Official Protocol Title:	A Phase III, Randomized, Active-Controlled, Parallel-Group Clinical Trial to Study the Efficacy and Long-Term Safety of Mometasone Furoate / Formoterol Fumarate (MF/F, MK-0887A [SCH418131]), Compared with Mometasone Furoate (MF, MK-0887 [SCH032088]), in Children with Persistent Asthma
NCT number:	NCT02741271
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TITLE:

A Phase III, Randomized, Active-Controlled, Parallel-Group Clinical Trial to Study the Efficacy and Long-Term Safety of Mometasone Furoate / Formoterol Fumarate (MF/F, MK-0887A [SCH418131]), Compared with Mometasone Furoate (MF, MK-0887 [SCH032088]), in Children with Persistent Asthma

IND NUMBER: 70,283 and IND 52,214

EudraCT NUMBER: 2009–010110–30

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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number	Section Title	Description of Change	Rationale
8.0	Statistical Analysis Plan	The control-based imputation of missing %-predicted FEV_1 data is now part of the primary analysis (it was originally proposed as a sensitivity analysis). The original, primary method of imputation based on the Missing-At-Random assumption, has been moved to one of the supportive analyses. Note that the primary endpoint, %-predicted FEV_1, remains the same.	FDA request to modify SAP on handling of missing data by reversing the roles of primary and sensitivity imputation methods.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
2.1 7.1.2.7	Trial Design Airway Reversibility	Added reference to section on rescue medication. Clarified visits and timeframe on when reversibility procedure can occur with related text: "The reversibility testing prior to Visit 3 must be performed at least two days prior to the Visit 3 due to the timeframe for the over-read of the spirometry report from the central vendor."	Changes were made for reference and further clarification purposes on the reversibility procedure.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
		Removed text with details of prior reversibility procedure and added reference to Appendix 12.8 for updated procedure.	
4.2.1	Rationale for the Trial and Selected Subject Population	Clarified timing of the reversibility procedure post-bronchodilator administration to within "approximately" 30 minutes instead of 'within 30 minutes'.	Changes were made based upon feedback from field operations as timing of updated reversibility procedure may vary and not be exactly within 30 minutes of SABA administration.
5.1.2 12.5	Subject Inclusion Criteria Pharmacokinetic Sub-Trial: MK-0887A Protocol 087	Criteria #1: Removed text in parenthesis related to age of assent: "(subjects ages 7 to 11 years, would provide an assent, or provide consent in accordance with local regulations)".	Per guidelines, age for assent would be determined by IRB/ERC. Change does not impact ICF.
5.1.2 5.1.3	Subject Inclusion Criteria Subject Exclusion Criteria	Table 1 (Medications to be withheld prior to Spirometry Testing), Table 2 (Medications Excluded Prior to the Screening Visit [Visit 1]): Updated column header to 'Minimum' Excluded Timeframe instead of 'Excluded Timeframe".	Provide clarification for flexibility to washout timeframes.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
5.1.3	Subject Exclusion Criteria	Criteria #4: Clarified compliance measurement is based off of MDI: "…and will be determined by comparing the change in dose counter readings relative to the duration of treatment as entered on the eCRF".	To provide emphasis on use of MDI dose counter for compliance measure.
5.2 and throughout protocol	Trial Treatment Other related sections	Changed Trial 'Treatment' to Trial 'Medication'.	Updated wording for consistency in terminology throughout the protocol.
5.2 5.2.2 5.6 7.1.2.7 7.1.2.17	Trial Treatment(s) Timing of Dose Administration Rescue Medication & Supportive Care Airway Reversibility Rescue Medications	Clarified when use of spacers are permitted and not permitted: "Spacer devices are not permitted with the open-label and double-blinded trial medication as well as the training inhalers." "Spacers are only permitted for SABA used as rescue medication (as well as for SABA administered for the purposes of demonstrating reversibility [Section 7.1.2.7])."	To emphasize that use of spacer is not allowed with trial medication. To clarify of spacers are only allowed for use with rescue SABA and during reversibility.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
5.8	Subject Withdrawal/Discontinuation Criteria	Organizational changes to reflect separate subsections beneath Section 5.8 for discontinuation of treatment/vaccination (5.8.1) and withdrawal from trial (5.8.2). Application of consistent terminology to refer to 'treatment/vaccination discontinuation' vs. 'withdrawal from trial'. Brief rationale added to describe the importance of monitoring beyond treatment discontinuation.	Template update as well as in alignment with FDA request to follow subjects who discontinue treatment during the trial.
6.0	Trial Flowchart	Clarification to Footnotes k, m, and n: k: Referenced Section 7.1.2.7 for details on reversibility procedure. m & n: Clarified that females of child bearing potential need both dipstick and HCG urine testing.	Further clarify procedures for females of child-bearing potential.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
7.1.1.6	Assignment of Screening Number	Updated text to 'Any subject who is rescreened…." from "Any subject who is screened multiple times."	In the protocol we do not allow for multiple re-screenings.
7.1.1.8	Trial Compliance	Added clarifying text on: A rescheduled visit should be "in accordance with the appropriate visit window." For the eDiary: "Daily assessment data must be reviewed by the investigator."	To clarify guidance on rescheduled visit and emphasize review of diary data by investigators.
7.1.2.3	Height and Weight	Clarified that equipment used to measure height and weight does not need to have a separate calibration for the purposes of the trial.	To clarify that not all devices need to be calibrated.
7.1.2.6	Spirometry, also known as Pulmonary Function Testing (PFT)	Provided information to sites that "if the site and the central vendor cannot agree on the data value(s), the sponsor should be consulted." Also, "In order to receive timely receipt of the vendor's selected measurements, the PFT data should be transmitted, by the site, at the end of each	Provided specific information to sites on vendor review of PFT data.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
		testing day." Note: The Investigator should consider the safety and well-being of the subject if reversibility is repeated more than once. In addition, the Investigator should have a clinical rationale for why reversibility should be repeated.	
7.1.2.10	eDiary (IVRS/IWRS) and Peak Flow Meter: Instructions	Clarified that SABA as prevention for exercise-induced bronchospasm (EIB) is not considered rescue use; it should not be captured in the eDiary. This should be capture in the CM eCRF.	Clarify procedure of capturing SABA use for EIB.
7.1.2.13	Asthma Baseline Pediatric Profile	Added section on completing ABPP eCRF.	Provided specific information on completion of standard respiratory eCRF.
7.1.2.17	Rescue Medications: Dispense/Retrieve Oral Prednisone/Prednisolone Medication (as needed): All visits	Clarified for oral steroids that "The course of steroid treatment will be determined by the prescribing health care provider".	Clarify the definition of 'course'.
7.1.3.1	Laboratory Safety Evaluations (Hematology, Chemistry and	Female subjects of child bearing potential will be required at all visits to perform	Clarified urine collection procedure for females of child-

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
	Urinalysis)	a urine pregnancy test with a dipstick as well as HCG urine testing. Sites will submit HCG urine testing to the central lab regardless of the outcome from the site performed dipstick testing. Table 7 Removed duplicate for Alanine aminotransferase (ALT).	bearing potential. Removed duplicate test name.
7.1.4.1.2	Lost to Follow-up	Added section for procedures for Lost to Follow-up.	Added section per template as Section 5.8 was updated.
7.1.5.1	Re-Screening	Clarified definition of re-screening to subjects who do not meet one or more criteria required for participation in a trial.	Clarified to be consistent with eCRF guidance.
7.1.5.2	Discontinued Subjects Continuing to be Monitored in the Trial	Updated section title from "Follow-up after Premature Discontinuation of Treatment" to match updated to template.	Updated title of section per template update.
8.2.4.1	Statistical Methods for Efficacy Analyses	Added description of how missing data will be imputed.	Changed primary efficacy analysis.
8.2.4.1.2	Missing-Data Sensitivity Analysis	Added leading statement for statistical sensitivity analyses.	Help better justify rationale for sensitivity analyses.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
8.2.6.1	Sample-size Calculation for the Primary Analysis (using Multiple Imputation)	Added leading statement for statistical sensitivity analyses.	Help better understand scenarios for sample size estimation.
8.2.6.1	Sample-size Calculation for the Primary Analysis (using Multiple Imputation)	Moved sample size statement from end to beginning of section.	Have sample size up front to help reader get the resulting sample size faster.
8.2.7	Subgroup Analyses and Effect of Baseline Factors	Added clarification statement for analysis of subgroups.	Alignment of statistical method for analysis of subgroups with primary efficacy analysis.
9.1	Investigational Product	Updated text to remove text on similarity of placebo trainer to trial medication.	Updated/clarified to avoid confusion during CofA submissions.
10.4	Compliance with Trial Registration and Results Posting Requirements	Updated language within section 10.4 includes reference to trial registration and results posting obligations to the EMA.	Updated protocol template.
12.8 7.1.2.7	Method for Administering Short-Acting Beta-Agonist (SABA) During Post bronchodilator testing for Airway Reversibility Airway Reversibility	Clarification to reversibility procedure as per PCL (May 2016). Added text and listed procedure for using nebulization of SABA during reversibility.	Clarified procedure as it was not clear to sites. Use of nebulization added based on site feedback.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
12.10	Asthma Action Plan	Updated calculation text. Removed text on 'comment card' as these are not used in the trial. Formatted text to improve readability of calculations for each range.	Updated text errors and other formatting changes for easier readability.
12.13	List of Abbreviations	Added abbreviation for ABPP: Asthma Baseline Pediatric Profile.	Added as this was added to the protocol.

1.0 TRIAL SUMMARY

Abbreviated Title	MK-0887A efficacy and long-term safety in children with persistent asthma
Trial Phase	III
Clinical Indication	Treatment of persistent asthma in children ages 5 to 11 years
Trial Type	Interventional
Type of control	Active control without placebo
Route of administration	Oral inhalation
Trial Blinding	Double-blind
Treatment Groups	Mometasone furoate / formoterol fumarate (MF/F) 100/10 mcg twice daily given via a metered dose inhaler (MDI) MF 100 mcg twice daily given via a MDI
Number of trial subjects	Approximately 160 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 21 months from the time the first subject signs the informed consent until the last subject's last visit.
Duration of Participation	Each subject participates in the trial for approximately 29 weeks, from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase of ~1 week, each subject enters a ~2-week open-label run-in period, followed by a ~24-week double-blind active treatment period. After completion of the double-blind treatment period, each subject is followed for approximately 2 weeks.
Randomization Ratio	1:1

A list of abbreviations used in this document is in Section 12.13.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a multi-center, randomized, double-blind, active-controlled, parallel-group trial of mometasone furoate / formoterol fumarate (MF/F) 100/10 mcg and mometasone furoate (MF) 100 mcg, each given via a metered-dose inhaler (MDI) twice daily, in children ages 5 to 11 years with persistent asthma already receiving inhaled corticosteroid / long-acting beta-agonist (ICS/LABA) combination therapy, to be conducted in conformance with Good Clinical Practices (GCP). The trial consists of a 1-week Screening Period, a 2-week Open-label Run-in Period (during which all subjects receive MF), and a 24-week Double-blind Treatment Period (MF/F or MF, for assessment of efficacy and safety during the first 12 weeks and assessment of safety during the last 12 weeks); 2 weeks after completing treatment, there is a follow-up assessment for safety.

