Clinical Study Protocol with Amendment 02

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

NCT02980133

Protocol with Amendment 02 Approval Date: 5 June 2018

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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

Efficacy and Safety Study (Phase 3)

IND number: 108,838 and 72,240; EudraCT number: 2016-003835-39

Article 45 or 46 of 1901/2006 does not apply

Protocol Approval Date: 13 September 2016

Protocol with Amendment 02 Approval Date: 05 June 2018

Sponsor

Teva Branded Pharmaceutical
Products R&D, Inc.
41 Moores Road
Frazer, Pennsylvania 19355
United States of America

Information regarding clinical laboratories and other departments and institutions is found in Appendix A

Confidentiality Statement

This clinical study will be conducted in accordance with current Good Clinical Practice (GCP) as directed by the provisions of the International Council for Harmonisation (ICH); United States (US) Code of Federal Regulations (CFR), and European Union (EU) Directives (as applicable in the region of the study); national country legislation; and the sponsor's Standard Operating Procedures (SOPs).

This document contains confidential and proprietary information (including confidential commercial information pursuant to 21CFR§20.61) and is a confidential communication of Teva Branded Pharmaceutical Products R&D. The recipient agrees that no information contained herein may be published or disclosed without written approval from the sponsor.

AMENDMENT HISTORY

The protocol for Study FSS-AS-30003 (original protocol dated 13 September 2016) has been amended and reissued as follows:

Amendment 02	05 June 2018 572 patients randomized/enrolled to date
Letter of Clarification 02	21 February 2018
Letter of Clarification 01	21 September 2017
Local Protocol Amendment 01 for Russia	22 May 2017 126 patients randomized/enrolled to date
Amendment 01	31 October 2016 0 patients randomized/enrolled to date

The Summary of Changes to the Protocol includes the corresponding reason/justification for each change and is provided in Section 16.

INVESTIGATOR AGREEMENT

Original Protocol Dated 13 September 2016

Clinical Study Protocol with Amendment 02

IND number: 108,838 and 72,240; EudraCT number: 2016-003835-39

Article 45 or 46 of 1901/2006 does not apply

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

Principal Investigator: _____

Title: _____

Address of Investigational Center: _____

_____

_____

Tel: _____

I have read the protocol with Amendment 02 and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience, and training to conduct this clinical research study. The signature below constitutes approval of this protocol and attachments, and provides assurance that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to national or local legal and regulatory requirements and applicable regulations and guidelines.

I will make available the protocol and all information on the investigational medicinal product (IMP) that were furnished to me by the sponsor to all physicians and other study personnel responsible to me who participate in this study and will discuss this material with them to ensure that they are fully informed regarding the IMP and the conduct of the study. I agree to keep records on all patient information, investigational medicinal products (IMP) shipment and return forms, and all other information collected during the study, in accordance with national and local Good Clinical Practice (GCP) regulations.

Principal Investigator	**Signature**	**Date**

SPONSOR PROTOCOL APPROVAL

Sponsor's Authorized Representative [redacted]	**Sig** [redacted]	**Date** 06/05/2018

COORDINATING INVESTIGATOR AGREEMENT

Original Protocol Dated 13 September 2016

Clinical Study Protocol with Amendment 02

IND number: 108,838 and 72,240

Article 45 or 46 of 1901/2006 does not apply

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

I have read the protocol with Amendment 02 and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience, and training to conduct this clinical research study. The signature below constitutes approval of this protocol and attachments, and provides assurance that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to national and local legal and regulatory requirements and applicable regulations and guidelines.

I will make available the protocol and all information on the investigational medicinal product (IMP) that were furnished to me by the sponsor to all physicians and other study personnel responsible to me who participate in this study and will discuss this material with them to ensure that they are fully informed regarding the IMP and the conduct of the study. I agree to keep records on all patient information, IMPs shipment and return forms, and all other information collected during the study, in accordance with national and local Good Clinical Practice (GCP) regulations. In addition I will assume the responsibility of the coordinating investigator according to a separate contract.

Coordinating Investigator: [redacted]

Address of Investigational Center: [redacted]

Coordinating Investigator	Signature	Date
[redacted]		

CLINICAL STUDY PROTOCOL SYNOPSIS

with Amendment 02

Study FSS-AS-30003

Title of Study: 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

Sponsor: Teva Branded Pharmaceutical Products R&D, Inc.

Investigational New Drug (IND) Number: 108,838 and 72,240

Article 45 or 46 of 1901/2006 does not apply

Name of Test Investigational Medicinal Product (IMP): fluticasone propionate (Fp) multidose dry powder inhaler (MDPI), fluticasone propionate/salmeterol (FS) MDPI

EudraVigilance (EV) code for the IMP: SUB02241MIG (fluticasone propionate), SUB04314MIG (salmeterol xinafoate)

Type of the Study: Efficacy and Safety Study (Phase 3)

Indication: Asthma

Is this study conducted to investigate the New Use of an approved, marketed product? No

Number of Investigational Centers Planned: Approximately 130 investigational centers

Countries Planned: United States (US) and ex-US

Planned Study Period: Q4/2016 (first patient in) to Q2/2019 (last patient last visit)

Number of Patients Planned (total): A total of approximately 824 male and female patients, 206 patients in each of 4 treatment groups will be enrolled. Assuming a dropout rate of 12%, approximately 181 evaluable patients in each treatment group (724 total patients) will complete the 12-week treatment period.

Study Population: The population planned to be enrolled in this study comprises male and female patients 4 through 11 years of age who have a documented history of persistent asthma. The asthma diagnosis must be in accordance with the National Institutes of Health (NIH) definition.

Primary and Secondary 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.

Primary Efficacy Endpoints:

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

Secondary Efficacy Endpoints:

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 IMP for asthma exacerbation during the 12-week treatment period

The sequential order of the secondary endpoints for multiplicity will be described in the statistical analysis plan.

Other Efficacy and Safety 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 (the 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

The safety endpoints are as follows:

- Incidence of adverse events throughout the study
- Vital signs assessments throughout the study
- Oropharyngeal examination findings at each visit
- Physical examination findings at baseline and at week 12 or at the IMP discontinuation visit (IMPDV)

General Design: 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 short-acting β_2 agonist [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 12 inhalations permitted per day. Starting on day 1 of the run-in period, patients must discontinue all nonstudy 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

A prescreening visit may be conducted, if needed, before the SV to discuss study procedures and/or provide patient instructions about any required washout periods for prohibited medications. The SV may take place during several investigational center visits.

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 who are being treated with an inhaled corticosteroid (ICS) with or without a long-acting β_2-agonist (LABA) and/or with a noncorticosteroid (NCS) therapy are eligible to be included in the study. Patients must meet washout period requirements at the SV for their asthma and non-asthma disallowed medications according to Appendix H. The patient's asthma medication regimen must be stable for 30 days prior to the SV (except as adjusted at an optional prescreening visit to wash out prohibited medications). If the patient has taken asthma maintenance medication the morning of the SV or SABA within 6 hours of lung function assessments (FEV_1 and PEF) by handheld device, the visit must be rescheduled so that lung function assessments and response to bronchodilator testing can be completed as described (other assessments not involving lung function may be completed that day).

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. Screening lung function assessments (FEV_1 and PEF) by handheld device should be performed at the investigational center between the hours of 0530 and 1100. Patients will be permitted 8 attempts per test. The highest FEV_1 value from 3 technically acceptable and 2 repeatable maneuvers will be used to qualify patients for the placebo run-in period. Patients who have failed screening for inability to perform lung function assessments (FEV_1 and PEF) in a technically acceptable manner or due to FEV_1 not meeting the inclusion criterion or demonstrated <10% response to a bronchodilator may retest once within 7 days of their initial SV provided that they have met all other inclusion criteria and none of the exclusion criteria at the SV. The handheld device should be kept at the clinic for these patients until they meet the requirements to enter the run-in period.

At retest, patients (or patient's parent/legal guardian/caregiver) will report if there have been any adverse events, changes in medications, or changes in medical history since providing consent/assent (as applicable). Patients who fail again to demonstrate technically acceptable lung function assessments (FEV_1 and PEF) or due to FEV_1 not meeting the inclusion criterion or who demonstrate <10% response to a bronchodilator will be considered screen failures. The run-in period will not start until patients have met all inclusion criteria and none of the exclusion criteria. Patients who fail to meet the requirements to enter the run-in period at this visit will be considered screen failures and will not be allowed to be rescreened.

Patients who qualify for entry into the placebo run-in period must discontinue all currently administered asthma medications (including leukotriene modifiers prescribed for other conditions) until completion of the TV6 (week 12) visit or 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 (90 mcg ex-actuator) 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 patient diary built into the handheld device.

Patients who experience an upper respiratory infection (URI) or lower respiratory infection (LRI) during the run-in period should be classified as randomization failures and be discontinued from the study but may be rescreened 2 weeks after resolution of the infection. Patients who are rescreened will need to repeat all screening procedures and evaluations. Only 1 rescreening for each patient will be permitted.

Patients who entered the run-in period with response to a bronchodilator ≥10% and <14.50% must present for repeat lung function assessments and another bronchodilator test within 14±2 days, during which they must demonstrate at least a 15% response to a bronchodilator. If the criteria are not met, patients may continue in the run-in period for up to 14 additional days to meet the lung function assessment and response to bronchodilator criteria (1 final attempt) for randomization. Patients may only continue in the run-in period if the investigator determines, by assessing the patient's asthma status (at each investigational center visit), that it is safe for the patient to continue. Patients who have entered the run-in period but fail to demonstrate technically acceptable lung function assessments and response to a bronchodilator (as described) will be considered to have failed randomization. All patients must demonstrate at least a 15% response to a bronchodilator at the SV or during the run-in period. Patients who demonstrate the response to bronchodilator during the run-in period may present for randomization the following day at the earliest or at another later time as long as it is within the 30-day allowance for the run-in period. Responses to a bronchodilator of 14.50% to 14.99% will be rounded to 15%.

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 (ICS or 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 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. The highest FEV_1 value from 3 acceptable and 2 repeatable maneuvers (maximum of 8 attempts per test) will be obtained before and 1-hour after the morning dose.

At each visit, the investigational center staff 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.

A telephone call may be conducted as needed during the alternate, non-visit weeks (weeks 5, 7, etc) to monitor the patients' safety and to assess their asthma status or for any other relevant reason.

At the end of the study, a FV (which may be a follow-up investigational center visit or telephone call) will be conducted 7±2 days after TV6 (week 12) to monitor safety of the patients.

Patients who meet the alert criteria for worsening asthma as defined for this study or experience worsening of asthma including asthma exacerbation will present to the investigational center for an investigator assessment as soon as possible. If possible and when it is judged safe to do so, this visit should be conducted before a change in asthma therapy takes place. Following investigator assessment of the patient's asthma status a decision will be made whether or not it is safe for a patient to continue the IMP. In cases where the IMP is to be withdrawn and alternative therapy started, the investigational center staff should contact the medical monitor to confirm the findings. In the event that it is considered in the best interest of a patient to stop the IMP and initiate an alternative asthma therapy, the patient will undergo all visit procedures required for the IMPDV. After the IMPDV, IMP dosing will not occur. The investigator should discuss and implement alternative asthma treatment that is appropriate for the patient. These patients will

continue to participate in all study visits as scheduled and continue to complete all morning and evening study procedures except for the IMP dosing. Patients will be asked to perform 1-hour postdose lung function assessments at the remaining treatment visits; 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. If a patient or patient's parent/legal guardian/caregiver elects to completely withdraw from the study (ie, withdraw consent) prior to the investigator assessment or investigational center visit, irrespective of the reason for the study discontinuation, every attempt will be made to conduct the IMPDV subsequent to the patient's withdrawal from the IMP.

Asthma exacerbation 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.

At TV6 (week 12), or the IMPDV as applicable, the investigator will discuss asthma treatment with the patient after safety assessments have been completed, and any medication started for the purpose of newly recommended asthma treatment will not be considered a protocol violation. This asthma therapy will be recorded in the CRF following IMP discontinuation (planned or unplanned). Additionally, an investigational center visit may be conducted at any time at the request of the patient or parent/legal guardian/caregiver, as applicable or at the discretion of the investigator.

Safety will be monitored by vital signs, physical examination, oropharyngeal examination, and recording of adverse events. In addition, during the study, PEF and FEV_1 will be monitored as part of safety monitoring (alert criteria for worsening asthma). Any visual evidence of oral candidiasis during the treatment period will be confirmed by obtaining a swab for culture of the suspect area. Patients and parents/legal guardians/caregivers will be provided with guidelines for when to contact the investigational center in case of worsening asthma symptoms or rescue inhaler use. Patients who meet predefined alert criteria should be evaluated by the investigator to determine if the IMP should be discontinued. If a patient discontinues the IMP prematurely but remains in the study, all subsequent visits will include all assessments according to the study procedures and assessments table except for IMP dosing. Patients will be asked to perform 1-hour postdose lung function assessments at the remaining treatment visits; 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.

Alert criteria for individual patients have been designed to ensure patient safety. If any of the criteria listed below are met, during a scheduled or unplanned study visit, the investigator (after discussion with the sponsor) will determine whether the patient's overall clinical picture is consistent with worsening asthma and if the patient should be withdrawn from IMP (but not the study) to be placed on alternative asthma therapy in the interest of patient safety. Meeting 1 of these alert criteria does not automatically require a patient to be withdrawn from IMP, rather it requires a clinical evaluation to determine if the patient's asthma can continue to be managed in

a blinded manner per the study or necessitates a change in asthma therapy. All attempts will be made to safely continue to manage a patient in a blinded manner.

- Morning FEV_1 by handheld device measured at home falls below the FEV_1 stability limit (see Section 6.1.3) calculated at the SV for the run-in period and at baseline for the treatment period on 4 or more days (do not have to be consecutive) out of any 7-day period (7-day period is defined as any consecutive 7 days following the RV and can overlap with scheduled study investigational center visits).
- Based upon a review of patient data from the patient diary built into the handheld device, the patient has experienced any of the following during a 7-day period (7-day period is defined as any consecutive 7 days following a previous TV; 7 days can overlap with scheduled study investigational center visits):
  - 3 or more days in which 8 or more inhalations/day of rescue medication (albuterol/salbutamol HFA MDI [90 mcg ex-actuator] or equivalent) were used (any 3 days in the consecutive 7-day period)
  - 3 or more days in which the patient experienced a nighttime asthma symptom score of more than 2 (any 3 days in the consecutive 7-day period)

Patients who meet the alert criteria and/or who experience a clinically meaningful worsening of their asthma will be assessed by the investigator. If the investigator considers it is not possible to safely manage a patient in a blinded manner as patient's asthma warrants a change in his/her asthma treatment, the IMP will be stopped, and appropriate treatment (based on the investigator's judgment) should be offered. The medical monitor should be contacted to confirm the findings when alternative therapy is to be instituted. The patient should continue in the study until the patient has completed all remaining study visits and the FV.

- 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. Significant treatment includes the use of systemic corticosteroids and/or the addition of other ICS-containing asthma medications, LABAs, or other NCS asthma medications, for example, inhaled short-acting muscarinic antagonist; emergency room (ER)/urgent care clinic visit; or hospitalization. Note: A single dose of nebulized albuterol/salbutamol would not meet the criteria for an asthma exacerbation. ER/urgent care clinic visits where the treatment is limited to a single dose of nebulized albuterol/salbutamol will not meet the criteria of an asthma exacerbation.

After the last TV (TV6, week 12), the patient will enter the follow-up period. One week (±2 days) after the last TV, the patient will have a 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 addition to screening, run-in, and all TVs. Patients who stop IMP and return for safety evaluation at week 12 will not be considered to have completed the treatment period.

Brief Summary of Study Design for the Trial Registry(s): This study will evaluate the efficacy and safety of Fp MDPI and FS MDPI in pediatric patients with a documented history of persistent asthma.

Method of 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 Interactive Response Technology (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. 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.

Investigational Medicinal Products: Dose, Pharmaceutical Form, Route of Administration, and Administration Rate

Test IMP: Fp MDPI, 25 mcg, 1 inhalation twice daily; Fp MDPI, 50 mcg, 1 inhalation twice daily; FS MDPI, 50/12.5 mcg, 1 inhalation twice daily

Placebo IMP: Placebo MDPI, 1 inhalation twice daily

Duration of Patient Participation and Maximal Exposure to IMP: The total duration of patient participation in this study is approximately 15 to 17 weeks, which includes a patient-blinded run-in period (up to 30 days), a double-blind, randomized treatment period (12 weeks±2 days), and a follow-up period (7±2 days). Patients may also participate in an optional prescreening period for up to 15 days before the SV, during which no IMP will be administered.

Study Duration: Approximately from Q4 of 2016 to Q2 of 2019

End of Study: End of study is defined as the last visit of the last patient.

Plans for Treatment or Care after the Patient Has Ended Participation in the Study: No IMP will be provided beyond completion of the study. Patients should return to their primary care physician for treatment after study completion.

Inclusion Criteria: The SV can be broken into more than 1 visit. Patients may be included in the study run-in period if they meet all of the following inclusion criteria at screening:

a. The patient is a male or female patient 4 through 11 years of age, inclusive, when informed consent/assent (as applicable) is signed.

b. Written informed consent must be signed and dated by parent/legal guardian and the written informed assent form must be signed and dated by the patient (as applicable, per local regulations) before any study-related procedures are conducted.

c. The patient has a diagnosis of asthma as defined by the NIH. The asthma diagnosis has been present for a minimum of 3 months before SV.

d. The patient has persistent asthma with a FEV_1 ≥50% and ≤90% of the value predicted for age, height, sex, and race at the SV as measured by handheld device.

e. The patient's persistent asthma is stable and is currently being treated with stable asthma therapy (eg, ICS, ICS/LABA, leukotriene receptor antagonist, etc.) for at least 30 days before the SV. Patients who are currently on SABA regimen only or PRN only are not eligible for the study.

f. The patient has demonstrated ≥10% response to a bronchodilator from screening FEV_1 within 30 minutes (±5 min) after 2 to 4 inhalations of albuterol/salbutamol HFA MDI (90 mcg ex-actuator) or equivalent at SV as measured by handheld device. Patients who demonstrated <10% response to a bronchodilator may retest within 7 days of their initial SV.

   – Patients who demonstrate response to a bronchodilator ≥10% and <14.50% may enter the run-in period (provided that they meet the other inclusion and none of the exclusion criteria) and may present for repeat lung function assessments by handheld device and another bronchodilator test within 14±2 days, during which they must demonstrate at least a 15% response to a bronchodilator. If the criteria are not met, patients may continue in the run-in period for up to 14 additional days to meet the lung function assessment and response to bronchodilator criteria (1 final attempt) for randomization. Patients may only continue in the run-in period if the investigator determines, by assessing the patient's asthma status (at each investigational center visit), that it is safe for the patient to continue.

g. The patient (with assistance from parents/legal guardians/caregivers, as needed) is able to perform technically acceptable lung function assessments by handheld device. Patients who fail to demonstrate technically acceptable lung function assessments may retest within 7 days of their initial SV.

h. The patient (with assistance from parents/legal guardians/caregivers, as needed) is able to use an MDI device and an MDPI device.

i. The patient is able to withhold (as judged by the investigator) his/her rescue medication for at least 6 hours before SV and all TVs where lung function assessments are performed.

j. The patient is assessed as otherwise healthy, with clinically acceptable medical history, physical examination, and vital signs within acceptable ranges for children with asthma as assessed by the investigator.

k. All patients must be able to replace their current SABA with albuterol/salbutamol HFA MDI inhalation aerosol at the SV for use as needed for the duration of the study.

l. Female patients who have reached puberty and achieved menarche (as determined by the investigator) must be counseled regarding the possible unknown risks associated with IMP during pregnancy following permission of the parents/legal guardians. A urine pregnancy test must be negative for these patients at SV. Eligible female patients who are known to be sexually active will be excluded.

m. Eligible male patients who are known to be sexually active will be excluded.

Exclusion Criteria: Patients will be excluded from participating in this study if they meet any of the following criteria:

a. The patient has a history of life-threatening asthma exacerbation that is defined for this protocol as an asthma episode that required intubation and/or was associated with hypercapnia, respiratory arrest, or hypoxic seizures.

b. The patient is pregnant or lactating or plans to become pregnant during the study period or within 30 days after the patient's last study-related visit (for eligible patients only and if applicable).

c. The patient has participated as a randomized patient in any investigational drug study within the 30 days or within 5 half-lives (starting from the final FV of that study) preceding the SV (or prescreening visit, as applicable) or plans to participate in another investigational drug study at any time during this study.

d. The patient has a known hypersensitivity to any corticosteroid, salmeterol, or any of the excipients in the IMP or rescue medication formulation (ie, lactose). Dietary lactose intolerance does not exclude the patient from inclusion into the study or as per the investigator's medical discretion.

e. The patient has been treated with any known strong cytochrome P450 (CYP) 3A4 inhibitors (eg, ketoconazole, ritonavir, clarithromycin) within 30 days before the SV or plans to be treated with any strong CYP3A4 inhibitor during the study.

f. The patient has been treated with any of the prohibited medications during the prescribed (per protocol) washout periods before the SV.

g. The patient currently smokes or has a smoking history. The patient must not have used tobacco products within the past year (eg, cigarettes, cigars, chewing tobacco, or pipe tobacco).

h. The patient has a culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus, or middle ear that has not resolved at least 2 weeks before the SV (note: patients who develop a URI or LRI during the run-in period may be rescreened 2 weeks after symptoms resolve).

i. The patient has had an asthma exacerbation requiring systemic corticosteroids within 30 days before the SV or has had any hospitalization for asthma within 2 months before the SV.

j. Initiation or dose escalation of immunotherapy (administered by any route) is planned during the study period. However, patients who initiated immunotherapy 90 days or more before the SV and have been on a stable (maintenance) dose for 30 days or more before the SV may be considered for inclusion.

k. The patient has used immunosuppressive medications within 30 days before the SV.

l. The patient is unable to tolerate or unwilling to comply with the appropriate washout periods and withholding of all applicable medications.

m. The patient has untreated oral candidiasis at the SV. Patients with clinical visual evidence of oral candidiasis who agree to receive treatment and comply with appropriate medical monitoring may enter the run-in period.

n. The patient has a history of a positive test for human immunodeficiency virus, active hepatitis B virus, or hepatitis C infection.

o. The patient is an immediate relative of an employee of the clinical investigational center.

p. A member of the patient's household is participating in the study at the same time. However, after the enrolled patient completes or discontinues participation in the study, another patient from the same household may be screened.

q. The patient has a disease/condition that, in the medical judgment of the investigator, would put the safety of the patient at risk through participation or that could affect the efficacy or safety analysis if the disease/condition worsened during the study. Examples include, but are not limited to, the following:

- cardiovascular conditions including clinically significant cardiac arrhythmia, known aortic aneurysm, congenital heart disease, coronary heart disease, or vital signs clinically unacceptable for ranges in children with asthma as assessed by the investigator
- hepatic, renal, hematologic, neuropsychologic, or endocrine conditions (eg, sickle cell disease, uncontrolled diabetes mellitus, uncontrolled thyroid disorder, Addison's disease, Cushing's syndrome, stroke within 3 months before the SV)
- gastrointestinal conditions (eg, poorly controlled peptic ulcer disease, poorly controlled gastroesophageal reflux disease)
- infectious/immunologic conditions including untreated tuberculosis (a history of tuberculosis is acceptable only if a patient has received an approved prophylactic treatment regimen or an approved active treatment regimen and has had no evidence of active disease for a minimum of 2 years) and immunologic compromise
- ocular conditions including glaucoma, ocular herpes simplex, or cataracts
- oncologic conditions including any current malignancy, excluding basal cell carcinoma. History of malignancy is acceptable only if the patient has been in remission for 1 year before the SV. Remission is defined as no current evidence of malignancy and no treatment for the malignancy in the 12 months before the SV.
- pulmonary conditions including chronic bronchitis, emphysema, chronic bronchiectasis, cystic fibrosis, chronic lung disease, or chronic obstructive pulmonary disease

- renal conditions including chronic renal failure or ongoing dialysis
- history of or planned solid organ transplant

r. Vulnerable patients (ie, people kept in detention) are excluded from participation.

Randomization Criteria:

The following criteria must be fulfilled at the RV:

a. The patient continues to be in general good health, meeting the entry criteria.

n. The average of the 5 highest values for trough morning FEV_1 obtained at home (by handheld device) out of the last 7 days prior to RV is within 40% to 85% predicted for age, height, sex, and race (Quanjer et al 2012).

o. The patient's C-ACT score at the RV is ≤19.

p. The patient has demonstrated at least a 15% response to a bronchodilator from baseline FEV_1 within 30 minutes after 2 to 4 inhalations of albuterol/salbutamol HFA MDI (90 mcg ex-actuator) or equivalent at SV or during the run-in period as measured by handheld device. Note: The RV may not be conducted on the same day as the response to bronchodilator testing.

q. The patient has had no significant changes in asthma medications during run-in, excluding the albuterol/salbutamol HFA MDI (90 mcg ex-actuator) or equivalent used as rescue medication or run-in placebo MDPI as supplied per protocol.

r. The patient has not had a URI or LRI during the run-in period. Patients who develop a URI or LRI during the run-in period may be discontinued from the study and allowed to rescreen 2 weeks after resolution of symptoms.

s. The patient has had no asthma exacerbation during the run-in period, defined as any worsening of asthma requiring any significant treatment other than rescue albuterol/salbutamol HFA MDI (90 mcg ex-actuator) or equivalent or the patient's run-in MDPI. This includes requiring the use of systemic corticosteroids, inhaled corticosteroids or other medications used to control asthma or are prohibited medications (Appendix H), and/or ER/urgent care clinic visit or hospitalization. Note: A single dose of nebulized albuterol/salbutamol will not meet the criteria for an asthma exacerbation. Emergency room/urgent care clinic visits where the treatment is limited to a single dose of nebulized albuterol/salbutamol will not meet the criteria of an asthma exacerbation.

t. The patient has no clinical visual evidence (on oropharyngeal examination) of oropharyngeal candidiasis.

u. The patient has not experienced an adverse event that would result in failure to continue to meet selection criteria.

v. The patient has not used any of the prohibited concomitant medications during the run-in period.

w. The patient has complied with home lung function assessments and patient diary (built into the handheld device) entry on at least 5 of the last 7 days prior to RV, including the following:

- completion of daytime and nighttime asthma symptom scores
- completion of daytime and nighttime rescue medication (albuterol/salbutamol HFA MDI) use (whether used or not)
- completion of the morning and evening lung function assessments (FEV_1 and PEF) by handheld device on 5 or more of the 7 days immediately preceding the RV
- recording of morning and evening IMP use on 5 or more of the 7 days immediately preceding RV

Statistical Considerations:

Sample Size Rationale: 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%.

This study FSS-AS-30003 is the first Teva's study in which the handheld spirometry is utilized as an endpoint and this hanheld device is being used in a pediatric asthma patient population, the target population of this study. A blinded sample size reassessment was not planned for this study. However, routine blinded data monitoring of this study FSS-AS-30003 revealed that a few

patietnts showed nonphysiologic (~200% of percent predicted FEV_1) changes from baseline. This triggered a blinded sample size reassessment that showed that the overall mean change from baseline and SD for the overall study population is higher than the initial assumptions based on the office spirometry in adult asthma patients. In addition, monitoring of FEV_1 stability throughout the study revealed challenges in obtaining consistent morning trough FEV_1 values with best efforts in this young patient population, despite the rigorous training and coaching provided by the investigators. Therefore, 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.

Assuming a dropout rate of 12%, then 206 patients per treatment group in the 4 treatment groups, for a total of 824 patients, will be randomized (initial assumption for dropout rate was 15%).

Primary Estimands and Efficacy Analysis:

The specific 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 in order to collect data after IMP discontinuation.

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. 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. In light of this, 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.

Analysis of the change from baseline in weekly average of the percent predicted trough morning FEV_1 at week 12

The baseline percent predicted FEV_1 will be the weekly average of the morning FEV_1 prior to the first IMP dose. The first day before randomization consists of the entry on the morning of the RV in the patient diary built into the handheld device. The weekly average of the percent predicted FEV_1 at week 12 will be the average values based on the available data at that week.

The primary analysis of the change from baseline in weekly average of percent predicted morning FEV_1 at week 12 due to the initially randomized treatment as actually taken 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 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% confidence interval (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. Details on the implementation of the multiple imputations will be provided in the statistical analysis plan.

Analysis of the change from baseline in 1-hour postdose percent predicted morning FEV_1 at week 12

For the endpoint of change from baseline in 1-hour postdose percent predicted morning FEV_1 (measured at the clinic) at week 12, baseline is defined as predose FEV_1 measurements obtained at the clinic at the RV with the handheld device immediately prior to the IMP administration.

The primary analysis of the change from baseline in 1-hour postdose percent predicted morning FEV_1 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 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 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. Missing data caused by early dropouts will be handled similarly to the above analysis.

Sensitivity Analysis

To assess the impact of missing data, several sensitivity analyses will be conducted for the 2 endpoints by evaluating alternative estimands. More details will be provided in Section 9 of the protocol and the statistical analysis plan.

- The primary analysis for the 2 endpoints will be repeated using data collected after IMP discontinuation (retrieved dropout data). Reference-based imputation will be used only for patients with no retrieved dropout data. This analysis estimates different estimands, namely the change from baseline as actually taken.
- The primary analysis for the 2 endpoints will be repeated on completers with no major protocol violations.

- A tipping point analysis will be performed as a sensitivity analysis to missing data by utilizing multiple imputations assuming MNAR for the active arms. Only data collected prior to IMP discontinuation will be utitlized in this analysis.
- "2-dimensional tipping point" will also be performed to assess shifts to the distribution apply to both placebo and active arms.
- The primary analysis for the 2 endpoints will be repeated when missing data will be imputed using a mixed approach of last observation carried forward and baseline observation carried forward (see Section 9.5.4.2 of the protocol).
- For the first primary endpoint of change from baseline in the weekly average of percent predicted trough morning FEV_1 over the 12-week treatment period, analysis will be performed using a mixed model for repeated measures (MMRM). This analysis will not use retrieved dropout data. This analysis represents a missing at random assumption.

Secondary Efficacy Analysis:

For all secondary endpoints, analyses will be performed using the ITT analysis set and will not include retrieved dropout data in the analysis.

Analyses of change from baseline in weekly average of daily trough morning PEF, total daily use of albuterol/salbutamol, total daily asthma symptom score, and C-ACT score over the 12-week treatment period will be analyzed using an MMRM analysis with effects due to baseline, sex, age, (pooled) investigational center, previous therapy (ICS or NCS), treatment, time, and time-by-treatment interaction. For all of these endpoints, the MMRM will use only observations collected until IMP discontinuation.

The time to first onset of effect, defined as the first decrease from baseline in daily rescue medication use, will be analyzed using a log-rank test. Median and mean time to first onset of effect and associated 95% CIs will be estimated. Time to first onset of effect will also be displayed graphically with a Kaplan-Meier figure.

The proportion of patients who 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. These patients will be considered as nonresponders in this analysis.

Other Efficacy Analysis: Statistical methods to be used for other efficacy endpoints will be described and detailed in the statistical analysis plan.

Multiple Comparisons and Multiplicity: A fixed-sequence testing procedure will be employed to control the overall Type I error rate at the 2-sided 0.05 level for the co-primary endpoints. The sequential order of comparisons will be as follows:

1. 1-hour postdose percent predicted FEV_1 comparing FS MDPI 50/12.5 mcg versus Fp MDPI 50 mcg
2. Trough percent predicted FEV_1 comparing Fp MDPI 50 mcg versus placebo
3. Trough percent predicted FEV_1 comparing Fp MDPI 25 mcg versus placebo

Each test will be 2-sided and performed at the 0.05 level of significance. However, if a test is not significant at the 2-sided 0.05 level, no further tests will be performed.

