
mnar adjust( wk10 / shift=&sj  adjustobs=(trt='B' ));
mnar adjust( wk11 / shift=&sj  adjustobs=(trt='B' ));
mnar adjust( wk12 / shift=&sj  adjustobs=(trt='B' ));

mnar adjust( wk1 / shift=&sj  adjustobs=(trt='C' ));
mnar adjust( wk2 / shift=&sj  adjustobs=(trt='C' ));
mnar adjust( wk3 / shift=&sj  adjustobs=(trt='C' ));
mnar adjust( wk4 / shift=&sj  adjustobs=(trt='C' ));
mnar adjust( wk5 / shift=&sj  adjustobs=(trt='C' ));
mnar adjust( wk6 / shift=&sj  adjustobs=(trt='C' ));
mnar adjust( wk7 / shift=&sj  adjustobs=(trt='C' ));
mnar adjust( wk8 / shift=&sj  adjustobs=(trt='C' ));
mnar adjust( wk9 / shift=&sj  adjustobs=(trt='C' ));
mnar adjust( wk10 / shift=&sj  adjustobs=(trt='C' ));
mnar adjust( wk11 / shift=&sj  adjustobs=(trt='C' ));
mnar adjust( wk12 / shift=&sj  adjustobs=(trt='C' ));

mnar adjust( wk1 / shift=0  adjustobs=(trt='D' ));
mnar adjust( wk2 / shift=0  adjustobs=(trt='D' ));
mnar adjust( wk3 / shift=0  adjustobs=(trt='D' ));
mnar adjust( wk4 / shift=0  adjustobs=(trt='D' ));
mnar adjust( wk5 / shift=0  adjustobs=(trt='D' ));
mnar adjust( wk6 / shift=0  adjustobs=(trt='D' ));
mnar adjust( wk7 / shift=0  adjustobs=(trt='D' ));
mnar adjust( wk8 / shift=0  adjustobs=(trt='D' ));
```

```
    mnar adjust( wk9 / shift=0  adjustobs=(trt='D' ));
    mnar adjust( wk10 / shift=0  adjustobs=(trt='D' ));
    mnar adjust( wk11 / shift=0  adjustobs=(trt='D' ));
    mnar adjust( wk12 / shift=0  adjustobs=(trt='D' ));

    var trt &covlist wk1 – wk12;
run;
where: the order of &covlist includes: sex, (pooled investigational
center, previous therapy, base, and age
Note: wk1 – wk12 is the AVAL raw data, change from baseline values
should not be used in PROC MI procedure.
```

The same shift will be assumed for all weekly average and all treatment groups.

2. The MMRM model will be fitted to the completed datasets using the model that was used for analysis. The difference will be estimated in adjusted LS means and p-value. SAS code similar to the following will be used:

```
ods output diffs=middiffs;
proc mixed data=dateset;
     by shift;
     class usubjid sex center therapy visit trt;
     model chg=base sex age center therapy visit trt visit*trt /
               ddfm=KR alpha=0.05;
     repeated visit / type=un sub=usubjid(trt) r;
               ** repeated visit / type=cs sub=usubjid(trt) r;
               ** if type=un fails to converge;
     lsmeans trt / diff cl;
run;
```

3. The results from the MMRM models will be combined using the following code:

```
data diffdt;
      set midiffs;
      comparison=trt||' vs '||left(_trt);
run;
proc sort data=diffdt;
      by comparison shift;
run;
ods output parameterestimates=miparm1;
proc mianalyze data=diffdt alpha=0.05 theta0=0;
```

```
        by comparison shift;

        modeleffects estimate;

        stderr stderr;

run;
```

4. Repeat steps 1 through 3 using the same values for the shift parameter for active arms but with a different positive value for placebo group. For example, SAS code below indicated a shift of 2 for placebo group.