Screening Period (Visit 1 to Visit 2)

At the Screening Visit (Visit 1), after providing consent, subjects will undergo general screening procedures. Subjects will enter the trial having been adequately controlled on a stable dose of ICS/LABA fixed-dose combination (FDC) therapy, such as Advair®,[1] for at least 4 weeks prior to Visit 1. During the Screening Period, subjects will remain on their pre-trial ICS/LABA combination therapy. At Visit 1, subjects will practice inhalation technique with a MDI training inhaler under supervision at the trial site, in order to demonstrate appropriate MDI inhalation technique. At Visit 1, the site will review, with the subjects/caregivers, the proper completion of an electronic diary (eDiary) that is based on an interactive voice-response system / integrated web-response system (IVRS/IWRS). The eDiary (IVRS/IWRS) is to be used daily to capture the subject's use of trial medication and use of rescue medication(s). Rescue medications (short-acting beta-agonist [SABA, albuterol/salbutamol] and oral corticosteroid [prednisone or prednisolone]) will be made available for the subject at Visit 1 (Section 5.6). Rescue medication is to be used for worsening asthma per the Asthma Action Plan (AAP [Appendix 12.10]). An individualized written AAP is provided at Visit 1, by the investigator to the subject and the caregiver, to provide guidance on effectively managing the subject's asthma symptoms, as recommended by clinical practice guidelines. Subjects should have access to a peak expiratory flow (PEF) meter to use daily for the duration of the trial. Subjects must perform PEF measurements every morning (AM) upon rising. Based on once-daily PEF measurements (AM only) reported during the Screening Period, a PEF "stability limit" will be calculated at Visit 2, prior to entering the Open-label Run-in Period.

Run-in Period (Visit 2 to Visit 3)

Beginning at Visit 2, there will be an approximately 2-week Open-label Run-in Period, during which subjects will receive MF 100 mcg given via a MDI twice daily. Subjects will have taken the last dose of their pre-trial ICS/LABA combination therapy the night before Visit 2. The morning of Visit 2, subjects will receive their first dose of MF 100 mcg in the clinic, as a witnessed dose.

[1] ADVAIR® is a registered trademark of the GlaxoSmithKline group of companies, Research Triangle Park, NC 27709 USA

The purpose of the Run-in Period is to ascertain that the subject acceptably performs all necessary procedures and can be eligible for randomization. The rationale for treating with MF MDI is to standardize treatment prior to randomization. This may also afford a greater opportunity to demonstrate airway reversibility (since subjects will likely demonstrate higher FEV_1 and lower reversibility on FDC at Screening). If the subject does not meet reversibility criteria at Visit 1, repeat assessments can be performed at least two days prior to Visit 3. (Section 7.1.2.7)

Double-blind Treatment Period (Visit 3 to Visit 8)

At Visit 3, subjects meeting all the inclusion criteria and none of the exclusion criteria will be randomized to enter an approximately 24-week Double-blind Treatment Period, during which they will receive either MF/F 100/10 mcg or MF 100 mcg, given via a MDI twice daily. Approximately 160 subjects will be randomized to receive MF/F or MF in a 1:1 ratio, according to the Sponsor's computer-generated randomization schedule. To ensure adequate and balanced representation of younger subjects, randomization is stratified by age (5-to-7 versus 8-to-11 years of age). Ongoing trial monitoring will be used to target approximately 20% of randomized subjects in the 5- to 7-year-old age stratum. To ensure that treatment allocation is balanced across geographic regions of the world in this large multinational trial, randomization is also stratified by region. At each visit during this treatment period (Visit 3 to Visit 7), blinded trial medication is administered as a witnessed dose, followed by one hour of serial spirometry measurements. Further, at Visit 3 and at Visit 7, spirometry will also be performed at two hours and four hours after the witnessed dose.

At Visit 3 (or any visit prior to Visit 7), subjects at selected sites (and after signing consent to participate in the main trial) will have the option to sign a separate informed consent to participate in a pharmacokinetic (PK) sub-trial. At Visit 7, blood samples will be collected from approximately 20 subjects, to characterize the plasma concentration-time profile of MF ($AUC_{0\text{-}12h}$, $AUC_{0\text{-}last}$, C_{max}, and T_{max}) following repeated twice-daily oral inhalations of MF/F or MF. Specific procedures and timing of the PK assessments are further described in Appendix 12.5.

After Visit 8 (which ends the approximately 24-week Double-blind Treatment Period), all subjects will be followed for a post-treatment assessment approximately 2 weeks later. The post-treatment assessment captures any adverse events or other reportable events occurring after the final dose of trial medication (Section 7.1.5.3).

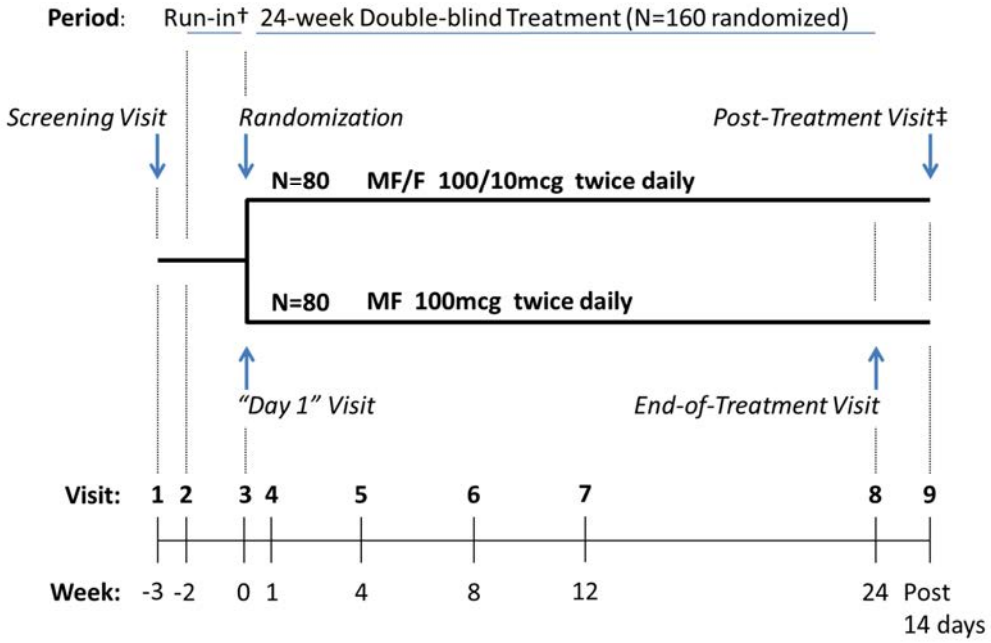
Assessments during all periods

Throughout the trial, the site will evaluate the subject's asthma status (based on PEF measurement and rescue medication use) and medication usage (based on eDiary [IVRS/IWRS] data). During the trial, PEF measurements will be obtained once daily, AM only. Subjects must perform PEF measurements every morning upon rising. The eDiary (IVRS/IWRS) will be utilized to alert the investigator to changes in PEF assessments that may indicate asthma worsening. The investigators should review and reach out to the subject for follow up.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

2.2 Trial Diagram

The trial design is depicted in Figure 1.



†During Run-in (between Visits 2 and 3), all subjects receive open-label MF MDI 100mcg twice daily.
‡For the Post-Treatment Visit, only female subjects of child-bearing potential return to the clinic. All other subjects are contacted by telephone.

Figure 1 Trial design for Protocol MK-0887A-087

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

Primary Efficacy Objective

To demonstrate the efficacy of MF/F 100/10 mcg twice daily, compared with MF 100 mcg twice daily, by evaluating lung function during the first 12 weeks of double-blind treatment in children ages 5–11 years with persistent asthma.

Primary Efficacy Hypothesis

MF/F 100/10 mcg twice daily is superior to MF 100 mcg twice daily on AM post-dose %-predicted FEV_1 (measured during 60 minutes post-dose), and analyzed as the mean post-dose change from baseline across Day 1, Week 1, Week 4, Week 8, and Week 12 in children ages 5 to 11 years with persistent asthma.

Trial success is defined by demonstrating a statistically significant improvement in the primary endpoint (AM post-dose change in %-predicted FEV_1 after a witnessed dose) for MF/F compared with MF.

Primary Safety Objective

To characterize the safety and tolerability of MF/F 100/10 mcg twice daily and MF 100 mcg twice daily based on adverse events reported in association with up to 24 weeks of treatment in children ages 5 to 11 years with persistent asthma.

There is no hypothesis for the safety objective.

3.2 Secondary Objective(s) & Hypothesis(es)

Key Secondary Efficacy Objective

To determine the onset of action for the efficacy of MF/F 100/10 mcg twice daily, compared with MF 100 mcg twice daily, by evaluating %-predicted FEV_1 in the AM of Day 1 of dosing, analyzed beginning at 4 hours post-dose and continuing to 2 hours, 60, 30, 15, and 5 minutes post-dose, and measured as the change from baseline (AM pre-dose on Day 1).

Secondary Efficacy Hypothesis

MF/F 100/10 mcg has an onset of action more rapid than that of MF 100 mcg, evaluated as %-predicted FEV_1 in the AM of Day 1 of dosing (analyzed beginning at 4 hours post-dose and continuing to 2 hours, 60, 30, 15, and 5 minutes post-dose) and measured as the change from baseline (AM pre-dose on Day 1), by comparing MF/F 100/10 mcg versus MF 100 mcg in children ages 5 to 11 years with persistent asthma.

Secondary Objectives

(1) To demonstrate the efficacy of MF/F 100/10 mcg twice daily, compared with MF 100 mcg twice daily, on the change from baseline in AM post-dose %-predicted FEV_1 as measured during 4 hours post-dose, at Day 1 and Week 12.