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 to 11 years of age), an unplanned blinded sample size reassement was conducted. Since the adjustment to sample size was based on blinded standard deviation, no adjustment to the multiplicity control is warrented.

Multiplicity control for the secondary endpoints and the sequential order of the secondary endpoints will be described in the statistical analysis plan.

No multiplicity adjustments will be made for other efficacy analyses.

Safety Analyses: Safety data will be summarized using descriptive statistics by treatment group.

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LIST OF ABBREVIATIONS

List of Abbreviations

Abbreviation	Term
ADL	activities of daily living
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AUC_{0-t}	area under the concentration-time curve from time 0 to the time of the last measurable drug concentration
BOCF	baseline observation carried forward
BP	blood pressure
C-ACT	Childhood Asthma Control Test
CDC	Centers for Disease Control and Prevention
CDMS	clinical data management system
CFR	Code of Federal Regulations (US)
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum observed plasma drug concentration
CRF	case report form (refers to any media used to collect study data [ie, paper or electronic])
CI	confidence interval
CRO	contract research organization
CSR	clinical study report
CYP	cytochrome P450
ePRO	electronic patient-reported outcome
ER	emergency room
EU	European Union
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
Fp	fluticasone propionate
Fp MDPI	fluticasone propionate multidose dry powder inhaler
FS	fluticasone propionate/salmeterol
FS MDPI	fluticasone propionate/salmeterol multidose dry powder inhaler
FSH	follicle stimulating hormone
FV	follow-up visit
GCP	Good Clinical Practice
GPSP	Global Patient Safety and Pharmacovigilance

Abbreviation	Term
GQA	Global Quality Assurance
HFA	hydrofluoroalkane
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICS	inhaled corticosteroid
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IMPDV	investigational medicinal product discontinuation visit
IND	Investigational New Drug
INN	international nonproprietary name
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent-to-treat
IUD	intrauterine device
LABA	long-acting β_2 agonist
LOCF	last observation carried forward
LRI	lower respiratory infection
LSO	local safety officer
MA	Marketing Authorisation
MAR	missing at random
MDI	metered-dose inhaler
MDPI	multidose dry powder inhaler
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
MNAR	missing not at random
n	number
NAEPP	National Asthma Education and Prevention Program
NCS	noncorticosteroid
NDA	New Drug Application
NIH	National Institutes of Health
PEF	peak expiratory flow
PP	per-protocol
PT	preferred term
PRN	Pro re nata/when needed

Abbreviation	Term
RSI	reference safety information
RV	randomization visit
SABA	short-acting β_2 agonist
SD	standard deviation
SmPC	Summary of Product Characteristics
SOC	system organ class
SOP	Standard Operating Procedure
SUSAR	suspected unexpected serious adverse reaction
SV	screening visit
Sx	salmeterol xinafoate
TV	treatment visit
ULN	upper limit of normal
URI	upper respiratory infection
US	United States
XML	Extensible Markup Language

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1. Introduction

An estimated 300 million people worldwide suffer from asthma, with the prevalence of asthma increasing in industrialized countries and in developing countries (Beasley et al 2000, Masoli et al 2004). The number of persons with asthma is estimated to reach 400 million by the year 2025, and the estimated worldwide death rate from asthma is 1 in every 250 deaths (Masoli et al 2004).

In the United States (US), research by the National Center for Health Statistics, Centers for Disease Control and Prevention (CDC) shows that asthma has been diagnosed in more than 39 million people at some time (National Health Interview Survey 2011), and in 2010, 25.7 million residents have asthma (Akinbami et al 2012). In *"Asthma's Impact on the Nation,"* the CDC estimates that in 2010 over 7 million children in the USA had asthma, equal to 1 in 11 children; there were 10.5 million missed days of school due to asthma in 2008; and nearly 1 in 5 children went to an emergency department for care in 2009. Estimates in the adult population for 2010 were over 18.7 million adults with asthma, equal to 1 in 12 adults, with 14.2 million missed days of work due to asthma in 2008. Asthma limits daily activity for 3 in 5 persons with asthma, and about 9 people die from asthma each day (CDC 2012).

The characteristic feature of asthma is chronic airway inflammation. This inflammatory process includes mast cells, eosinophils, macrophages, neutrophils, lymphocytes, and epithelial cells (National Asthma Education and Prevention Program [NAEPP] 2007). Symptoms of asthma include wheezing, shortness of breath, chest tightness, and coughing, with symptoms often worse at night and in the early morning. The main pathological features of asthma are airway inflammation and airway smooth muscle dysfunction resulting in airway hyperresponsiveness with the predominant physiological feature being episodes of airway obstruction with limited expiratory airflow (NAEPP 2007). Chronic inflammation in the airways may lead to permanent alterations to the airway structure, a process known as airway remodeling (NAEPP 2007).

The goal of pharmacologic therapy in asthma is to control chronic and nocturnal symptoms, maintain normal activity levels (including exercise), maintain near-normal pulmonary function, prevent acute episodes of asthma, minimize emergency room (ER) visits and hospitalizations, and avoid adverse effects of asthma medications (NAEPP 2007). Quick relief medications, such as short-acting β_2 agonists (SABAs) and anticholinergics are used to treat acute symptoms by rapidly reversing airflow limitation and bronchoconstriction. Long-term control medications such as inhaled corticosteroids (ICSs), cromolyn, immunomodulators, leukotriene modifiers, and long-acting β_2 agonists (LABAs) are used to achieve daily control of persistent asthma symptoms. Because of the complementary mechanisms of action of ICSs and LABAs, many asthma patients require treatment with both for optimal control of their asthma. Clinical programs conducted with currently marketed combination products have demonstrated that ICS/LABA combination products provide greater improvement in forced expiratory volume in 1 second (FEV_1), peak expiratory flow (PEF), and decreased exacerbations than either individual component alone in patients older than 12 years with persistent asthma (Shrewsbury et al 2000). The rationale for use of such a combination therapy for the treatment of asthma is that it is scientifically sound (counteracting airway inflammation and smooth muscle dysfunction),

justifiable on therapeutic grounds (potential for improved compliance and convenience), and offers significant clinical benefits.

Teva Branded Pharmaceutical Products R&D, Inc. (Teva) is developing fluticasone propionate (Fp) inhalation powder products and a fixed-dose combination of fluticasone propionate/salmeterol (FS) inhalation powder products, using Teva's proprietary multidose dry powder inhaler (MDPI). Fluticasone propionate is a synthetic trifluorinated corticosteroid with potent anti-inflammatory activity. Salmeterol xinafoate (Sx) is a LABA. Inflammation is an important component of the pathophysiology of asthma, and corticosteroids have been shown to inhibit multiple inflammatory cells and mediators involved in the pathophysiology of asthma.

The fluticasone propionate multidose dry powder inhaler (Fp MDPI) is supplied in multiple dosage strengths of Fp (25, 50, and 100 mcg twice daily) for doses of 50, 100, and 200 mcg daily to patients ages 12 years and older requiring ICS therapy for treatment of asthma. The Fp MDPI contains the same active ingredient as FLOVENT® DISKUS® (GlaxoSmithKline plc[1]), which is marketed at strengths of 50, 100, and 250 mcg for doses of 100 to 1000 mcg twice daily (adolescents and adults) and is the reference drug. The proposed Fp dose for study in patients 4 through 11 years of age is based on the adult dose-ranging study demonstrating efficacy of the 25 and 50 mcg twice daily doses that are the same or lower than the currently approved doses of FLOVENT DISKUS and ADVAIR® DISKUS® (GlaxoSmithKline plc[2]) in pediatric patients. Similarly, the proposed dose for salmeterol is based on the adult Phase 2 study, which demonstrated that the dose of 12.5 mcg twice daily was the optimal dose and resulted in less systemic exposure. Based on the results from the adult and adolescent Phase 3 clinical trials (New Drug Applications [NDAs] submitted for Food and Drug Administration [FDA] review in March 2016), the 25- and 50-mcg twice daily doses (50/12.5 and 100/12.5 mcg, respectively) of fluticasone propionate/salmeterol multidose dry powder inhaler (FS MDPI) were confirmed as appropriate for studies in patients 4 through 11 years of age.

The fixed-dose combination product, FS MDPI, is supplied in multiple dosage strengths of Fp with a fixed dosage of salmeterol (50/12.5, 100/12.5, and 200/12.5 mcg) to allow for treatment of the entire spectrum of asthma patients ages 12 years and older for whom combination therapy is appropriate. The FS MDPI contains the same active ingredients as ADVAIR DISKUS, which is marketed at doses of 100/50, 250/50, and 500/50 mcg and is the reference drug. Exposure to Fp and salmeterol is similar or lower for the FS MDPI doses to the higher doses administered for the marketed product ADVAIR DISKUS. The salmeterol in FS MDPI and ADVAIR DISKUS is Sx (the conversion factor from salmeterol xinafoate salt to salmeterol free base is 0.6883). Salmeterol xinafoate will dissolve and dissociate into salmeterol free base (active moiety) in the lung to exert a therapeutic effect.

The Teva device-formulation combination allows for concentrations of drug in the formulation to be significantly lower than ADVAIR DISKUS while achieving similar systemic exposure and clinical benefits.

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[1] FLOVENT® DISKUS® is a trademark, the property of the GlaxoSmithKline group of companies.
[2] ADVAIR® DISKUS® is a trademark, the property of the GlaxoSmithKline group of companies.

The 100/12.5-cg dose of FS MDPI provides approximately twice the exposure to Fp than the 100/50-mcg dose of ADVAIR DISKUS. The availability of the lowest FS MDPI dose, 50/12.5 mcg (which corresponds to the commonly used 100/50-mcg ADVAIR DISKUS dose), allows for lower exposure to Fp, as well as considerably less exposure to salmeterol. In a Phase 2 clinical study evaluating the dose response, efficacy, and safety of FS MDPI, the Teva formulation of FS MDPI demonstrated lower Sx exposure when compared with ADVAIR DISKUS (FS MDPI 100/12.5 mcg area under the concentration-time curve from time 0 to the time of the last measurable drug concentration [AUC_{0-t}]=69.9 pg•hr/mL and maximum observed plasma drug concentration [C_{max}]=35.8 pg/mL versus ADVAIR DISKUS 100/50 mcg AUC_{0-t}=173.5 pg•hr/mL and C_{max}=42.3 pg/mL; Study FSS-AS-201).

Multiple FS doses, with increasing levels of Fp, allow for treatment of patients with varying asthma severities and is consistent with asthma guidelines recommending a stepwise approach to ongoing asthma treatment; treatment is stepped up in patients with persistent symptoms or exacerbations and is stepped down once good asthma control is achieved and maintained (eg, the optimal step-up from Fp MDPI 50 mcg would be FS MDPI 50/12.5 mcg).

The availability of multiple dose levels is therefore advantageous to allow for adjustment of treatment in a stepwise approach across a spectrum of asthma patients and symptoms, and helps to avoid underdosing or overdosing with ICS in the presence of a LABA. The goal of this study is to confirm the optimal dose of Fp MDPI and demonstrate the superiority of FS MDPI versus Fp MDPI on bronchodilation in patients 4 through 11 years old with persistent asthma.

1.2. Findings from Nonclinical and Clinical Studies

Brief summaries of nonclinical pharmacology, pharmacokinetics, and toxicology studies and clinical studies are provided in the following sections. More detailed information is provided in the Fp MDPI and FS MDPI Investigator's Brochures (IBs).

1.2.1. Nonclinical Studies

Information about nonclinical findings may be found in the current IBs for Fp MDPI and FS MDPI.

1.2.2. Clinical Studies

1.2.2.1. Fluticasone Propionate Efficacy

The efficacy of Fp in asthma is due, in part, to its local anti-inflammatory activity. Specifically, these effects include inhibition of multiple cell types (mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils) and inhibition of mediator production/secretion (histamine, eicosanoids, leukotrienes, and cytokines).

Clinical studies on Fp, marketed as FLOVENT, have shown the benefit of Fp in the maintenance treatment of all severities of persistent asthma. For pediatric asthmatic patients ages 4 through 11 years, the recommended starting dosage is 1 inhalation of the 50-mcg strength product twice daily. Information about these studies is contained in the FLOVENT prescribing information. The Fp MDPI IB contains information about previous Teva clinical studies performed to determine the optimal dose of Fp using the Teva MDPI versus FLOVENT.

1.2.2.2. Fluticasone Propionate/Salmeterol Efficacy

Salmeterol (SEREVENT® DISKUS®[3]) is a selective LABA that has demonstrated a prolonged duration of bronchodilator action. As a class, LABAs have been widely used in combination with ICS for the long-term maintenance treatment of asthma. Salmeterol inhalation aerosol was approved in 1994 for the long-term maintenance treatment of asthma and the prevention of bronchospasm in adolescent and adult patients with reversible airway obstruction. As a result of the chlorofluorocarbon phase out, only a dry powder formulation of salmeterol as a monoproduct is currently available in the US.

In the NDA submitted in March 2016, the proposed indication for Teva's FS MDPI is for the treatment of asthma in patients aged 12 years and older. FS (ADVAIR DISKUS) is indicated for the long-term, twice-daily, maintenance treatment of asthma in patients 4 years of age and older. For pediatric asthmatic patients ages 4 through 11 years, the recommended starting dosage is 1 inhalation of the 100/50-mcg strength product twice daily. ADVAIR DISKUS is not indicated for the relief of acute bronchospasm.

Teva has conducted a dose-ranging study in asthmatic patients to determine the optimal dose of salmeterol in FS MDPI. This study, FSS-AS-201, was performed in patients with mild asthma. Study FSS-AS-201 was performed as a blinded, single-dose, crossover study with 4 different strengths of salmeterol (all with 100 mcg of Fp) in the Teva MDPI device compared with Fp 100 mcg in the Teva MDPI device and ADVAIR DISKUS 100/50 mcg. Results showed that the 12.5- and 25-mcg strengths of salmeterol in Teva's FS MDPI device were comparable in clinical efficacy (as determined by serial spirometry) with 50 mcg of salmeterol in ADVAIR DISKUS 100/50 mcg. The peak salmeterol concentration and exposure for FS MDPI 100/12.5 mcg was lower than ADVAIR DISKUS 100/50 mcg (data on file).

Additional information about clinical studies with ADVAIR DISKUS in asthma patients is provided in the prescribing information, which is included as an appendix in the Teva FS MDPI IB.

1.3. Known and Potential Benefits and Risks to Patients

1.3.1. Known and Potential Benefits and Risks of the Test Investigational Medicinal Product(s)

Additional information regarding benefits and risks to patients may be found in the Fp MDPI and FS MDPI IBs.

In summary, the benefit and risk assessment for Fp MDPI and FS MDPI is favorable following review of the outlined data.

1.3.1.1. Benefits of Test Investigational Medicinal Product Treatment

These known and potential risks described below are balanced against known benefits. Clinical data demonstrate that use of Fp and salmeterol in combination in both adults and children with

[3] SEREVENT® DISKUS® is a trademark, the property of the GlaxoSmithKline group of companies.

persistent asthma provides greater improvement in pulmonary function and overall asthma control than either component alone. The use of such a combination is recommended for the maintenance treatment of asthma in children, adolescents, and adults who remain symptomatic despite low-to-medium doses of an ICS in accordance with current guidelines for the management of asthma.

1.3.1.2. Risks of Test Investigational Medicinal Product Treatment

The class effects of systemic and local corticosteroids include *Candida albicans* infection, immunosuppression, hypercorticism and adrenal suppression, paradoxical bronchospasm, growth effects, and glaucoma and cataracts.

The class of LABAs, such as salmeterol, increases the risk of asthma-related death. Data from a large placebo-controlled study that compared the safety of salmeterol (SEREVENT Inhalation Aerosol [GlaxoSmithKline plc]) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. Currently available data are inadequate to determine whether concurrent use of ICSs with other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABAs. Available data from controlled clinical trials suggest that LABAs increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Excessive beta-adrenergic stimulation has been associated with cardiovascular and central nervous system (CNS) effects, such as seizures, angina, hypertension or hypotension, tachycardia, arrhythmia, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise and insomnia.

Based on extensive clinical experience with Fp alone and in combination with salmeterol, Fp MDPI and FS MDPI are expected to have safety profiles (incidence, severity, and seriousness) that are comparable to those of FLOVENT DISKUS and ADVAIR DISKUS, respectively. However, Teva is developing Fp MDPI and FS MDPI for use at lower dose strengths of both active ingredients, but with comparable efficacy, relative to these currently marketed products.

In studies in which all patients were ≥12 years of age the most common treatment-emergent adverse events in ≥3% of patients in the Fp MDPI and FS MDPI groups (Teva Studies FpS-AS-101, FpS-AS-102, FpS-AS-201, FpS-AS-202, and FSS-AS-201) included nasopharyngitis, upper respiratory infection (URI), headache, and nasal congestion.

The most common adverse reactions (≥3%) in Phase 3, placebo-controlled clinical trials with Fp MDPI and FS MDPI products in adults included nasopharyngitis, oral candidiasis, back pain, headache, and cough.

In Studies FSS-AS-301 and FSS-AS-30017, asthma exacerbations were reported at a similar frequency among patients treated with Fp MDPI and FS MDPI treatment groups (<1% to 4%), while the incidence of asthma exacerbation was 11% in patients treated with placebo.

For Study FSS-AS-305 in the ICS cohort, the incidence of asthma exacerbations was balanced between the mid-strength groups, while the incidence of severe asthma exacerbations was 6% for Fp MDPI and 0 for FLOVENT hydrofluoroalkane (HFA). For Study FSS-AS-305 in the ICS/LABA cohort, the incidence of asthma exacerbations was 15% in the FS MDPI 200/12.5 mcg group and 7% in the ADVAIR DISKUS group, while the incidence of severe asthma exacerbations was 6% and 5%, respectively. Four patients had treatment

discontinued, 3 patients were hospitalized in response to a severe asthma exacerbation, and 5 patients had an ER/urgent care clinic visit (but were not hospitalized) because of an asthma exacerbation. There was no apparent relationship with treatment group for these events. This open-label safety study was not designed to evaluate treatment differences in asthma exacerbation incidence. Prior history of asthma exacerbations was not collected and was not used to ensure proper balance in randomization across the treatment groups. Ad hoc statistical analyses were performed and confirmed the incidences were not different among all groups. The most likely explanation for the apparent differences are the rarity of the events and the smaller numbers of patients in the active comparator groups relative to the study drug groups (3:1 randomization ratio).

The most common adverse events noted in adult and adolescent asthmatic patients receiving ADVAIR DISKUS in repeat-dose, controlled clinical trials included URI, pharyngitis, headaches, upper respiratory inflammation, bronchitis, cough, and nausea and vomiting.

In a study of pediatric patients randomly assigned to either ADVAIR DISKUS 100/50 mcg or Fp inhalation powder 100 mcg twice daily, aged 4 through 11 years who were receiving ICS at study entry, common adverse reactions (≥3% and greater than placebo) seen in the pediatric patients receiving ADVAIR DISKUS but not reported in the adult and adolescent clinical trials included throat irritation and ear, nose, and throat infections.

Complete safety information is available in the Fp MDPI and FS MDPI IBs.

1.3.2. Overall Benefit and Risk Assessment for This Study

Based on extensive clinical experience with Fp and FS, Fp MDPI and FS MDPI are expected to have safety profiles (incidence, severity, and seriousness) that are comparable to those of ADVAIR DISKUS. However, Teva is developing Fp MDPI and FS MDPI for use at lower dose strengths of both active ingredients, but with comparable efficacy, relative to these currently marketed products.

The most common adverse events noted in adult and adolescent asthmatic patients receiving ADVAIR DISKUS in repeat-dose, controlled clinical trials included URI, pharyngitis, headaches, upper respiratory inflammation, bronchitis, cough, and nausea and vomiting. The most common adverse reactions noted in pediatric patients aged 4 through 11 years receiving ADVAIR DISKUS 100/50 mcg or Fp 100 mcg twice daily but not in adults or adolescents were throat irritation, and ear, nose, and throat infections. The most common adverse events noted in asthmatic patients 4 years and older receiving FLOVENT DISKUS included URI, throat irritation, sinusitis, rhinitis, oral candidiasis, nausea and vomiting, gastrointestinal discomfort, fever, cough, bronchitis, and headache. The safety profile in the pediatric population is similar to that of adults.

The most common adverse reactions (≥3%) in Phase 3, placebo-controlled clinical trials with Fp MDPI and FS MDPI products in adults and adolescents included nasopharyngitis, oral candidiasis, back pain, headache, and cough. The safety profile is consistent with the known class of drugs and underlying diseases.

The potential benefits will likely outweigh the risks for this study. Efficacy results of the well-controlled Phase 3 and Phase 2 studies demonstrated that Fp MDPI (50, 100, and 200 mcg bid) and FS MDPI (50/12.5, 100/12.5, and 200/12.5 mcg bid) significantly improved

lung function, reduced rescue bronchodilator use, and improved asthma symptoms and quality of life in patients with asthma 12 years of age and older. Thus, Fp MDPI and FS MDPI represent effective, easily administered treatment options for these patients.

Use of placebo-controlled study design in evaluating ICSs and other molecules is commonly used in developing these drug products and is required by FDA towards supporting the efficacy of the molecule (eg, Kerwin et al 2008, Woodcock et al 2013). The design of this study is very similar to other pediatric placebo-controlled trials where adverse events in the placebo arm were similar to those in the treatment arms. The study has been designed to minimize the risks of placebo use to the intended population of patients 4 through 11 years of age. The patient inclusion and exclusion criteria were selected to ensure that patients with severe asthma or history of life-threatening exacerbations would not be eligible. In this study, the patients' lung function, symptom scores, and rescue medication use will be monitored daily with use of a handheld device/electronic diary. The handheld device/electronic diary will provide alerts to the study center and medical monitor for the trial so that patients whose asthma status may be deteriorating will be captured early (Section 4.3.2). This will minimize the risk and asthma exacerbation as well as any discomfort that might come from an exacerbation. Additionally, use of the handheld device/electronic diary minimizes the burden of requiring patients to travel to the study center for monitoring. Patients assigned to placebo therapy often demonstrate improvement in lung function, suggesting that frequent contact with medical providers may be of benefit. Additionally, all patients are provided with rescue albuterol/salbutamol for use as needed. Rescue albuterol/salbutamol usage will be followed closely for signs of deterioration.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary and Secondary Study Objectives and Endpoints

The primary and secondary study objectives and endpoints are:

Objectives	Endpoints
The **primary objective** of the 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 primary efficacy endpoints are as follows: • For Fp MDPI versus placebo: the change from baseline in weekly average of the percent predicted trough morning 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) 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]) 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 IMP for asthma exacerbation during the 12-week treatment period The sequential order of the secondary endpoints for multiplicity will be described in the statistical analysis plan.
The **secondary objective** of this study is to evaluate the safety and tolerability of Fp MDPI and FS MDPI.	The safety endpoints are as follows: • Incidence of adverse events throughout the study • Vital signs assessments throughout the study • Oropharyngeal examination findings at each visit • Physical examination findings at baseline and at week 12 or at the IMP discontinuation visit (IMPDV)

2.1.1. Justification of Primary Endpoint

The co-primary endpoints selected for this study are consistent with those previously used in the selected population by other combination products and in the Fp MDPI and FS MDPI program in the adult and adolescent asthma population. They reflect the distinct mechanism of action of the 2 different drug components.

2.2. Other Efficacy and Safety Endpoints

2.2.1. 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

3. STUDY DESIGN

3.1. General Design and Study Schematic Diagram

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 12 inhalations permitted per day. Starting day 1 of the run-in period, patients must discontinue all nonstudy 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

A prescreening visit may be conducted, if needed, before the SV to discuss study procedures and/or provide patient instructions about any required washout periods for prohibited medications. SV may take place during several investigational center visits.

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 who are being treated with an ICS with or without a LABA and/or with a noncorticosteroid (NCS) therapy are eligible to be included in the study. Patients must meet washout period requirements at the SV for their asthma and non-asthma disallowed medications according to Appendix H. The patient's asthma medication regimen must be stable for 30 days prior to the SV (except as adjusted at an optional prescreening visit to wash out prohibited medications). If the patient has taken asthma maintenance medication the morning of the SV or SABA within 6 hours of lung function assessments (FEV_1 and PEF) by handheld device, the visit must be rescheduled so that lung function assessments and response to bronchodilator testing can be

completed as described (other assessments not involving lung function may be completed that day).

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. Screening lung function assessments (FEV_1 and PEF) by handheld device should be performed at the investigational center between the hours of 0530 and 1100. Patients will be permitted 8 attempts per test. The highest FEV_1 value from 3 technically acceptable and 2 repeatable maneuvers will be used to qualify patients for the placebo run-in period. Patients who have failed screening for inability to perform lung function assessments (FEV_1 and PEF) in a technically acceptable manner or due to FEV_1 not meeting the inclusion criterion or demonstrated <10% response to a bronchodilator may retest once within 7 days of their initial SV provided that they have met all other inclusion criteria and none of the exclusion criteria at the SV. The handheld device should be kept at the clinic for these patients until they meet the requirements to enter the run-in period.

At retest, patients (or patient's parent/legal guardian/caregiver) will report if there have been any adverse events, changes in medications, or changes in medical history since providing consent/assent. Patients who fail again to demonstrate technically acceptable lung function assessments (FEV_1 and PEF) or due to FEV_1 not meeting the inclusion criterion or who demonstrate <10% response to a bronchodilator will be considered screen failures. The run-in period will not start until patients have met all inclusion criteria and none of the exclusion criteria. Patients who fail to meet the requirements to enter the run-in period at this visit will be considered screen failures and will not be allowed to be rescreened.

Patients who qualify for entry into the placebo run-in period must discontinue all currently administered asthma medications (including leukotriene modifiers prescribed for other conditions) until completion of the TV6 (week 12) visit or 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 (90 mcg ex-actuator) 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 patient diary built into the handheld device.

Patients who experience an URI or lower respiratory infection (LRI) during the run-in period should be classified as randomization failures and be discontinued from the study but may be rescreened 2 weeks after resolution of the infection. Patients who are rescreened will need to repeat all screening procedures and evaluations. Only 1 rescreening for each patient will be permitted.

Patients who entered the run-in period with response to a bronchodilator ≥10% and <14.50% must present for repeat lung function assessments and another bronchodilator test within 14±2 days, during which they must demonstrate at least a 15% response to a bronchodilator. If

the criteria are not met, patients may continue in the run-in period for up to 14 additional days to meet the lung function assessment and response to bronchodilator criteria (1 final attempt) for randomization. Patients may only continue in the run-in period if the investigator determines, by assessing the patient's asthma status (at each investigational center visit), that it is safe for the patient to continue. Patients who have entered the run-in period but fail to demonstrate technically acceptable lung function assessments and response to a bronchodilator (as described) will be considered to have failed randomization. All patients must demonstrate at least a 15% response to a bronchodilator at the SV or during the run-in period. Patients who demonstrate the response to bronchodilator during the run-in period may present for randomization the following day at the earliest or at another later time as long as it is within the 30-day allowance for the run-in period. Responses to a bronchodilator of 14.50% to 14.99% will be rounded to 15%.

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 (ICS or 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 2). Patients will be instructed to take 1 inhalation from the assigned device twice daily approximately 12 hours apart.

Table 2: 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 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. The highest FEV_1 value from 3 acceptable and 2 repeatable maneuvers (maximum of 8 attempts per test) will be obtained before and 1-hour after the morning dose.

At each visit, the investigational center staff 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.

A telephone call may be conducted as needed during the alternate, non-visit weeks (weeks 5, 7, etc) to monitor the patients' safety and to assess their asthma status or for any other relevant reason.

At the end of the study, a FV (which may be a follow-up investigational center visit or telephone call) will be conducted 7±2 days after TV6 (week 12) to monitor safety of the patients.

Patients who meet the alert criteria for worsening asthma as defined for this study or experience worsening of asthma including asthma exacerbation will present to the investigational center for an investigator assessment as soon as possible. If possible and when it is judged safe to do so, this visit should be conducted before a change in asthma therapy takes place. Following investigator assessment of the patient's asthma status, a decision will be made whether or not it is safe for a patient to continue the IMP. In cases where the IMP is to be withdrawn and alternative therapy started, the investigational center staff should contact the medical monitor to confirm the findings. In the event that it is considered in the best interest of a patient to stop the IMP and initiate an alternative asthma therapy, the patient will undergo all visit procedures required for the IMPDV. After the IMPDV, IMP dosing will not occur. The investigator should discuss and implement alternative asthma treatment that is appropriate for the patient. These patients will continue to participate in all study visits as scheduled and continue to complete all morning and evening study procedures except for IMP dosing. Patients will be asked to perform 1-hour postdose lung function assessments at the remaining treatment visits; 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. If a patient or patient's parent/legal guardian elects to completely withdraw from the study (ie, withdraw consent) prior to the investigator assessment or investigational center visit, irrespective of the reason for the study discontinuation, every attempt will be made to conduct the IMPDV subsequent to the patient's withdrawal from the IMP.

Asthma exacerbation 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.

At TV6 (week 12), or the IMPDV as applicable, the investigator will discuss asthma treatment with the patient after safety assessments have been completed, and any medication started for the purpose of newly recommended asthma treatment will not be considered a protocol violation. This asthma therapy will be recorded in the CRF following IMP discontinuation (planned or unplanned). Additionally, an investigational center visit may be conducted at any time at the request of the patient or parent/legal guardian/caregiver, as applicable or at the discretion of the investigator.

Safety will be monitored by vital signs, physical examination, oropharyngeal examination, and recording of adverse events. In addition, during the study, PEF and FEV_1 will be monitored as part of safety monitoring (alert criteria for worsening asthma). Any visual evidence of oral candidiasis during the treatment period will be confirmed by obtaining a swab for culture of the suspect area. Patients and parents/legal guardians/caregivers will be provided with guidelines for when to contact the investigational center in case of worsening asthma symptoms or rescue inhaler use. Patients who meet predefined alert criteria should be evaluated by the investigator to determine if the IMP should be discontinued. If a patient discontinues the IMP prematurely but remains in the study, all subsequent visits will include all assessments according to Table 3 except for IMP dosing. Patients will be asked to perform 1-hour postdose lung function assessments at the remaining treatment visits; 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.

Alert criteria for individual patients have been designed to ensure patient safety. If any of the criteria listed below are met, during a scheduled or unplanned study visit, the investigator (after discussion with the sponsor) will determine whether the patient's overall clinical picture is consistent with worsening asthma and if the patient should be withdrawn from IMP (but not the study) to be placed on alternative asthma therapy in the interest of patient safety. Meeting 1 of these alert criteria does not automatically require a patient to be withdrawn from IMP, rather it requires a clinical evaluation to determine if the patient's asthma can continue to be managed in a blinded manner per the study or necessitates a change in asthma therapy. All attempts will be made to safely continue to manage a patient in a blinded manner.

- Morning FEV_1 by handheld device measured at home falls below the FEV_1 stability limit (see Section 6.1.3) calculated at the SV for the run-in period and at baseline for the treatment period on 4 or more days (do not have to be consecutive) out of any 7-day period (7-day period is defined as any consecutive 7 days following the RV and can overlap with scheduled study investigational center visits).
- Based upon a review of patient data from the patient diary built into the handheld device, the patient has experienced any of the following during a 7-day period (7-day

period is defined as any consecutive 7 days following a previous TV; 7 days can overlap with scheduled study investigational center visits):

- 3 or more days in which 8 or more inhalations/day of rescue medication (albuterol/salbutamol HFA MDI [90 mcg ex-actuator] or equivalent) were used (any 3 days in the consecutive 7-day period)
- 3 or more days in which the patient experienced a nighttime asthma symptom score of more than 2 (any 3 days in the consecutive 7-day period)

Patients who meet the alert criteria and/or who experience a clinically meaningful worsening of their asthma will be assessed by the investigator. If the investigator considers it is not possible to safely manage a patient in a blinded manner as patient's asthma warrants a change in his/her asthma treatment, the IMP will be stopped, and appropriate treatment (based on the investigator's judgment) should be offered. The medical monitor should be contacted to confirm the findings when alternative therapy is to be instituted. The patient should continue in the study until the patient has completed all remaining study visits and the FV.