```
mnar adjust( wk1 / shift=2  adjustobs=(trt='D' ));
mnar adjust( wk2 / shift=2  adjustobs-(trt='D' ));
mnar adjust( wk3 / shift=2  adjustobs-(trt='D' ));
mnar adjust( wk4 / shift=2  adjustobs=(trt='D' ));
mnar adjust( wk5 / shift=2  adjustobs-(trt='D' ));
mnar adjust( wk6 / shift=2  adjustobs-(trt='D' ));
mnar adjust( wk7 / shift=2  adjustobs=(trt='D' ));
mnar adjust( wk8 / shift=2  adjustobs-(trt='D' ));
mnar adjust( wk9 / shift=2  adjustobs-(trt='D' ));
mnar adjust( wk10 / shift=2  adjustobs-(trt='D' ));
mnar adjust( wk11 / shift=2  adjustobs-(trt='D' ));
mnar adjust( wk12 / shift=2  adjustobs-(trt='D' ));
```

5. Repeat step 6 with a few different positive values for placebo group.
6. Steps 2 through 5 will be repeated using different values for the shift parameter. After this step,, a treatment effect (difference in adjusted means from placebo) and associated p-value will be estimated for each shift parameter.

Since the tipping point analysis is to find out how much of a change is required to "tip" the result from statistically significant to not statistically significant, it will not be performed for any comparison that is not statistically significant at the onset.

Change from Baseline in 1-hour Postdose Percent Predicted Morning FEV_1 at Week 12:

The 1-hour postdose percent predicted morning FEV_1 measurement will be performed at the investigational center at the RV, TV2 (week 1), TV3 (week 2), TV4 (week 4), TV5 (week 8) and TV6 (week 12). MI method will be applied similarly to impute the 1-hour postdose missing data that are caused by early dropouts, then tipping point analysis will be performed.

APPENDIX D. SENSITIVITY ANALYSIS: MIXED APPROACH OF LOCF AND BOCF

With this approach, missing data caused by early dropouts from the study will be handled by two parts: a positive change from baseline score will be penalized by using the BOCF method. This will assign patient's change from baseline score to zero. Discontinued patient that has negative change from baseline with last nonmissing score (LOCF) will not have his/her result adjusted, since his/her score will be poor already.

Change from Baseline in Weekly Average of the Percent Predicted Trough Morning FEV_1 at Week 12:

The approach will be implemented as follows. Let C denote the change from baseline in percent predicted trough morning FEV_1, then

$$C = f_i - f_0 \qquad [1]$$

where f_i is the last nonmissing FEV_1, and f_0 is the baseline of percent predicted FEV_1.

The primary analysis variable that accounts for early dropout, $\boldsymbol{S}$, will be defined as follows:

$$\boldsymbol{S} = \begin{cases} C, & \text{if } C \le 0 \\ CP, & \text{if } C > 0 \end{cases} \qquad [2]$$

where C is given by equation [1], P=1, if a patient completes the study by protocol or if a patient's final FEV_1 is measured at week 12, and P=0, otherwise. Note that retrieved dropout data will not be used for this analysis.

The primary analysis of change from baseline in weekly average of percent predicted trough morning FEV_1 at week 12 of $\boldsymbol{S}$, as defined in equation [2] above, will be analyzed using an analysis of covariance (ANCOVA) model with effects due to baseline percent predicted trough morning FEV_1, sex, age, (pooled) investigational center, previous therapy (ICS or NCS), and treatment. Contrasts for pairwise treatment comparisons of interest will be constructed. The estimated treatment difference between each contrast of interest (i.e, Fp MDPI vs Placebo) will be presented together with the 2-sided 95% confidence interval (CI) for the difference and the p-value. The following SAS code pertains to the analysis:

```
proc mixed data=fev1cfb;
      class sex center therapy trt;
      model S=bfev sex age center therapy trt;

      /* Compare active Fp treatment to Placebo at Week 12 */
      estimate 'Fp 25 mcg BID vs Placebo'      trt  1 0 0 -1 /cl;
      estimate 'Fp 50 mcg BID vs Placebo'      trt  0 1 0 -1 /cl;
```

```
      lsmeans trt / diff cl;

      ods output Estimates=Est LSMeans=lsmeans Diffs=Diffs;

run;
```

where: ***S*** is defined as in equation [2] above; bfev is the baseline value of FEV1; and trt is the treatment for the primary analysis:

A = Fp MDPI 50 mcg BID

B = Fp MDPI 100 mcg BID

C = FS MDPI 50/12.5 mcg BID

D = Placebo

Change from Baseline in 1-hour Postdose Percent Predicted Morning FEV_1 at Week 12:

The 1-hour postdose percent predicted morning FEV_1 measurement will be performed at the investigational center at the RV, TV2 (week 1), TV3 (week 2), TV4 (week 4), TV5 (week 8) and TV6 (week 12). Mixed approach of LOCF and BOCF method will be applied similarly to impute the 1-hour postdose missing data that are caused by early dropouts from the study IMP.

APPENDIX E. SENSITIVITY ANALYSIS: MMRM

Similar to the primary estimand, retrieved dropout data will not be used in this sensitivity analysis. Missing data are not implicitly imputed in the MMRM analysis; however, all nonmissing data for a patient will be used within the analysis to estimate the time-averaged difference between treatment groups over 12 weeks. This analysis represents a MAR assumption.

Change from Baseline in Weekly Average of the Percent Predicted Trough Morning FEV_1 Over Week 12:

The sensitivity analysis will be performed using a MMRM with effects due to baseline FEV_1, sex, age, (pooled) center, previous therapy (ICS or NCS), week, treatment, and week-by-treatment interaction. No explicit structure will be assumed for the covariance among the repeated measures. However, if there is a convergence problem with unstructured covariance, then a compound symmetry covariance structure will be assumed.

The estimated treatment means and treatment mean difference derived from the MMRM analysis between each treatment will be presented together with 2-sided 95% CI for the means and the mean difference with corresponding p-value. An example of the SAS codes is as followed:

```
proc mixed data=fev1cfb;

      class usubjid sex center therapy week trt;

      model cfev=bfev sex age center therapy week trt week*trt
      /ddfm=KR;

      repeated week / type=un sub=usubjid(trt) r;

                      ***repeated week / type=cs sub=usubjid(trt) r;

                      ***If type=un fails to converge;


      /* Compare active Fp treatment to Placebo over 12 weeks */

      estimate 'Fp 25 mcg BID vs Placebo'    trt  1 0 0 -1 /cl;

      estimate 'Fp 50 mcg BID vs Placebo'    trt  0 1 0 -1 /cl;


      lsmeans trt week*trt / diff cl;

      ods output Estimates=Est LSMeans=lsmeans Diffs=Diffs;

run;
where: cfev and bfev denote change from baseline and baseline value of
percent predicted FEV1 respectively; week = 1, 2, 3, 4, 5, 6, 7, 8, 9,
10, 11, 12 representing weeks 1 to 12 respectively; and trt is the
treatment for the primary analysis:

            A = Fp MDPI 25 mcg BID

            B = Fp MDPI 50 mcg BID
```

```
C = FS MDPI 50/12.5 mcg BID
D = Placebo
```