(2) To demonstrate the efficacy of MF/F 100/10 mcg twice daily, compared with MF 100 mcg twice daily, on the change from baseline in AM pre-dose %-predicted FEV_1, averaged over weeks 4, 8, and 12 of treatment.

(3) To demonstrate the efficacy of MF/F 100/10 mcg twice daily, compared with MF 100 mcg twice daily, on the change from baseline in total daily short-acting beta-agonist (SABA) use across the first 12-weeks of double-blind treatment.

(4) To characterize the plasma pharmacokinetics (PK) profile of MF and to determine the PK parameters (e.g., AUC_{0-12h}, AUC_{0-last}, C_{max}, and T_{max}) at steady state after multiple oral inhalations via MDI device in children ages 5-11 years old with persistent asthma.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB) and/or approved labeling for detailed background information on MK-0887A.

4.1.1 Pharmaceutical and Therapeutic Background

Asthma is the leading cause of chronic illness in many countries of the world, and there is concern that the prevalence of asthma is rising in developed countries, as well as in the developing world [1]. In the United States (US) in 2012, an estimated 18.7 million adults and 6.8 million children were reported to have asthma, equivalent to 9.3% of children under age 18 years in the US (National Health Interview Survey [NHIS], National Center for Health Statistics, Centers for Disease Control and Prevention, 2014 [NHIS 2014] [Available from: URL: http://www.cdc.gov/nchs/fastats/asthma.htm]). The economic impact of childhood asthma is reflected in hospitalization and medication costs, as well as the cost of parental work absences. The impact of asthma on school-age children is immense; among persons with at least one asthma attack in the previous 12 months for 2008, there were 10.5 million school days missed due to asthma among children aged 5–17 years (Available from: URL: http://www.cdc.gov/nchs/data/series/sr_03/sr03_035.pdf). Inhaled corticosteroids (ICSs) are currently the most effective anti-inflammatory medications for the treatment of persistent childhood asthma and are recommended as the initial asthma therapy for children ages 5 years and older by current asthma guidelines (Global Initiative for Asthma [GINA] Guidelines [Available from: http://www.ginasthma.org/]). Current asthma guidelines also recommend the use of long-acting β-agonist (LABAs) as add-on therapy in children ages 5 years and older whose asthma is insufficiently controlled by ICS alone.

LABA monotherapy is not recommended as an asthma controller therapy since studies have suggested that LABAs increase the risk of asthma-related death and other serious asthma outcomes. In June 2010, the US Food and Drug Administration (FDA) announced labeling recommendations stating that use of a LABA alone without a long-term asthma controller medication, such as ICS, is contraindicated in the treatment of asthma. When subjects are treated concomitantly with ICS, the risk of LABAs is uncertain; however in this trial, the risk is manageable because the safety of all subjects is closely monitored.

Mometasone furoate (MF) is a synthetic glucocorticosteroid that binds to the glucocorticoid receptor (GR) with very high affinity. It is a potent corticosteroid with a low potential to cause systemic side effects. Controlled clinical trials in children with asthma have demonstrated that inhaled MF via dry powder inhaler (DPI) is efficacious in improving lung

function, reducing symptoms, and reducing frequency and severity of asthma exacerbations at doses of 100 to 200 mcg/day in children ages 4 to 11 years with no unusual or unexpected treatment-emergent adverse events (AEs) reported.

Formoterol (F), a LABA, has been shown to quickly increase lung function within 5 minutes of administration and to maintain efficacy over 24 hours at a dose of 10 mcg twice daily (BID). Results of Phase III clinical trials in children with asthma indicated that F at doses of 10 or 20 mcg BID was effective in children ages 5 years and older [2].

Co-administration (in a single inhaler) of an ICS and a long-acting bronchodilator in glucocorticosteroid-dependent asthma subjects is clinically superior to the same dose of ICS administered alone and clinically equivalent to the separate administration of the ICS and LABA, as acknowledged in GINA guidelines. For drugs providing rapid onset of relief from asthma symptoms, adherence to prescribed medication is likely to be higher than when there is no perceived effect on breathing. Thus, the addition of F to MF in a single inhaler may improve adherence to prescribed medication.

Successful formulation of the combination of MF plus F (MF/F) in a single metered-dose inhaler (MDI) has made it possible to establish the twice-daily efficacy and safety profile of this fixed-dose combination (FDC) in adults and adolescents ages 12 years and older. Collectively, results from Phase III clinical trials showed that in subjects who were inadequately controlled on ICS, MF/F delayed the time-to-first asthma exacerbation, compared with F alone and placebo [3]; [4]. In addition, MF/F provided rapid and sustained improvement in lung function, improved asthma control and quality of life, and reduced nocturnal awakenings requiring use of SABA when compared with placebo. Based on those trials, MF/F has been approved in the US (DULERA®[2] MF/F MDI 100/5 mcg and 200/5 mcg, two inhalations twice daily), Canada (ZENHALE®[3] MF/F MDI 50/5 mcg, 100/5 mcg, and 200/5 mcg, two inhalations twice daily), and other countries for the treatment of asthma in adults and adolescents ages 12 years and older.

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[2] DULERA®, ASMANEX® HFA, and ASMANEX® TWISTHALER® are registered trademarks of Merck Sharp & Dohme Corp., Whitehouse Station, NJ 08889 USA

[3] ZENHALE® is a trademark of MSD International Holdings Gmbh. Merck Canada Inc., a subsidiary of Merck & Co., Inc., Canada.

The current Phase III trial evaluates MF/F MDI 100/10 mcg and MF MDI 100 mcg in children ages 5 to 11 years with persistent asthma. This trial builds on the documented safety and efficacy of MF DPI in children ages 5–11 years for ASMANEX® TWISTHALER®[3] and the documented efficacy of MF/F MDI versus MF MDI with acceptable safety that is well-established in adults and adolescents ages 12 years and older. The current trial is expected to generate data to support that MF/F MDI is superior to MF MDI for efficacy and to support that both MF/F MDI and MF MDI are safe for patients ages 5–11 years.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Current asthma guidelines recommend the use of LABAs as add-on therapy in children ages 5 years and older whose asthma is not adequately controlled on ICS alone. Based on this established clinical practice, there is a substantial pediatric patient population that has been determined by their physician to require an ICS/LABA combination to obtain adequate control of their asthma, and this trial will exclusively select subjects for enrollment from this population. This trial will include children, of any race and either sex, 5 to 11 years of age, with persistent asthma, who are receiving an ICS/LABA combination and whose asthma is adequately controlled, as defined by the Global Initiative for Asthma (GINA) guidelines (at http://www.ginasthma.org/). Subjects must have been diagnosed with asthma for at least 6 months prior to Visit 1 and treated with a stable dose of ICS/LABA combination for at least 4 weeks prior to Visit 1. Subjects are included in this trial based on an appropriate level of lung function at baseline, as well as demonstrating reversibility of airway obstruction within approximately 30 minutes of bronchodilator.

4.2.2 Rationale for Dose Selection/Regimen

Dose of Mometasone Furoate

Controlled clinical trials have demonstrated that inhaled MF (MK-0887) via DPI is efficacious in improving lung function, reducing symptoms and reducing the frequency and severity of exacerbations at doses of 100 to 200 mcg/day in children 4 to 11 years of age. MF DPI 100 mcg once daily (QD) in the evening (PM) is approved in the US for the maintenance treatment of asthma in patients 4 to 11 years of age. MF DPI 200 mcg QD is approved for use in patients 12 years of age and older in the US and European Union (EU).

Previous clinical trials in children have demonstrated that a total daily dose of MF 100 mcg and MF 200 mcg – when given via DPI – significantly improved lung function. The incidence and nature of AEs reported were similar to those observed for other ICSs in children and were not notably different from those observed with MF DPI in adults and adolescents.

However, in trials C97-380 and C98-005, that assessed MF 100 mcg in the DPI formulation, MF DPI 100 mcg once daily in the morning or once daily in the evening did not achieve

statistical significance in improving lung function in children ages 4 to 11 years. In contrast, MF 100 mcg BID – both via DPI and via MDI – was significantly better than placebo in improving lung function. These results suggest that when MF is formulated as a MDI, a higher and/or BID dose may be necessary to achieve a comparable therapeutic effect to MF when given via DPI.

A phase II dose-ranging trial (P086) was conducted to demonstrate dose-related efficacy of MF, by evaluating morning lung function at the end of the dosing interval (AM pre-dose %-predicted forced expiratory volume in one second [FEV1]) after 12 weeks of treatment. Three dose levels of MF MDI (50 mcg, 100 mcg, and 200 mcg) BID were each compared with placebo in children 5 to 11 years of age with persistent asthma. The trial demonstrated that each of the three doses of MF MDI was statistically superior to placebo. Among the 3 dose levels, however, 50 mcg BID showed sub-maximal efficacy, while both 100 mcg BID and 200 mcg BID showed statistically significant and clinically meaningful efficacy. The effects of 100 mcg BID and 200 mcg BID were similar (wherein the effect of 200 mcg BID was numerically slightly smaller than the effect of 100 mcg BID). Finally, all 3 doses of MF MDI showed a numerically greater effect on FEV1 compared with MF DPI 100 mcg QD in the evening.

P086 also demonstrated that each of the 3 doses of MF MDI was well tolerated. Across all the treatment arms in P086, there were no reports of the prespecified AEs of oropharyngeal candidiasis or dysphonia. Overall, the types and frequencies of AEs in P086 were generally similar across the treatment arms, with no dose-responsive pattern of reporting.

The data from P086 support MF 100 mcg BID (via MDI) as the minimum dose providing clinically meaningful efficacy that is also expected to have an acceptable safety profile when combined with formoterol. Based on these results, this trial will evaluate MF 100 mcg BID versus MF/F 100/10 mcg BID.

Dose of Formoterol

In the US, formoterol is currently approved for asthma maintenance in patients 5 years or older, with a total daily dose not to exceed 24 mcg. Outside the US, the dosage in children is approved up to 40 mcg (ex-actuator) daily maximum dose.

In a phase II trial (P06476), the bronchodilatory effect of a single administration of MF/F MDI 100/10 mcg (with or without a spacer) was compared with F DPI 10 mcg, and with placebo MDI (with/without spacer) in children ages 5–11 years. The trial showed no difference in bronchodilation between a single administration of MF/F MDI 100/10 versus the approved formulation of F DPI, thus supporting the dose selection of F 10 mcg for this trial [4]; [5].