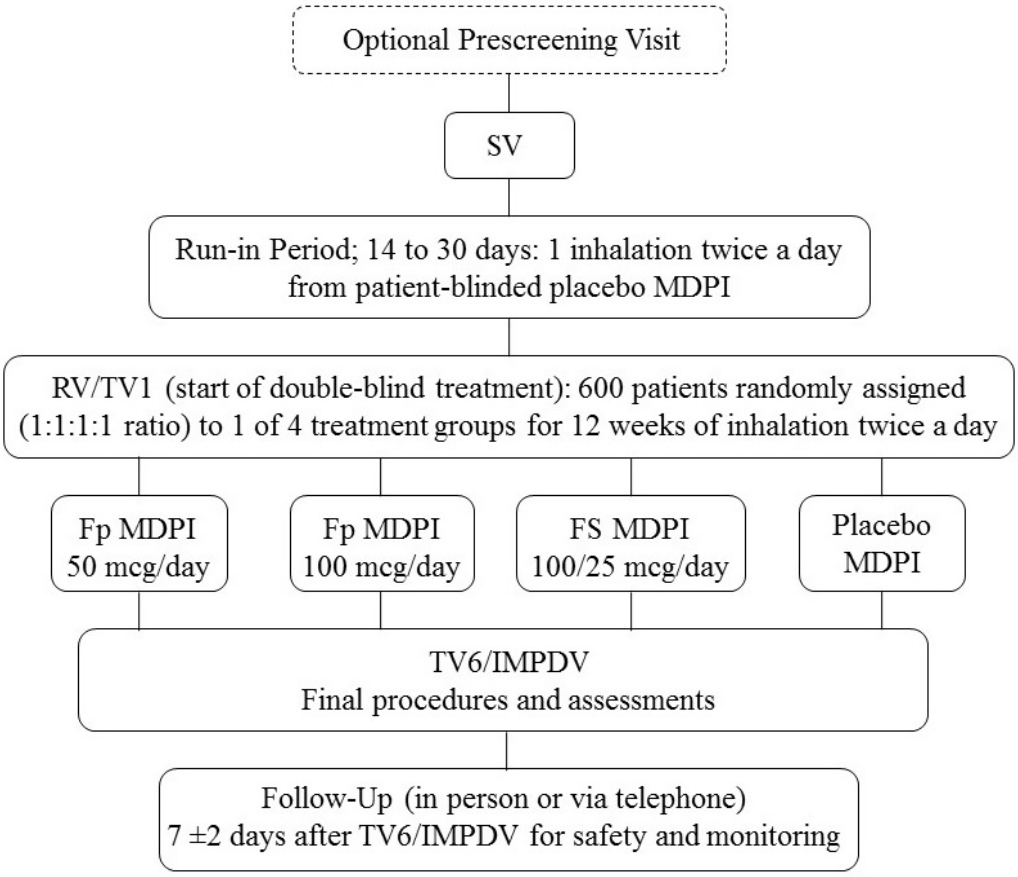
- For the purpose of this study, an asthma exacerbation is defined as worsening of asthma requiring any significant treatment other than IMP and study rescue medication. Significant treatment includes the use of systemic corticosteroids and/or the addition of other ICS-containing asthma medications, LABAs, or other NCS asthma medications, for example, inhaled short-acting muscarinic antagonist; ER/urgent care clinic visit(s); or hospitalization. Note: A single dose of nebulized albuterol/salbutamol would not meet the criteria for an asthma exacerbation. ER/urgent care clinic visits where the treatment is limited to a single dose of nebulized albuterol/salbutamol will not meet the criteria of an asthma exacerbation.

After the last TV (TV6, week 12), the patient will enter the follow-up period. One week (±2 days) after the last TV, the patient will have a 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 addition to screening, run-in, and all TVs. Patients who stop IMP and return for safety evaluation at week 12 will not be considered to have completed the treatment period.

The assessments and procedures performed during each study visit are detailed in Table 3 and Appendix B.

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.

3.2. Planned Number of Patients and Countries

The population planned to be enrolled in this study comprises male and female patients 4 through 11 years of age who have a documented history of persistent asthma. Approximately 824 male and female patients, 206 patients in each of 4 treatment group, will be enrolled. Assuming a dropout rate of 12%, approximately 181 evaluable patients in each treatment group (724 total patients) will complete the 12-week treatment period.

Details on the definition of evaluable patients and sample size are given in Section 9.

The study is planned to be conducted in the US and ex-US in approximately 130 investigational centers. The study is expected to start in the fourth quarter of 2016 (first patient in) and last until approximately the second quarter of 2019 (last patient last visit).

3.3. Justification for Study Design and Selection of Population

This is a standard study design used to determine the safety and efficacy of 3 investigational treatments in pediatric patients aged 4 through 11 years old with persistent asthma.

The study is part of a pediatric program to investigate the efficacy and safety in pediatric patients. This study follows completion of a pharmacokinetic study with Fp MDPI and FS MDPI in the target study population of asthmatic patients 4 through 11 years of age. The population planned to be enrolled in this study comprises male and female patients 4 through 11 years of age who have a documented history of persistent asthma. The asthma diagnosis must be in accordance with the National Institutes of Health (NIH) definition.

3.4. Stopping Rules for the Study

There are no formal rules for early termination of this study. During the conduct of the study, serious adverse events will be reviewed (see Section7.1.5) as they are reported from the investigational centers to identify safety concerns.

The study may be terminated by the sponsor for any reason at any time.

A patient may discontinue participation in the study at any time for any reason by withdrawal of consent; every effort should be undertaken to find out the reason for discontinuation. The investigator or sponsor can withdraw a patient from the study IMP at any time for any reason (eg, protocol violation or deviation as defined in Appendix C, noncompliance, or adverse event). However, patients that do not withdraw consent should remain in the study (as counseled during the informed consent process) and complete the remaining study procedures and visits, with the exception of IMP dosing. Patients will be asked to perform 1-hour postdose lung function assessments at the remaining treatment visits; 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.

3.5. Schedule of Study Procedures and Assessments

Study procedures and assessments with their time points are summarized in Table 3. Detailed by-visit information is provided starting with Appendix B, Part 11. Detailed descriptions of each assessment are provided in Section 6 (efficacy assessments) and Section 7 (safety assessments). Study procedures and assessments by visit are listed in Appendix B.

Table 3: Study Procedures and Assessments

Study period	**Placebo run-in**		**Double-blind treatment period (visit week)**						**Follow-up**
Visit number	**SV[a]**	**RV/TV1[b]**	**TV2**	**TV3**	**TV4**	**TV5**	**TV6**	**IMPDV**	**FV**
Procedures and assessments	**Screening**	**Baseline**	**W1**	**W2**	**W4**	**W8**	**W12**	**IMP discontinuation**	**W13**
Allowed time windows	**-30 to -14 days**	**Day 1**	**Day 8 ±2 days**	**Day 15 ±2 days**	**Day 29 ±2 days**	**Day 57 ±2 days**	**Day 85 ±2 days**	**±2 days**	**Day 92 ±2 days**
Informed consent/assent	X								
Medical history[c]	X								
Prior medication history	X								
Inclusion and exclusion criteria	X								
Demography	X								
Begin run-in	X								
Perform randomization and treatment assignment in IRT[b]		X							
Randomization criteria		X							
Adverse event inquiry and recording	X	X	X	X	X	X	X	X	X
Concomitant medication inquiry	X	X	X	X	X	X	X	X	X
Vital signs measurement[d]	X	X	X	X	X	X	X	X	
Full physical examination, including weight and height	X						X	X	
Directed cardiopulmonary examination		X							
Oropharyngeal examination[e]	X	X	X	X	X	X	X	X	
Urine pregnancy test (female patients of childbearing potential)	X	X	X	X	X	X	X	X	
Perform lung function assessments (FEV_1 and PEF) by handheld device with response to bronchodilator testing[f]	X								
Perform lung function assessments (FEV_1 and PEF) by handheld device predose [g]	X	X	X	X	X	X	X (morning only)	X	
Perform lung function assessments (FEV_1) by handheld device 1-hour postdose at the investigational center[h]		X	X	X	X	X	X (morning only)	X	
Conduct training for use of handheld device	X	X	X	X	X	X		X	

Study period	**Placebo run-in**		**Double-blind treatment period (visit week)**						**Follow-up**
Visit number	**SV[a]**	**RV/TV1[b]**	**TV2**	**TV3**	**TV4**	**TV5**	**TV6**	**IMPDV**	**FV**
Procedures and assessments	**Screening**	**Baseline**	**W1**	**W2**	**W4**	**W8**	**W12**	**IMP discontinuation**	**W13**
Allowed time windows	**-30 to -14 days**	**Day 1**	**Day 8 ±2 days**	**Day 15 ±2 days**	**Day 29 ±2 days**	**Day 57 ±2 days**	**Day 85 ±2 days**	**±2 days**	**Day 92 ±2 days**
Asthma control questionnaire (C-ACT)		X			X	X	X	X	
Dispense/collect run-in IMP kit	X	X						X	
Conduct training for IMP administration and have patient demonstrate proper technique using the provided training inhaler[i]	X	X	X	X	X	X			
Observe patient dosing with IMP		X	X	X	X	X	X		
Dispense/collect rescue medication[j]	X	X	X	X	X	X	X		
Dispense/collect double-blind IMP kit		X		X	X	X	X	X	
Assess alert criteria for worsening asthma		X	X	X	X	X	X	X	
Distribute/collect handheld device[k]	X	X	X	X	X	X	X	X	
Discuss and record recommended asthma therapy[l]							X	X	
End IMP in IRT system							X	X	
End study participation in IRT system[m]							X	X[l]	

[a] Patients may attend a prescreening visit up to 15 days before the SV. The SV may occur up to 30 days prior to the RV. Patients who fail to meet baseline lung function assessments by handheld device requirements may retest within 7 days of their initial SV. Patients who demonstrate a response to a bronchodilator ≥10% and <14.50% may enter the run-in period but must undergo repeat lung function assessments and another bronchodilator test in 14±2 days and may attempt lung function assessments and response to a bronchodilator within 14 more days if needed (as applicable). Patient-blinded drug should be dispensed at each visit until the patient qualifies for or fails randomization. Informed consent/assent should be done at the SV unless already completed at a prescreening visit.

[b] The RV may occur up to 30 days following the SV. The patient's home FEV_1 by handheld device should be reviewed, and the average of the 5 highest daily values (3 attempts) for trough morning FEV_1 out of the last 7 days prior to RV must be 40% to 85% predicted for age, height, sex and race (Quanjer et al 2012) with asthma symptom criteria, the C-ACT score must be ≤19 to be eligible for randomization. The patient must also meet the lung function assessment requirements at the investigational center and all other study criteria. Eligible patients will be assigned a patient randomization identification number via the IRT system that is different than the one received at screening.

[c] The medical history is to be obtained by the investigator or designated study personnel. If there are no prior medical records available, the investigator must document the history of asthma, as reported by the patient, in the source document. Prior medical records must be requested, or the reason if not requested must be documented in the source documents. This will be considered adequate history if it meets the inclusion criteria.

[d] Vital signs (BP and pulse rate) should be obtained with the patient in the sitting position after a 5-minute rest period.

[e] An oropharyngeal examination is to be conducted by a qualified medical provider (as required by local regulation) at each visit. Clinical visual evidence of oropharyngeal candidiasis at the RV will exclude the patient from participating in the treatment period. Evidence of oropharyngeal candidiasis at any study TV or end of study TV should be evaluated by obtaining a swab for culture. Patients who agree to treatment may continue to receive IMP. Treatment should not be delayed for results of the culture.

[f] Lung function assessments (FEV_1 and PEF) by handheld device and response to bronchodilator testing should be conducted. Patients unable to perform lung function assessments will be allowed to retest once within 7 days. Patients who meet lung function assessment and response to a bronchodilator requirements may enter the run-in period. Patients who entered the run-in period with response to a bronchodilator ≥10% and <14.50% must present for repeat lung function assessments and another bronchodilator test within 14±2 days, during which they must demonstrate at least a 15% response to a bronchodilator. Responses to bronchodilator of 14.50% to 14.99% will be rounded to 15%. If the criteria are not met, patients may continue in the run-in period for up to 14 additional days to meet the lung function assessment and response to a bronchodilator criteria (1 final attempt) for randomization. Patients who have failed screening for inability to perform lung function assessments in a technically acceptable manner or due to FEV_1 not meeting the inclusion criterion or demonstrated <10% response to a bronchodilator may retest once within 7 days of their initial SV provided that they have met all other inclusion criteria and none of the exclusion criteria at the SV. Patients who enter the run-in period with response to a bronchodilator ≥15% do not need to retest at the RV. For patients who need to demonstrate the response to bronchodilator during the run-in, the RV must be on another day.

[g] Daily morning and evening lung function assessments (FEV_1 and PEF) by handheld device (after the patient is trained on its use and has demonstrated proper technique using the provided training device) will be performed, except as indicated. The patient will be instructed to perform 3 trough morning FEV_1 maneuvers and 3 evening FEV_1 maneuvers at home each day during participation in the run-in period and the treatment period (morning only on the final TV [TV6 (week 12)]). The highest FEV_1 obtained at the SV will be used to calculate the home FEV_1 stability limit, which will be used for review of alert criteria during the run-in period. The average FEV_1 over 5 days prior to RV will be used to calculate the alert criteria for the treatment period.

[h] 60-minute (±10 minutes) postdose lung function assessments will be performed at the investigational center at all visits (excluding patients placed on alternative therapy where the patient will not dose but a 1-hour assessment will still be collected).

[i] Except patients who have been placed on alternative therapy.

[j] Rescue medication will be dispensed for all patients entering the run-in period. At each visit, the study personnel should determine if the patient has adequate rescue medication remaining (based on current use) or dispense a new albuterol/salbutamol HFA MDI. A second inhaler may be provided for use at school or camp, as applicable. Rescue medication dispensed at SV will be used for response to a bronchodilator test.

[k] The investigational center staff must verify that the information from the patient diary built into the handheld device is up to date and identify any potential missing data or deviations upon review of the patient diary built into the handheld device at that visit. The device will be collected and inspected to make sure it is not damaged and the data will be downloaded at each clinic visit. Once inspected, the same handheld device will be redispensed to the patient unless it needs to be replaced.

[l] The investigator will discuss ongoing asthma treatment with the patient after lung function assessments have been completed, and any medication started for the purpose of ongoing asthma treatment will not be considered a protocol violation. This treatment, if instituted, should be entered in the CRF as ongoing therapy.

[m] End of study participation in the IRT system will take place at the last visit during the treatment period (ie, at TV6 for patients who complete the treatment period, or at the IMPDV for patients who discontinue the study prematurely [patients who withdraw consent]).

BP=blood pressure; C-ACT=Childhood Asthma Control Test; CRF=case report form; FEV_1=forced expiratory volume in 1 second; FV=follow-up visit; HFA MDI=hydrofluoroalkane metered-dose inhaler; IMP=investigational medicinal product; IMPDV=investigational medicinal product discontinuation visit; IRT=Interactive Response Technology; PEF=peak expiratory flow; RV=randomization visit; SV=screening visit; TV=treatment visit.

4. SELECTION AND WITHDRAWAL OF PATIENTS

Prospective waivers (exceptions) from study inclusion and exclusion criteria to allow patients to be enrolled are not granted by Teva (Appendix C).

4.1. Patient Inclusion Criteria

The SV can be broken into more than 1 visit. Patients may be included in the study run-in period if they meet all of the following inclusion criteria at screening:

a. The patient is a male or female patient 4 through 11 years of age, inclusive, when informed consent/assent (as applicable) is signed.

b. Written informed consent must be signed and dated by parent/legal guardian and the written informed assent form must be signed and dated by the patient (as applicable, per local regulations) before any study-related procedures are conducted.

c. The patient has a diagnosis of asthma as defined by the NIH. The asthma diagnosis has been present for a minimum of 3 months before SV.

d. The patient has persistent asthma with a FEV_1 ≥50% and ≤90% of the value predicted for age, height, sex, and race at the SV as measured by handheld device.

e. The patient's persistent asthma is stable and is currently being treated with stable asthma therapy (eg, ICS, ICS/LABA, leukotriene receptor antagonist, etc.) for at least 30 days before the SV. Patients who are currently on SABA regimen only or PRN only are not eligible for the study.

f. The patient has demonstrated ≥10% response to a bronchodilator from screening FEV_1 within 30 minutes (±5 min) after 2 to 4 inhalations of albuterol/salbutamol HFA MDI (90 mcg ex-actuator) or equivalent at SV as measured by handheld device. Patients who demonstrated <10% response to a bronchodilator may retest within 7 days of their initial SV.

   – Patients who demonstrate response to a bronchodilator ≥10% and <14.50% may enter the run-in period (provided that they meet the other inclusion and none of the exclusion criteria) and may present for repeat lung function assessments by handheld device and another bronchodilator test within 14±2 days, during which they must demonstrate at least a 15% response to a bronchodilator. If the criteria are not met, patients may continue in the run-in period for up to 14 additional days to meet the lung function assessment and response to bronchodilator criteria (1 final attempt) for randomization. Patients may only continue in the run-in period if the investigator determines, by assessing the patient's asthma status (at each investigational center visit), that it is safe for the patient to continue.

g. The patient (with assistance from parents/legal guardians/caregivers, as needed) is able to perform technically acceptable lung function assessments by handheld device. Patients who fail to demonstrate technically acceptable lung function assessments may retest within 7 days of their initial SV.

h. The patient (with assistance from parents/legal guardians/caregivers, as needed) is able to use an MDI device and an MDPI device.

i. The patient is able to withhold (as judged by the investigator) his/her rescue medication for at least 6 hours before SV and all TVs where lung function assessments are performed.

j. The patient is assessed as otherwise healthy, with clinically acceptable medical history, physical examination, and vital signs within acceptable ranges for children with asthma as assessed by the investigator.

k. All patients must be able to replace their current SABA with albuterol/salbutamol HFA MDI inhalation aerosol at the SV for use as needed for the duration of the study.

l. Female patients who have reached puberty and achieved menarche (as determined by the investigator) must be counseled regarding the possible unknown risks associated with IMP during pregnancy following permission of the parents/legal guardians. A urine pregnancy test must be negative for these patients at SV. Eligible female patients who are known to be sexually active will be excluded.

m. Eligible male patients who are known to be sexually active will be excluded.

4.2. Patient Exclusion Criteria

Patients will be excluded from participating in this study if they meet any of the following criteria:

a. The patient has a history of life-threatening asthma exacerbation that is defined for this protocol as an asthma episode that required intubation and/or was associated with hypercapnia, respiratory arrest, or hypoxic seizures.

b. The patient is pregnant or lactating or plans to become pregnant during the study period or within 30 days after the patient's last study-related visit (for eligible patients only and if applicable).

c. The patient has participated as a randomized patient in any investigational drug study within the 30 days or within 5 half-lives (starting from the final FV of that study) preceding the SV (or prescreening visit, as applicable) or plans to participate in another investigational drug study at any time during this study.

d. The patient has a known hypersensitivity to any corticosteroid, salmeterol, or any of the excipients in the IMP or rescue medication formulation (ie, lactose). Dietary lactose intolerance does not exclude the patient from inclusion into the study or as per the investigator's medical discretion.

e. The patient has been treated with any known strong cytochrome P450 (CYP) 3A4 inhibitors (eg, ketoconazole, ritonavir, clarithromycin) within 30 days before the SV or plans to be treated with any strong CYP3A4 inhibitor during the study.

f. The patient has been treated with any of the prohibited medications during the prescribed (per protocol) washout periods before the SV.

g. The patient currently smokes or has a smoking history. The patient must not have used tobacco products within the past year (eg, cigarettes, cigars, chewing tobacco, or pipe tobacco).

h. The patient has a culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus, or middle ear that has not resolved at least 2 weeks before the SV (note: patients who develop a URI or LRI during the run-in period may be rescreened 2 weeks after symptoms resolve).

i. The patient has had an asthma exacerbation requiring systemic corticosteroids within 30 days before the SV or has had any hospitalization for asthma within 2 months before the SV.

j. Initiation or dose escalation of immunotherapy (administered by any route) is planned during the study period. However, patients who initiated immunotherapy 90 days or more before the SV and have been on a stable (maintenance) dose for 30 days or more before the SV may be considered for inclusion.

k. The patient has used immunosuppressive medications within 30 days before the SV.

l. The patient is unable to tolerate or unwilling to comply with the appropriate washout periods and withholding of all applicable medications.

m. The patient has untreated oral candidiasis at the SV. Patients with clinical visual evidence of oral candidiasis who agree to receive treatment and comply with appropriate medical monitoring may enter the run-in period.

n. The patient has a history of a positive test for human immunodeficiency virus, active hepatitis B virus, or hepatitis C infection.

o. The patient is an immediate relative of an employee of the clinical investigational center.

p. A member of the patient's household is participating in the study at the same time. However, after the enrolled patient completes or discontinues participation in the study, another patient from the same household may be screened.

q. The patient has a disease/condition that, in the medical judgment of the investigator, would put the safety of the patient at risk through participation or that could affect the efficacy or safety analysis if the disease/condition worsened during the study. Examples include, but are not limited to, the following:

   – cardiovascular conditions including clinically significant cardiac arrhythmia, known aortic aneurysm, congenital heart disease, coronary heart disease, or vital signs clinically unacceptable for ranges in children with asthma as assessed by the investigator

   – hepatic, renal, hematologic, neuropsychologic, or endocrine conditions (eg, sickle cell disease, uncontrolled diabetes mellitus, uncontrolled thyroid disorder, Addison's disease, Cushing's syndrome, stroke within 3 months before the SV)

   – gastrointestinal conditions (eg, poorly controlled peptic ulcer disease, poorly controlled gastroesophageal reflux disease)

- infectious/immunologic conditions including untreated tuberculosis (a history of tuberculosis is acceptable only if a patient has received an approved prophylactic treatment regimen or an approved active treatment regimen and has had no evidence of active disease for a minimum of 2 years) and immunologic compromise
- ocular conditions including glaucoma, ocular herpes simplex, or cataracts
- oncologic conditions including any current malignancy, excluding basal cell carcinoma. History of malignancy is acceptable only if the patient has been in remission for 1 year before the SV. Remission is defined as no current evidence of malignancy and no treatment for the malignancy in the 12 months before the SV.
- pulmonary conditions including chronic bronchitis, emphysema, chronic bronchiectasis, cystic fibrosis, chronic lung disease, or chronic obstructive pulmonary disease
- renal conditions including chronic renal failure or ongoing dialysis
- history of or planned solid organ transplant

r. Vulnerable patients (ie, people kept in detention) are excluded from participation.

4.3. Withdrawal Criteria and Procedures for the Patient

In accordance with the Declaration of Helsinki (in accordance with the applicable country's acceptance), each patient (parent/legal guardian) is free to withdraw from the study at any time. The investigator also has the right to withdraw a patient from the study in the event of serious intercurrent illness, pregnancy (see Section 7.2), or other reasons concerning the health or well-being of the patient, or in the event of repeated and documented lack of cooperation. Patients who are withdrawn from IMP may choose not to withdraw consent and to continue their participation in the study. These patients should complete the remaining study procedures and visits, with the exception of IMP dosing. Patients will be asked to perform 1-hour postdose lung function assessments at the remaining treatment visits; 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.

In addition, a patient may be withdrawn from the study as described in Section 3.4.

Should a patient (parent/legal guardian) decide to withdraw after administration of IMP, all efforts will be made to complete and report all observations up to the time of withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made and an explanation given as to why the patient is withdrawing from the study.

The reason for and date of withdrawal from the study must be recorded on the source documentation and transcribed to the CRF. If a patient withdraws consent, every attempt will be made to determine the reason. If consent is withdrawn because of an adverse event, monitoring will be continued at the discretion of the investigator (eg, until the event has resolved or stabilized, until the patient is referred to the care of a health care professional, or until a

determination of a cause unrelated to the IMP or study procedure is made). The specific event or test result must be recorded on the source documentation and transcribed to the CRF.

All assessments should be performed according to the protocol on the last day the patient takes IMP, or as soon as possible thereafter.

If the final visit is conducted more than 7 ±2 days after the last dose of IMP, all safety assessments will be performed, but efficacy assessments will not be made (see Appendix B, Part 16).

4.3.1. Withdrawal for Worsening Asthma

Patients who meet the alert criteria and/or who experience a clinically meaningful worsening of their asthma will be assessed by the investigator. If the investigator considers it is not possible to safely manage a patient in a blinded manner as patient's asthma warrants a change in his/her asthma treatment, the IMP will be stopped, and appropriate treatment (based on the investigator's judgment) should be offered. The medical monitor should be contacted to confirm the findings when alternative therapy is to be instituted. The patient should continue in the study until the patient has completed all remaining study visits and the FV.

- 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. Significant treatment includes the use of systemic corticosteroids and/or the addition of other ICS-containing asthma medications, LABAs, or other NCS asthma medications, for example, inhaled short-acting muscarinic antagonist; ER/urgent care clinic visit; or hospitalization. Note: A single dose of nebulized albuterol/salbutamol would not meet the criteria for an asthma exacerbation. ER/urgent care clinic visits where the treatment is limited to a single dose of nebulized albuterol/salbutamol will not meet the criteria of an asthma exacerbation.

4.3.2. Alert Criteria for Worsening Asthma

Alert criteria for individual patients with worsening asthma have been designed to ensure patient safety. If any of the criteria listed below are met, during scheduled or unplanned study visit, the investigator will determine whether the patient's overall clinical picture is consistent with worsening asthma and if the patient should be withdrawn from IMP (but not the study) to be placed on alternative asthma therapy in the interest of patient safety. In cases where the IMP is to be withdrawn and alternative therapy started, the investigational center staff should contact the medical monitor to confirm the findings. Meeting 1 of these alert criteria does not automatically require a patient to be withdrawn from IMP, rather it requires a clinical evaluation to determine if the patient's asthma can continue to be managed in a blinded manner per the study or necessitates a change in asthma therapy. All attempts will be made to safely continue to manage a patient in a blinded manner.

- Morning FEV_1 by handheld device measured at home falls below the FEV_1 stability limit (see Section 6.1.3) calculated at the SV for the run-in period and at baseline for the treatment period on 4 or more days (do not have to be consecutive) out of any 7-day period (7-day period is defined as any consecutive 7 days following the RV and can overlap with scheduled study investigational center visits).

- Based upon a review of patient data from the patient diary built into the handheld device, the patient has experienced any of the following during a 7-day period (7-day period is defined as any consecutive 7 days following a previous TV; 7 days can overlap with scheduled study investigational center visits):
  - 3 or more days in which 8 or more inhalations/day of rescue medication (albuterol/salbutamol HFA MDI [90 mcg ex-actuator] or equivalent) were used (any 3 days in the consecutive 7-day period)
  - 3 or more days in which the patient experienced a nighttime asthma symptom score of more than 2 (any 3 days in the consecutive 7-day period)

4.4. Replacement of Patients

A patient who is randomized but does not complete the treatment period will not be replaced.

4.5. Rescreening

Patients who have not met inclusion criteria for response to a bronchodilator and cannot return within 7 days for a retest should be classified as screen failures but may be rescreened. Patients who experience an URI or LRI during the run-in period should be classified as randomization failures and be discontinued from the study, but may be rescreened 2 weeks after resolution of the infection. Patients who are rescreened will need to repeat all screening procedures and evaluations. Only 1 retest and 1 rescreening for each patient will be permitted.

The decision to retest or rescreen patients will be based on the investigator's judgment and the study protocol. In cases of rescreening, the sponsor or designee should be notified of the pending rescreening. Patients may retest/rescreen for lung function assessments and response to a bronchodilator only if they meet all other nonspirometric inclusion/exclusion criteria. At the retest, patients will be asked if they have had any adverse events, changes in medications, or changes in medical history. Patients will not be eligible to enter the run-in period until all inclusion/exclusion criteria are met.

4.6. Screening Failure

Screening failures are defined as participants who consent to participate in the clinical study but do not subsequently enter the placebo run-in period. Minimal information includes but is not limited to demography, screening failure details, eligibility criteria, and any serious adverse events.

Randomization failures are defined as participants who enter the placebo run-in period but are not subsequently randomized (ie, do not meet the randomization criteria).

5. TREATMENTS

5.1. Investigational Medicinal Products Used in the Study

IMP is defined as the test IMPs, reference IMPs, and matching placebo IMPs to the respective test and reference IMPs. Details for each IMP are provided below and in Table 4. (Note: The use of spacers or chambers for inhalers is not permitted with IMP inhalers [test or placebo] or rescue inhalers.)

5.1.1. Test Investigational Medicinal Product

The investigation products include the following:

- **Treatment A:** Fp MDPI 25 mcg, 1 inhalation twice daily
- **Treatment B:** Fp MDPI 50 mcg, 1 inhalation twice daily
- **Treatment C:** FS MDPI 50/12.5 mcg, 1 inhalation twice daily

5.1.2. Placebo Investigational Medicinal Product

The placebo used in this study includes the following:

- **Treatment D:** Placebo MDPI 0 mcg, 1 inhalation twice daily

Table 4: Investigational Medicinal Products Used in the Study

IMP Name	Fp MDPI	FS MDPI	Placebo IMP
Trade name and INN, if applicable, or company-assigned number	Fluticasone Propionate Inhalation Powder	Fluticasone Propionate/Salmeterol Inhalation Powder	Placebo inhalation powder
Formulation	Inhalation powder	Inhalation powder	Inhalation powder
Unit dose strength(s)/Dosage level(s)	25 mcg or 50 mcg	50/12.5 mcg	0 mcg
Route of administration	Inhalation	Inhalation	Inhalation
Dosing instructions	1 inhalation twice daily approximately 12 hours apart	1 inhalation twice daily approximately 12 hours apart	1 inhalation twice daily approximately 12 hours apart
Packaging	Inhaler device	Inhaler device	Inhaler device
Manufacturer	[redacted]	[redacted]	[redacted]

Fp=fluticasone propionate; FS=fluticasone propionate/salmeterol; IMP=investigational medicinal product; INN=international nonproprietary name; MDPI=multidose dry powder inhaler.

5.2. Preparation, Handling, Labeling, Storage, and Accountability for Investigational Medicinal Products

5.2.1. Storage and Security

For the purposes of the study, test IMPs (Fp MDPI, FS MDPI) and placebo with Teva MDPI devices must be stored between 15° and 25°C (59° and 77°F) in a dry place away from direct heat and sunlight, and in a securely locked, substantially constructed cabinet or enclosure. All rescue medication (albuterol/salbutamol HFA) will be stored according to the manufacturer's drug product stipulation, in a dry place, and in a securely locked, substantially constructed cabinet or enclosure. Maintenance of a daily temperature log (manual or automated) is required.

Each IMP shipment will include a packing slip listing the contents of the shipment and a device for monitoring and recording temperatures. The investigator is responsible for ensuring that deliveries of IMP and other study materials from the sponsor are treated as follows:

- correctly received and recorded
- handled and stored safely and properly in accordance with the Code of Federal Regulations (CFR) or local regulations
- used in accordance with this protocol

The investigational center personnel are responsible for the acknowledgement of the receipt using the interactive response technology (IRT).

Detailed instructions regarding labeling (eg, investigational centers indicating the use by date) of the IMP are provided in the study operations manual.

5.2.2. Labeling

Supplies of IMPs will be labeled according to the current International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practice and will include any locally required statements. If necessary, labels will be translated into the local language.

5.2.3. Accountability

Each IMP shipment will include a packing slip listing the contents of the shipment, drug return instructions, and any applicable forms.

The investigator is responsible for ensuring that deliveries of IMP and other study materials from the sponsor are correctly received, recorded, handled, and stored safely and properly in accordance with the CFR or national and local regulations, and used in accordance with this protocol.

The IMP for this study must be used in accordance with the protocol and may be dispensed to patients only by authorized study investigational center personnel. The investigator is responsible for drug accountability, reconciliation, and record maintenance. In accordance with applicable regulatory requirements, the investigator or designated study investigational center personnel must maintain IMP accountability records.

A record of IMP accountability (ie, IMP and other materials received, used, retained, returned, or destroyed) should be documented in the IRT and signed by the principal investigator or designee, with an account given for any discrepancies. Empty, partially used, and unused IMP will be returned to the sponsor or designee.

5.3. Justification for Investigational Medicinal Products

5.3.1. Justification for Dose of Test Investigational Medicinal Product

The Fp MDPI doses to be evaluated in this study (25 mcg twice daily and 50 mcg twice daily) were selected for study in patients 4 through 11 years of age based on the adult dose-ranging study. Based on the results from the adult and adolescent Phase 3 clinical trials (submitted for FDA review in March 2016), the 25- and 50-mcg twice-daily doses were confirmed as reasonable for studies in patients 4 through 11 years of age.

The FS MDPI dose to be evaluated in this study (50/12.5 mcg twice daily) was selected for study in patients 4 through 11 years of age based on the adult and adolescent dose-ranging study, which showed that FS MDPI at a total daily dose of 100/50 mcg was superior to ADVAIR DISKUS in its effects on FEV_1 over the 12 hours after a single dose, while lower doses of FS MDPI were generally comparable.

A detailed description of IMP administration is presented in Section 5.1.

5.3.2. Justification for Use of Placebo Investigational Medicinal Product

A placebo was elected to be used in this study in order to evaluate the efficacy of treatment with Fp MDPI or FS MDPI versus rescue treatment only in patients with persistent asthma.

5.4. Other Medicinal Products/Non-Investigational Medicinal Products

Not applicable.

5.5. Treatment After the End of the Study

No IMP will be provided beyond completion of the study. Patients should return to their primary care physician for treatment after study completion.

5.6. Restrictions

Medication restrictions are described in Section 5.7 and Appendix H. Patients will be required to comply with the following activity restrictions:

- Patients are not to engage in strenuous exercise on the mornings of any scheduled investigational center visits.
- If possible, patients should avoid cold air exposure on the mornings of any scheduled investigational center visits. Patients who experience bronchial symptoms related to exposure to cold air should be adequately stabilized at room temperature before performance of any study-related lung function assessments.

5.7. Prior and Concomitant Medication or Therapy

All patients will be required to be on a stable dose of asthma therapy for a minimum of 30 days before the SV. At the SV, all nonstudy asthma-related medications will be discontinued and replaced with placebo run-in medication and rescue medication for use during the run-in period. At the RV (TV1), these medications will be replaced with double-blind IMP and rescue medication for randomized patients for use during the double-blind period.

Allowed Medications: In addition to rescue medication use (albuterol/salbutamol inhalation aerosol), the following medications will be permitted, but with restrictions, during the study:

- Chronic and as-needed doses of low potency topical corticosteroids (eg, 1% hydrocortisone cream, desonide, fluocinolone cream 0.01%) are permitted for dermatologic diseases, not to exceed 20% of the body surface area; no occlusive dressing is permitted.
- Short-acting or long-acting antihistamine use (with a washout period of 24 hours before any visit) is permitted for the treatment of allergic rhinitis, as needed.
- Chronic stable doses of intranasal corticosteroids of at least 7 days' duration before the SV and stable throughout the study duration for the treatment of allergic rhinitis are allowed throughout the study.
- Chronic stable doses of ocular steroids of at least 7 days duration, with doses expected to remain stable throughout the study, are allowed.
- Immunotherapy for the treatment of allergies by any route is permitted as long as therapy was initiated 90 days or more before the SV and the patient has been on a stable dose for 30 days or more before the SV. The regimen must remain stable throughout the study.

Prohibited/Disallowed Medications:

The medications in Appendix H are not allowed during the study. The washout period is also defined. Initiation of immunotherapy (administered by any route) during this study is prohibited, as is the escalation of the dose of maintenance immunotherapy (administered by any route).

Patients who require continuous treatment with β-blockers, monoamine oxidase inhibitors, tricyclic antidepressants, anticholinergics, and/or systemic corticosteroids are excluded.

5.8. Procedures for Monitoring Patient Compliance

The investigator will be responsible for monitoring patient compliance. A check of IMP compliance will be performed during each visit after the initial dispensation of IMP; and IMP accountability records will be completed. If the investigator or the sponsor determines that the patient is not in compliance with the study protocol, the investigator and the sponsor should determine whether the patient should be withdrawn. The Independent Ethics Committee/Institutional Review Board (IEC/IRB) should be notified.

5.9. 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. 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.

The following criteria must be fulfilled at the RV:

a. The patient continues to be in general good health, meeting the entry criteria.

n. The average of the 5 highest values for trough morning FEV_1 obtained at home (by handheld device) out of the last 7 days prior to RV is within 40% to 85% predicted for age, height, sex, and race (Quanjer et al 2012).

o. The patient's C-ACT score at the RV is ≤19.

p. The patient has demonstrated at least a 15% response to a bronchodilator from baseline FEV_1 within 30 minutes after 2 to 4 inhalations of albuterol/salbutamol HFA MDI (90 mcg ex-actuator) or equivalent at SV or during the run-in period as measured by handheld device. Note: The RV may not be conducted on the same day as the response to bronchodilator testing.

q. The patient has had no significant changes in asthma medications during run-in, excluding the albuterol/salbutamol HFA MDI (90 mcg ex-actuator) or equivalent used as rescue medication or run-in placebo MDPI as supplied per protocol.

r. The patient has not had a URI or LRI during the run-in period. Patients who develop a URI or LRI during the run-in period may be discontinued from the study and allowed to rescreen 2 weeks after resolution of symptoms.

s. The patient has had no asthma exacerbation during the run-in period, defined as any worsening of asthma requiring any significant treatment other than rescue albuterol/salbutamol HFA MDI (90 mcg ex-actuator) or equivalent or the patient's

run-in MDPI. This includes requiring the use of systemic corticosteroids, inhaled corticosteroids or other medications used to control asthma or are prohibited medications (Appendix H), and/or ER/urgent care clinic visit or hospitalization. Note: A single dose of nebulized albuterol/salbutamol will not meet the criteria for an asthma exacerbation. Emergency room/urgent care clinic visits where the treatment is limited to a single dose of nebulized albuterol/salbutamol will not meet the criteria of an asthma exacerbation.

t. The patient has no clinical visual evidence (on oropharyngeal examination) of oropharyngeal candidiasis.

u. The patient has not experienced an adverse event that would result in failure to continue to meet selection criteria.

v. The patient has not used any of the prohibited concomitant medications during the run-in period (see Section 5.7 and Appendix H).

w. The patient has complied with home lung function assessments and patient diary (built into the handheld device) entry on at least 5 of the last 7 days prior to RV, including the following:

- completion of daytime and nighttime asthma symptom scores
- completion of daytime and nighttime rescue medication (albuterol/salbutamol HFA MDI) use (whether used or not)
- completion of the morning and evening lung function assessments (FEV_1 and PEF) by handheld device on 5 or more of the 7 days immediately preceding the RV
- recording of morning and evening IMP use on 5 or more of the 7 days immediately preceding RV

5.10. Maintenance of Randomization and Blinding

5.10.1. Maintenance of Randomization

Patient randomization codes will be maintained in a secure location at the service provider. At the time of analysis (after the end of study), after receiving unblinding request from the Teva statistician, the service provider will provide the unblinded treatment assignment according to the processes defined in the relevant Standard Operating Procedure (SOP).

5.10.2. Blinding and Unblinding

For information about personnel who may be aware of treatment assignments, see Section 5.9. These individuals will not be involved in conduct of any study procedures or assessment of any adverse events.

In case of a serious adverse event, pregnancy, or in cases when knowledge of the treatment assignment is needed to make treatment decisions, the investigator may unblind the patient's treatment assignment as deemed necessary, mainly in emergency situations, through specialized access in the IRT system. If possible, the sponsor should be notified of the event before breaking

of the code. If this is not possible, the sponsor should be notified immediately afterwards, and the patient's treatment code should not be revealed. Breaking of the treatment code can always be performed by the investigational center without prior approval by the sponsor.

When a blind is broken, the patient will be withdrawn from the study and the event will be recorded on the CRF. The circumstances leading to the breaking of the code should be fully documented in the investigator's study files and in the patient's source documentation. Treatment assignment should not be recorded in any study documents or source document.

In blinded studies, for an adverse event defined as a suspected unexpected serious adverse reaction (SUSAR) (ie, reasonable possibility; see Section 7.1.4), Global Patient Safety and Pharmacovigilance (GPSP) may independently request that the treatment code be broken (on a case-by-case basis) to comply with regulatory requirements. The report will be provided in an unblinded manner for regulatory submission. If this occurs, blinding will be maintained for the investigator and for other personnel involved in the conduct of the study, and analysis and reporting of the data.

5.10.3. Data Monitoring Committee

There will be no Data Monitoring Committee in this study.

5.11. Total Blood Volume

No laboratory tests or serum pregnancy tests will be performed in this study unless clinically indicated, and no blood is planned to be collected.

6. ASSESSMENT OF EFFICACY

6.1. Primary Efficacy Measure and Justification

The primary efficacy measures are as follows:

- For Fp MDPI versus placebo: the change from baseline in weekly average of the percent predicted trough morning 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

6.1.1. Lung Function Assessments (FEV_1 and PEF) by Handheld Device

Preferably, all lung function assessment (FEV_1 and PEF) are to be conducted consistently, using standardized equipment, time of day (±1 hour), and posture. Patients will be provided with a handheld device at the SV, which will be used to measure lung function assessments and will serve as an electronic patient diary to collect asthma symptom scores, rescue medication, and IMP use. The same handheld device should be used for a patient throughout the study, whenever possible. The device will be collected and inspected to make sure it is not damaged and the data will be downloaded at each clinic visit. Once inspected, the same handheld device will be redispensed to the patient unless it needs to be replaced.

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 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 instructions and training (competent handheld device use and dosing technique using the training devices provided), patients will repeat 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. 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 a 1-hour postdose FEV_1 measurement using the handheld device. The 1-hour postdose assessment should be conducted 60 ±10 minutes after IMP dosing (or as described for patients on alternative asthma

treatment; see Section 3.1). The highest FEV_1 value from 3 acceptable and 2 repeatable maneuvers (maximum of 8 attempts per test) will be obtained before and 1-hour after the morning dose. The acceptability and repeatability of each maneuver will be automatically determined as programmed by the handheld device. Patients will be allowed 1 retest for screening lung function assessments. Predicted FEV_1 will be computed and adjusted for age, height, race, and sex using the criteria of Quanjer (Quanjer et al 2012). A standard method for calculating FEV_1 will be provided to all investigational centers.

In cases of lung function assessment-induced bronchospasm (ie, successively lower values with good technique), the largest valid FEV_1 may be used.

The baseline lung function assessments are defined as the weekly average of the morning FEV_1 prior to the RV.

6.1.2. Response to a Bronchodilator

At SV, FEV_1 will be measured immediately before and within 30 minutes after administration of 2 to 4 inhalations of albuterol/salbutamol HFA MDI (90 mcg ex-actuator) or equivalent. Nebulized albuterol/salbutamol at a total dose of 2.5 mg may be used at the investigator's discretion. Spacers are also allowed during this time, but their use is only allowed for the test of response to bronchodilator. Patients who meet the criteria to enter the run-in but who have not demonstrated the required response to bronchodilator my repeat this testing 14 ±2 days after the SV and may have 1 final attempt if needed within 14 days. The run-in period should not exceed 30 days. Responses to a bronchodilator of 14.50% to 14.99% will be rounded to 15%. The percent response to a bronchodilator is calculated using the following equations, as applicable:

$$\frac{(\text{Post-bronchodilator } FEV_1 - \text{Pre-bronchodilator } FEV_1)}{\text{Pre-bronchodilator } FEV_1} \times 100\%$$

6.1.3. FEV_1 Stability Limit

At SV, the FEV_1 stability limit will be calculated for patients who qualify to enter the run-in period as 80% of the highest acceptable pre-albuterol/salbutamol FEV_1. This value will be used during the run-in period.

The FEV_1 stability limit for the treatment period will be calculated for each patient at the RV, as applicable, using the following equation:

Mean best pre-albuterol/salbutamol FEV_1 available from 5 of 7 days (the baseline value) preceding RV × 80%

This value will be used for the remainder of the study and will be used to determine alert criteria for worsening asthma, as applicable. The FEV_1 stability limit is automatically calculated and stored in the handheld device software. If a patient falls below the FEV_1 stability limit, an alert will appear on the handheld device screen.

6.2. Secondary Efficacy Measures

The secondary efficacy measures and time points for this study are as follows:

- PEF will be measured by the patient (with assistance from the parents/legal guardians/caregivers, as needed) with a handheld device in the morning and evening before administration of IMP or rescue medications. The time points for assessment of PEF as a secondary efficacy endpoint are specifically the morning (predose and pre-rescue bronchodilator) evaluation over the 12-week treatment period.
- The total daily (24-hour) use of albuterol/salbutamol inhalation aerosol will be calculated based on information recorded in the daily patient diary built into the handheld device by the patient (with assistance from the parents/legal guardians/caregivers, as needed) over weeks 1 through 12.
- Daytime and nighttime asthma symptom scores will be recorded in the daily patient diary built into the handheld device by the patient (with assistance from the parents/legal guardians/caregivers, as needed) over weeks 1 through 12.
- The C-ACT will be completed at weeks 4, 8, and 12 and at the IMPDV.
- The time to first onset of effect, defined as the first decrease from baseline in daily rescue medication use, will be calculated based on information recorded in the daily patient diary built into the handheld device by the patient (with assistance from the parents/legal guardians/caregivers, as needed).
- The proportion of patients who discontinued from IMP for asthma exacerbation during the 12-week treatment period will be evaluated over the 12-week treatment period.

6.2.1. Weekly Average of Daily Trough Morning Peak Expiratory Flow

Peak expiratory flow will be determined twice daily, in the morning before administration of IMP or rescue medications and in the evening. A handheld device will be provided to patients at the SV and used to determine the morning and evening PEF throughout the course of the study. The patient will record the highest value of 3 measurements obtained in the morning in the patient diary built into the handheld device.

On mornings for which a TV is scheduled (RV through TV6/IMPDV), patients will perform their morning PEF measurement as usual using the handheld device at home and will then repeat their PEF measurement (using the handheld device) at the investigational center. Symptom scores should always be assessed before any PEF measurements are obtained. The morning administration of IMP will take place and be recorded at the visit.

6.2.2. Weekly Average of Total Daily Rescue Medication Use

The 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 patient diary built into the handheld device. If there is no rescue medication usage, patients should enter 0 in the patient diary built into the handheld device. The average number of daily inhalations over the 7 days before the RV will be the baseline value and will be compared to the rescue aerosol over weeks 1 through 12.

6.2.3. Weekly Average of the Total Daily Asthma Symptom Score

The change from baseline in the weekly average of the total daily asthma symptom score will be assessed over weeks 1 through 12. The total daily asthma symptom score is the average of the daytime and nighttime scores.

Asthma symptom scores will be recorded in the patient diary built into the handheld device each morning and each evening before determining PEF and FEV_1 and before administration of study or rescue medications.

Each patient will assess the symptoms of cough, wheeze, shortness of breath, and chest tightness and enter a single score that is inclusive of all symptoms.

On mornings for which a TV is scheduled (SV through TV6), the symptom scores and recording of the morning administration of IMP will be completed at the investigational center visit. Symptom scores should always be assessed before lung function assessments (FEV_1 and PEF) by handheld device are obtained.

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 school 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

6.2.4. Change from Baseline in Asthma Control (measured by C-ACT) 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 questions are scored on a 3-point scale (0 to 3) and the last 3 questions are scored on a 5-point scale (0 to 5), with summation of all items providing scores ranging from 0 to 27. These scores span the continuum of poor control of asthma (score ≤5) to complete control of asthma (score ≥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 parent/legal guardian/caregiver (as applicable) at the investigational center, before any other assessments are performed, at the specified visits.

The investigators and personnel will be provided with detailed instructions for administering the C-ACT (in the study reference manual) in order to achieve maximum compliance in a clinical study environment and maximum data quality. After completion of the C-ACT, investigational center personnel will check the questionnaires for completeness and legibility.

The C-ACT should be completed during a study visit and should precede any discussion of asthma status between the patient/parent/caregiver and investigational center personnel.

6.2.5. Time to First Onset of Effect

The time to first onset of effect, defined as the first decrease from baseline in daily rescue medication use, will be calculated based on the number of inhalations of rescue medication (albuterol/salbutamol HFA MDI [90 mcg ex-actuator] or equivalent) recorded by the patient each morning and evening in the patient diary built into the handheld device.

6.2.6. Proportion of Patients who Discontinued from IMP for Asthma Exacerbation During the 12-week Treatment Period

The proportion of patients who discontinued from IMP for asthma exacerbation during the 12-week treatment period will be assessed.

6.3. Other Efficacy Measures

The other efficacy measures for this study are as follows:

- The total daily (24-hour) use of albuterol/salbutamol inhalation aerosol will be calculated based on information recorded in the daily patient diary built into the handheld device by the patient (with assistance from the parents/legal guardians/caregivers, as needed) at weeks 4, 8, and 12.
- The percentage of rescue-free days and symptom-free days will be calculated based on information recorded in the daily patient diary built into the handheld device by the patient (with assistance from the parents/legal guardians/caregivers, as needed) over the 12-week treatment period.
- The percentage of asthma-control days will be calculated based on information recorded in the daily patient diary built into the handheld device by the patient (with assistance from the parents/legal guardians/caregivers, as needed) over the 12-week treatment period.
- FEV_1 will be measured by the patient (with assistance from the clinic staff) with a handheld device in the clinic before administration of IMP or rescue medications at the morning evaluation on weeks 1, 2, 4, 8, and 12. The change from baseline in 1-hour postdose percent predicted morning FEV_1 at week 1 and in the weekly average of percent predicted trough morning FEV_1 will be based on the measurements obtained in the clinic.
- PEF will be measured by the patient (with assistance from the parents/legal guardians/caregivers, as needed) with a handheld device before administration of IMP or rescue medications at the evening evaluation over the 12-week treatment period. The change from baseline in the weekly average of daily evening PEF will be

calculated based on information recorded in the daily patient diary built into the handheld device by the patient (with assistance from the parents/legal guardians/caregivers, as needed).

- The change from baseline in asthma control (measured by C-ACT) score will be evaluated over the 12-week treatment period. C-ACT will be completed at weeks 4, 8, and 12.
- The time to consistent onset of effect defined as the decrease from baseline in daily rescue medication use on 3 consecutive days will be calculated based on the number of inhalations of rescue medication recorded by the patient each morning and evening in the patient diary built into the handheld device.

6.3.1. Change from Baseline in Weekly Average of Total Daily Rescue Medication Use

The change from baseline in the weekly average of total daily use of albuterol/salbutamol inhalation aerosol will be assessed at weeks 4, 8, and 12.

6.3.2. Change from Baseline in Percentage of Rescue-Free Days

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 the evening) as recorded in the patient diary built into the handheld device during the 12-week treatment period will be summarized.

6.3.3. Change from Baseline in Percentage of Symptom-Free Days

The change from baseline in the percentage of symptom-free days (defined as 24-hour periods with asthma symptom score of 0) as recorded in the patient diary built into the handheld device during the 12-week treatment period will be summarized.

6.3.4. Change from Baseline in Percentage of Asthma-Control Days

The 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 use) as recorded in the patient diary built into the handheld device during the 12-week treatment period will be summarized.

6.3.5. Change from Baseline in 1-hour Postdose Percent Predicted Morning FEV_1 at Week 1

The change from baseline in 1-hour postdose percent predicted morning FEV_1 at week 1 will be assessed at TV2.

6.3.6. Change from Baseline in Weekly Average of Daily Evening Peak Expiratory Flow

The change from baseline in the weekly average of daily evening PEF over the 12-week treatment period will be assessed.

6.3.7. Change from Baseline in Weekly Average of Percent Predicted Trough Morning FEV_1

The change from baseline in weekly average of the percent predicted trough morning FEV_1 will be assessed at weeks 1, 2, 4, and 8.

6.3.8. Proportion of Patients Who Achieve At Least a 15% Increase in Morning FEV_1

The proportion of patients who achieve at least a 15% increase in FEV_1 at 1-hour postdose at day 1 (the RV/TV1), week 1 (TV2), and week 12 (TV6) will be assessed.

6.3.9. Change from Baseline in Asthma Control (measured by C-ACT) Score

The change from baseline in C-ACT score at weeks 4, 8, and 12 will be assessed.

6.3.10. Time to Consistent Onset of Effect

The time to consistent onset of effect (defined as the decrease from baseline in daily rescue medication use on 3 consecutive days) will be calculated based on the number of inhalations of rescue medication recorded by the patient each morning and evening in the patient diary built into the handheld device and will be summarized.

6.4. Safety Measures and Time Points

Safety measures and time points for this study are as follows:

- inquiries about adverse events at all visits
- vital signs measurements at all visits
- oropharyngeal examinations at all visits
- physical examinations at baseline and week 12 or at the IMPDV

7. ASSESSMENT OF SAFETY

In this study, safety will be assessed by qualified study personnel by evaluating reported adverse events, vital signs measurements, physical examination findings (including body weight measurements), and oropharyngeal examination findings. In addition, during the study, PEF and FEV_1 will be monitored as part of safety monitoring (alert criteria for worsening asthma). Any visual evidence of oral candidiasis during the treatment period will be confirmed by obtaining a swab for culture of the suspect area. Patients and parents/legal guardians/caregivers will be provided with guidelines for when to contact the investigational center in case of worsening asthma symptoms or rescue inhaler use. Patients who meet predefined alert criteria should be evaluated by the investigator. The investigator will determine whether the patient's overall clinical picture is consistent with worsening asthma and if the patient should be withdrawn from IMP (but not the study) to be placed on alternative asthma therapy in the interest of patient safety.

7.1. Adverse Events

7.1.1. Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

In this study, any adverse event occurring after the clinical study patient has signed the informed consent form/assent form (as applicable) should be recorded and reported as an adverse event.

An adverse event can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of this study, or significant worsening of the disease under study, or of any concurrent disease, whether or not considered related to the IMP. (Note: Asthma exacerbations in this study will not be considered adverse events unless they meet the criteria for serious adverse events.) A new condition or the worsening of a pre-existing condition will be considered an adverse event. Stable chronic conditions (such as arthritis) that are present before study entry and do not worsen during this study will not be considered adverse events (but should be recorded as medical history).

Accordingly, an adverse event can include any of the following:

- intercurrent illnesses
- physical injuries
- events possibly related to concomitant medication
- significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions
- drug interactions
- events occurring during diagnostic procedures or during any washout phase of this study

- laboratory or diagnostic test abnormalities that result in the withdrawal of the patient from the study, are associated with clinical signs and symptoms or a serious adverse event, require medical treatment or further diagnostic work-up, or are considered by the investigator to be clinically significant (Note: Abnormal laboratory test results at the SV that preclude a patient from entering the study or receiving IMP are not considered 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. Significant treatment includes the use of systemic corticosteroids and/or the addition of other ICS-containing asthma medications, LABAs, or other NCS asthma medications, for example, inhaled short-acting muscarinic antagonist, ER/urgent care clinic visit(s), or hospitalization. Note: A single dose of nebulized albuterol/salbutamol would not meet the criteria for an asthma exacerbation. ER/urgent care clinic visits where the treatment is limited to a single dose of nebulized albuterol/salbutamol will not meet the criteria of an asthma exacerbation.

Asthma exacerbation 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.

Any occurrence of oropharyngeal candidiasis that is confirmed by culture during the study will be reported as an adverse event. A patient who agrees to be treated may continue in the study at the discretion of the investigator.

If any patient dies during the study, a listing of deaths will be provided, and all relevant information will be discussed in the patient narrative included in the clinical study report (CSR).

7.1.2. Recording and Reporting of Adverse Events

For recording of adverse events, the study period is defined for each patient as that time period from signature of the informed consent/assent form (as applicable) to the end of the follow-up period. The follow-up period is defined as 7±2 days after the last dose of IMP.

All adverse events that occur during the defined study period must be recorded on the source documentation and transcribed to the CRF, regardless of the severity of the event or judged relationship to the IMP. For serious adverse events, the Serious Adverse Event Form must be completed and the serious adverse event must be reported immediately. The investigator does not need to actively monitor patients for adverse events once the study has ended. Serious adverse events occurring in a patient (after the treatment of that patient has ended) should be reported to the sponsor if the investigator becomes aware of them, following the procedures described in Section 7.1.5.3.1.

At each contact with the patient, the investigator or designee must question the patient about adverse events by asking an open-ended question such as “Have you had any unusual symptoms or medical problems since the last visit? If yes, please describe”. All reported or observed signs

and symptoms will be recorded individually, except when considered manifestations of a medical condition or disease state. A precise diagnosis will be recorded whenever possible. When such a diagnosis is made, all related signs, symptoms, and any test findings will be recorded collectively as a single diagnosis on the CRF and, if it is a serious adverse event, on the serious adverse event form.

The clinical course of each adverse event will be monitored at suitable intervals until resolved, stabilized, or returned to baseline; or until the patient is referred for continued care to a health care professional; or until a determination of a cause unrelated to the IMP or study procedure is made.

The onset and end dates, duration (in case of adverse event duration of less than 24 hours), action taken regarding IMP, treatment administered, and outcome for each adverse event must be recorded on the source documentation and transcribed to the CRF.

The relationship of each adverse event to IMP and study procedures, and the severity and seriousness of each adverse event as judged by the investigator, must be recorded as described below.

7.1.3. Severity of an Adverse Event

The severity of each adverse event must be recorded as 1 of the following:

Mild: No limitation of usual activities

Moderate: Some limitation of usual activities

Severe: Inability to carry out usual activities

7.1.4. Relationship of an Adverse Event to the Test Investigational Medicinal Product

The relationship of an adverse event to the test IMP is characterized in Table 5.

Table 5: The Relationship of an Adverse Event to the Test Investigational Medicinal Product

Term	Definition	Clarification
No reasonable possibility (not related)	This category applies to adverse events that, after careful consideration, are clearly due to extraneous causes (disease, environment, etc) or to adverse events that, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the IMP.	The relationship of an adverse event may be considered "no reasonable possibility" if it is clearly due to extraneous causes or if at least 2 of the following apply: • It does not follow a reasonable temporal sequence from the administration of the IMP. • It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It does not follow a known pattern of response to the IMP. • It does not reappear or worsen when the IMP is re-administered.
Reasonable possibility (related)	This category applies to adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the administration of IMP cannot be ruled out with certainty.	The relationship of an adverse event may be considered "reasonable possibility" if at least 2 of the following apply: • It follows a reasonable temporal sequence from administration of the IMP. • It cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear after discontinuation of the IMP, yet an IMP relationship clearly exists. • It follows a known pattern of response to the IMP.

IMP=investigational medicinal product.

7.1.5. Serious Adverse Events

For recording of serious adverse events, the study period is defined for each patient as that time period from signature of the informed consent form to the end of the follow-up period. Serious adverse events occurring in a patient after the end of the follow-up period should be reported to the sponsor if the investigator becomes aware of them, following the procedures described in Section 7.1.5.3.1.

7.1.5.1. Definition of a Serious Adverse Event

A serious adverse event is an adverse event occurring at any dose that results in any of the following outcomes or actions:

- death

- is life-threatening adverse event (ie, the patient was at risk of death at the time of the event); it does not refer to an event which hypothetically might have caused death if it were more severe
- requires inpatient hospitalization or prolongation of existing hospitalization, which means that hospital inpatient admission or prolongation of hospital stay were required for treatment of an adverse event, or that they occurred as a consequence of the event

  Hospitalizations scheduled before the patient signed the informed consent form will not be considered serious adverse events, unless there was worsening of the pre-existing condition during the patient's participation in this study.
- persistent or significant disability/incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- is a congenital anomaly/birth defect
- an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the patient and may require medical intervention to prevent one of the outcomes listed in this definition

  Examples of such events are intensive treatment in an ER or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.

7.1.5.2. Expectedness

A serious adverse event that is not included in the Adverse Reaction section of the relevant reference safety information (RSI) by its specificity, severity, outcome, or frequency is considered an unexpected adverse event. The RSI for this study are the Teva Fp MDPI and FS MDPI IBs.

The sponsor's GPSP will determine the expectedness for all serious adverse events.

For the purpose of SUSAR reporting, the version of the IB at the time of occurrence of the SUSAR applies.

7.1.5.3. Reporting a Serious Adverse Event

7.1.5.3.1. Investigator Responsibility

To satisfy regulatory requirements, all serious adverse events that occur during the study, regardless of judged relationship to administration of the test IMP, must be reported to the sponsor by the investigator. The event must be reported within 24 hours of when the investigator learns about it. Completing the serious adverse event form and reporting the event must not be delayed, even if not all the information is available. The investigator does not need to actively monitor patients for adverse events once this study has ended.

Serious adverse events occurring to a patient after the last administration of IMP of that patient has ended should be reported to the sponsor if the investigator becomes aware of them.

The serious adverse event form should be sent to the local safety officer (LSO) or designee (a contract research organization [CRO] in a country without a sponsor LSO) (contact information is in the Clinical Study Personnel Contact Information section); the LSO will forward the report to the sponsor's GPSP.

The following information should be provided to record the event accurately and completely:

- study number
- investigator and investigational center identification
- patient number
- onset date and detailed description of adverse event
- investigator's assessment of the relationship of the adverse event to the test IMP (no reasonable possibility, reasonable possibility)

Additional information includes:

- age and sex of patient
- date of first dose of IMP
- date and amount of last administered dose of IMP
- action taken
- outcome, if known
- severity
- explanation of assessment of relatedness
- concomitant medication (including doses, routes of administration, and regimens) and treatment of the event
- pertinent laboratory or other diagnostic test data
- medical history
- results of dechallenge/rechallenge, if known
- for an adverse event resulting in death
  - cause of death (whether or not the death was related to IMP)
  - autopsy findings (if available)

Each report of a serious adverse event will be reviewed and evaluated by the investigator and the sponsor to assess the nature of the event and the relationship of the event to the test IMP, study procedures, and to underlying disease.

Additional information (follow-up) about any serious adverse event unavailable at the initial reporting should be forwarded by the investigator within 24 hours of when it becomes known to the same address as the initial report.

For all countries, the sponsor's GPSP will distribute the Council for International Organizations of Medical Sciences (CIOMS) form/Extensible Markup Language (XML) file to the LSO/CRO

for submission to the competent authorities, IEC/IRBs, and investigators, according to regulations. The investigator is responsible for ensuring that the IEC/IRB is also informed of the event, in accordance with national and local regulations.

For double-blind studies, blinding will be maintained for all study personnel. Therefore, in case of a SUSAR, only the LSO/CRO will receive the unblinded report for regulatory submission; the others will receive a blinded report.

7.1.5.3.2. Sponsor Responsibility

If a SUSAR is believed to be related to the IMP or study procedures, the sponsor will take appropriate steps to notify all investigators participating in sponsored clinical studies of Fp MDPI and FS MDPI and the appropriate competent authorities (and IEC/IRB, as appropriate).

In addition to notifying the investigators and competent authorities (and IEC/IRB, as appropriate), other measures may be required, including:

- altering existing research by modifying the protocol
- discontinuing or suspending the study
- altering the process of informed consent by modifying the existing consent form and informing all study participants of new findings
- modifying listings of expected toxicities to include adverse events newly identified as related to Fp MDPI and FS MDPI

7.1.6. Protocol-Defined Adverse Events not for Expedited Reporting

No protocol-defined adverse events not for expedited reporting were identified for this study.