4.2.2.1 Rationale for the Use of Comparator

To assess the efficacy of MF/F combination therapy, MF monotherapy is the comparator chosen, allowing the trial to demonstrate the contribution of the formoterol component to the clinical benefits of the fixed-dose combination of MF/F in children. The safety and effectiveness of MF monotherapy has already been assessed in controlled clinical trials in adults and adolescents, and most recently, in children 5-11 years of age (P086). The MF comparator product has the same formulation as the MF/F combination product, with the exception that the drug substance F has been removed and replaced with the equivalent amount of HFA-227 propellant, dehydrated alcohol and oleic acid. This trial will not include F monotherapy as a control arm because of general safety concerns associated with the use of a LABA as monotherapy in subjects with asthma.

Placebo is not a comparator in this trial because it is believed that a placebo control arm is not required to support the efficacy or safety assessments of MF/F or MF, particularly in this population of asthmatic children who all enter the trial being treated with ICS/LABA combination therapy. Furthermore, efficacy and safety of both MF/F and MF have already been well shown in previous studies. For MF/F in adults, 21 clinical studies (9 Phase-1 studies, 4 Phase-2 studies, and 8 Phase-3 studies) assessing the safety, tolerability, clinical pharmacology, patient handling (of the MDI with an integrated dose counter), and clinical effectiveness of the MF/F MDI combination product have been completed. For MF in children, the efficacy and safety of MF have already been shown in placebo-controlled trials, both in studies of MF DPI in children ages 5–11 years and in P086, the recently completed MF MDI dose-ranging trial in children ages 5–11 years.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

Primary

The primary efficacy endpoint is the AM post-dose %-predicted FEV_1 (measured as the change from AM pre-dose %-predicted FEV_1). The AM post-dose %-predicted FEV_1 is calculated as the area under the curve from zero to 60 minutes (using the trapezoid rule) after a witnessed dose and divided by the time interval (to preserve the unit, %-predicted). This method of calculation provides an aggregate bronchodilatory effect during 1 hour post-dose. A separate AM post-dose %-predicted FEV_1 measurement is calculated for each visit, and is evaluated as a change from baseline of the mean across Day 1, Week 1, Week 4, Week 8 and Week 12.

Based on previous clinical studies (in adults and in children), the maximal bronchodilator effect of formoterol is achieved at 1 hour after dosing and is sustained for 12 hours (see also Section 8.2.6.) Therefore, a series of measurements up to 60 minutes post-dose will adequately capture the effect of the addition of F to MF for the efficacy evaluation of MF/F compared with MF.

Secondary

Formoterol is characterized by a rapid bronchodilator effect, which may be observed within 5 minutes of administration [4]. The key secondary endpoint of AM %-predicted FEV_1 at each of the 5-, 15-, 30-, and 60-minute, 2- and 4 hour post-dose evaluations on Day 1 of dosing will assess the onset of action of MF/F.

To further examine the overall contribution of F to the MF/F combination, an additional secondary endpoint, the AM post-dose %-predicted FEV_1 measured during 4 hours post-dose will be analyzed on Day 1 and Week 12 (see also Section 8.2.2.1). The secondary endpoint of AM pre-dose FEV_1 (as averaged over weeks 4, 8, and 12 of treatment) specifically supports the primary endpoint evaluation by assessing the effect of the bronchodilator at the end of the 12-hour dosing interval. Finally, the secondary endpoint of SABA use across the initial 12-weeks of double-blind treatment provides a clinically relevant measure of asthma control during treatment.

4.2.3.2 Pharmacokinetic Endpoints

Blood samples from a subgroup of subjects will be collected to characterize the plasma concentration-time profile of MF following multiple oral inhalations of MF/F or MF via MDI device administered to approximately steady state in children ages 5–11 years old with persistent asthma. Plasma MF concentrations, obtained after approximately 12 weeks of twice-daily dosing of MF/F MDI or MF MDI, will be used to characterize PK parameters including steady-state Area Under the concentration-time Curve from 0 to 12 hours (AUC_{0-12h}), area under the curve from 0 to last concentration observed (AUC_{0-last}), maximum concentration (C_{max}), and time to C_{max} (T_{max}) of MF in children with persistent asthma.

The PK sampling times were optimized based on the one-compartment nature of the PK profile of MF. Evaluation suggests that the reduced sampling scheme being used in this sub-trial, when compared to the dense samplings used in historic clinical PK studies in adults, will provide adequate assessment of the non-compartmental PK parameters (C_{max} and AUC_{0-12h}) of MF with minimum bias (<5%).

Please refer to the PK Sub-trial details in Appendix 12.5.

4.2.3.3 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on buccal swab DNA specimens collected during this clinical trial.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. For instance, exploratory pharmacogenetic (PGt) studies may be performed if significant

Pharmacokinetic/Pharmacodynamic (PK/PD) relationships are observed or adverse events are identified. Genomic markers of disease may also be investigated. Such retrospective pharmacogenetic studies will be conducted with appropriate biostatistical design and analysis and compared to PK/PD results or clinical outcomes. Any significant PGt relationships to outcome would require validation in future clinical trials. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 - Collection and Management of Specimens for Future Biomedical Research. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

4.3 Benefit/Risk

Subjects in clinical trials generally cannot expect to receive direct benefit from treatment during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

As acknowledged in Section 4.1.1, there are general safety concerns associated with the use of LABA. In the US, the product labeling for all ICS/LABA combination therapies includes a boxed warning regarding the risk of asthma-related death and other serious asthma outcomes in association with use of LABAs for asthma. All subjects eligible for this trial have been determined by their physician to have needed ICS/LABA combination therapy for adequate control of their asthma. Asthma treatment guidelines (both from GINA and from US National Institutes of Health, National Heart Lung and Blood Institute http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines) recommend to step down therapy as tolerated in patients whose asthma is controlled. The design of this trial allows assessment of the need for ICS/LABA while ensuring that subjects' safety is monitored closely, during both the 2-week Run-in Period with ICS alone and during the Double-blind Treatment Period. The level of clinical monitoring during this trial (as described in the next paragraph) may be even greater than is generally available in standard clinical practice. If a subject is randomized to receive ICS alone and remains well controlled, this supports the opportunity to maintain treatment with ICS and without LABA. If a subject does not do well on ICS alone during the trial, this may confirm a clinical need to maintain treatment with ICS/LABA. Alternatively, if a subject is randomized to receive ICS/LABA, this remains consistent with the clinical decision of his/her physician to place the child on ICS/LABA combination therapy.

Some subjects in the trial may show a modest asthma worsening during the trial period. The trial design ensures that subjects' safety will be carefully monitored during the Run-in Period and the Double-blind Treatment Period. Each subject will have access to a supply of bronchodilator rescue medication to be used on an as-needed basis. In addition, each subject will be given a supply of oral prednisone/prednisolone in case of an asthma exacerbation; any subject requiring the use of systemic steroid treatment more than once for worsening asthma will be discontinued from trial medication immediately (and should continue to be monitored

through the end of the trial). Explicit instructions on when to use these additional medications will be provided to the subject. Trial subjects will use their PEF meter (a lung function measurement device) as a self-monitoring tool, as guided by a written Asthma Action Plan (AAP Appendix 12.10), to increase awareness of asthma control and to alert the subjects to changes in lung function that might require medical intervention. Subjects will be given an individualized written AAP containing very specific instructions on actions to take when symptoms increase and/or PEF reductions are recorded or perceived. The protocol also stipulates rules for calculating stability limits based on PEF measurements, which the investigator will use during the course of the trial to help ascertain if there is a need for asthma rescue medication and/or additional medical management. Finally, subjects will be provided with contact information for physician/medical support at all times and will have around-the-clock access to physicians.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigators Brochure (IB) and Informed Consent documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Subjects ages 5–11 years with a diagnosis of persistent asthma on ICS/LABA combination therapy will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Be willing to give written informed consent/assent (in accordance with local regulations) prior to Screening; and the subject's legal representative must also give written informed consent for the subject to participate in the trial. The subject's legal representative may also provide written informed consent and the subject provide assent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.

   For the PK Sub-trial: subject and the subject's legal representative must be willing to actively participate in the main trial and indicate understanding and willingness to participate in the sub-trial by signing the sub-trial specific informed consent/assent.
2. Be between 5 and 11 years of age (inclusive) at Visit 1, of either sex, and of any race.
3. Have a diagnosis of asthma according to the international guidelines of at least 6 months prior to Visit 1 (Global Initiative for Asthma [GINA] Guidelines Available from: http://www.ginasthma.org/).

4. Have asthma that is adequately controlled on a stable dose of ICS/LABA combination therapy for at least 4 weeks prior to Visit 1 according to the clinical judgment of the investigator.
5. Demonstrate at Visit 1, an FEV_1 >60% and ≤90% predicted when all restricted medications have been withheld for the appropriate intervals (Table 1).

Table 1 Medications to be withheld prior to Spirometry Testing (All Visits with Spirometry)

Medication	Minimum Excluded Timeframes
Beta-adrenergic bronchodilators, sustained-release tablets	48 hours
Beta-adrenergic bronchodilators, syrups and tablets	24 hours
Beta-adrenergic bronchodilators, long-acting, inhaled	12 hours
Ipratropium bromide inhaled, aerosol or nebulized or combination with albuterol/salbutamol	12 hours
Beta-adrenergic bronchodilators, short-acting, inhaled, or nebulized	6 hours

6. Demonstrate at Visit 1, an increase in absolute FEV_1 of at least 12% within 30 minutes after administration of albuterol/salbutamol (must be demonstrated according to the procedure specifically defined in Appendix 12.8). If the 12% reversibility criterion is not met at Visit 1, reversibility must be demonstrated prior to the randomization visit (Visit 3).
7. Demonstrate the ability to: use an MDI (without spacer) correctly according to protocol-defined procedures at Visit 1 (Screening Visit) and Visit 2 (Run-in Visit); use a peak flow meter correctly and perform spirometry correctly before Visit 2 (Run-in Visit).
8. Be willing (with consent of their parent(s)/guardian [i.e., caregiver]) to discontinue his/her prescribed asthma medication before beginning the Run-in Period, if based upon the medical judgment of the investigator, there is no inherent harm in changing the subject's current asthma therapy.
9. Demonstrate an ability to follow trial procedures (including use of MDI training inhaler, use of open-label run-in medication, use of PEF meter, and use of eDiary [IVRS/IWRS]) to the satisfaction of the investigator/qualified designee prior to randomization.

   Note: Subjects may be rescreened once if they do not meet inclusion/exclusion criteria at Visit 1 or Visit 2. A subject may not be rescreened once they have entered the open-label Run-in Period in the trial.