7.1.7. Protocol-Defined Adverse Events of Special Interest

No protocol-defined adverse events of special interest were identified for this study.

7.1.8. Protocol Deviations Because of an Adverse Event

If a patient experiences an adverse event or medical emergency, deviations from the protocol may be allowed on a case-by-case basis. To ensure patient safety, after the event has stabilized or treatment has been administered (or both), the investigator or other physician in attendance must contact the physician identified in the Clinical Study Personnel Contact Information section of this protocol as soon as possible to discuss the situation. The investigator, in consultation with the sponsor, will decide whether the patient should continue to receive study IMP, continue in the study on alternative treatment, or be withdrawn from the study in the interest of patient safety.

7.2. Pregnancy

All pregnancies of females participating in the study that occur during the study, or within 30 days of completion of the study, are to be reported immediately to the physician identified in the Clinical Study Personnel Contact Information section of this protocol, and the investigator must provide the LSO/CRO with the pregnancy form. The process for reporting a pregnancy is

the same as that for reporting a serious adverse event but using the pregnancy form (see Section 7.1.5.3.1).

Any female patient becoming pregnant during the study will discontinue treatment. All patients who become pregnant will be monitored for the outcome of the pregnancy (including spontaneous or voluntary termination). If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), including details of birth and presence or absence of any birth defect, congenital abnormalities, or maternal and newborn complications, will be reported to the sponsor. Any complication of pregnancy during the study and any complication of pregnancy that the investigator becomes aware of after withdrawal from the study will be reported as an adverse event or serious adverse event, as appropriate.

If the pregnancy does not continue to term, 1 of the following actions will be taken:

- For a spontaneous abortion, report as a serious adverse event.
- For an elective abortion due to developmental anomalies, report as a serious adverse event.
- For an elective abortion **not** due to developmental anomalies, report on the pregnancy form; do not report as an adverse event.

7.3. Medication Error and Special Situations Related to the Investigational Medicinal Products

Any administration of IMP that is not in accordance with the study protocol should be reported either as a violation, if it meets the violation criteria specified in the protocol (Appendix C), or as a deviation, in the patient's source documents, regardless of whether or not an adverse event occurs as a result. When meeting protocol violation criteria, all instances of incorrect IMP administration should be categorized as "Non-Compliance to investigational medicinal product (IMP)."

The following are types of medication errors and special situations, as reported by the investigator:

1. Medication error: Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient, or consumer.
4. Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information. Clinical judgment should always be applied. Any dose of IMP (whether the test IMP, reference IMP, or placebo IMP), whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to the sponsor.
5. Abuse: Persistent or sporadic, intentional excessive use of IMP which is accompanied by harmful physical or psychological effects.
6. Off-label use: Situations where an IMP is intentionally used for a medical purpose not in accordance with the authorized product information.

7. Occupational exposure: Exposure to an IMP as a result of one's professional or nonprofessional occupation.
8. Breastfeeding: Suspected adverse reactions which occur in infants following exposure to a medicinal product from breast milk.

When the identification of the IMP is required, the investigator must follow the procedures for unblinding outlined in Section 5.10.2.

7.4. Clinical Laboratory Tests

Since the IMPs in this trial are well-established molecules and are not known to influence clinical laboratory tests at doses to be studied in this trial, optional clinical laboratory evaluation, if needed at the discretion of the investigator, may be performed during the study at a local laboratory. These clinical laboratory tests may be performed to ensure the health and wellbeing of the patients but will not be used to assess the safety of the IMP.

All clinical laboratory test results outside of the reference range will be judged by the investigator as belonging to one of the following categories:

- abnormal but not clinically significant
- abnormal and clinically significant

A laboratory test result that is judged by the investigator as clinically significant will be recorded on the source documentation, transcribed to the CRF as an adverse event, and monitored as described in Section 7.1.2. An event may include a laboratory or diagnostic test abnormality (once confirmed by repeated testing) that results in patient continuing study participation, the withdrawal of the patient from the study, the temporary or permanent cessation of treatment with IMP or medical treatment, or further diagnostic work-up.

7.4.1. Human Chorionic Gonadotropin Tests

Human chorionic gonadotropin tests in urine will be performed for all female patients who have reached puberty and achieved menarche at the SV and, if clinically indicated, thereafter. Any female patient who becomes pregnant during the study will be withdrawn. Procedures for reporting the pregnancy are provided in Section 7.2.

7.5. Physical Examinations

Physical examinations, including weight and height, will be performed at the time points detailed in Table 3. Any physical examination finding that is judged by the investigator as clinically significant will be considered an adverse event, recorded on the CRF, and monitored as described in Section 7.1.2.

7.6. Vital Signs

Vital signs (blood pressure [BP] and pulse) will be measured at the time points detailed in Table 3. All vital signs results outside of the reference ranges will be judged by the investigator as belonging to 1 of the following categories:

- abnormal but not a clinically significant worsening from baseline

- abnormal and a clinically significant worsening from baseline

Before BP and pulse are measured, the patient must be in a supine or semi-erect/seated position and resting for at least 5 minutes (the same position and arm should be used each time vital signs are measured for a given patient). For any abnormal vital sign finding, the measurement should be repeated as soon as possible. Any vital sign value that is judged by the investigator as clinically significant will be recorded on the source documentation, transcribed to the CRF as an adverse event, and monitored as described in Section 7.1.2.

In addition, potentially clinically significant values may be predefined by the sponsor for selected vital signs (see Section 9.7) and, if so, will be documented in the statistical analysis plan or other relevant documents (eg, medical monitoring plan).

7.7. Oropharyngeal Examinations

Oropharyngeal examinations will be performed at every visit (SV through TV6). The examination must be performed by a qualified healthcare professional. Whenever possible, the same qualified healthcare professional should complete the assessment for the same patient throughout that patient's participation in the study.

Patients with clinical visual evidence of oral candidiasis at SV who agree to receive treatment and comply with appropriate medical monitoring may participate in the run-in period and may return for randomization. However, if the oral candidiasis is not controlled at that time, the patient will not be allowed to enter the study treatment period.

Any visual evidence of oral candidiasis during the treatment period of the study (after RV through TV6, inclusive) will be evaluated by obtaining and analyzing a swab of the suspect area. Appropriate therapy should be initiated immediately at the discretion of the investigator and should not be delayed for culture confirmation.

Patients with a culture-positive infection may continue participation in the study on appropriate anti-infective therapy, provided this therapy is not prohibited by the protocol. If a patient requires a protocol-prohibited medication for therapy, the patient will be discontinued from the study and provided appropriate therapy.

8. ASSESSMENT OF PHARMACOKINETICS / PHARMACODYNAMICS / BIOMARKERS / PHARMACOGENOMICS / IMMUNOGENICITY / ANCILLARY STUDIES

8.1. Pharmacokinetic Assessment

Pharmacokinetic parameters are not evaluated in this study.

8.2. Pharmacodynamics Assessment

Pharmacodynamic parameters are not evaluated in this study.

8.3. Assessment of Exploratory Biomarkers

Biomarkers are not evaluated in this study.

9. STATISTICS

This section describes the statistical analysis planned for this study. Changes, additions, and further details about the analyses will be described in the statistical analysis plan (SAP). After finalization of the statistical analysis plan, any additional analyses or changes to analyses that may be required will be fully disclosed in the CSR.

9.1. 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%.

This study FSS-AS-30003 is the first Teva's study in which the handheld spirometry is utilized as an endpoint and this hanheld device is being used in a pediatric asthma patient population, the target population of this study. A blinded sample size reassessment was not planned for this study. However, routine blinded data monitoring of this study FSS-AS-30003 revealed that a few patietnts showed nonphysiologic (~200% of percent predicted FEV_1) changes from baseline. This triggered a blinded sample size reassessment that showed that the overall mean change from baseline and SD for the overall study population is higher than the initial assumptions based on the office spirometry in adult asthma patients. In addition, monitoring of FEV_1 stability throughout the study revealed challenges in obtaining consistent morning trough FEV_1 values with best efforts in this young patient population, despite the rigorous training and coaching

provided by the investigators. Therefore, 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.

Assuming a dropout rate of 12%, then 206 patients per treatment group in the 4 treatment groups, for a total of 824 patients, will be randomized (initial assumption for dropout rate was 15%).

9.2. Analysis Sets

9.2.1. 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 efficacy analyses.

9.2.2. 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.

9.2.3. Per-Protocol Analysis Set

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 both data collected in the IMP dose counter and diary. Details will be provided in the SAP. 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 PP analysis set will serve as the supportive population for the primary efficacy analysis only.

9.3. Data Handling Conventions

Data imputation rules will be described in the statistical analysis plan, as appropriate for each endpoint.

9.4. Study Population

The ITT analysis set (Section 9.2.1) will be used for all study population summaries unless otherwise specified. Summaries will be presented by treatment group and for all patients.

9.4.1. 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; patients in the ITT, safety, and PP analysis sets; patients who complete the study; and patients who withdraw from the treatment period of the study and the reason for withdrawal.

9.4.2. Demographic and Baseline Characteristics

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. For continuous variables, descriptive statistics (number [n], mean, SD, median, minimum, and maximum) will be provided. For categorical variables, patient counts and percentages will be provided. Categories for missing data will be presented if necessary.

Patient demographics will be presented for all 3 analysis sets defined in Section 9.2.

9.5. Efficacy Analysis

9.5.1. Primary Endpoint

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 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

9.5.2. Secondary Endpoints

The 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 the statistical analysis plan.

9.5.3. Other Efficacy Endpoints

The other efficacy endpoints include the following:

- 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 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

9.5.4. Planned Method of Analysis

The ITT analysis set (Section 9.2.1) will be the primary analysis set to be used for all efficacy analyses. The PP analysis set will serve as the sensitivity analysis set for primary efficacy analyses only. Details will be provided in the statistical analysis plan. Subgroup (sex, age group,

previous therapy [ICS or NCS], and race) analyses will be provided for the primary efficacy endpoints.

9.5.4.1. Primary Estimands and Efficacy Analysis

The specific 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 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 (Little and Kang 2015, Mallinckrodt et al 2016, Mallinckrodt 2013, 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, such as systemic corticosteroids, additional medications containing ICS, or both, which would 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 or exceeding 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. In light of this, 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 in Mallinckrodt et al 2016 (Sections 3.2 and 3.4 for estimand 2 in the paper).

Analysis of the change from baseline in weekly average of the percent predicted trough morning FEV_1 at week 12

The baseline percent predicted FEV_1 will be the weekly average of the morning FEV_1 prior to the first IMP dose. The first day before randomization consists of the entry on the morning of the RV in the patient diary built into the handheld device. The weekly average of the percent predicted FEV_1 at week 12 will be the average values based on the available data at that week.

The primary analysis of the change from baseline in weekly average of percent predicted morning FEV_1 at week 12 due to the initially randomized treatment as actually taken 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 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% confidence interval (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. Details on the implementation of the multiple imputations will be provided in the statistical analysis plan.

Analysis of the change from baseline in 1-hour postdose percent predicted morning FEV_1 at week 12

For the endpoint of change from baseline in 1-hour postdose percent predicted morning FEV_1 (measured at the clinic) at week 12, baseline is defined as predose FEV_1 measurements obtained at the clinic at the RV with the handheld device immediately prior to the IMP administration.

The primary analysis of the change from baseline in 1-hour postdose percent predicted morning FEV_1 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 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 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. Missing data caused by early dropouts will be handled similarly to the above analysis.

9.5.4.2. Sensitivity Analysis to Missing Data

To assess the impact of missing data, several sensitivity analyses will be conducted for the 2 endpoints by evaluating alternative estimands. More details will be provided in the statistical analysis plan.

- The primary analysis for the 2 endpoints will be repeated when using data collected after IMP discontinuation (retrieved dropout data). Reference-based imputation will be used only for patients with no retrieved dropout data. This analysis estimates different estimands, namely the change from baseline as actually taken (see estimand 1 in Mallinckrodt et al 2016).
- The primary analysis for the 2 endpoints will be repeated on completers with no major protocol violations (see estimand 3 in Mallinckrodt et al 2016).
- A tipping point analysis will be performed as a sensitivity analysis to missing data by utilizing multiple imputations under different missing mechanism. For placebo patients, in all applications of multiple imputations, missing at random (MAR) will be assumed. 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. This analysis will utilize only data collected prior to IMP discontinuation. Additional details will be provided in the SAP.

- "2-dimensional tipping point" multiple imputation will be performed similar to above, the shifts to the distribution will apply to both placebo and active arms, to represent different degrees of effect loss. This analysis will utilize only data collected prior to IMP discontinuation. Additional details will be provided in the SAP.
- The primary analysis for the 2 endpoints will be repeated when missing data will be imputed using a mixed approach of last observation carried forward (LOCF) and baseline observation carried forward (BOCF) as follows: BOCF will be used for patients who had a positive change from baseline at the time of study or IMP discontinuation (ie, a change of 0), while LOCF will be used for patients that have negative change from baseline. In this imputation method, the imputed value is the lower between LOCF and BOCF for each patient. No adjustments will be made to other patients.
- For the first primary endpoint of change from baseline in the weekly average of percent predicted trough morning FEV_1 over the 12-week treatment period, analysis will be performed using a mixed model for repeated measures (MMRM). This analysis will not use retrieved dropout data. This analysis represents a MAR assumption.

9.5.4.3. Secondary Efficacy Analysis

For all secondary endpoints, analyses will be performed using the ITT analysis set and will not include retrieved dropout data in the analysis.

Analysis of change from baseline in weekly average of daily trough morning PEF, total daily use of albuterol/salbutamol, total daily asthma symptom score, and C-ACT score over the 12-week treatment period will be analyzed using an MMRM analysis with effects due to baseline, sex, age, (pooled) investigational center, previous therapy (ICS or NCS), treatment, time, and time-by-treatment interaction. For all of these endpoints, the MMRM will use only observations collected until IMP discontinuation.

The time to first onset of effect, defined as the first decrease from baseline in daily rescue medication use, will be analyzed using a log-rank test. Median and mean time to first onset of effect and associated 95% Cis will be estimated. Time to first onset of effect will also be displayed graphically with a Kaplan-Meier figure.

The proportion of patients who 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. These patients will be considered as nonresponders in this analysis.

9.5.4.4. Other Efficacy Analysis

Statistical methods to be used for other efficacy endpoints will be described and detailed in the statistical analysis plan.

9.6. Multiple Comparisons and Multiplicity

A fixed-sequence testing procedure will be employed to control the overall Type I error rate at the 2-sided 0.05 level for the co-primary endpoints. The sequential order of comparisons will be as follows:

1. 1-hour postdose percent predicted FEV_1 comparing FS MDPI 50/12.5 mcg versus Fp MDPI 50 mcg

9. Trough percent predicted FEV_1 comparing Fp MDPI 50 mcg versus placebo

10. Trough percent predicted FEV_1 comparing Fp MDPI 25 mcg versus placebo

Each test will be 2-sided and performed at the 0.05 level of significance. However, if a test is not significant at the 2-sided 0.05 level, no further tests will be performed.

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 to 11 years of age), an unplanned blinded sample size reassement was conducted. Since the adjustment to sample size was based on blinded standard deviation, no adjustment to the multiplicity control is warrented.

Multiplicity control for the secondary endpoints and the sequential order of the secondary endpoints will be described in the statistical analysis plan.

No multiplicity adjustments will be made for other efficacy analyses.

9.7. Safety Analysis

Safety analyses will be performed on the safety analysis set (Section 9.2.2).

Safety assessments and time points are provided in Table 3.

Safety data will be summarized using descriptive statistics by treatment group.

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Each patient will be counted only once in each preferred term (PT) or system organ class (SOC) category for the analyses of safety. 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 (ie, reasonable possibility; see Section 7.1.4) (defined as related or with missing relationship, overall and by severity), serious treatment-emergent adverse events, and treatment-emergent adverse events causing withdrawal from the study.

Summaries will be presented by treatment group and for all patients. Incidence and event counts will be summarized for the SOC and PT summary table. Patient listings of serious adverse events and treatment-emergent adverse events leading to withdrawal will be presented.

Shifts from baseline to the final TV (TV6/IMPDV) in physical examination findings will be summarized descriptively.

Changes in vital signs measurement data will be summarized descriptively. All values will be compared with predefined criteria to identify potentially clinically significant values or changes, and such values will be summarized and listed in separate tables and listings. Although such

values will be summarized and listed, clinical significance will be determined independently by the investigator.

The use of concomitant medications will be summarized by therapeutic class using descriptive statistics. Concomitant medications will include all medications taken while the patient is being treated with IMP.

For continuous variables, descriptive statistics (n, mean, SD, median, minimum, and maximum) will be provided for actual values and changes from baseline to each time point. For categorical variables, patient counts and percentages will be provided. Descriptive summaries of serious adverse events, patient withdrawals due to adverse events, and potentially clinically significant abnormal values (vital signs) based on predefined criteria will be provided as well.

If any patient dies during the study, a listing of deaths will be provided and all relevant information will be discussed in the patient narrative included in the CSR.

9.8. Tolerability Analysis

Tolerability will be assessed via other endpoints.

9.9. Planned Interim Analysis

There will be no interim analysis.

9.10. Reporting Deviations from the Statistical Plan

Deviations from the statistical plan, along with the reasons for the deviations, will be described in protocol amendments, the statistical analysis plan, the CSR, or any combination of these, as appropriate, and in accordance with applicable national, local, and regional requirements and regulations.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Refer to Appendix C for information regarding quality control and quality assurance. This includes information about protocol amendments, deviations and violations, responsibilities of the investigator to study personnel, study monitoring, and audit and inspection.

Refer to **Error! Reference source not found.** for the definition of a clinical product complaint and investigator responsibilities in the management of a clinical product complaint.

Details are given in a Study Manual.

11. COMPLIANCE STATEMENT

This study will be conducted in full accordance with the ICH Harmonised Tripartite Guideline for GCP E6 and any applicable national and local laws and regulations (eg, Title 21 CFR Parts 11, 50, 54, 56, 312, and 314, Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use). Any episode of noncompliance will be documented.

The investigator is responsible for performing the clinical study in accordance with this protocol and the applicable GCP guidelines referenced above for collecting, recording, and reporting the data accurately and properly. Agreement of the investigator to conduct and administer this clinical study in accordance with the protocol will be documented in separate clinical study agreements with the sponsor and other forms as required by national competent authorities in the country where each investigational center is located.

The investigator is responsible for ensuring the privacy, health, and welfare of the patients during and after the clinical study; and must ensure that trained personnel are immediately available in the event of a medical emergency. The investigator and the involved clinical study personnel must be familiar with the background and requirements of the study; and with the properties of the IMPs as described in the IB or prescribing information.

The principal investigator at each investigational center has the overall responsibility for the conduct and administration of the clinical study at that investigational center and for contacts with study management, with the IEC/IRB, and with competent authorities.

See Appendix D for the ethics expectations of informed consent or assent, competent authorities and IEC/IRB, confidentiality regarding study patients, and requirements for registration of the clinical study.

12. DATA MANAGEMENT AND RECORD KEEPING

See **Error! Reference source not found.** for information regarding data management and record keeping. This includes direct access to source data and documents, data collection, data quality control, and archiving of CRFs and source documents.

13. FINANCING AND INSURANCE

A separate clinical study agreement, including a study budget, will be signed between each principal investigator and the sponsor (or the CRO designated by the sponsor) before the IMP is delivered.

The patients in this clinical study are insured in accordance with applicable legal provisions. The policy coverage is subject to the full policy terms, conditions, extensions, and exclusions. Excluded from the insurance coverage are inter alia, damages to health, and worsening of previous existing disease that would have occurred or continued if the patient had not taken part in the clinical study.

The policy of Clinical Trials Insurance will be provided to the investigational centers by the sponsor.

For covered clinical studies (see 21CFR54), the investigator will provide the sponsor with financial information required to complete FDA 3454 form. Each investigator will notify the sponsor of any relevant changes during the conduct of the study and for 1 year after the study has been completed.

14. PUBLICATION POLICY

See **Error! Reference source not found.** for information regarding the publication policy.

15. REFERENCES

Akinbami LJ, Moorman JE, Bailey C, Zahran HS, King M, Johnson CA, et al. Trends in asthma prevalence, health care use, and mortality in the United States, 2001-2010. NCHS Data Brief. 2012 May;(94):1-8.

Beasley R, Crane J, Lai CK, Pearce N. Prevalence and etiology of asthma. J Allergy Clin Immunol 2000;105(2 Pt 2):S466-72.

Centers for Disease Control and Prevention. Asthma's impact on the nation: data from the CDC National Asthma Control Program. http://www.cdc.gov/asthma/impacts_nation/asthmafactsheet.pdf. 2012. Accessed [April 2014].

Corren J, Korenblat PE, Miller CJ, O'Brien CD, Mezzanotte WS. Twelve-week, randomized, placebo-controlled, multicenter study of the efficacy and tolerability of budesonide and formoterol in one metered-dose inhaler compared with budesonide alone and formoterol alone in adolescents and adults with asthma. Clin Ther 2007;29(5):823–43.

Kerwin EM, Pearlman DS, de Guia T, Carlsson LG, Gillen M, Uryniak T, et al. Evaluation of efficacy and safety of budesonide delivered via two dry powder inhalers. Curr Med Res Opin. 2008;24(5):1497–510.

Little R, Kang S. Intention-to-treat analysis with treatment discontinuation and missing data in clinical trials. Stat Med 2015;34(16):2381–90.

Mallinckrodt C. Choosing primary estimands and analyses. In: Preventing and treating missing data in longitudinal clinical trials: A practical guide. New York: Cambridge University Press, 2013.

Mallinckrodt C, Molenberghs G, Rathmann S. Choosing estimands in clinical trials with missing data. Pharm Stat 2016.

Masoli M, Fabian D, Holt S, Beasley R for the Global Initiative for Asthma (GINA) Program. The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy 2004;59(5):469-78.

National Health Interview Survey (NHIS), National Center for Health Statistics, Centers for Disease Control and Prevention. Data: 2011 Lifetime Asthma, Current Asthma, Asthma Attacks among those with Current Asthma. Available at http://www.cdc.gov/asthma/nhis/2011/table1-1.htm. Accessed 25 August 2013.

National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program (NAEPP). Expert Panel Report 3: Guidelines for the diagnosis and management of asthma—full report 2007, August 28 2007. National Institutes of Health publication 07-4051. Available at http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf. Accessed 26 September 2013.

O'Neill RT, Temple R. The prevention and treatment of missing data in clinical trials: an FDA perspective on the importance of dealing with it. Clin Pharmacol Ther 2012;91(3):550–4.

Pearlman DS, Stricker W, Weinstein S, Gross G, Chervinsky P, Woodring A, et al. Ann Allergy Asthma Immunol 1999;82(3):257–65.

Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J 2012;40(6):1324-43.

Shrewsbury S, Pyke S, Britton M. Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA). BMJ 2000;320(7246):1368-73.

Szefler SJ, Boushey HA, Pearlman DS, Togias A, Liddle R, Furlong A, et al. Time to onset of effect of fluticasone propionate in patients with asthma. J Allergy Clin Immunol 1999;103(5):780–8.

Woodcock A, Bleecker ER, Lötvall J, O'Byrne PM, Bateman ED, Medley H, et al. Efficacy and safety of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma. Chest 2013;144(4):1222–9.

16. SUMMARY OF CHANGES TO PROTOCOL

16.1. Amendment 02 Dated 05 June 2018

The primary reason for this amendment is to address the observed larger variability in the overall blinded patient population in morning trough FEV_1 at home values than the initial protocol assumptions.

The initial assumptions of the treatment effect and variability were based on data collected in previous Teva studies with the same Fp MDPI and FS MDPI product in adult asthma patients. The relationship between the handheld and clinic-based spirometry was analysed using data from a previous Teva study (a double-blinded, placebo controlled study of beclomethasone diproprionate via breath-actuated inhaler for persisten asthma in adults and adolescents aged ≥12 yeas) in which both handheld and clinic-based spirometry were used to measure FEV_1. Analysis of the relationship between handheld and clinic-based spirometry demonstrated that handheld spirometery provided consistent and reliable results with reduced placebo response in the home setting.

However, this study FSS-AS-30003 is the very first study in which handheld spirometry 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 Section 6.1.3 for a description of how FEV_1 stability alert criteria were used to monitor patient safety related to worsening of asthma). 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. Based on the observed blinded 410 completed patients, the initial assumptions for SD and power calculation and the sample size have been revised as detailed in Section 9.

Other minor or editorial changes have been made to the protocol (and protocol synopsis, as appropriate). These changes are unlikely to affect the safety or rights (physical or mental integrity) of the patients in this clinical study or the scientific value of the clinical study.

Original text with changes shown	New wording	Reason/justification for change
Section 3.1 affected by this change:		
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.	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 (FEV1 and PEF) by handheld device as usual, but to delay IMP dosing until they get to the investigational center.	Adding IMP for clarity
Section 3.2 affected by this change:		
The population planned to be enrolled in this study comprises male and female patients 4 through 11 years of age who have a documented history of persistent asthma. Approximately ~~600~~ 824 male and female patients, ~~150~~ 206 patients in each of 4 treatment group, will be enrolled. Assuming a dropout rate of ~~15~~12%, approximately ~~127~~ 181 evaluable patients in each treatment group (~~508~~ 724 total patients) will complete the 12-week treatment period.	The population planned to be enrolled in this study comprises male and female patients 4 through 11 years of age who have a documented history of persistent asthma. Approximately 824 male and female patients, 206 patients in each of 4 treatment group, will be enrolled. Assuming a dropout rate of 12%, approximately 181 evaluable patients in each treatment group (724 total patients) will complete the 12-week treatment period.	Increase in number of patients enrolled (for details, see above)
The study is expected to start in the fourth quarter of 2016 (first patient in) and last until approximately the ~~third~~second quarter of ~~2018~~2019 (last patient last visit).	The study is expected to start in the fourth quarter of 2016 (first patient in) and last until approximately the second quarter of 2019 (last patient last visit).	Increase in number of patients enrolled (for details, see above)
Section 3.5 "Table 3 Study Procedures and Assessments" affected by this change:		
Row: allowed time windows *Column: RT/TV1* Day ~~0~~1	*Row: allowed time windows* *Column: RT/TV1* Day ~~0~~1	Letter of Clarification 01
Row: Perform lung function assessments (FEV_1) by handheld device 1 hour postdose at the investigational center *Column: SV* ~~X~~	*Row: Perform lung function assessments (FEV_1) by handheld device 1 hour postdose at the investigational center* Column: SV	Letter of Clarification 01
Row: End study participation in IRT system *Column: TV6* X^{n}	*Row: End study participation in IRT system* *Column: TV6* X	Letter of Clarification 01

Original text with changes shown	**New wording**	**Reason/justification for change**
Table 3: Study Procedures and Assessments; footnote a Patients who fail to meet baseline lung function assessments by handheld device requirements may retest ~~after~~ within 7 days of their initial SV.	*Table 3: Study Procedures and Assessments; footnote a* Patients who fail to meet baseline lung function assessments by handheld device requirements may retest within 7 days of their initial SV.	Letter of Clarification 01
Table 3 Study Procedures and Assessments; footnote b The patient's home FEV_1 by handheld device should be reviewed, and the average of the 5 ~~most recent~~ highest daily values (3 attempts) for trough morning FEV_1 ~~over~~ out of the last 7 days prior to RV must be 40% to 85% predicted for age, height, sex and race	*Table 3: Study Procedures and Assessments; footnote a* The patient's home FEV_1 by handheld device should be reviewed, and the average of the 5 highest daily values (3 attempts) for trough morning FEV_1 out of the last 7 days prior to RV must be 40% to 85% predicted for age, height, sex and race	Letter of Clarification 02
Section 4.1 affected by this change:		
The patient's persistent asthma is stable and is currently being treated with stable asthma therapy (eg, ICS, ICS/LABA, leukotriene receptor antagonist, etc.) for at least 30 days before the SV. Patients who are currently on SABA regimen only or PRN only are not eligible for the study.	The patient's persistent asthma is stable and is currently being treated with stable asthma therapy (eg, ICS, ICS/LABA, leukotriene receptor antagonist, etc.) for at least 30 days before the SV. Patients who are currently on SABA regimen only or PRN only are not eligible for the study.	Letter of Clarification 02
The patient has demonstrated ≥10% response to a bronchodilator from screening FEV1 within 30 minutes (±5 min) after 2 to 4 inhalations of albuterol/salbutamol HFA MDI (90 mcg ex actuator) or equivalent at SV as measured by handheld device.	The patient has demonstrated ≥10% response to a bronchodilator from screening FEV1 within 30 minutes (±5 min) after 2 to 4 inhalations of albuterol/salbutamol HFA MDI (90 mcg ex actuator) or equivalent at SV as measured by handheld device.	Adding time window
Section 5.7 affected by this change:		
Chronic stable doses of ocular steroids of at least ~~30~~7 days duration, with doses expected to remain stable throughout the study, are allowed.	Chronic stable doses of ocular steroids of at least 7 days duration, with doses expected to remain stable throughout the study, are allowed.	Letter of Clarification 01
Section 5.9 affected by this change		
Approximately ~~150~~ 206 patients will be randomized into each treatment group.	Approximately 206 patients will be randomized into each treatment group.	Increase in number of patients enrolled (for details, see above)
The average of the 5 ~~most recent~~ highest ~~daily~~ values for trough morning FEV_1 obtained at home (by handheld device) ~~over 5~~ out of the last 7 days prior to RV is within 40% to 85%	The average of the 5 highest values for trough morning FEV_1 obtained at home (by handheld device) out of the last 7 days prior to RV is within 40% to 85% predicted for age, height,	Letter of Clarification 02

Original text with changes shown	New wording	Reason/justification for change
predicted for age, height, sex, and race	sex, and race	
Section 7.7 affected by this change:		
Patients with a culture positive infection may continue participation in the study on appropriate anti infective therapy, provided this therapy is not prohibited by the protocol. ~~Azole antifungal medications are prohibited.~~ If a patient requires a protocol prohibited medication for therapy, the patient will be discontinued from the study and provided appropriate therapy.	Patients with a culture positive infection may continue participation in the study on appropriate anti infective therapy, provided this therapy is not prohibited by the protocol. If a patient requires a protocol prohibited medication for therapy, the patient will be discontinued from the study and provided appropriate therapy.	Letter of Clarification 01
Section 9 affected by this change:		
This section describes the statistical analysis ~~as foreseen at the time of planning the~~planned for this study. Changes, additions, and further details about the analyses will be described in the statistical analysis plan~~.~~ (SAP).	This section describes the statistical analysis planned for this study. Changes, additions, and further details about the analyses will be described in the statistical analysis plan (SAP).	Increase in number of patients enrolled (for details, see above)
Section 9.1 affected by this change:		
Sample size and power calculations are driven by demonstrating superiority of ~~Fp MDPI 50 mcg twice daily over placebo in change from baseline in percent predicted trough morning FEV_1 at week 12 and the 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 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, that a true treatment difference is 5% between Fp MDPI 50 mcg twice daily and placebo, and that a common standard deviation (SD) is 13.25%, then 127~~	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	Increase in number of patients enrolled (for details, see above)

Original text with changes shown	New wording	Reason/justification for change
~~patients per treatment group will yield an approximate statistical power of 85%, at a significance level of 0.05, for the 2-sided test of Fp MDPI 50 mcg twice daily versus placebo. The treatment effect and variability assumptions made for this power calculation are based on data collected in Teva studies.~~ 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, ~~that a true treatment difference is 4.5% between FS MDPI 50/12.5 mcg twice daily and Fp MDPI 50 mcg twice daily, and that a common SD is 9.3%, then 127 patients per treatment group will yield a statistical power of 97%, at a significance level of 0.05, for the 2-sided test of FS MDPI 50/12.5 mcg twice daily versus Fp MDPI 50 mcg twice daily. The treatment effect and variability assumptions made for this power calculation are based on data collected in studies conducted by Teva.~~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	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%. This study FSS-AS-30003 is the first Teva's study in which the handheld spirometry is utilized as an endpoint and this hanheld device is being used in a pediatric asthma patient	

Original text with changes shown	New wording	Reason/justification for change
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%. This study FSS-AS-30003 is the first Teva's study in which the handheld spirometry is utilized as an endpoint and this hanheld device is being used in a pediatric asthma patient population, the target population of this study. A blinded sample size reassessment was not planned for this study. However, routine blinded data monitoring of this study FSS-AS-30003 revealed that a few patietnts showed nonphysiologic (~200% of percent predicted FEV_1) changes from baseline. This triggered a blinded sample size reassessment that showed that the overall mean change from baseline and SD for the overall study population is higher than the initial assumptions based on the office spirometry in adult asthma patients. In addition, monitoring of FEV_1 stability throughout the study revealed	population, the target population of this study. A blinded sample size reassessment was not planned for this study. However, routine blinded data monitoring of this study FSS-AS-30003 revealed that a few patietnts showed nonphysiologic (~200% of percent predicted FEV_1) changes from baseline. This triggered a blinded sample size reassessment that showed that the overall mean change from baseline and SD for the overall study population is higher than the initial assumptions based on the office spirometry in adult asthma patients. In addition, monitoring of FEV_1 stability throughout the study revealed challenges in obtaining consistent morning trough FEV_1 values with best efforts in this young patient population, despite the rigorous training and coaching provided by the investigators. Therefore, 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	

Original text with changes shown	New wording	Reason/justification for change
challenges in obtaining consistent morning trough FEV_1 values with best efforts in this young patient population, despite the rigorous training and coaching provided by the investigators. Therefore, 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. Assuming a dropout rate of ~~15~~12%, then ~~150~~206 patients per treatment group in the 4 treatment groups, for a total of ~~600~~824 patients, will be randomized~~.~~ (initial assumption for	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. Assuming a dropout rate of 12%, then 206 patients per treatment group in the 4 treatment groups, for a total of 824 patients, will be randomized (initial assumption for dropout rate was 15%).	

Original text with changes shown	New wording	Reason/justification for change
dropout rate was 15%).		

Original text with changes shown	New wording	Reason/justification for change
Section 9.2.3 affected by this change:		
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 both data collected in the IMP dose counter and diary. Details will be provided in the SAP. 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 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 both data collected in the IMP dose counter and diary. Details will be provided in the SAP. 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."	Patients compliance might not be captured accurately by using data from the diary alone. Therefore, treatment compliance will be assessed on both data from the dose counter and the diary.
Section 9.5.4.2 affected by this change:		
•A tipping point analysis will be performed as a sensitivity analysis to missing data by utilizing multiple imputations under different missing mechanism. For placebo patients, in all applications of multiple imputations, missing at random (MAR) will be assumed. 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. This analysis will utilize only data collected prior to IMP discontinuation. Additional details will be provided in the SAP.	•A tipping point analysis will be performed as a sensitivity analysis to missing data by utilizing multiple imputations under different missing mechanism. For placebo patients, in all applications of multiple imputations, missing at random (MAR) will be assumed. 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. This analysis will utilize only data collected prior to IMP discontinuation. Additional details will be provided in the SAP.	In response to FDA feedback
•"2-dimensional tipping point" multiple imputation will be performed similar to above, the shifts to the distribution will apply to both placebo and active arms, to represent different degrees of effect loss. This analysis will utilize only data collected prior to IMP discontinuation. Additional details will be provided in the SAP.	•"2-dimensional tipping point" multiple imputation will be performed similar to above, the shifts to the distribution will apply to both placebo and active arms, to represent different degrees of effect loss. This analysis will utilize only data collected prior to IMP discontinuation. Additional details will be provided in the SAP.	Adding the 2-dimensional tipping point in response to FDA feedback
Section 9.5.4.3 affected by this change:		
Analysis of change from baseline in weekly average of daily trough morning PEF, total daily use of albuterol/salbutamol,	Analysis of change from baseline in weekly average of daily trough morning PEF, total daily use of albuterol/salbutamol,	Text was change to include the appropriate statistical analysis.

Original text with changes shown	New wording	Reason/justification for change
~~and~~ total daily asthma symptom score, and C-ACT score over the 12-week treatment period will be analyzed using an MMRM analysis with effects due to baseline, sex, age, (pooled) investigational center, previous therapy (ICS or NCS), treatment, time, and time-by-treatment interaction. ~~The change from baseline in C-ACT score over the 12-week treatment period will be analyzed using an ANCOVA model with effects due to sex, age, (pooled) investigational center, previous therapy (ICS or NCS), and treatment. Patients who drop out or discontinue IMP will be considered as nonresponders in this analysis.~~	total daily asthma symptom score, and C-ACT score over the 12-week treatment period will be analyzed using an MMRM analysis with effects due to baseline, sex, age, (pooled) investigational center, previous therapy (ICS or NCS), treatment, time, and time-by-treatment interaction.	
Section 9.6 affected by this change:		
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 to 11 years of age), an unplanned blinded sample size reassement was conducted. Since the adjustment to sample size was based on blinded standard deviation, no adjustment to the multiplicity control is warrented.	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 to 11 years of age), an unplanned blinded sample size reassement was conducted. Since the adjustment to sample size was based on blinded standard deviation, no adjustment to the multiplicity control is warrented.	Increase in number of patients enrolled (for details, see above)
Appendix A affected by this change:		
[redacted] Teva Pharmaceuticals [redacted]	[redacted] Teva Pharmaceuticals [redacted]	Update title and phone number
[redacted] Teva Pharmaceuticals [redacted]	[redacted] Teva Pharmaceuticals [redacted]	Update of study personnel
[redacted] Merckle GmbH	[redacted] Merckle GmbH	Updated legal representative of the sponsor in the EU

Original text with changes shown	New wording	Reason/justification for change
Graf-Arco-Str. 3 89079 Ulm Germany [redacted] ~~Teva GmbH~~ ~~Graf-Arco-Str. 3~~ ~~89079 Ulm~~ ~~Germany~~	Graf-Arco-Str. 3 89079 Ulm Germany	

16.2. Letter of Clarification 02 Dated 21 February 2018

LETTER OF CLARIFICATION 02

Study number: FSS-AS-30003

Clinical Study Protocol with Amendment 01 and local Amendment 01 for Russia

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

Dated 31 October 2016

IND number: 108,838 and 72,240; NDA number: 208798 and 208799;

EudraCT number: 2016-003835-39

21 Feb 2018

Dear Investigator:

The purpose of this letter of clarification is to clarify the below in the Clinical Study Protocol Amendment 01 and Local Amendment 01 for Russia:

- Page 14 and 51 – Inclusion Criteria: There were questions regarding whether patients who are currently on SABA only regimen or on PRN basis are eligible for the study. Teva has instructed the sites since July 2017 that such patients were eligible. However, after further review, based on the protocol inclusion criterion "The patient's persistent asthma is stable and is currently being treated with stable asthma therapy for at least 30 days before the SV", a decision has been made that patients must have persistent asthma and must currently being treated with a stable asthma therapy, eg ICS, ICS/LABA, LABA, leukotriene receptor antagonist, cromolyn, theophylline, etc. for at least 30 days. **Patients who are currently on SABA regimen only or PRN only are not eligible for the study.** For those patients being randomized based on the previous instruction, protocol deviations will need to be documented along with reference to this letter of clarification; however, it is acknowledged that the sponsor guidance on this matter previously allowed these subjects to be randomized and is the cause of the deviations.
- Page 17 and 61 – Randomization Criteria: "The average of the 5 most recent highest daily values for trough morning FEV_1 obtained at home (by handheld device) over 5 out of the last 7 days prior to RV is within 40% to 85% predicted for age, height, sex, and race (Quanjer et al 2012)", and

  Page 49 (Table, Study Procedures and Assessments) – subscript "b": "The patient's home FEV_1 by handheld device should be reviewed, and the average of the 5 most recent highest daily values (3 attempts) for trough morning FEV_1 over the last 7 days

prior to RV must be 40% to 85% predicted for age, height, sex and race (Quanjer et al 2012)…":

Due to lack of clarity in this language, the current calculation of FEV_1 eligibility in the ERT system has been mistakenly based on the most recent 5 days FEV_1 values, instead of the protocol intended **the 5 highest values** out of the last 7 days. This has resulted in some patients being randomized to the study without meeting the criteria; and some patients may have met the eligibility criteria but were failed to be randomized. For the patients being randomized without meeting the eligibility criteria, protocol deviations will need to be documented along with reference to this letter of clarification; however, it is acknowledged that ERT system programming caused the deviations.

These changes will be incorporated into the protocol during the next amendment, as applicable. Please ensure that this letter is maintained with the study protocol. Also, please provide a copy of this letter to your IRB/IEC for review and acknowledgement.

Please feel free to contact me at [redacted] or by email to [redacted] if you have any questions or concerns regarding this letter.

[redacted]

Teva Pharmaceuticals

16.3. Letter of Clarification 01 Dated 21 September 2017

Pharmaceuticals

LETTER OF CLARIFICATION 01

Study number: FSS-AS-30003

Clinical Study Protocol with Amendment 01

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

Dated 31 October 2016

IND number: 108,838 and 72,240; NDA number: 208798 and 208799;

EudraCT number: 2016-003835-39

21Sep 2017

Dear Investigator:

The purpose of this letter of clarification is to address the following discrepancies in the Clinical Study Protocol Amendment 01:

- Page 48, Table 3 (Study Procedures and Assessments) – visit window: The Randomization/Treatment Visit 1 is currently noted as **Day 0** in row "Allowed time windows"; it should state **Day 1** instead.
- Page 48, Table 3 (Study Procedures and Assessments) – 1-hour post dose lung function at screening visit is not a required procedure at screening; the entry in the table was an error.
- Page 48, Table 3 (Study Procedures and Assessments) – subscript "n": End of Study participation in IRT system – there is nothing associated in the key for letter "n."
- Section 5.1 indicates "the use of spacers or chambers for inhalers is not permitted with IMP inhalers or rescue inhalers." It has been confirmed that spacers are only allowed during the screening response to a bronchodilator test (section 6.1.2).
- The language on ocular steroid use differs between Section 5.7 ("Chronic stable doses of ocular steroids of at least **30 days** duration are allowed") and Appendix H ("Chronic stable doses of ocular steroids of at least **7 days** duration, with doses expected to remain stable throughout the study, are allowed"): The wording in Appendix H is correct, ie ocular corticosteroids are allowed if stable for **7 days** rather than 30 days.

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TEVA Pharmaceuticals

- Per inclusion criteria f "Patients who demonstrated < 10% response to a bronchodilator may retest within 7 days of their initial SV". Per schedule of events "Patients who fail to meet baseline lung function assessments by handheld device requirements may retest after 7 days". The correct timeframe is **within 7 days of their initial SV**.
- Page 80, Section 7.7 (Oropharyngeal Examinations) – The statement "Azole antifungal medications are prohibited" can be deleted from this section, as it is covered in the list of prohibited medications.

These changes will be incorporated into the protocol during the next amendment, as applicable. Please ensure that this letter is maintained with the study protocol. Also, please provide a copy of this letter to your IRB/IEC for review and acknowledgement.

Please feel free to contact me at [redacted] or by email to [redacted] if you have any questions or concerns regarding this letter.

[redacted]

Teva Pharmaceuticals

16.4. Country-specific (Russia) Amendment 01 Dated 22 May 2017

The primary reason for this amendment is to respond to feedback from the Ministry of Health (MOH) of the Russian Federation. This amendment is considered to be nonsubstantial by the sponsor's Authorized Representative. The protocol is being locally amended to include safety and efficacy data on Fp MDPI and FS MDPI in children 12 years of age and older. These changes are unlikely to affect the safety or rights (physical or mental integrity) of the patients in this clinical study or the scientific value of the clinical study.

Original text with changes shown	New wording	Reason/Justification for change
APPENDIX B EFFICACY AND SAFETY DATA FOR PHASE 2 AND 3 STUDIES FOR ADOLESCENT PATIENTS (Other section affected by this change: Section 1.2)		
New appendix added.	New appendix added.	This appendix was added in response to feedback from the MOH of the Russian Federation.

16.5. Amendment 01 Dated 31 October 2016

The primary reason for this amendment is to respond to FDA feedback. This amendment is considered to be substantial (ie, requires approval by CA, IEC, and/or IRB) by the sponsor's Authorized Representative. Other nonsubstantial changes have been made to the protocol (and protocol synopsis, as appropriate). These changes are unlikely to affect the safety or rights (physical or mental integrity) of the patients in this clinical study or the scientific value of the clinical study.

Table 3 (Study Procedures and Assessments) has been revised to reflect changes described below.

Changes to the Protocol

Original text with changes shown	New wording	Reason/justification for change
SECTION 1.1 INTRODUCTION (Other sections affected by this change: Section 3.2, Section 3.3, and Section 5.3.1)		
The proposed Fp dose for study in ~~children~~patients 4 through 11 years of age is based on the adult dose-ranging study demonstrating efficacy of the 25 and 50 mcg twice daily doses that are the same or lower than the currently approved doses of FLOVENT DISKUS and ADVAIR® DISKUS® (GlaxoSmithKline plc) in pediatric patients.	The proposed Fp dose for study in patients 4 through 11 years of age is based on the adult dose-ranging study demonstrating efficacy of the 25 and 50 mcg twice daily doses that are the same or lower than the currently approved doses of FLOVENT DISKUS and ADVAIR® DISKUS® (GlaxoSmithKline plc) in pediatric patients.	This change was made in order to use uniform language throughout the protocol.
SECTION 1.3.2 OVERALL BENEFIT AND RISK ASSESSMENT FOR THIS STUDY		
Use of placebo-controlled study design in evaluating ICSs and other molecules is commonly used in developing these drug products and is required by FDA towards supporting the efficacy of the molecule (eg, Kerwin et al 2008, Woodcock et al 2013). The design of this study is very similar to other pediatric placebo-controlled trials where adverse events in the placebo arm were similar to those in the treatment arms. The study has been designed to minimize the risks of placebo use to the intended population of patients 4 through 11 years of age. The patient inclusion and exclusion criteria were selected to ensure that patients with severe asthma or history of life-threatening exacerbations would not be eligible. In this study, the patients' lung function, symptom scores, and rescue medication use will be monitored daily with use of a handheld device/electronic diary. The handheld device/electronic diary will provide alerts to the study center and medical monitor for the trial so that patients whose asthma status may be deteriorating will be captured early (Section 4.3.2). This will minimize the risk and asthma exacerbation as well as any discomfort that might come from an exacerbation. Additionally, use of the handheld device/electronic diary minimizes the burden of requiring patients to travel to the study center for monitoring. Patients assigned to placebo therapy often demonstrate improvement in lung function, suggesting that frequent contact with medical providers may be of benefit. Additionally, all patients are provided with rescue	Use of placebo-controlled study design in evaluating ICSs and other molecules is commonly used in developing these drug products and is required by FDA towards supporting the efficacy of the molecule (eg, Kerwin et al 2008, Woodcock et al 2013). The design of this study is very similar to other pediatric placebo-controlled trials where adverse events in the placebo arm were similar to those in the treatment arms. The study has been designed to minimize the risks of placebo use to the intended population of patients 4 through 11 years of age. The patient inclusion and exclusion criteria were selected to ensure that patients with severe asthma or history of life-threatening exacerbations would not be eligible. In this study, the patients' lung function, symptom scores, and rescue medication use will be monitored daily with use of a handheld device/electronic diary. The handheld device/electronic diary will provide alerts to the study center and medical monitor for the trial so that patients whose asthma status may be deteriorating will be captured early (Section 4.3.2). This will minimize the risk and asthma exacerbation as well as any discomfort that might come from an exacerbation. Additionally, use of the handheld device/electronic diary minimizes the burden of requiring patients to travel to the study center for monitoring. Patients assigned to placebo therapy often demonstrate improvement in lung function, suggesting that frequent contact with medical providers may be of benefit.	This change was made to elaborate and expand on the benefit-risk text in the protocol.

Original text with changes shown	New wording	Reason/justification for change
albuterol/salbutamol for use as needed. Rescue albuterol/salbutamol usage will be followed closely for signs of deterioration.	Additionally, all patients are provided with rescue albuterol/salbutamol for use as needed. Rescue albuterol/salbutamol usage will be followed closely for signs of deterioration.	
SECTION 2.2.1 OTHER EFFICACY ENDPOINTS (Other sections affected by this change: Section 6.3, Section 6.3.1, Section 6.3.7, Section 6.3.8, Section 6.3.9, and Section 9.5.3)		
• 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 ~~and at the last postbaseline observation~~ • Change from baseline in the weekly average of the percent predicted trough morning FEV_1 at weeks 1, 2, 4, and 8~~, and at the last postbaseline observation~~ • 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~~, and at the last postbaseline observation~~ • Change from baseline in asthma control (measured by C-ACT) score at weeks 4, 8, and 12 ~~and at the last postbaseline observation~~	• 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 weekly average of the percent predicted trough morning FEV1 at weeks 1, 2, 4, and 8 • Proportion of patients who achieve at least a 15% increase in morning FEV1 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	This change was made to remove the last postbaseline observation as a time point for these other efficacy endpoints since it is not a meaningful time point for this evaluation.

Original text with changes shown	New wording	Reason/justification for change
SECTION 3.1 GENERAL DESIGN AND STUDY SCHEMATIC DIAGRAM (Other section affected by this change: Appendix B)		
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~~12 inhalations permitted per day.	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 12 inhalations permitted per day.	This change was made to correct the maximum amount of inhalations permitted per day.
SECTION 3.1 GENERAL DESIGN AND STUDY SCHEMATIC DIAGRAM (Other section affected by this change: Appendix B)		
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.	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.	This change was made to emphasize that after providing consent, patients are expected to complete all study procedures and visits (unless they choose to withdraw consent).
SECTION 3.1 GENERAL DESIGN AND STUDY SCHEMATIC DIAGRAM (Other sections affected by this change: Section 6.1.1 and Appendix B)		
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~~ so that lung function assessments and response to bronchodilator testing can be completed as described (other assessments not involving lung function may be completed that day)~~. 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.	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.	Text was removed to correct that if a patient takes the morning IMP dose or rescue medication within 6 hours of the planned lung function assessments, the entire treatment visit must be rescheduled. Text was also added to provide instructions on taking other medications prior to treatment visit assessments for patients who have been

Original text with changes shown	New wording	Reason/justification for change
		withdrawn from IMP.
SECTION 3.1 GENERAL DESIGN AND STUDY SCHEMATIC DIAGRAM (Other sections affected by this change: Section 3.4, Section 3.5 [Table 3, footnote h] Section 4.3, Section 6.1.1, and Appendix B)		
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. ~~For patients who need to demonstrate the response to bronchodilator during the run-in, the RV must be on another day.~~	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.	Text was added to provide instructions for performing lung function assessments for patients who have been withdrawn from IMP. Text was also removed for better flow and to avoid redundancy with other paragraphs in this section.
SECTION 3.1 GENERAL DESIGN AND STUDY SCHEMATIC DIAGRAM (Other sections affected by this change: Section 3.5 [Table 3, footnote k], Section 4.3.2, Appendix B, and Appendix E)		
In cases where the IMP is to be withdrawn and alternative therapy started, the ~~site~~investigational center staff should contact the medical monitor to confirm the findings.	In cases where the IMP is to be withdrawn and alternative therapy started, the investigational center staff should contact the medical monitor to confirm the findings.	This change was made because "investigational center" is the term preferred by the sponsor, rather than "site." The term "staff" was added for clarity.
SECTION 3.1 GENERAL DESIGN AND STUDY SCHEMATIC DIAGRAM		
If a patient or patient's parent/legal guardian elects to completely withdraw from the study (ie, withdraw consent) prior to the investigator assessment or investigational center	If a patient or patient's parent/legal guardian elects to completely withdraw from the study (ie, withdraw consent) prior to the investigator assessment or investigational center	This text was added to clarify that withdrawing completely from the study involves

Original text with changes shown	New wording	Reason/justification for change
visit, irrespective of the reason for the study discontinuation, every attempt will be made to conduct the IMPDV subsequent to the patient's withdrawal from the IMP.	visit, irrespective of the reason for the study discontinuation, every attempt will be made to conduct the IMPDV subsequent to the patient's withdrawal from the IMP.	withdrawing consent.
SECTION 3.1 GENERAL DESIGN AND STUDY SCHEMATIC DIAGRAM (Other section affected by this change: Section 7.1.1)		
Asthma worsening including asthma exacerbations with a change to alternative asthma therapy~~, will be recorded as an efficacy endpoint and~~ 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 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.	This text was changed to remove incorrect wording.
SECTION 3.1 GENERAL DESIGN AND STUDY SCHEMATIC DIAGRAM		
This asthma therapy will be recorded in the CRF ~~as recommended asthma therapy~~ following IMP discontinuation (planned or unplanned).	This asthma therapy will be recorded in the CRF-following IMP discontinuation (planned or unplanned).	This change was made to clarify the procedure for recording asthma therapy in the CRF following IMP discontinuation.
SECTION 3.1 GENERAL DESIGN AND STUDY SCHEDMATIC DIAGRAM (Other sections affected by this change: Section 3.5 [Table 3, foonote g], and Appendix B)		
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 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 addition 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~~not be considered to have completed the treatment period~~ for the purposes of primary analysis.~~	After the last TV (TV6, week 12), the patient will enter the follow-up period. One week (±2 days) after the last TV, the patient will have a 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 addition to screening, run-in, and all TVs. Patients who stop IMP and return for safety evaluation at week 12 will not be considered to have completed the treatment period.	This change was made to reflect that patients who discontinue IMP are still expected to attend treatment visits (although they will not be given IMP). Text was also revised to correct which patients will not be considered to have completed the treatment period.
SECTION 3.4 EARLY STOPPING RULES		
A patient may discontinue participation in the study at any time for any reason ~~(eg, lack of efficacy,~~by withdrawal of consent~~, and adverse event)~~; every effort should be undertaken to find	A patient may discontinue participation in the study at any time for any reason by withdrawal of consent; every effort should be undertaken to find out the reason for	These changes were made to correct the reasons for discontinuing participation in

Original text with changes shown	New wording	Reason/justification for change
out the reason for discontinuation.	discontinuation.	the study.
SECTION 3.4 EARLY STOPPING RULES (Other section affected by these changes: Section 4.3)		
The investigator or sponsor can withdraw a patient from the study IMP at any time for any reason (eg, protocol violation or deviation as defined in Appendix C~~, noncompliance, or adverse event~~). However, patients that do not withdraw consent should remain in the study (as counseled during the informed consent process) and complete the remaining study procedures and visits, with the exception of IMP dosing.	The investigator or sponsor can withdraw a patient from the study IMP at any time for any reason (eg, protocol violation or deviation as defined in Appendix C, noncompliance, or adverse event). However, patients that do not withdraw consent should remain in the study (as counseled during the informed consent process) and complete the remaining study procedures and visits, with the exception of IMP dosing.	These changes were made to emphasize that patients who discontinue study IMP should still participate in study procedures and visits.
SECTION 3.5 SCHEDULE OF STUDY PROCEDURES AND ASSESSMENTS (TABLE 3)		
Allowed time windows: TV2: Day 8±2 days TV3: Day 15±2 days TV4: Day 29±2 days TV5: Day 57±2 days TV6: Day 85±2 days FV: Day 92±2 days	Allowed time windows: TV2: Day 8±2 days TV3: Day 15±2 days TV4: Day 29±2 days TV5: Day 57±2 days TV6: Day 85±2 days FV: Day 92±2 days	This change was made to include the days of the study visits, where applicable.
SECTION 3.5 SCHEDULE OF STUDY PROCEDURES AND ASSESSMENTS (TABLE 3)		
Perform lung function assessments (FEV1~~ and PEF~~) by handheld device 1-hour postdose at the investigational center	Perform lung function assessments (FEV1) by handheld device 1-hour postdose at the investigational center	This change was made to correct that PEF will not be performed as a 1-hour postdose lung function assessment.
SECTION 3.5 SCHEDULE OF STUDY PROCEDURES AND ASSESSMENTS (TABLE 3, FOOTNOTE B)		
The RV may occur up to 30 days following the SV. The patient's home FEV_1 by handheld device should be reviewed, and the average of the 5 most recent highest daily values (3 attempts) for trough morning FEV_1 over the 7 days prior to RV must be 40% to 85% predicted for age, height, sex and race (Quanjer et al 2012) with asthma symptom criteria, the C-ACT score must be ≤19 to be eligible for randomization. The patient	The RV may occur up to 30 days following the SV. The patient's home FEV_1 by handheld device should be reviewed, and the average of the 5 most recent highest daily values (3 attempts) for trough morning FEV_1 over the 7 days prior to RV must be 40% to 85% predicted for age, height, sex and race (Quanjer et al 2012) with asthma symptom criteria, the C-ACT score must be ≤19 to be eligible for	This change was made to clarify that 2 different randomization identification numbers will be assigned at SV and at RV.

Original text with changes shown	New wording	Reason/justification for change
must also meet the lung function assessment requirements at the investigational center and all other study criteria. ~~Assign~~ Eligible patients will be assigned a patient randomization identification number via the IRT system ~~unless already completed~~that is different than the one received at ~~a prescreening visit~~screening.	randomization. The patient must also meet the lung function assessment requirements at the investigational center and all other study criteria. Eligible patients will be assigned a patient randomization identification number via the IRT system that is different than the one received at screening.	
SECTION 3.5 SCHEDULE OF STUDY PROCEDURES AND ASSESSMENTS (TABLE 3, FOOTNOTE E)		
Evidence of oropharyngeal candidiasis at any study TV or end of study TV should be evaluated by obtaining a swab for culture. Patients who agree to treatment may continue ~~in the study.~~to receive IMP.	Evidence of oropharyngeal candidiasis at any study TV or end of study TV should be evaluated by obtaining a swab for culture. Patients who agree to treatment may continue to receive IMP.	This change was made to clarify that patients who receive treatment for oropharyngeal candidiasis may continue receiving IMP.
SECTION 3.5 SCHEDULE OF STUDY PROCEDURES AND ASSESSMENTS (TABLE 3, FOOTNOTE G)		
The patient will be instructed to perform 3 trough morning FEV_1 maneuvers and 3 evening FEV_1 maneuvers at home each day during participation in the run-in period and the treatment period (morning only on the final TV [TV6 (week 12~~) or IMPDV]).~~)]). The highest FEV_1 obtained at the SV will be used to calculate the home FEV_1 stability limit, which will be used for review of alert criteria during the run-in period. The average FEV_1 over 5 days prior to RV will be used to calculate the alert criteria for the treatment period.	The patient will be instructed to perform 3 trough morning FEV_1 maneuvers and 3 evening FEV_1 maneuvers at home each day during participation in the run-in period and the treatment period (morning only on the final TV [TV6 (week 12)]). The highest FEV_1 obtained at the SV will be used to calculate the home FEV_1 stability limit, which will be used for review of alert criteria during the run-in period. The average FEV_1 over 5 days prior to RV will be used to calculate the alert criteria for the treatment period.	This text was changed to clarify that patients will continue to participate in study visits and procedures even after discontinuing IMP. Text was also added to clarify how the alert criteria will be calculated.
SECTION 3.5 SCHEDULE OF STUDY PROCEDURES AND ASSESSMENTS (TABLE 3, FOOTNOTE M)		
End of study participation in the IRT system will take place at the last visit during the treatment period (ie, at TV6 for patients who complete the treatment period, or at the IMPDV for patients who discontinue the study prematurely [patients who withdraw consent]).	End of study participation in the IRT system will take place at the last visit during the treatment period (ie, at TV6 for patients who complete the treatment period, or at the IMPDV for patients who discontinue the study prematurely [patients who withdraw consent]).	This change was made to clarify the reason for discontinuing the study.
SECTION 4.2 PATIENT EXCLUSION CRITERIA		
b. The patient is pregnant or lactating or plans to become pregnant during the study period or within 30 days after the patient's last study-related visit (for	b. The patient is pregnant or lactating or plans to become pregnant during the study period or within 30 days after the patient's last study-related visit	These changes were made to remove exclusion criterion that are not relevant.

Original text with changes shown	New wording	Reason/justification for change
eligible patients only and if applicable). ~~Any patient who becomes pregnant during the study will be withdrawn from the study.~~ d. ~~The patient has previously participated as a randomized patient in an Fp MDPI or FS MDPI study.~~	(for eligible patients only and if applicable).	
SECTION 4.2 PATIENT EXCLUSION CRITERIA		
k. The patient has used immunosuppressive medications within ~~4 weeks~~30 days before the SV.	k. The patient has used immunosuppressive medications within 30 days before the SV.	This change was made for consistency throughout the protocol.
SECTION 4.3 WITHDRAWAL CRITERIA AND PROCEDURES FOR THE PATIENT		
In accordance with the Declaration of Helsinki (in accordance with the applicable country's acceptance), each patient (parent/legal guardian) is free to withdraw from the study at any time. The investigator also has the right to withdraw a patient from the study in the event of serious intercurrent illness, ~~adverse events,~~ pregnancy (see Section 7.2), or other reasons concerning the health or well-being of the patient, or in the event of repeated and documented lack of cooperation	In accordance with the Declaration of Helsinki (in accordance with the applicable country's acceptance), each patient (parent/legal guardian) is free to withdraw from the study at any time. The investigator also has the right to withdraw a patient from the study in the event of serious intercurrent illness, pregnancy (see Section 7.2), or other reasons concerning the health or well-being of the patient, or in the event of repeated and documented lack of cooperation	This change was made to clarify that the parent/legal guardian of the patient may withdraw the patient from the study. Changes were also made to the text to clarify the circumstances under which the investigator may wish to withdraw a patient from the study.
SECTION 4.3 WITHDRAWAL CRITERIA AND PROCEDURES FOR THE PATIENT		
Should a patient (parent/legal guardian) decide to withdraw after administration of IMP~~(s), or should the investigator decide to withdraw the patient~~, all efforts will be made to complete and report all observations up to the time of withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made and an explanation given as to why the patient is withdrawing ~~or being withdrawn~~ from the study. The reason for and date of withdrawal from the study must be recorded on the source documentation and transcribed to the	Should a patient (parent/legal guardian) decide to withdraw after administration of IMP, all efforts will be made to complete and report all observations up to the time of withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made and an explanation given as to why the patient is withdrawing from the study. The reason for and date of withdrawal from the study must be recorded on the source documentation and transcribed to the CRF. If a patient withdraws consent, every attempt will	These changes to the text were made to clarify the circumstances under which a patient may withdraw from the study. This text was also changed to reflect that laboratory tests will not be performed during

Original text with changes shown	New wording	Reason/justification for change
CRF. If a patient withdraws consent, every attempt will be made to determine the reason. If ~~the reason for withdrawal~~consent is withdrawn because of an adverse event ~~or a clinically significant abnormal laboratory test result~~, monitoring will be continued at the discretion of the investigator (eg, until the event has resolved or stabilized, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the IMP or study procedure is made).	be made to determine the reason. If consent is withdrawn because of an adverse event, monitoring will be continued at the discretion of the investigator (eg, until the event has resolved or stabilized, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the IMP or study procedure is made).	this study.
SECTION 5.9 RANDOMIZATION AND BLINDING		
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.	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.	This change was made to add detail about stratification procedures.
SECTION 5.10.1 MAINTENANCE OF RANDOMIZATION		
Patient randomization codes will be maintained in a secure location at the service provider ~~contracted to generate the codes~~.	Patient randomization codes will be maintained in a secure location at the service provider.	This change was made to clarify the location of the patient randomization codes.
SECTION 6.3 OTHER EFFICACY MEASURES		
• FEV_1 will be measured by the patient (with assistance from the ~~parents/legal guardians/caregivers, as needed~~clinic staff) with a handheld device in the clinic before administration of IMP or rescue medications at the morning evaluation on weeks 1, 2, 4, ~~and 8 and the last postbaseline observation.~~8, and 12. The change from baseline in 1-hour postdose percent predicted morning FEV_1 at week 1 and in the weekly average of percent predicted trough morning FEV_1 will be ~~calculated based on information recorded in the daily patient diary built into the handheld device by the patient (with assistance from the parents/legal guardians/caregivers, as needed).~~based on	• FEV_1 will be measured by the patient (with assistance from the clinic staff) with a handheld device in the clinic before administration of IMP or rescue medications at the morning evaluation on weeks 1, 2, 4, 8, and 12. The change from baseline in 1-hour postdose percent predicted morning FEV_1 at week 1 and in the weekly average of percent predicted trough morning FEV_1 will be based on the measurements obtained in the clinic.	These changes were made to clarify the procedures for measuring FEV_1 and to emphasize that the endpoints involving FEV_1 will be based on measurements taken in the clinic.