10. Have clinical laboratory tests (complete blood count [CBC], blood chemistries, including urine pregnancy for female subjects of child-bearing potential [i.e., who have started menstruating], and urinalysis) conducted at Visit 1 documented to be clinically acceptable to the investigator before beginning the Run-in Period. A female subject of childbearing potential (i.e., who has started menstruating) must have a negative urine pregnancy test at Visit 1 to be considered eligible for the trial.

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Requires the use of >8 inhalations per day of albuterol, 100 mcg per actuation (or its equivalent), and/or >2 nebulized treatments per day of 2.5 mg albutero1 (or its equivalent), on any 2 consecutive days between the Screening Visit (Visit 1) and the Randomization Visit (Visit 3). If a subject uses both MDI and nebulized formulations of SABA in the same day, then one nebulized treatment is considered equivalent to 4 inhalations of the MDI in order to calculate if the subject has exceeded the equivalent of 8 inhalations in total SABA use for that day.
2. Experiences a clinical worsening of asthma between the Screening Visit (Visit 1) and the Randomization Visit (Visit 3), that results in emergency room visit (for an asthma exacerbation), hospitalization due to asthma, or treatment with additional, excluded asthma medication (other than SABA).
3. Has experienced an upper or lower respiratory tract infection within the 4 weeks prior to Visit 1. If there is evidence of an upper or lower respiratory tract infection at Visit 1 or at Visit 2 (prior to the subject entering the Run-in Period), the subject may be treated as appropriate, and Visit 1 or Visit 2 can be rescheduled to be at least 4 weeks after resolution.
4. Demonstrates <80% compliance with use of trial medication during the 2 week Run-in Period. Compliance will be determined prior to randomization at Visit 3 and will be determined by comparing the change in dose counter readings relative to the duration of treatment as entered on the eCRF.
5. Is considered to have unstable asthma at the end-of the Run-in Period, based on the clinical judgment of the investigator.
6. Has had greater than 4 asthma exacerbations (defined as a worsening of asthma requiring systemic corticosteroid use and/or a 24-hour or longer stay in an emergency department, urgent care center, and/or hospital) within the 52 weeks prior to Visit 1.
7. Has had a history of life-threatening asthma, including an asthma episode that required intubation and/or was associated with hypercapnia requiring non-invasive ventilatory support.
8. Has been taking any restricted medications (listed in Table 2) prior to the Screening Visit (Visit 1) without meeting the required washout timeframes.

Table 2 Medications Excluded Prior to the Screening Visit (Visit 1)

Medication	Minimum Excluded Timeframes
Investigational antibodies for asthma or rhinitis	6 months
Monoclonal antibodies (for example, Xolair®/Omalizumab)	6 months
Methotrexate, cyclosporine, gold, and other cytotoxic agents	3 months
Investigational drugs or vaccines	1 month
Any systemic glucocorticosteroids (intravenous, intra-articular, or intramuscular)	12 weeks
Any oral glucocorticosteroid (eg, prednisone/prednisolone)	4 weeks
Glucocorticosteroids, high potency dermatologicals, plain and/or combination classifications of mid-strength, or potent or super potent by Stoughton-Cornell Scale (Appendix 12.7)	1 month
Theophylline	2 weeks
Cromolyn sodium, nedocromil, inhaled	2 weeks
Leukotriene modifiers (e.g., montelukast, zafirlukast, zileuton)	2 weeks
Beta-adrenergic bronchodilators, sustained-release tablets	48 hours
Beta-adrenergic bronchodilators, syrups and tablets	24 hours
Ipratropium bromide inhaled, aerosol or nebulized or combination with albuterol/salbutamol	12 hours
Beta-adrenergic bronchodilators, short-acting, inhaled or nebulized	6 hours

9. Has a clinically significant condition or situation, other than the condition being studied which, in the opinion of the investigator, may interfere with trial evaluations, subject safety or optimal participation in the trial (e.g. hypoxic seizures).
10. Has a known or suspected hypersensitivity to ICS, beta2 agonists, or any components of the trial medications.
11. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial.

5.2 Trial Treatment(s)

The treatments to be used in this trial are outlined below in Table 3. Rescue Medication is also described in this table, but is expected to be locally sourced (i.e., generally not provided directly by the Sponsor).

Table 3 Trial Medication/Rescue Medication

Trial Medication					
Drug	**Total Dose/Potency**	**Dose Frequency**	**Route of Administration**	**Regimen/ Treatment Period**	**Use**
MF/F via MDI	100/10 mcg	Twice daily	Orally inhaled	24-week double-blind period	Experimental
MF via MDI	100 mcg	Twice daily	Orally inhaled	24-week double-blind period	Experimental
MF via MDI	100 mcg	Twice daily	Orally inhaled	2-week open-label period	Run In
MDI Training Inhaler	0 mcg	Twice daily	Orally inhaled	All Visits	Training
Rescue Medication†					
Drug	**Total Dose/Potency**	**Dose Frequency**	**Route of Administration**	**Regimen/ Treatment Period**	**Use**
SABA [albuterol/ salbutamol]	NA	PRN (when necessary)	Orally inhaled (with or without a spacer)	NA	Rescue
oral corticosteroid [prednisone/ prednisolone])	NA	PRN	Oral	NA	Rescue
†Rescue Medication is expected to be locally sourced by the site, with cost re-imbursement by the Sponsor.					

At Visit 1 and Visit 2, subjects will practice taking "inhaled trial medication" with a MDI training inhaler, perform AM PEF measurements, and complete the eDiary (IVRS/IWRS). Subjects will continue to use their current ICS/LABA combination therapy between Visit 1 and Visit 2. Subjects will also be provided with SABA and oral prednisone/prednisolone, which are for potential use as rescue medications during the Screening, Run-in and Double-blind Treatment periods (Appendix 12.10- Asthma Action Plan).

Note: Spacers **are** only permitted for SABA used as rescue medication as well as SABA administered for the purposes of demonstrating reversibility (Section 7.1.2.7). Spacers are not permitted for use with trial medication.

Open-label MF MDI will be provided at Visit 2 for use during the Run-in Period. Trial medication during the Run-in Period should be taken twice daily (2 puffs in the morning upon awakening and 2 puffs in the evening), approximately 12 hours apart.

Blinded trial medication will begin at the Randomization Visit (Visit 3). Trial medication during the approximately 24-week Double-blind Treatment Period should be taken twice daily (2 puffs in the morning upon awakening and 2 puffs in the evening), approximately 12 hours apart.

In general, the morning dose of trial medication should be taken **after** the subject completes the AM PEF measurements and **prior** to the eDiary (IVRS/IWRS) entries. But, on the day of an in-clinic visit, the morning dose should *not* be taken at home and instead will be given as a witnessed dose in the clinic (this includes the open-label trial medication at Visit 2, as well as the first dose of blinded trial medication after randomization at Visit 3), after observing the subject using the MDI training inhaler.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

5.2.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background & Rationale. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each subject.

5.2.2 Timing of Dose Administration

Screening Visit (Visit 1)

At Visit 1, the subject will be trained on the proper inhalation technique using an MDI training inhaler without a spacer. The caregiver will also be trained to ensure the subject performs proper inhalation techniques. Spacer devices are not permitted with the open-label and double-blinded trial medication as well as the training inhalers.

These training inhalers should not be dispensed to the subject and should be retained by the investigational site personnel. The investigator or qualified designee should be satisfied that the subject is properly trained on how to inhale the medication through the MDI training inhaler. A training inhaler should be used at every visit as appropriate in order to check and reinforce proper dosing technique. The investigator or qualified designee should observe the subject's dosing technique with the MDI training inhaler and should make adjustments to their technique, if necessary. Verbal and written instructions for proper use of the MDI will be provided to the subject.

At Visit 1, subjects will receive supplies of rescue medications (SABA [albuterol/salbutamol] and oral corticosteroid [prednisone/prednisolone]) to be used, with investigator instructions, for worsening asthma per the Asthma Action Plan (Appendix 12.10). Subjects will be reminded to contact the investigator if they notice any worsening of their asthma symptoms. Rescue medication supplies will be assessed at every visit throughout the Screening, Run-in and Double-blind Treatment periods.

At Visit 1, subjects will also be instructed to bring their previous asthma medication(s) at the next visit (Visit 2) for verification. Subjects will be reminded that they will discontinue their prior medication (pre-trial ICS/LABA combination therapy) before starting the Open-label Run-in medication; the last dose of pre-trial medication should be taken the night before Visit 2.

Throughout this protocol, the caregiver is expected to be an active participant and oversee and assist with, as appropriate, compliance with the subject's dosing/visit schedule and proper use of the inhaler, PEF meter, and eDiary (IVRS/IWRS).

Open-Label Run-in (Between Visit 2 and Randomization Visit [Visit 3])

At Visit 2, if the investigator determines that laboratory results, including urine pregnancy results for female subjects of child-bearing potential, are clinically acceptable, a subject may enter the Run-in Period. The subject will then be instructed to start taking the first dose of their Run-in open-label MF MDI medication, as a witnessed dose in the clinic.

Trial medication should be taken twice a day (two puffs in the morning upon awakening and 2 puffs in the evening, approximately 12 hours apart), after the subject completes the PEF measurement (AM only) and prior to the eDiary (IVRS/IWRS) entries.

Run-in treatment is as follows:

- MF MDI 50 mcg: 2 puffs twice daily, approximately 12 hours apart, for a total daily dose of 200 mcg (100 mcg twice daily).

At in-clinic visits, the morning dose of trial medication will be given as a witnessed dose.

During the Run-in Period (Visit 2 to Visit 3), investigator must evaluate if the subject has a decrease in AM PEF below the stability limit on any 2 consecutive days prior to randomization. If yes, the investigator must determine if the subject can continue based on his/her clinical judgment; the decision should be clearly documented in the subject's trial files.

Note: The AM Run-in Period stability limit is calculated by the eDiary (IVRS/IWRS) based on the reported PEF data. The best PEF value (i.e., the highest of 3 efforts) will be entered by the subject/caregiver in the eDiary [IVRS/IWRS]), in the morning on each day when the assessment was completed (Section 7.1.2.10). The calculation for the PEF stability limit is as follows: the AM PEF values from each of the 7 days prior to the Run-in Period are added, divided by the number of non-missing values, and multiplied by 0.70.

Double-Blind Treatment Period

At the Randomization Visit (Visit 3), a subject meeting all inclusion criteria and none of the exclusion criteria will be randomly allocated to treatment with MF/F 100/10 mcg or MF 100 mcg for approximately 24 weeks.