Original text with changes shown	New wording	Reason/justification for change
the measurements obtained in the clinic.		
SECTION 7.1.1 DEFINITION OF AN ADVERSE EVENT		
~~Asthma~~For the purpose of this study, an asthma exacerbation is defined as ~~any~~ worsening of asthma requiring any significant treatment other than IMP and study rescue ~~albuterol (salbutamol) or the patient's regular ICS maintenance~~medication. Significant treatment~~. As~~ includes the use of systemic corticosteroids and/or the addition of other ICS-containing asthma medications, LABAs, or other NCS asthma medications, for example, inhaled short-acting muscarinic antagonist, ER/urgent care clinic visit(s), or hospitalization. Note: A single dose of nebulized albuterol/salbutamol would not meet the criteria for an asthma exacerbation. ER/urgent care clinic visits where the treatment is limited to a single dose of nebulized albuterol/salbutamol will not meet the criteria of an asthma exacerbation. Asthma exacerbation 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 ~~are~~with a change to alternative asthma therapy, will be recorded ~~separately in the CRFs,~~as an ~~asthma exacerbation is~~efficacy endpoint and will not be considered an adverse event ~~unless~~for this study since it ~~meets the definition of~~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. Any occurrence of oropharyngeal candidiasis that is confirmed by culture during the study will be reported as an adverse event. A patient who agrees to be treated may continue in the study at the discretion of the investigator.	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. Significant treatment includes the use of systemic corticosteroids and/or the addition of other ICS-containing asthma medications, LABAs, or other NCS asthma medications, for example, inhaled short-acting muscarinic antagonist, ER/urgent care clinic visit(s), or hospitalization. Note: A single dose of nebulized albuterol/salbutamol would not meet the criteria for an asthma exacerbation. ER/urgent care clinic visits where the treatment is limited to a single dose of nebulized albuterol/salbutamol will not meet the criteria of an asthma exacerbation. Asthma exacerbation 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 be recorded as an efficacy endpoint and 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. Any occurrence of oropharyngeal candidiasis that is confirmed by culture during the study will be reported as an adverse event. A patient who agrees to be treated may continue in the study at the discretion of the investigator.	These changes were made so that the language describing asthma exacerbation in this section is consistent with Section 3.1. Text was also added to discuss the occurrence of oropharyngeal candidiasis in greater detail.
SECTION 7.1.3 SEVERITY OF ADVERSE EVENT		

Original text with changes shown	New wording	Reason/justification for change
The severity of each adverse event must be recorded as 1 of the following: **Mild:** No limitation of usual activities **Moderate:** Some limitation of usual activities **Severe:** Inability to carry out usual activities ~~**Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated~~ ~~**Grade 2:** Moderate; minimal, local intervention or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money)~~ ~~**Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (eg, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)~~ ~~**Grade 4:** Life-threatening consequences; urgent intervention indicated~~ ~~**Grade 5:** Death related to adverse event~~	The severity of each adverse event must be recorded as 1 of the following: **Mild:** No limitation of usual activities **Moderate:** Some limitation of usual activities **Severe:** Inability to carry out usual activities	This change was made to remove text that is not relevant to this study.
SECTION 7.1.8 PROTOCOL DEVIATIONS BECAUSE OF AN ADVERSE EVENT		
The investigator, in consultation with the sponsor, will decide whether the patient should continue to ~~participate~~receive study IMP, continue in the study on alternative treatment, or be withdrawn from the study in the interest of patient safety.	The investigator, in consultation with the sponsor, will decide whether the patient should continue to receive study IMP, continue in the study on alternative treatment, or be withdrawn from the study in the interest of patient safety.	These changes were made to clarify the options available to the investigator for patients who experience a protocol deviation because of an adverse event.
SECTION 7.3 MEDICATION ERROR AND SPECIAL SITUATIONS RELATED TO THE INVESTIGATIONAL MEDICINAL PRODUCT (Other section affected by these changes: Appendix C)		
Any administration of IMP that is not in accordance with the study protocol should be reported ~~on the CRF~~ either as a violation, if it meets the violation criteria specified in the	Any administration of IMP that is not in accordance with the study protocol should be reported either as a violation, if it meets the violation criteria specified in the protocol	This text was changed to reflect that protocol violations will no longer be captured in

Original text with changes shown	New wording	Reason/justification for change
protocol (Appendix C), or as a deviation, in the patient's source documents, regardless of whether or not an adverse event occurs as a result. When meeting protocol violation criteria, all instances of incorrect IMP administration should be categorized ~~on the CRF~~ as "Non-Compliance to investigational medicinal product (IMP)." The following are types of medication errors and special situations, as reported by the investigator: 1. Medication error: Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient, or consumer. 2. Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information. Clinical judgment should always be applied. Any dose of IMP (whether the test IMP, reference IMP, or placebo IMP), whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to the sponsor. ~~When the identification of the IMP is required, the investigator must follow the procedures for unblinding outlined in Section .~~ 3. ~~Misuse: Situations where the IMP is intentionally and inappropriately used not in accordance with the authorized product information.~~ 4. Abuse: Persistent or sporadic, intentional excessive use of IMP which is accompanied by harmful physical or psychological effects. 5. Off-label use: Situations where an IMP is intentionally used for a medical purpose not in accordance with the	(Appendix C), or as a deviation, in the patient's source documents, regardless of whether or not an adverse event occurs as a result. When meeting protocol violation criteria, all instances of incorrect IMP administration should be categorized as "Non-Compliance to investigational medicinal product (IMP)." The following are types of medication errors and special situations, as reported by the investigator: 1. Medication error: Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient, or consumer. 2. Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information. Clinical judgment should always be applied. Any overdose of IMP (whether the test IMP, reference IMP, or placebo IMP), whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to the sponsor. 3. Abuse: Persistent or sporadic, intentional excessive use of IMP which is accompanied by harmful physical or psychological effects. 4. Off-label use: Situations where an IMP is intentionally used for a medical purpose not in accordance with the authorized product information. 5. Occupational exposure: Exposure to an IMP as a result of one's professional or nonprofessional occupation. 6. Breastfeeding: Suspected adverse reactions which	the CRF. This text was also changed to incorporate updated template language from the sponsor regarding medication errors.

Original text with changes shown	New wording	Reason/justification for change
authorized product information. 6. Occupational exposure: Exposure to an IMP as a result of one's professional or non-professional occupation. 7. Breastfeeding: Suspected adverse reactions which occur in infants following exposure to a medicinal product from breast milk. When the identification of the IMP is required, the investigator must follow the procedures for unblinding outlined in Section 5.10.2.	occur in infants following exposure to a medicinal product from breast milk. When the identification of the IMP is required, the investigator must follow the procedures for unblinding outlined in Section 5.10.2.	
SECTION 7.4.1 SERUM CHEMISTRY, HEMATOLOGY, AND URINALYSIS		
~~Clinical laboratory tests (serum chemistry, hematology and coagulation, urinalysis), if needed at the discretion of the investigator, may be performed during the trial.~~	None	This section was removed from the protocol because it is not relevant to the study.
SECTION 7.4.2. OTHER CLINICAL LABORATORY TESTS		
~~Other clinical laboratory tests will be performed as needed to ensure the safety of the patients.~~	None	This section was removed from the protocol because it is not relevant to the study.
SECTION 7.7 OROPHARYNGEAL EXAMINATIONS		
Oropharyngeal examinations will be performed at every visit (SV through TV6). The examination must be performed by a qualified healthcare professional. Whenever possible, the same qualified healthcare professional should complete the assessment for the same patient throughout that patient's participation in the study. Patients with clinical visual evidence of oral candidiasis at SV who agree to receive treatment and comply with appropriate medical monitoring may participate in the run-in period and may return for randomization. However, if the oral candidiasis is not controlled at that time, the patient will not be allowed to enter the study treatment period. Any visual evidence of oral candidiasis during the treatment period of the study (after RV through TV6, inclusive) will be	Oropharyngeal examinations will be performed at every visit (SV through TV6). The examination must be performed by a qualified healthcare professional. Whenever possible, the same qualified healthcare professional should complete the assessment for the same patient throughout that patient's participation in the study. Patients with clinical visual evidence of oral candidiasis at SV who agree to receive treatment and comply with appropriate medical monitoring may participate in the run-in period and may return for randomization. However, if the oral candidiasis is not controlled at that time, the patient will not be allowed to enter the study treatment period. Any visual evidence of oral candidiasis during the treatment period of the study (after RV through TV6, inclusive) will be	This text was added to provide a detailed description of oropharyngeal examinations to the protocol.

Original text with changes shown	New wording	Reason/justification for change
evaluated by obtaining and analyzing a swab of the suspect area. Appropriate therapy should be initiated immediately at the discretion of the investigator and should not be delayed for culture confirmation. Patients with a culture-positive infection may continue participation in the study on appropriate anti-infective therapy, provided this therapy is not prohibited by the protocol. Azole antifungal medications are prohibited. If a patient requires a protocol-prohibited medication for therapy, the patient will be discontinued from the study and provided appropriate therapy.	evaluated by obtaining and analyzing a swab of the suspect area. Appropriate therapy should be initiated immediately at the discretion of the investigator and should not be delayed for culture confirmation. Patients with a culture-positive infection may continue participation in the study on appropriate anti-infective therapy, provided this therapy is not prohibited by the protocol. Azole antifungal medications are prohibited. If a patient requires a protocol-prohibited medication for therapy, the patient will be discontinued from the study and provided appropriate therapy.	
SECTION 9.2.2 Modified Intent-to-Treat Analysis Set (Other section affected by these changes: Section 9.4.1)		
~~The modified intent-to-treat (mITT) analysis set will include all patients in the ITT population and will include the available data for those patients until they discontinue IMP.~~ ~~The mITT analysis set will serve as the main analysis set for the primary, secondary, and other efficacy endpoints.~~	None	This section was removed because the mITT analysis set will no longer be used for analysis in this study.
SECTION 9.4.2 DEMOGRAPHIC AND BASELINE CHARACTERISTICS		
Patient demographics will be presented for all 4~~3~~ analysis sets defined in Section 9.2.	Patient demographics will be presented for all 3 analysis sets defined in Section 9.2.	The number of analysis sets was corrected.

Original text with changes shown	New wording	Reason/justification for change
SECTION 9.5.4 PLANNED METHOD OF ANALYSIS (Other section affected by these changes: Section 9.2.1)		
The ~~mITT~~ITT analysis set (Section 9.2.1) will be the primary analysis set to be used for all efficacy analyses. ~~The ITT analysis set will serve as the supportive analysis set for all efficacy analyses.~~ The PP analysis set will serve as the ~~supportive~~sensitivity analysis set for primary efficacy analyses only. Details will be provided in the statistical analysis plan. Subgroup (sex, age group, previous therapy [ICS or NCS], and race) analyses will be provided for the primary efficacy endpoints.	The ITT analysis set (Section 9.2.1) will be the primary analysis set to be used for all efficacy analyses. The PP analysis set will serve as the sensitivity analysis set for primary efficacy analyses only. Details will be provided in the statistical analysis plan. Subgroup (sex, age group, previous therapy [ICS or NCS], and race) analyses will be provided for the primary efficacy endpoints.	This text was revised to reflect that the ITT analysis set will be the primary analysis set for efficacy analyses, since the mITT analysis set will no longer be used in this study.
SECTION 9.5.4.1 PRIMARY ESTIMANDS AND EFFICACY ANALYSIS		
The specific 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 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 (Little and Kang 2015, Mallinckrodt et al 2016, Mallinckrodt 2013, 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	The specific 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 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 (Little and Kang 2015, Mallinckrodt et al 2016, Mallinckrodt 2013, 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	These changes were made to update the primary efficacy analysis in response to FDA feedback.

Original text with changes shown	New wording	Reason/justification for change
therapies, such as systemic corticosteroids, additional medications containing ICS, or both, which would 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 or exceeding 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. In light of this, 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 in Mallinckrodt et al 2016~~Change from Baseline in Weekly Average of the Percent Predicted Trough Morning FEV_1 at Week 12~~ (Sections 3.2 and 3.4 for estimand 2 in the paper). **Analysis of the change from baseline in weekly average of the percent predicted trough morning FEV_1 at week 12** The baseline percent predicted FEV_1 will be the weekly average of the morning FEV_1 prior to the first IMP dose. The first day before randomization consists of the entry on the morning of the RV in the patient diary built into the handheld device. The weekly average of the percent predicted FEV_1 at week 12 will be the average values based on the available data at that week.	be placed on alternative asthma therapies, such as systemic corticosteroids, additional medications containing ICS, or both, which would 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 or exceeding 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. In light of this, 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 in Mallinckrodt et al 2016 (Sections 3.2 and 3.4 for estimand 2 in the paper). **Analysis of the change from baseline in weekly average of the percent predicted trough morning FEV_1 at week 12** The baseline percent predicted FEV_1 will be the weekly average of the morning FEV_1 prior to the first IMP dose. The first day before randomization consists of the entry on the morning of the RV in the patient diary built into the handheld device. The weekly average of the percent predicted FEV_1 at week 12 will be the average values based	

Original text with changes shown	New wording	Reason/justification for change
The primary analysis of the change from baseline in weekly average of percent predicted morning FEV_1 at week 12 due to the initially randomized treatment as actually taken 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 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% confidence interval (CI) for the difference and the p-value. In this analysis, missing data ~~for the primary endpoint~~ that are caused by early dropouts from the study or from IMP (regardless of availability of retrieved dropout data) will be ~~handled by penalizing a positive~~ imputed using reference-based multiple imputations. Details on the implementation of the multiple imputations will be provided in the statistical analysis plan. **Analysis of the change from baseline in 1-hour postdose percent predicted** ~~FEV_1 score using a baseline observation carried forward method. This method will assign these patients a change from baseline percent predicted FEV_1 score of 0; thus, the discontinued patients are treated as failures and are assigned a poor score. Discontinued patients that have negative change from baseline with last nonmissing percent predicted FEV_1 score will not have their results adjusted, since their scores are already poor. The same adjustment will be made for patients who discontinue IMP but continued the study assessment using the last assessment prior to discontinuation of IMP~~**morning FEV_1 at week 12**~~. No adjustments will be made to other patients.~~ ~~A supporting analysis of change from baseline in the weekly average of percent predicted trough morning FEV_1 over the 12-week treatment period will be performed using a mixed model for repeated measures (MMRM).~~ ~~Change from Baseline in 1-hour Postdose Percent Predicted~~	on the available data at that week. The primary analysis of the change from baseline in weekly average of percent predicted morning FEV_1 at week 12 due to the initially randomized treatment as actually taken 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 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% confidence interval (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. Details on the implementation of the multiple imputations will be provided in the statistical analysis plan. **Analysis of the change from baseline in 1-hour postdose percent predicted morning FEV_1 at week 12** The co-primary For the endpoint of change from baseline in 1-hour postdose percent predicted morning FEV_1 (measured at the clinic) at week 12, baseline is defined as predose FEV_1 measurements obtained at the clinic at the RV with the handheld device immediately prior to the IMP administration. The primary analysis of the change from baseline in 1-hour postdose percent predicted morning FEV_1 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 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 difference between each IMP treatment	

Original text with changes shown	New wording	Reason/justification for change
~~Morning FEV_1 at Week 12~~ ~~The co-primary~~ For the endpoint of change from baseline~~,~~ in 1-hour postdose percent predicted morning FEV_1 (measured at the clinic) at week 12, baseline is defined as ~~pre-dose~~predose FEV_1 measurements obtained at the clinic at the RV with the handheld device immediately prior to the IMP administration~~,~~. The primary analysis of the change from baseline in 1-hour postdose percent predicted morning FEV_1 ~~(measured at the clinic)~~ 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 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 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. Missing data caused by early dropouts will be handled similarly to the above analysis.	group and the placebo group will be presented together with the 2-sided 95% CI for the difference and the p-value. Missing data caused by early dropouts will be handled similarly to the above analysis.	
SECTION 9.5.4.2 SENSITIVITY ANALYSIS TO MISSING DATA		
To assess the impact of missing data, several sensitivity analyses will be conducted for the 2 endpoints by evaluating alternative estimands. More details will be provided in the statistical analysis plan. • The primary ~~endpoint~~analysis for the 2 endpoints will be repeated when using data collected after IMP discontinuation ~~and penalizing~~(retrieved dropout data). Reference-based imputation will be used only for patients ~~for whom~~with no retrieved dropout data. This analysis estimates different estimands, namely the change from baseline as actually taken (see estimand 1 in Mallinckrodt et al 2016). • The primary analysis for the 2 endpoints will be repeated on completers with no major protocol violations (see estimand 3 in Mallinckrodt et al	To assess the impact of missing data, several sensitivity analyses will be conducted for the 2 endpoints by evaluating alternative estimands. More details will be provided in the statistical analysis plan. • The primary analysis for the 2 endpoints will be repeated when using data collected after IMP discontinuation (retrieved dropout data). Reference-based imputation will be used only for patients with no retrieved dropout data. This analysis estimates different estimands, namely the change from baseline as actually taken (see estimand 1 in Mallinckrodt et al 2016). • The primary analysis for the 2 endpoints will be repeated on completers with no major protocol violations (see estimand 3 in Mallinckrodt et al	These changes were made to update the handling of missing data in response to FDA feedback.

Original text with changes shown	New wording	Reason/justification for change
2016~~assessment after IMP discontinuation is available. In addition, a~~). • A tipping point analysis will be performed as a sensitivity analysis to missing data by utilizing multiple imputations under ~~the missing not at random (MNAR) assumption.~~ different missing mechanism. For placebo patients, in all applications of multiple imputations, missing at random (MAR) will be assumed. 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. ~~An additional analysis to assess the robustness of the results will be conducted by applying the primary efficacy analysis to the PP analysis set.~~ • The primary analysis for the 2 endpoints will be repeated when missing data will be imputed using a mixed approach of last observation carried forward (LOCF) and baseline observation carried forward (BOCF) as follows: BOCF will be used for patients who had a positive change from baseline at the time of study or IMP discontinuation (ie, a change of 0), while LOCF will be used for patients that have negative change from baseline. In this imputation method, the imputed value is the lower between LOCF and BOCF for each patient. No adjustments will be made to other patients. • For the first primary endpoint of change from baseline in the weekly average of percent predicted trough morning FEV_1 over the 12-week treatment period, analysis will be performed using a mixed model for repeated measures (MMRM). This analysis will not use retrieved dropout data. This analysis represents a MAR assumption.	2016). • A tipping point analysis will be performed as a sensitivity analysis to missing data by utilizing multiple imputations under different missing mechanism. For placebo patients, in all applications of multiple imputations, missing at random (MAR) will be assumed. 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. • The primary analysis for the 2 endpoints will be repeated when missing data will be imputed using a mixed approach of last observation carried forward (LOCF) and baseline observation carried forward (BOCF) as follows: BOCF will be used for patients who had a positive change from baseline at the time of study or IMP discontinuation (ie, a change of 0), while LOCF will be used for patients that have negative change from baseline. In this imputation method, the imputed value is the lower between LOCF and BOCF for each patient. No adjustments will be made to other patients. • For the first primary endpoint of change from baseline in the weekly average of percent predicted trough morning FEV_1 over the 12-week treatment period, analysis will be performed using a mixed model for repeated measures (MMRM). This analysis will not use retrieved dropout data. This analysis represents a MAR assumption.	

Original text with changes shown	New wording	Reason/justification for change
SECTION 9.5.4.3 SECONDARY EFFICACY ANALYSIS		
For all secondary endpoints, analyses will be performed using the ITT analysis set and will not include retrieved dropout data in the analysis.	For all secondary endpoints, analyses will be performed using the ITT analysis set and will not include retrieved dropout data in the analysis.	Text was added to clarify the analyses of the secondary endpoints.
SECTION 15 REFERENCES		
Corren J, Korenblat PE, Miller CJ, O'Brien CD, Mezzanotte WS. Twelve-week, randomized, placebo-controlled, multicenter study of the efficacy and tolerability of budesonide and formoterol in one metered-dose inhaler compared with budesonide alone and formoterol alone in adolescents and adults with asthma. Clin Ther 2007;29(5):823–43. Kerwin EM, Pearlman DS, de Guia T, Carlsson LG, Gillen M, Uryniak T, et al. Evaluation of efficacy and safety of budesonide delivered via two dry powder inhalers. Curr Med Res Opin. 2008;24(5):1497–510. Little R, Kang S. Intention-to-treat analysis with treatment discontinuation and missing data in clinical trials. Stat Med 2015;34(16):2381–90. Mallinckrodt C. Choosing primary estimands and analyses. In: Preventing and treating missing data in longitudinal clinical trials: A practical guide. New York: Cambridge University Press, 2013. Mallinckrodt C, Molenberghs G, Rathmann S. Choosing estimands in clinical trials with missing data. Pharm Stat 2016. O'Neill RT, Temple R. The prevention and treatment of missing data in clinical trials: An FDA perspective on the importance of dealing with it. Clin Pharmacol Ther 2012;91(3):550–4. Pearlman DS, Stricker W, Weinstein S, Gross G, Chervinsky P, Woodring A, et al. Ann Allergy Asthma Immunol 1999;82(3):257–65. Szefler SJ, Boushey HA, Pearlman DS, Togias A, Liddle R, Furlong A, et al. Time to onset of effect of fluticasone propionate in patients with asthma. J Allergy Clin Immunol	Corren J, Korenblat PE, Miller CJ, O'Brien CD, Mezzanotte WS. Twelve-week, randomized, placebo-controlled, multicenter study of the efficacy and tolerability of budesonide and formoterol in one metered-dose inhaler compared with budesonide alone and formoterol alone in adolescents and adults with asthma. Clin Ther 2007;29(5):823–43. Kerwin EM, Pearlman DS, de Guia T, Carlsson LG, Gillen M, Uryniak T, et al. Evaluation of efficacy and safety of budesonide delivered via two dry powder inhalers. Curr Med Res Opin. 2008;24(5):1497–510. Little R, Kang S. Intention-to-treat analysis with treatment discontinuation and missing data in clinical trials. Stat Med 2015;34(16):2381–90. Mallinckrodt C. Choosing primary estimands and analyses. In: Preventing and treating missing data in longitudinal clinical trials: A practical guide. New York: Cambridge University Press, 2013. Mallinckrodt C, Molenberghs G, Rathmann S. Choosing estimands in clinical trials with missing data. Pharm Stat 2016. O'Neill RT, Temple R. The prevention and treatment of missing data in clinical trials: An FDA perspective on the importance of dealing with it. Clin Pharmacol Ther 2012;91(3):550–4. Pearlman DS, Stricker W, Weinstein S, Gross G, Chervinsky P, Woodring A, et al. Ann Allergy Asthma Immunol 1999;82(3):257–65. Szefler SJ, Boushey HA, Pearlman DS, Togias A, Liddle R,	Additional references were inserted into the list of references as additional sources were included in the text.

Original text with changes shown	New wording	Reason/justification for change
1999;103(5):780–8. Woodcock A, Bleecker ER, Lötvall J, O'Byrne PM, Bateman ED, Medley H, et al. Efficacy and safety of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma. Chest 2013;144(4):1222–9.	Furlong A, et al. Time to onset of effect of fluticasone propionate in patients with asthma. J Allergy Clin Immunol 1999;103(5):780–8. Woodcock A, Bleecker ER, Lötvall J, O'Byrne PM, Bateman ED, Medley H, et al. Efficacy and safety of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma. Chest 2013;144(4):1222–9.	
APPENDIX A CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS		
~~Not applicable~~ Q Squared Solutions LLC 27027 Tourney Road, Suite 2E Valencia, CA 91355 USA Q Squared Solutions Limited The Alba Campus (Rosebank) Livingston West Lothian EH54 7EG Scotland, United Kingdom	Q Squared Solutions LLC 27027 Tourney Road, Suite 2E Valencia, CA 91355 USA Q Squared Solutions Limited The Alba Campus (Rosebank) Livingston West Lothian EH54 7EG Scotland, United Kingdom	The information for the central clinical laboratories was inserted into the document.
APPENDIX B STUDY PROCEDURES AND ASSESSMENTS BY VISIT		
The intent of the run-in period is to complete baseline safety evaluations, establish patient compliance, and obtain baseline measures of asthma symptoms, rescue use, and ~~PEF~~lung function assessment values. Patients (with assistance from parents/legal guardians/caregivers, as needed) will record symptoms, rescue use, and ~~PEF~~lung function assessments (FEV_1 and PEF) in the patient diary built into the handheld device throughout the 14- to 30-day run-in period to establish their baseline profiles.	The intent of the run-in period is to complete baseline safety evaluations, establish patient compliance, and obtain baseline measures of asthma symptoms, rescue use, and lung function assessment values. Patients (with assistance from parents/legal guardians/caregivers, as needed) will record symptoms, rescue use, and lung function assessments (FEV_1 and PEF) in the patient diary built into the handheld device throughout the 14- to 30-day run-in period to establish their baseline profiles.	This change was made to correct which lung function assessments should be recorded in the patient diary during the run-in period.
APPENDIX B STUDY PROCEDURES AND ASSESSMENTS BY VISIT (Other section affected by these changes: Section 3.5 [Table 3, footnote i])		
The training inhaler is to be kept at the clinic and not provided to the patient to keep at home. Inhaler device training is not	The training inhaler is to be kept at the clinic and not provided to the patient to keep at home. Inhaler device	This text was added to exempt patients who discontinue the

Original text with changes shown	New wording	Reason/justification for change
required for patients placed on alternative asthma therapy and who are no longer taking IMP per protocol.	training is not required for patients placed on alternative asthma therapy and who are no longer taking IMP per protocol.	study IMP from inhaler device training.
APPENDIX D ETHICS		
~~The investigator, or a qualified person designated by the investigator, should fully inform the patient of all pertinent aspects of the study, including the written information approved by the IEC/IRB. All written and oral information about the study will be provided in a language as nontechnical as practical to be understood by the patient. The patient should be given ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. The above should be detailed in the source documents.~~ ~~Written informed consent will be obtained from each patient before any study specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained. The patient's willingness to participate in the study will be documented in the informed consent form, which will be signed and personally dated by the patient and by the person who conducted the informed consent discussion. The investigator will keep the original informed consent forms, and copies will be given to the patients. It will also be explained to the patients that the patient is free to refuse participation in the study and free to withdraw from the study at any time without prejudice to future treatment.~~ The investigator, or a qualified person designated by the investigator, should fully inform the patient and each parent/legal guardian of all pertinent aspects of the study, including the written information approved by the IEC/IRB. All written and oral information about the study will be provided in a language as nontechnical as practical to be understood by the ~~each~~ parent/legal guardian and the patient. The patient and each parent/ legal guardian should be given ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. The above should be detailed in the source documents.	The investigator, or a qualified person designated by the investigator, should fully inform the patient and each parent/legal guardian of all pertinent aspects of the study, including the written information approved by the IEC/IRB. All written and oral information about the study will be provided in a language as nontechnical as practical to be understood by the parent/legal guardian and the patient. The patient and each parent/legal guardian should be given ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. The above should be detailed in the source documents. A personally signed and dated informed consent form will be obtained from the parent/legal guardian, and a signed and dated assent form will be obtained from each patient (as applicable and as may be specified by local regulations) before any study specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained; according to IEC/IRB requirements. The forms will be signed and dated also by the person who conducted the informed consent discussion. The investigator will keep the original informed consent and assent forms, and copies will be given to the patients (and each parent/legal guardian). It will also be explained to the patients (and each parent/legal guardian) that they are free to refuse participation in the study and free to withdraw from the study at any time without prejudice to future treatment.	The first 2 paragraphs of this text were deleted to avoid redundancy with the next 2 paragraphs. The text was also changed to modify the circumstances under which a signed and dated assent form may be collected from each patient.

Original text with changes shown	New wording	Reason/justification for change
A personally signed and dated informed consent form will be obtained from the parent/legal guardian, and a signed and dated assent form will be obtained from each patient (~~if the patient is able~~as applicable and as may be specified by local regulations) before any study specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained; according to IEC/IRB requirements. The forms will be signed and dated also by the person who conducted the informed consent discussion. The investigator will keep the original informed consent and assent forms, and copies will be given to the patients (and each parent/legal guardian). It will also be explained to the patients (and each parent/legal guardian) that they are free to refuse participation in the study and free to withdraw from the study at any time without prejudice to future treatment.		
APPENDIX E LOST TO FOLLOW-UP		
• The investigational center must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study. This includes using alternative contact information supplied by the parent/legal guardian as outlined in the informed consent (as allowed by local regulation).	• The investigational center must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study. This includes using alternative contact information supplied by the parent/legal guardian as outlined in the informed consent (as allowed by local regulation).	This text was added to specify the manner in which the investigational center will attempt to contact patients who do not return to the investigational center for a required study visit.

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APPENDIX A. CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS

Sponsor's Authorized Representative	[redacted] Teva Pharmaceuticals [redacted]
Legal Representative of the sponsor in the EU	[redacted] Merckle GmbH Graf-Arco-Str. 3 89079 Ulm Germany
Sponsor's Medical Expert/Contact Point designated by the sponsor for Further Information on the Study	[redacted] Teva Pharmaceuticals [redacted]
Coordinating Principal Investigator	[redacted]
Sponsor's Representative of Global Patient Safety and Pharmacovigilance **For serious adverse events:** Send by email to the LSO/CRO. The email address will be provided in the serious adverse event report form. In the event of difficulty transmitting the form, contact the sponsor's study personnel identified above for further instruction.	[redacted] Teva Pharmaceuticals [redacted]
Contract Research Organization	PRA Health Sciences 4130 Parklake Ave, #400 Raleigh, NC 27612
Central Clinical Laboratory	Q Squared Solutions LLC 27027 Tourney Road, Suite 2E Valencia, CA 91355 USA Q Squared Solutions Limited The Alba Campus (Rosebank) Livingston West Lothian EH54 7EG Scotland, United Kingdom
Central Electrocardiogram Evaluation	Not applicable

Bioanalytical Pharmacokinetics Evaluation	Not applicable
Bioanalytical Immunogenicity Evaluation	Not applicable
Pharmacogenomics/Biomarker Evaluation	Not applicable
Randomization and Trial Supply Management (RTSM) vendor	Y-Prime 263 Great Valley Parkway Malvern, PA 19355

APPENDIX B. STUDY PROCEDURES AND ASSESSMENTS BY VISIT

1. Procedures for Optional Prescreening Visit

An optional prescreening visit may be scheduled up to 15 days prior to the screening visit (SV). During this visit and after informed consent/assent (as applicable) is obtained, the investigator will discuss with the patient and parents/legal guardians/caregivers study procedures and potential study-specific changes to the patient's current asthma therapy if a patient decides to participate in the study and qualifies for study entry; the investigator will also discuss any required washout periods for prohibited medications before the SV.

At the time of informed consent (at the prescreening visit or SV), 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.

An SV will be scheduled, which should occur in the morning (0530 to 1100) and instruct patients to refrain from taking their morning inhaled corticosteroid (ICS)/long-acting β2 agonist (LABA) and to avoid taking rescue medication for at least 6 hours before the appointment time on the day of the SV.

11. Procedures for Screening and Enrollment (Visit 1)

A signed and dated informed consent form (unless already obtained at a prescreening visit) will be obtained from the parent/legal guardian, and a signed and dated assent form will be obtained from each patient (as applicable) before any screening procedures commence, according to national laws and local Independent Ethics Committee/Institutional Review Board (IEC/IRB) requirements. Each parent/legal guardian will acknowledge and agree to the possible use of this information for the study by giving informed consent.

After informed consent is obtained, interactive response technology (IRT) will be used to assign screened patients an 8-digit permanent identification.

Note that if the patient has a prescreening visit, a permanent identification number would have been assigned at that time.

Lung function assessments by handheld device at the SV are to be performed a minimum of 6 hours after the last SABA use and should not be conducted if the patient has taken routine maintenance asthma medication on that day. Screening lung function assessments should be performed at the investigational center between the hours of 0530 and 1100. Patients will be permitted 8 attempts per test. The highest forced expiratory volume in 1 second (FEV_1) value from 3 technically acceptable and 2 repeatable maneuvers will be used. Patients who have failed screening for FEV_1 or response to a bronchodilator may retest once within 7 days of the SV provided that they have met all other inclusion criteria and none of the exclusion criteria. At retest, patients will report if there have been any adverse events, changes in medications, or changes in medical history since providing consent/assent (as applicable). The run-in period will not start until patients have passed all screening procedures (including a retest, if needed).

Patients who have not met inclusion criteria for response to a bronchodilator and cannot return within 7 days for a retest should be classified as screen failures but may be rescreened. Patients who experience an upper respiratory infection (URI) or lower respiratory infection (LRI) during the run-in period should be classified as randomization failures and be discontinued from the study, but may be rescreened 2 weeks after resolution of the infection. Patients who are rescreened will need to repeat all screening procedures and evaluations. Only 1 retest and 1 rescreening for each patient will be permitted.

The SV will take place up to 30 days before the RV. The following procedures will be performed at SV:

- obtain written informed consent/assent (as applicable) before any study-related procedures are performed (unless already obtained at a prescreening visit)
- review medical history
- collect prior medication history
- review inclusion and exclusion criteria
- collect demographic data
- inquire and record adverse events and concomitant medications
- perform vital signs measurements
- perform full physical examination (including weight and height)
- perform oropharyngeal examination
- perform urine pregnancy test (for females of childbearing potential, as applicable)
- perform predose lung function assessments (FEV_1 and peak expiratory flow [PEF]) by handheld device, followed by response to a bronchodilator test within 30 minutes after 2 to 4 inhalations of albuterol/salbutamol HFA. Patients who fail to meet lung function assessments or response to a bronchodilator requirements may retest once within 7 days.
- dispense run-in drug kit
- dispense rescue medication
- provide training on handheld device
- provide patient handheld device
- provide training on investigational medicinal product (IMP) and have patient demonstrate proper technique using the provided training device. The training inhaler is to be kept at the clinic and not provided to the patient to keep at home.

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 throughout the course of the study. A single training inhaler will be assigned to each patient at the SV and will be kept at the investigational center for use at each investigational center visit.

12. **Retesting and Rescreening**

Patients who have not met inclusion criteria for response to a bronchodilator and cannot return within 7 days for a retest should be classified as screen failures but may be rescreened. Patients who experience an URI or LRI during the run-in period should be classified as randomization failures and be discontinued from the study, but may be rescreened 2 weeks after resolution of the infection. Patients who are rescreened will need to repeat all screening procedures and evaluations. Only 1 retest and 1 rescreening for each patient will be permitted.

The decision to retest or rescreen patients will be based on the investigator's judgement and the study protocol. In cases of rescreening, the sponsor or designee should be notified of the pending rescreening. Patients may retest/rescreen for lung function assessments and response to a bronchodilator only if they meet all other nonspirometric inclusion/exclusion criteria. At the retest, patients will be asked if they have had any adverse events, changes in medications, or changes in medical history. Patients will not be eligible to enter the run-in period until all inclusion/exclusion criteria are met.

13. **Run-in Period (Between Screening Visit and Treatment Visit [TV] 1)**

Patients meeting all of the inclusion criteria and none of the exclusion criteria at the SV will begin a 14- to 30-day run-in period. 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 symptomatic relief of asthma symptoms during the run-in and treatment periods, with a maximum of 12 inhalations permitted per day.

Starting day 1 of the run-in period, patients must discontinue their current ICS or ICS/LABA therapy and all other nonstudy asthma-related drugs and instead take a patient-blinded MDPI placebo device (1 inhalation twice daily).

The intent of the run-in period is to complete baseline safety evaluations, establish patient compliance, and obtain baseline measures of asthma symptoms, rescue use, and lung function assessment values. Patients (with assistance from parents/legal guardians/caregivers, as needed) will record symptoms, rescue use, and lung function assessments (FEV_1 and PEF) in the patient diary built into the handheld device throughout the 14- to 30-day run-in period to establish their baseline profiles. Patients and parents/legal guardians/caregivers will be instructed to contact their investigator if they have met predefined asthma alert criteria.

14. **Procedures Before Investigational Medicinal Product Treatment (Baseline [Randomization Visit (RV)/TV1])**

Patients who meet the inclusion and exclusion criteria at visit SV will continue to RV/TV1. At the RV/TV1, patient will be assessed for randomization. Patients who meet all of the randomization criteria will be randomized into the double-blind treatment period of the study. Note: response to bronchodilator testing may not be conducted on the same day as the randomization visit.

The following procedures will be performed at the RV/TV1:

- review randomization criteria
- inquire about adverse events and concomitant medications
- perform vital signs measurements

- perform directed cardiopulmonary examination
- perform oropharyngeal examination
- perform urine pregnancy test (for females of childbearing potential, as applicable)
- perform predose lung function assessments (FEV_1 and PEF) by handheld device
- provide training on IMP and have patient demonstrate proper technique using the provided training device before dosing with IMP. The training inhaler is to be kept at the clinic and not provided to the patient to keep at home.
- dispense IMP
- observe patient dosing with IMP
- perform 1-hour postdose lung function assessments (FEV_1 and PEF) by handheld device
- collect Childhood Asthma Control Test (C-ACT) asthma questionnaire
- collect run-in drug kit
- dispense/collect rescue medication (if needed)
- dispense and provide training on handheld device
- assess alert criteria for worsening asthma

A patient who is not enrolled in the study on the basis of results of baseline assessments (eg, because inclusion and exclusion criteria were not met or enrollment did not occur within the specified time) may be considered for screening again if there is a change in the patient's medical background, a modification of study inclusion and exclusion criteria, or other relevant change. (Note: Details of rescreening criteria and procedures are included in the monitoring plan.)

Patients who continue to meet the inclusion and exclusion criteria will be assigned a permanent unique randomization number.

15. **Procedures During Investigational Medicinal Product Treatment**

a. Double-Blind Treatment Period (TV1 to TV6)

During the treatment period (TV1 though TV6), daily in the morning and evening at approximately the same time each day, patients (with assistance from parents/legal guardians/caregivers, as needed) 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 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 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 instructions and training (competent handheld device use and dosing technique using the training devices provided), patients will repeat 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 a 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. The highest FEV_1 value from 3 acceptable and 2 repeatable maneuvers (maximum of 8 attempts per test) will be obtained before and 1-hour after the morning dose. The postdose measurements should be taken at 60 minutes ±10 minutes from the time of IMP dosing.

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 or caregiver should complete assessments at each visit. Specific instructions are provided in the study reference manual.

Safety will be monitored by physical examination, oropharyngeal examination, vital signs, lung function assessments, and recording of adverse events. Any visual evidence of oral candidiasis during the treatment period will be confirmed by obtaining a swab for culture of the suspect area. Patients and parents/legal guardians/caregivers will be provided with guidelines for when to contact the investigational center in case of worsening asthma symptoms or rescue inhaler use. Patients who meet predefined alert criteria should be evaluated by the investigator to determine if they should be withdrawn from the study either at the next scheduled TV or an IMP discontinuation visit (IMPDV). In cases where the IMP is to be withdrawn and alternative therapy started, the investigational center staff should contact the medical monitor to confirm the findings. If a patient discontinues the study prematurely but remains in the study, all subsequent visits will include all assessments according to Table 3.

– **Treatment Visits 2, 3, 4, 5, and 6 (Weeks 1, 2, 4, 8, and 12) and IMPDV**

Patients will attend the investigational center at weeks 1, 2, 4, 8, and 12. The following procedures/assessments will be performed at these visits:

- inquiry and recording of adverse events and concomitant medications
- measurements of vital signs
- perform oropharyngeal examination
- perform urine pregnancy test (for females of childbearing potential, as applicable)
- perform predose lung function assessments (FEV_1 and PEF) by handheld device

- provide training on IMP (at all but TV6 and the IMPDV) and have patient demonstrate proper technique using the provided training inhaler. The training inhaler is to be kept at the clinic and not provided to the patient to keep at home. Inhaler device training is not required for patients placed on alternative asthma therapy and who are no longer taking IMP per protocol.
- observe patient dosing with IMP
- perform 1-hour postdose lung function assessments (FEV_1 and PEF) by handheld device (morning only at TV6)
- provide handheld device training (at all but TV6)
- collect C-ACT asthma questionnaire (at TV4, TV5, TV6, and IMPDV only)
- dispense/collect rescue medication (as needed)
- dispense/collect IMP (at TV3, TV4, TV5, TV6, and the IMPDV only)
- assess alert criteria for worsening asthma
- discuss and record recommended asthma therapy (TV6 and the IMPDV only)
- end IMP in IRT system (TV6 and the IMPDV only)
- end study participation in IRT system (IMPDV only)

16. **Procedures After Investigational Medicinal Product Treatment**

Patients who participate in the study in compliance with the protocol for the entire duration of the study (screening, run-in, and all TVs) will be considered to have completed the study.

a. Follow-up

For patients who complete the study or withdraw prematurely, final evaluations will be performed at the IMPDV or on the last day the patient receives the IMP, or as soon as possible thereafter. Procedures for patients who withdraw prematurely from the study are described in Section 4.3. Patients should be treated with standard of care after termination of the study as appropriate.

Patients may attend a follow-up visit one week (±2 days) after the last TV. The follow-up visit may be in person or over the telephone. The following assessments will be performed during the follow-up visit:

- inquiry of adverse events
- inquiry of concomitant medication

The patients will be deemed to have completed the treatment period if they have completed all periods of treatment, including screening, run-in, and all treatments visits. The patient will be deemed to have completed the study period if they have completed all periods of the study, including FV in addition to screening, run-in, and all TVs. Patients who stop IMP and return for safety evaluation at week 12 will not be considered to have completed the treatment period.

Patients with ongoing adverse events will be monitored as described in Section 7.1.2. Otherwise, the follow-up visit will be the last study visit.

17. **Unscheduled Visits**

An unscheduled visit may be performed at any time during the study at the patient's request and as deemed necessary by the investigator. The date and reason for the unscheduled visit will be recorded on the case report form as well as any other data obtained (eg, adverse events, concomitant medications and treatments, and results from procedures or tests).

Procedures performed during unscheduled visits include the following:

- concomitant medication inquiry
- vital signs measurements
- adverse event inquiry

Other procedures may be performed at the discretion of the investigator.

APPENDIX C. QUALITY CONTROL AND QUALITY ASSURANCE

Protocol Amendments and Protocol Deviations and Violations

Protocol Amendments

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favorable opinion of a written amendment by the IEC/IRB and national and local competent authorities, as applicable, except when necessary to address immediate safety concerns to the patients or when the change involves only nonsubstantial logistics or administration. The principal investigator at each investigational center, the coordinating investigator (if applicable), and the sponsor will sign the protocol amendment.

Protocol Violations

Any deviation from the protocol that affects, to a significant degree, (a) the safety, physical, or mental integrity of the patients in the study and/or (b) the scientific value of the study will be considered a protocol violation. Protocol violations may include nonadherence on the part of the patient, the investigator, or the sponsor to protocol-specific inclusion and exclusion criteria, primary objective variable criteria, or GCP guidelines; noncompliance to IMP administration; and use of prohibited medications. All protocol violations will be reported to the responsible IEC/IRB, as required.

When a protocol violation is reported, the sponsor will determine whether to discontinue the patient from the study or permit the patient to continue in the study, with documented approval from the medical expert. The decision will be based on ensuring the safety of the patient and preserving the integrity of the study.

Changes in the inclusion and exclusion criteria of the protocol are **not** prospectively granted by the sponsor. If investigational center personnel learn that a patient who did not meet protocol inclusion and exclusion criteria was entered in a study, they must immediately inform the sponsor of the protocol violation. If such patient has already completed the study or has withdrawn early, no action will be taken but the violation will be recorded.

Information to Study Personnel

The investigator is responsible for giving information about the study to all personnel members involved in the study or in any element of patient management, both before starting the study and during the course of the study (eg, when new personnel become involved). The investigator must ensure that all study personnel are qualified by education, experience, and training to perform their specific task. These study personnel members must be listed on the investigational center authorization form, which includes a clear description of each personnel member’s responsibilities. This list must be updated throughout the study, as necessary.

The study monitor is responsible for explaining the protocol to all study personnel, including the investigator, and for ensuring they comply with the protocol.

Study Monitoring

To ensure compliance with GCP guidelines, the study monitor or representative is responsible for ensuring that patients have signed the informed consent form and the study is conducted according to applicable SOPs, the protocol, and other written instructions and regulatory guidelines.

The study monitor is the primary association between the sponsor and the investigator. The main responsibilities of the study monitor(s) are to visit the investigator before, during, and after the study to ensure adherence to the protocol, that all data are correctly and completely recorded and reported, and that informed consent is obtained and recorded for all patients before they participate in the study and when changes to the consent form are warranted, in accordance with IEC/IRB approvals.

The study monitor(s) will contact the investigator and visit the investigational center according to the monitoring plan. The study monitor will be permitted to review and verify the various records (CRFs and other pertinent source data records, including specific electronic source document relating to the study) to verify adherence to the protocol and to ensure the completeness, consistency, and accuracy of the data being recorded.

As part of the supervision of study progress, other sponsor personnel may, on request, accompany the study monitor on visits to the investigational center. The investigator and assisting personnel must agree to cooperate with the study monitor to resolve any problems, errors, or possible misunderstandings concerning the findings detected during the course of these monitoring visits or provided in follow-up written communication.

Audit and Inspection

The sponsor may audit the investigational center to evaluate study conduct and compliance with protocols, SOPs, GCP guidelines, and applicable regulatory requirements. The sponsor's Global Clinical Quality Assurance, independent of Global Specialty Development, is responsible for determining the need for (and timing of) an investigational center audit.

The investigator must accept that competent authorities and sponsor representatives may conduct inspections and audits to verify compliance with GCP guidelines.

APPENDIX D. ETHICS

Informed Consent/Assent

The investigator, or a qualified person designated by the investigator, should fully inform the patient and each parent/legal guardian of all pertinent aspects of the study, including the written information approved by the IEC/IRB. All written and oral information about the study will be provided in a language as nontechnical as practical to be understood by the parent/legal guardian and the patient. The patient and each parent/legal guardian should be given ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. The above should be detailed in the source documents.

A personally signed and dated informed consent form will be obtained from the parent/legal guardian, and a signed and dated assent form will be obtained from each patient (as applicable and as may be specified by local regulations) before any study specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained; according to IEC/IRB requirements. The forms will be signed and dated also by the person who conducted the informed consent discussion. The investigator will keep the original informed consent and assent forms, and copies will be given to the patients (and each parent/legal guardian). It will also be explained to the patients (and each parent/legal guardian) that they are free to refuse participation in the study and free to withdraw from the study at any time without prejudice to future treatment. The parent/legal guardian will be counseled about the importance of the patient completing all visits even if the patient is withdrawn from IMP but chooses to continue their participation in the study (ie, does not withdraw consent). The parent/legal guardian will be asked to provide alternative contact information (as allowed by local regulation) in the event that the study center is unable to contact the parent/legal guardian to encourage continued participation in the study.

Competent Authorities and Independent Ethics Committees/Institutional Review Boards

Before this study starts, the protocol will be submitted to the national competent authority and to the respective IEC/IRB for review. As required, the study will not start at a given investigational center before the IEC/IRB and competent authority (as applicable) for the investigational center give written approval or a favorable opinion.

Confidentiality Regarding Study Patients

The investigator must ensure that the privacy of the patients, including their identity and all personal medical information, will be maintained at all times. In CRFs and other documents or image material submitted to the sponsor, patients will be identified not by their names, but by an identification number.

Personal medical information may be reviewed for the purpose of patient safety or for verifying data in the source and the CRF. This review may be conducted by the study monitor, properly authorized persons on behalf of the sponsor, Global Quality Assurance (GQA), or competent authorities. Personal medical information will always be treated as confidential.

In compliance with national and local regulations and in accordance with Teva standard procedures, this clinical study will be registered on trials registry websites.

APPENDIX E. LOST TO FOLLOW-UP

A patient will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the investigational center.

The following actions must be taken if a patient fails to return to the investigational center for a required study visit:

- The investigational center staff must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study. This includes using alternative contact information supplied by the parent/legal guardian as outlined in the informed consent (as allowed by local regulation).
- In cases in which the patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of 'lost to follow-up'.

APPENDIX F. INSTRUCTIONS FOR USE OF MEDICAL DEVICES

All patients will be provided training on use of the Teva MDPI device during the SV. The training will be done after all screening procedures and lung function assessments have been completed and the patient has been deemed eligible for inclusion. Directions for use of the device will be reviewed with each patient. Patients will then be provided with a Teva MDPI training device. The training devices are empty and do not contain active medication. Patients will practice using the device and will be required to demonstrate their understanding of correct technique. Directions for use of each device should be reviewed with each patient at randomization and at each TV. Training procedures should be repeated at each TV to ensure that patients continue to use correct technique for the device over the duration of the study.

APPENDIX G. HANDLING, LABELING, STORAGE, AND ACCOUNTABILITY FOR IMPS

Storage and Security

For the purposes of the study, test IMPs (Fp MDPI, Fs MDPI) and placebo with Teva MDPI devices must be stored between 15°C and 25°C (59°F and 77°F) in a dry place away from direct heat and sunlight, and in a securely locked, substantially constructed cabinet or enclosure. All rescue medication (albuterol/salbutamol HFA) will be stored according to the manufacturer's drug product stipulation, in a dry place, and in a securely locked, substantially constructed cabinet or enclosure. Maintenance of a daily temperature log (manual or automated) is required.

Each IMP shipment will include a packing slip listing the contents of the shipment and a device for monitoring and recording temperatures. The investigator is responsible for ensuring that deliveries of IMP and other study materials from the sponsor are treated as follows:

- Correctly received and recorded
- Handled and stored safely and properly in accordance with the Code of Federal Regulations (CFR) or local regulations
- Used in accordance with this protocol

The investigational center personnel are responsible for the acknowledgement of the receipt using the IRT.

Labeling

Detailed instructions regarding labeling (eg, investigational centers indicating the use by date) of the investigational product are provided in the study operations manual.

Supplies of IMPs will be labeled in accordance with the current ICH guidelines on GCP and Good Manufacturing Practice and will include any locally required statements. If necessary, labels will be translated into the local language.

Accountability

Each IMP shipment will include a packing slip listing the contents of the shipment, return instructions, and any applicable forms.

The investigator is responsible for ensuring that deliveries of IMPs and other study materials from the sponsor are correctly received, recorded, handled, and stored safely and properly in accordance with the CFR or national and local regulations, and used in accordance with this protocol.

Only patients enrolled in the study may receive IMPs and only authorized staff at the investigational center may supply or administer IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions or appropriate instructions with access limited to the investigator and authorized staff at the investigational center.

The investigator (or designee) will instruct the patient to store the IMP according to the instructions on the label, if applicable; or will give instructions in an appropriate form.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for IMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

A record of IMP accountability (ie, IMP and other study materials received, used, retained, returned, or destroyed) must be prepared and signed by the principal investigator or designee, with an account given for any discrepancies. Empty, partially used, and unused IMP will be returned to the sponsor or designee.

APPENDIX H. LIST OF PROHIBITED MEDICATIONS

Type of medication	**Washout period before the screening visit (unless otherwise specified)**
Anti-immunoglobulin E therapy (omalizumab)	5 half-lives
Any other investigational drug	30 days or 5 half-lives, whichever is longer
Aspirin[a]	1 day
Beta-adrenergic receptor blocking agents	30 days
Bisphosphonates oral or intravenous (eg, alendronate, ibandronate)	30 days
Corticosteroids (oral, intravenous, intra-articular, or intramuscular)[b]	30 days
Cromones	14 days
Decongestants (eg, pseudoephedrine, phenylpropanolamine, phenylephrine)	Discontinue 24 hours before SV, RV, and TV1 to TV6 (week 12) and resume use after the visit
Immunologically active biologic medications (eg, anti-tumor necrosis factor alpha, abatacept)	5 half-lives
Immunosuppressive therapy (eg, methotrexate, gold, azathioprine)	30 days
Immunotherapy[c]	Initiation within 90 days or change in dose within 30 days
Inhaled anticholinergic medication (eg, tiotropium bromide)	7 days
ICSs other than IMP	Permitted at SV, but discontinue upon entering run-in
Inhaled LABA	Permitted at SV, but discontinue upon entering run-in
Leukotriene modifiers	Permitted at SV, but discontinue upon entering run-in
Monoamine oxidase inhibitors	14 days
Oral β_2-agonists (tablets, syrup)	7 days
Oral or nasal antihistamines (eg, loratadine, diphenhydramine, cetirizine)	Discontinue 24 hours before SV, RV, and TV1 to TV6 (week 12) and resume use after completion of the visit
Strong CYP3A4 inhibitors (eg, oral ketoconazole, itraconazole, ritonavir, clarithromycin)	30 days
Theophyllines	Permitted at SV, but discontinue upon entering run-in
Topical dermatologic corticosteroids (intermediate to high potency; eg, CUTIVATE® [PharmaDerm], ELOCON® [Schering Corporation])[d]	14 days
Marijuana (medical, legal, and illegal)	30 days before the SV and throughout the study
Electronic cigarettes	Discontinue 24 hours before the SV and do not resume use during the study

Type of medication	**Washout period before the screening visit (unless otherwise specified)**
Tricyclic antidepressants	14 days

[a] Chronic stable doses of aspirin (≤325 mg/day) for cardiovascular prophylaxis are allowed.

[b] Chronic stable doses of ocular steroids of at least 7 days duration, with doses expected to remain stable throughout the study, are allowed.

[c] Immunotherapy for the treatment of allergies by any route is permitted as long as therapy was initiated 90 days or more before the SV and the patient has been on a stable dose for 30 days or more before the SV. The patient must remain on this stable regimen throughout the study.

[d] Chronic and as-needed doses of low potency topical corticosteroids (eg, 1% hydrocortisone cream, desonide, fluocinolone cream 0.01%) covering <20% of body surface area are allowed; no occlusive dressings are allowed.

CYP=cytochrome P450; ICS=inhaled corticosteroid; IMP=investigational medicinal product; LABA=long-acting β_2-agonist; RV=randomization visit; SV=screening visit; TV=treatment visit.

APPENDIX I. PHARMACOGENETIC ASSESSMENTS

Pharmacogenomics is not evaluated in this study.

APPENDIX J. PRODUCT COMPLAINTS

Clinical Product Complaints

A clinical product complaint is defined as a problem or potential problem with the physical quality or characteristics of clinical IMP supplies or clinical device supplies used in a clinical research study sponsored by Teva. Examples of a product complaint include but are not limited to:

- suspected contamination
- questionable stability (eg, color change, flaking, crumbling, etc)
- defective components
- missing or extra units (eg, primary container is received at the investigational center with more or less than the designated number of units inside)
- incorrect packaging, or incorrect or missing labeling/labels
- unexpected or unanticipated taste or odor, or both
- device not working correctly or appears defective in some manner

Each investigational center will be responsible for reporting a possible clinical product complaint by completing the product complaint form provided by Teva and emailing it to [redacted] within 48 hours of becoming aware of the issue.

For complaints involving a device or other retrievable item, it is required that the device (or item) be sent back to the sponsor for investigative testing whenever possible. For complaints involving an IMP, all relevant samples (eg, the remainder of the patient's IMP supply) should be sent back to the sponsor for investigative testing whenever possible.

2. **Product Complaint Information Needed from the Investigational Center**

In the event that the product complaint form cannot be completed, the investigator will provide the following information, as available:

- investigational center number and principal investigator name
- name, phone number, and address of the source of the complaint
- clinical protocol number
- patient identifier (patient study number) and corresponding visit numbers, if applicable
- product name and strength for open label studies
- patient number, bottle, and kit numbers (if applicable) for double blind or open label studies
- product available for return (Yes/No)
- product was taken or used according to protocol (Yes/No)

- description or nature of complaint
- associated serious adverse event (Yes/No)
- clinical supplies unblinded (for blinded studies) [Yes/No]
- date and name of person receiving the complaint

Note: Reporting a product complaint must not be delayed even if not all the required information can be obtained immediately. Known information must be reported immediately. The sponsor will collaborate with the investigator to obtain any outstanding information.

2. **Handling of Investigational Medicinal Product(s) at the Investigational Center(s)**

The investigator is responsible for retaining the product in question in a location separate from the investigator's clinical study supplies. The sponsor may request that the investigator return the product for further evaluation and/or analysis. If this is necessary, the clinical study monitor or designee will provide the information needed for returning the IMP.

If it is determined that the investigational center must return all IMP, the sponsor will provide the information needed to handle the return.

The integrity of the randomization code and corresponding blinded clinical supplies will be maintained whenever possible. A serious adverse event or the potential for a product quality problem existing beyond the scope of the complaint may be a reason to unblind the clinical supplies for an affected patient.

3. **Adverse Events or Serious Adverse Events Associated with a Product Complaint**

If there is an adverse event or serious adverse event due to product complaint, the protocol should be followed for recording and reporting (Section Section 7.1.2 and Section Section 7.1.5.3, respectively).

4. **Documenting a Product Complaint**

The investigator will record in the source documentation a description of the product complaint, and any actions taken to resolve the complaint and to preserve the safety of the patient. Once the complaint has been investigated by the sponsor and the investigator, if necessary, an event closure letter may be sent to the investigational center where the complaint originated or to all investigational centers using the product.

Medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study.

APPENDIX K. DOCUMENTING A PRODUCT COMPLAINT

Direct Access to Source Data and Documents

All patient data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed to the CRF. Data may not be recorded directly on the CRF and considered as source data unless the sponsor provides written instructions specifying which data are permitted to be recorded directly to the CRF.

If data are processed from other institutions or by other means (eg, clinical laboratory, central image center, or data from the patient diary built into the handheld device) the results will be sent to the investigational center, where they will be retained but not transcribed to the CRF, unless otherwise noted in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management).

The medical experts, study monitors, auditors, IEC/IRB, and inspectors from competent authority (or their agents) will be given direct access to source data and documents (eg, medical charts/records, laboratory test results, printouts, videotapes) for source data verification, provided that patient confidentiality is maintained in accordance with national and local requirements.

The investigator must maintain the original records (ie, source documents) of each patient's data at all times. The investigator must maintain a confidential patient identification list that allows the unambiguous identification of each patient.

Data Collection

Data will be collected using CRFs that are specifically designed for this study. The data collected on the CRFs will be captured in a clinical data management system (CDMS) that meets the technical requirements described in 21CFR Part 11 (USA) and documents of other concerned competent authorities. Before using the CDMS, it will be fully validated and all users will receive training on the system and study specific training. After they are trained, users will be provided with individual system access rights.

Data will be collected at the investigational center by appropriately designated and trained personnel, and CRFs must be completed for each patient who provided informed consent. Patient identity should not be discernible from the data provided on the CRF.

If data are processed from other sources (eg, central laboratory, bioanalytical laboratory, central image center, data from the patient diary built into the handheld device, electronic patient-reported outcome [ePRO] tablet), these data will be sent to the investigational center, where they will be retained but not transcribed to the CRF, unless otherwise noted in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management). All patient data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed to the CRF. Data may not be recorded directly on the CRF and considered as source data unless the sponsor provides written instructions specifying which data are permitted to be recorded directly to the CRF.

For patients who enter a study but do not meet entry criteria, at a minimum, data for screening failure reason, demography, and adverse events from the time of informed consent will be entered in the CRF.

Data Quality Control

Data Management is responsible for the accuracy, quality, completeness, and internal consistency of the data from this study. Oversight will be carried out as described in the sponsor's SOPs for clinical studies. Day to day data management tasks for this study are delegated to a contract organization, and these functions may be carried out as described in the SOPs for clinical studies at that organization. These SOPs will be reviewed by the sponsor before the start of data management activities.

Data will be verified by the study monitor using the data source, and reviewed by Data Management using both automated logical checks and manual review. Data identified as erroneous, or data that are missing, will be referred to the investigational center for resolution through data queries. Any necessary changes will be made in the clinical database, and data review and validation procedures will be repeated as needed. Data from external sources will be compared with the information available in the CDMS and any discrepancies will be queried.

Applicable terms will be coded according to the coding conventions for this study.

At the conclusion of the study, the CDMS and all other study data will be locked to further additions or corrections. Locking the study data represents the acknowledgement that all data have been captured and confirmed as accurate. All data collected will be approved by the investigator at the investigational center. This approval acknowledges the investigator's review and acceptance of the data as being complete and accurate.

Archiving of Case Report Forms and Source Documents

Sponsor Responsibilities

The sponsor will have final responsibility for the processing and quality control of the data. Data management oversight will be carried out as described in the sponsor's SOPs for clinical studies.

Day to day data management tasks for this study are delegated to a contract organization, and these functions may be carried out as described in the SOPs for clinical studies at that organization. These SOPs will be reviewed by the sponsor before the start of data management activities. The original CRFs will be archived by the sponsor. Investigational center specific CRFs will be provided to the respective investigational centers for archiving.

Investigator Responsibilities

The investigator must maintain all written and electronic records, accounts, notes, reports, and data related to the study and any additional records required to be maintained under country, state/province, or national and local laws, including, but not limited to:

- full case histories
- signed informed consent forms
- patient identification lists
- case report forms for each patient on a per visit basis
- data from other sources (eg, central laboratory, bioanalytical laboratory, central image center, patient diary built into the handheld device)
- safety reports

- financial disclosure reports/forms
- reports of receipt, use, and disposition of the IMPs
- copies of all correspondence with sponsor, the IEC/IRB, and any competent authority

The investigator will retain all records related to the study and any additional records required, as indicated by the protocol and according to applicable laws and regulations, until the CRO or sponsor notifies the institution in writing that records may be destroyed. If, after 25 years from study completion, or earlier in the case of the investigational center closing or going out of business, the investigator reasonably determines that study record retention has become unduly burdensome, and sponsor has not provided written notification of destruction, then the investigator may submit a written request to sponsor at least 60 days before any planned disposition of study records. After receipt of such request, the sponsor may make arrangements for appropriate archival or disposition, including requiring that the investigator deliver such records to the sponsor. The investigator shall notify the sponsor of any accidental loss or destruction of study records.

APPENDIX L. DOCUMENTING A PRODUCT COMPLAINT

All unpublished information given to the investigator by the sponsor shall not be published or disclosed to a third party without the prior written consent of the sponsor.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results: "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" (www.ICMJE.org). Publication of the results will occur in a timely manner according to applicable regulations. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual investigational center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements:

- substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work
- drafting the work or revising it critically for important intellectual content
- final approval of the version to be published
- agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

The publications committee established by the sponsor will oversee this process. Additional publications may follow. Policies regarding the publication of the study results are defined in the financial agreement.

No patent applications based on the results of the study may be made by the investigator nor may assistance be given to any third party to make such an application without the written authorization of the sponsor.

APPENDIX M. DOCUMENTING A PRODUCT COMPLAINT