At in-clinic visits, the morning dose of trial medication will be given as a witnessed dose.

At home between visits, trial medication should be taken twice a day (two puffs in the morning upon awakening and 2 puffs in the evening, approximately 12 hours apart), after the subject completes the PEF measurement (AM only) and prior to the eDiary (IVRS/IWRS) entries, as outlined in Section 5.2.

During the Double-blind Treatment Period, if the subject has a decrease in AM PEF below the stability limit on any 2 consecutive days, the investigator must determine if the subject can continue based on his/her clinical judgment; the decision should be clearly documented in the subject's trial files.

Subjects will be reminded to bring their blinded inhalers and all other trial medication to the clinic (whether used or not).

Double-blind treatments are listed in Table 4.

Table 4 Double-Blind Treatment

MF/F MDI 50/5 mcg (per actuation ["puff"])
• 2 puffs (100/10 mcg) twice daily, approximately 12 hours apart, for a total daily dose of 200/20 mcg
MF MDI 50 mcg (per actuation ["puff"])
• 2 puffs (100 mcg) twice daily, approximately 12 hours apart, for a total daily dose of 200 mcg

5.2.3 Trial Blinding/Masking

A double-blind/masking technique will be used during the Double-Blind Treatment Period. MF/F 100/10 mcg and MF 100 mcg will be packaged identically so that blind/masking is maintained. The subject, the investigator and Sponsor personnel or delegate(s) who are involved in the treatment or clinical evaluation of the subjects are unaware of the group assignments.

The Run-in Period is open-label therefore; the Sponsor, investigator, and subject will know the treatment administered.

See Section 7.1.4.2, Blinding/Unblinding, for a description of the method of unblinding a subject during the trial, should such action be warranted.

5.3 Randomization or Treatment Allocation

Randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 treatment arms in the Double-blind Treatment Period. Subjects will be assigned randomly in a 1:1 ratio to MF/F 100/10 mcg and MF 100 mcg, respectively. Note that the IVRS/IWRS system functionality used by site personnel for randomization is distinct from the eDiary functionality used by subjects/caregivers.

5.4 Stratification

Randomization will be stratified according to the following factors:

- Age: Age stratification (5-to-7 versus 8-to-11 years of age) will be performed in order to ensure an adequate number of younger subjects balanced between each treatment group. The randomization IVRS/IWRS will be used to monitor the simultaneous enrollment of both age groups. Ongoing trial monitoring will be used to target approximately 20% of randomized subjects in the 5- to 7-year-old age group.

- Region: Region stratification will ensure that treatment allocation is balanced across geographic regions of the world in this large multinational trial. Details of the regions will be provided in a separate supplemental Statistical Analysis Plan (sSAP).

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

Over the counter (OTC) pain relief medications may be used for minor ailments without prior consultation with the Sponsor Clinical Monitor.

In addition, the following concomitant medications are also permitted without prior consultation with the Sponsor Clinical Monitor:

- Topical antimicrobials and systemic antibiotics.
- Albuterol 90 mcg/salbutamol 100 mcg HFA MDI (ex-actuator) (SABA) treatment to be used as rescue medication during the Run-in Period and during the Double-blind Treatment Period (with at least an 6-hour washout period before trial visits [which also includes 6- hour washout prior to spirometry testing).
- Nebulizations of 2.5 mg albuterol/salbutamol per treatment to be used as rescue medication during the Run-in Period and during the Double-blind Treatment Period (with at least an 6- hour washout period before trial visits which also includes 6- hour washout prior to spirometry testing]). For the purposes of this protocol, one nebulization treatment will be regarded as equivalent to four inhalations from an MDI.
- Oral prednisone/prednisolone, to be used per investigator's instructions and the subject's Asthma Action Plan (Appendix 12.10), for an asthma exacerbation.
- Oral antihistamines for subjects with allergy symptoms.
- Ocular or nasal antihistamines.
- Oral, ocular, or nasal decongestant for subjects with allergy symptoms.

- Immunotherapy treatments if the subject is on a stable maintenance schedule for at least 4 weeks prior to Visit 1. However, doses should not be given within 24 hours prior to a trial visit. A subject can receive their immunotherapy dose while in the office for a trial visit after all protocol-specified procedures have been completed. Oral immunotherapy or short-course (rush) immunotherapy using escalating doses are prohibited. The Sponsor should be notified if rush venom immunotherapy is being considered for the subject.
- Vaccines (e.g., influenza, hepatitis, etc.) with a 1-week washout before a visit.
- Mild potency (Stoughton-Cornell Scale Appendix 12.7) topical glucocorticoids for dermatologic use only, for use in controlling eczema, etc. are allowed.
- Ocular, intra-nasal, and otic glucocorticosteroids.
- Thyroid replacement hormone if on a stable dose.

Listed below are some specific restrictions for concomitant therapy use during the course of the trial. If there is a clinical indication for any medication specifically prohibited during the trial, discontinuation from trial therapy may be required. The investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy requires the mutual agreement of the investigator, the Sponsor and the subject.

The following concomitant medications are prohibited:

Table 5 Medications Prohibited After Screening and for the Duration of the Trial

Leukotriene modifiers.
Oral immunotherapy or short-course rush immunotherapy or the initiation of immunotherapy treatment.
Medication linked with clinically significant incidence of hepatotoxicity (e.g., methotrexate, 17-alkylsteroids) or which may cause significant liver enzyme induction (e.g., barbiturates).
Beta blockers regardless of route of administration.
Theophylline.
Oral (permitted as outlined in section 5.5), intramuscular, intra-articular, intravenous, and inhaled glucocorticosteroids (not including trial medication).
Glucocorticosteroids, high potency dermatologicals, plain and/or combination classifications of mid-strength, potent or superpotent by Stoughton-Cornell Scale (Appendix 12.7).
Any therapeutic antibody treatment, including but not limited to omalizumab (Xolair®), or investigational antibodies.
Oral or inhaled bronchodilators e.g., salmeterol, formoterol, theophylline, and ipratropium bromide
Inhaled ipratropium bromide alone or in combination with albuterol/salbutamol (Combivent®), tiotropium.
Inhaled cromolyn sodium and nedocromil.
Amphetamines, methylphenidates and dextroamphetamines and lisdexamfetamine or similar stimulants with potential bronchodilatory effects used to treat ADHD/ADD (e.g., Ritalin, Concerta, Adderall, Dexedrine, Vyvanse).
Other investigational drugs and vaccines.

5.6 Rescue Medications & Supportive Care

Short-acting beta-agonist (SABA) (albuterol 90 mcg or salbutamol 100 mcg HFA MDI) and oral corticosteroid (prednisone or prednisolone) will be provided at the Screening Visit by sites to subjects for potential use at home as rescue medications. Throughout the trial, each subject will have access to a supply of bronchodilator rescue medication to be used on an as-needed basis. Nebulizations of albuterol/salbutamol 2.5 mg are also allowed for treatment of asthma symptoms, but are not provided by sites to subjects for potential use at home.

A **SABA MDI** (to be purchased locally by the site) will be provided to the subject for use as rescue medication. The SABA is to be used in accordance with the product labeling.

Note: Spacers **are** permitted for SABA used as rescue medication as well as SABA administered for the purposes of demonstrating reversibility (Section 7.1.2.7).

- The subject should be advised not to take SABA (via MDI or nebulizer) regularly or in anticipation of asthma symptoms. However, use of SABA as a prevention for exercise-induced bronchospasm (EIB) is permitted, only if previously taken in this manner, and should be discussed with the investigator at the Screening Visit. Because the use of SABA as prevention for EIB is not considered rescue use, it should not be captured in the IVRS/IWRS for the purpose of assessing asthma control.
- Once the subject consents to trial participation, the use of the SABA should be withheld at least 6 hours before each subsequent visit. If the subject used any SABA within 6 hours of the scheduled spirometry assessment at Screening (Visit 1), the assessment should be delayed (or rescheduled) until the appropriate washout is met. If the subject requires the use of SABA within 6 hours prior to a subsequent visit, they should be instructed to take the SABA and call the office to reschedule the visit.
- If the subject requires more than 8 inhalations per day on any 2 consecutive days, the subject/caregiver should be advised to contact the investigator.
- Nebulizations of 2.5 mg albuterol/salbutamol per treatment are permitted during the trial as directed by the protocol. If a subject uses both MDI and nebulized formulations of SABA in the same day, then one nebulized treatment is considered equivalent to 4 inhalations of the MDI in order to calculate if the subject has exceeded the equivalent of 8 inhalations in total SABA use for that day.
- Use of SABA in powder form (in lieu of the MDI provided) is prohibited.

Oral prednisone/prednisolone (to be purchased locally by the site) will also be provided to the subject. The subject should be advised not to take oral prednisone/prednisolone regularly or in anticipation of asthma symptoms. In case of an exacerbation of the subject's asthma, oral prednisone/prednisolone should be used as needed, in accordance with the prescribed dose and regimen as rescue medication. The oral prednisone/prednisolone should be taken only after the subject (or caregiver) calls the office and after investigator approval, if possible.

5.7 Diet/Activity/Other Considerations

At all visits with pre-dose measurement of FEV_1, visits should be scheduled so that lung function testing is performed in the morning between 6 am to 10 am, prior to the morning dose of trial medication (see Section 7.1.2.6).

Subjects will be allowed to consume their usual diet throughout the trial and engage in their usual level of exercise throughout the trial.

For the subjects who have signed consent to participate in the PK sub-trial, water may be administered ad libitum during the PK collection Visit (Visit 7).). Subjects may be provided meals (breakfast, lunch, and/or dinner) and snacks while at the trial site for the PK sub-trial. Food may be administered up to 1 hour prior to and as soon as 1 hour after trial drug administration. Grapefruit and grapefruit juice should be avoided. There are no other specific food restrictions prior to or after dosing, with the exception of ensuring a reasonable degree of consistency of any meals/snacks (with respect to content) and ensuring that meals/snacks do not interfere with clinical procedures during the trial.

5.8 Subject Withdrawal/Discontinuation Criteria

5.8.1 Discontinuation of Treatment

Discontinuation of treatment does not represent withdrawal from the trial.

As certain data on clinical events beyond treatment discontinuation may be important to the study, they must be collected through the subject's last scheduled follow-up, even if the subject has discontinued treatment. Therefore, all subjects who discontinue trial treatment prior to completion of the treatment period will still continue to participate in the trial as specified in Section 6.0 - Trial Flow Chart and Section 7.1.5.2 – Discontinued Subjects Continuing to be Monitored in the Trial.

Subjects may discontinue treatment at any time for any reason or be dropped from treatment at the discretion of the investigator should any untoward effect occur. In addition, a subject may be discontinued from treatment by the investigator or the Sponsor if treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at treatment discontinuation are provided in Section 7.1.4 – Other Procedures.

A subject must be discontinued from treatment but continue to be monitored in the trial for any of the following reasons:

- The subject or subject's legally acceptable representative requests to discontinue treatment.
- The subject has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, places the subject at unnecessary risk through continued treatment in the trial or does not allow the subject to adhere to the requirements to receive treatment in the trial.

- Any drug-related serious AE (SAE) or any SAE (including serious asthma exacerbation) which, in the opinion of the investigator and/or Sponsor, might affect the ability of the subject to safely continue to receive treatment.
- Chronic failure to comply with the dosing, evaluations, or other requirements of the trial, despite documentation at the site of repeated efforts to reinforce compliance.
- Any drug-related AE.
- The subject (menstruating female) has a confirmed positive serum pregnancy test. The pregnancy will be followed to resolution.
- Use of more than 1 course of oral prednisone/prednisolone for worsening asthma. The course of steroid treatment will be determined by the prescribing health care provider.
- If a subject is being treated (according to the Asthma Action Plan, Appendix 12.10) for worsening of asthma symptoms and is not stabilized within 14 days of initial treatment, based on the judgment of the Investigator.

For subjects who are discontinued from treatment but continue to be monitored in the trial, see Section 7.1.5.2 – Discontinued Subjects Continuing to be Monitored in the Trial for those procedures to be completed at each specified visit.

Discontinuation from treatment is "permanent." Once a subject is discontinued, he/she shall not be allowed to restart treatment.

5.8.2 Withdrawal from the Trial

A subject must be withdrawn from the trial if the subject or subject's legally acceptable representative withdraws consent from the trial.

If a subject withdraws from the trial, they will no longer receive treatment or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the trial including the procedures to be performed should a subject repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the subject, as well as specific details regarding withdrawal from Future Biomedical Research are outlined in Section 7.1.4 – Other Procedures.

5.9 Subject Replacement Strategy

A subject who discontinues from the trial will not be replaced.

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last study-related phone-call or visit, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

5.11 Clinical Criteria for Early Trial Termination

There are no pre-specified criteria for terminating the trial early.

6.0 TRIAL FLOW CHART

Trial Period:	**Screening**	**Run-In**	**Double-Blind Treatment**						**Post-Treatment**	
Visit Number:	**1**	**2**	**3**		**4**	**5**	**6**	**7**	**8**	**9** Follow-up (Phone)	Discon-tinuation[a]
Title:			Randomization								
			Pre	Post							
Scheduled Week:	**-3**	**-2**	**0**		**1**	**4**	**8**	**12**	**24**	Post 14 days (Day 183)	At time of Discon-tinuation
Day:	(Day-21)	(Day-14)	(Day 1)		(Day 8)	(Day 29)	(Day 57)	(Day 85)	(Day 169)		
Scheduling Window[b]:	NA	± 3 Days	± 3 Days		± 3 Days	± 3 Days	±3 Days	±3 Days	± 5 Days	±3 Days	
Administrative Procedures											
Informed Consent/Assent[c]	X										
Informed Consent for Future Biomedical Research[d]	X										
Inclusion/Exclusion Criteria	X	X	X								
Informed consent for PK sub-trial (at a subset of sites)[e]	X										
Subject Identification Card	X										
Medical History	X										
Prior/Concomitant Medication Review	X	X	X		X	X	X	X	X	X	X
Screening number assigned	X										
Treatment Allocation/ Randomization				X							
Telephone contact to remind subject of clinic visit (day before specified visit)[f]		X	X		X	X	X	X	X	X[n]	
Follow-up telephone contact: subjects who discontinue trial medication early[g]					X	X	X	X	X		
Clinical Procedures/Assessments											
Inhaler Training/Review with practice MDI training inhaler[h]	X	X	X		X	X	X	X			
Assess subject understanding of trial procedures	X	X	X		X	X	X	X	X		

Trial Period:	Screening	Run-In	Double-Blind Treatment						Post-Treatment	
Visit Number: Title:	**1**	**2**	**3** Randomization		**4**	**5**	**6**	**7**	**8**	**9** Follow-up (Phone)	Discon-tinuation[a]
Scheduled Week:	**-3**	**-2**	Pre **0**	Post	**1**	**4**	**8**	**12**	**24**	Post 14 days	At time of Discon-tinuation
Day:	(Day-21)	(Day-14)	(Day 1)		(Day 8)	(Day 29)	(Day 57)	(Day 85)	(Day 169)	(Day 183)	
Scheduling Window[b]:	NA	± 3 Days	± 3 Days		± 3 Days	± 3 Days	±3 Days	±3 Days	± 5 Days	±3 Days	
Run-in Period Medication (open-label MF): Dispensing/Collection[b]		X	X								
Double-blind Medication (MF/F or MF): Dispensing/Collection as required[b]				X		X	X	X	X		X
Compliance Measure Review			X		X	X	X	X	X		X
Dispense/Retrieve Rescue Medication as Needed[b]	X	X	X		X	X	X	X	X		X
Train eDiary (IVRS/IWRS)/ Peak Flow meter: Obtain/Review Data with Subject and Caregiver[i]	X	X	X		X	X	X	X	X		X
Dispense/Review Asthma Action Plan	X	X		X	X	X	X	X	X		
Full Physical Examination	X										
Directed Physical Examination[j]									X		X
Height and Weight	X							X[e]			
Oropharyngeal Examination	X	X	X		X	X	X	X	X		X
Vital Signs (heart rate, blood pressure, respiratory rate, oral/tympanic temperature) prior to spirometry, when applicable	X		X		X	X	X	X	X		X
Reversibility test[k]	X	X (if needed)									
Spirometry (Pulmonary Function Test)	X										
Serial Spirometry: Predose (-30 and 0 minutes); Postdose (5, 15, 30, 60 minutes)				X	X	X	X	X			

Trial Period:	Screening	Run-In	Double-Blind Treatment						Post-Treatment	
Visit Number:	**1**	**2**	**3**		**4**	**5**	**6**	**7**	**8**	**9** Follow-up (Phone)	Discon-tinuation[a]
Title:			Randomization								
			Pre	Post							
Scheduled Week:	**-3**	**-2**	**0**		**1**	**4**	**8**	**12**	**24**	Post 14 days (Day 183)	At time of Discon-tinuation
Day:	(Day-21)	(Day-14)	(Day 1)		(Day 8)	(Day 29)	(Day 57)	(Day 85)	(Day 169)		
Scheduling Window[b]:	NA	± 3 Days	± 3 Days		± 3 Days	± 3 Days	±3 Days	±3 Days	± 5 Days	±3 Days	
Serial Spirometry: Postdose (2 and 4 hours)				X				X			
In-Clinic Witnessed Dosing		X		X	X	X	X	X			
Adverse Events Monitoring	X	X	X		X	X	X	X	X	X	X
Laboratory Procedures / Assessments[l]											
Hematology/Chemistry/Urinalysis[m]	X	Review									
Urine Pregnancy Test[m]	X	X	X		X	X	X	X	X	X[n]	X
Blood Collection (PK sub-trial)[e]								X			
Buccal swab samples for Future Biomedical Research[d]				X							

All references to "subject(s)" in this pediatric trial imply that a caregiver/guardian will oversee, or be directly involved in, all procedures.

Note: If a subject is not able to visit the investigational site on the day or week as stipulated in the protocol, the visit may be re-scheduled at another time with prior agreement of the sponsor. Every attempt should be made to re-schedule as close as possible to the original visit date. **Throughout the trial, the site must ensure that the subject has sufficient trial drug to last until the next visit.**

a. Criteria for discontinuation from participation in the trial are in Section 5.8, and details regarding discontinuation procedures are in Section 7.1.4; criteria to consider discontinuation from treatment while continuing to monitor in the trial (i.e., not requiring a Discontinuation Visit) are also in Section 5.8. All subjects should be followed through trial completion regardless of premature discontinuation of treatment, unless the subject's caregiver withdraws consent.

b. The investigator will be responsible for providing and ensuring all subjects have adequate supplies of trial medication and rescue medication (inhaled SABA [albuterol/salbutamol], oral prednisone/prednisolone). Subjects who discontinue trial medication early will have access to a supply of bronchodilator rescue medication to be used on an as-needed basis. At Visit 8/Discontinuation Visit, supplies will only be collected and no further supplies will be dispensed.

c. Informed consent/assent forms MUST be obtained prior to the Visit 1 procedures including trial-specific medication washouts for spirometry. (Note: two separate calls to IVRS would need to be made [one to obtain the screening number at Visit 1, and one to obtain the allocation number for randomized subjects at Visit 3]).

d. Informed consent for future biomedical research must be obtained before buccal swab samples are collected. The buccal swab DNA samples should be obtained at Visit 3, as the last sample drawn, on randomized subjects only, or at a later date as soon as the informed consent is obtained. Specimens should only be collected at a scheduled visit.

e. A pharmacokinetic (PK) sub-trial will only be conducted at a subset of sites and only in subjects who consent to this sub-trial (see Appendix 12.5 for details). If consent for the sub-trial is not obtained at Visit 1, it is acceptable to obtain consent prior to the sub-trial Visit (Visit 7). For subjects participating in the PK sub-trial, height and weight must be performed at this PK Visit 7.

f. The site must contact the subject (caregiver) the day before each visit to remind them of the visit. Additionally, the telephone contact should serve as a reminder for ensuring restricted medication washout times will need to be observed. The appointment time for all visits should be established in advance to ensure that the subject is able to be at the site and begin spirometry assessments 12 hours after the prior evening's dose of trial medication.

g. All subjects should be followed through trial completion regardless of premature discontinuation of treatment, unless the subject's caregiver withdraws consent. Subjects who discontinue trial medication early will be contacted via telephone through the end of the trial for assessments of Adverse Events and concomitant medications as well assessments of daily eDiary (IVRS/IWRS) entries, if applicable.

h. The subject must demonstrate proper use of the MDI prior to entering the Run-in Period.

i. After receiving training on both electronic diary systems (i.e., IVRS and IWRS) at Screening (Visit 1), subjects will select to use either the IVRS or the IWRS to collect daily trial assessments. The daily eDiary (IVRS/IWRS) assessments will begin the morning of the Screening Visit and continue throughout the last in-clinic visit (Visit 8). Daily assessment data must be reviewed by the investigator. Subjects who discontinue trial medication early should be encouraged to continue to complete the daily eDiary (IVRS/IWRS) assessments through the end of the trial.

j. Directed (Focused) examination will be performed at Visit 8 and at Discontinuation Visit based on reason for discontinuation. (See Section 7.1.2.2)

k. Post β-agonist spirometry will be determined by administering 4 to 8 puffs of albuterol/salbutamol (Appendix 12.8). Subjects who meet pre-defined reversibility criteria at Visit 1 need not repeat reversibility testing at Visit 2. Subjects must meet pre-defined reversibility criteria prior to Visit 3 to be randomized at Visit 3. (See Section 7.1.2.7)

l. Once the laboratory results are received at the site, they should be promptly reviewed by the investigator and found to be clinically acceptable by the investigator in order to evaluate eligibility to begin run-in treatment at Visit 2. A single repeat test is permitted and must be reviewed and found to be clinically acceptable prior to Visit 2. Additional laboratory tests for drug-induced liver injury (DILI, see also Section 7.2.3.2) may be conducted if needed, based on investigator concern on initial DILI results.

m. Female subjects (or their Caregiver) must be asked at each visit if the subject has begun menses. Responses should be recorded in the eCRF. If a female subject reaches menarche (menstruates for the first time) during the trial, a urine pregnancy test (dipstick and HCG urine testing) must be done at that visit and every visit thereafter. Pregnancy tests will then be done at each visit. Post-menarche female subjects must have a negative urine pregnancy test at Screening. If urine test result is positive at any time during the trial, it would need to be confirmed with a serum β-hCG test.

n. Female subjects of child-bearing potential must return for a urine pregnancy test (dipstick and HCG urine testing) at the post-trial visit. All other subjects will receive a telephone contact for post-trial evaluation.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee, at Visits 1-3, to ensure that the subject qualifies for the trial.

7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject provides written informed consent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Subject Identification Card.

The subject identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about trial medication/vaccination in emergency situations where the investigator is not available.

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 30 days or longer as appropriate prior to Visit 1. Any prior medications are to be recorded on the electronic Case Report Form (eCRF). The identity of the therapy, the dose, route of administration, and regimen, the dates started and stopped (or notation of "continuing" if that is the case), and the reason for use must be recorded.

Section 5.1.3 provides a list of medications prohibited prior to the Screening Visit.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will review and record concomitant medications, if any, taken by the subject during the trial. Any concomitant therapy taken by the subject during the trial is to be recorded on the eCRF. The identity of the therapy, the dose, route of administration, the dates and times started and stopped (or notation of "continuing" if that is the case), and the reason for use must be recorded.

Section 5.5 outlines concomitant medications allowed and prohibited during the ongoing trial.

7.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is rescreened will retain the original screening number assigned at the initial screening visit

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 7.1.5

7.1.1.7 Assignment of Randomization Number

All eligible subjects will be randomly allocated and will receive a randomization number. The randomization number identifies the subject for all procedures occurring after randomization. Once a randomization number is assigned to a subject, it can never be re-assigned to another subject.

A single subject cannot be assigned more than 1 randomization number.

7.1.1.8 Trial Compliance (Medication/Other)

Interruptions from the protocol specified treatment plan for a total interruption of 5 consecutive days require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

Subjects and caregivers should be reminded of all appropriate medication washout times during telephone contact before any visits requiring spirometry testing.

If the subject uses the following medications:

- SABA rescue medication within 6 hours, or
- ICS/ LABA within 12 hours,

of a scheduled spirometry assessment at Visit 1, (Visit 2 or an unscheduled visit, if reversibility is being assessed) and Visit 3 through Visit 7; then, if necessary, the entire visit should be delayed or rescheduled (in accordance with the appropriate visit windows) until the appropriate washout is met. If the subject requires the use of the medications indicated above before a subsequent visit, he/she should be instructed to take the medication and call the office to reschedule the visit.

Verbal and written instruction for proper use of the MDI (Appendix 12.6) should be given to the subject and caregiver. As appropriate, the investigator or qualified designee should observe the subject at every visit as he/she doses themselves using the practice MDI training inhaler. Adjustment to their technique should be made, if necessary, until the subject is properly trained on how to use the inhaler. The MDI training inhaler will remain at the trial site and is not to be dispensed to the subject to take home.

At the Screening Visit (Visit 1) each subject will be instructed on an electronic diary (IVRS/IWRS) to use (the subject will use the eDiary with the assistance of their caregiver) for the duration of the trial (see Section 7.1.2.10 for details and Appendix 12.11). The caregiver designated for assistance of completion of the eDiary (IVRS/IWRS) must remain the same throughout the trial. At the Screening Visit and at all subsequent visits (except the subject's Final Visit), the subject and their caregiver should be instructed on how to properly use the eDiary (IVRS/IWRS) system to capture daily peak flow, trial medication use, and rescue medication use while in the trial. The subject and their caregiver should be instructed to ensure completeness of all required electronic data entries when returning for all subsequent visits. Daily assessment data must be reviewed by the investigator.

The subject's eDiary (IVRS/IWRS) data and PEF should be reviewed by the investigator or designee at each visit after Visit 1. The investigator's review should include an assessment by direct and open questions to the subject and caregiver. Overall completeness and accuracy of all recorded entries should be reviewed. Deficiencies should be immediately discussed with the subject and caregiver in order to improve the quality of information subsequently entered on the eDiary (IVRS/IWRS). The investigator and qualified designee should ensure that any relevant comments that refer to possible adverse events are discussed or clarified with the subject and caregiver, and are captured on the electronic Case Report Form (eCRF) for adverse events.

Compliance with eDiary (IVRS/IWRS) completion, trial medication use, and rescue medication usage or oral prednisone/prednisolone emergency use is essential, and any non-compliance noted by the investigator or designee should result in consultation with the subject and caregiver on corrective measures needed to ensure compliance.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Review Adverse Event

See Section 7.2 Assessing and Recording Adverse Events and Patient/ Device Events.

7.1.2.2 Physical Examination

A complete physical examination will be performed at Visit 1, and a directed/focused physical examination will be performed at Visit 8 or the Discontinuation Visit as indicated in the Trial Flow Chart (Section 6.0) . If the subject is discontinued for any reason during the Double-blind Treatment Period, every attempt should be made to perform a directed/focused physical examination as part of the discontinuation procedures.

A directed/focused physical exam will include the following: assessment of appearance, throat and nasal examination, and auscultation of heart and lungs. Other body systems may be examined as clinically indicated. Any abnormal physical findings (from visits other than at screening) should be recorded in the adverse event section of the eCRF.

7.1.2.3 Height and Weight

Height (cm) and weight (kg) will be measured prior to performing spirometry at Visit 1 as indicated in the Trial Flow Chart (Section 6.0). Height and weight will also be measured at Visit 7 only for the subjects participating in the PK Sub-trial; for all of these subjects, height and weight will be updated, but on the eCRF only. To avoid a difference in spirometry predicted values, height and weight collected at Visit 7 should not be updated in the spirometry equipment.

Note: Equipment used to measure height and weight does not need to have a separate calibration for the purposes of the trial.

7.1.2.4 Oropharyngeal Examination

An oropharyngeal examination will be performed at all in-clinic visits. Oropharyngeal candidiasis present (upon visual inspection, laboratory culture is not required) at the Screening Visit (Visit 1) or at the Randomization Visit (Visit 3) should be treated and the subject rescheduled when the candidiasis is resolved. During the treatment period, if there is suspected infection, therapy should be initiated as appropriate, and the occurrence should be captured as an adverse event on the eCRF. A subject with candidiasis may continue in the trial on appropriate treatment with approval of the investigator.

7.1.2.5 Vital Signs

Systolic and diastolic blood pressure (mm Hg), temperature (°C), pulse (beats/minute), and respiratory rate (breaths/minute) will be measured, (**just before spirometry measurements at Visit 1** [Visit 2 or an unscheduled visit, if reversibility is being assessed]**, Visits 3-7)**, with the subject in the sitting position. Vitals signs are to be performed at all in-clinic visits as specified in the Trial flowchart (Section 6.0). Any clinically significant abnormalities in vital signs noted after Visit 1 will be recorded as adverse events on the eCRF.

7.1.2.6 Spirometry, also known as Pulmonary Function Testing (PFT)

The subject and caregiver must be contacted (e.g. by phone) the day before each visit through to the subject's final visit [including discontinuation visit, if possible]. The primary purpose of this contact is to remind the subject and caregiver of the appointment time for the next day's visit and spirometry testing schedule (if applicable); and post-screening, to coordinate the timing of that evening's asthma medication dose to a specified time relative to his/her testing schedule the following day. Additionally, the phone contact should serve as a reminder for ensuring that restricted asthma medication washout times are observed. The appointment time for all visits should be established in advance to ensure that the subject is able to be at the investigational site and begin spirometry assessments 12 hours after the prior evening's dose of trial medication.

At all visits with pre-dose PFTs, PFTs should be performed in the morning, between 6 am to 10 am prior to the morning dose of trial medication. After restricted asthma medications have been withheld for the appropriate interval (Section 5.1.2), tests will be performed to measure FEV_1, and forced vital capacity (FVC). The subject will be given their dose of trial medication in the clinic following completion of the pre-dose spirometry testing at these visits. Post-dose spirometry measurements should be performed at the visits and times designated in the trial flow chart.

All PFTs will be captured and reported using centralized data services for diagnostic spirometry. Sites will be equipped with a trial-specific spirometer to perform spirometry at the specified visits. Every attempt must be made to use one spirometer consistently on each subject.

In this trial, Polgar reference ranges are to be used to determine percent predicted. If the subject self-reports his/her race as Black, appropriate adjustments will automatically be made for race by programming the spirometer using the formula:

FEV_1 predicted x 0.88 = FEV_1 predicted adjusted for race

Spirometry should be performed in accordance with guidelines established by the American Thoracic Society/European Respiratory Society (ATS/ERS) (Available from: http://www.thoracic.org/statements/). Additional details regarding spirometry procedures will be provided by the centralized spirometry vendor. For safety reasons, spirometry should be performed with the subject sitting, using a chair with arms and without wheels; however, if necessary to undertake the testing with the subject standing or in another position, this should

be noted on the spirometry report. For any subject, the position should be consistent throughout the trial.

Three measurements fulfilling the ATS/ERS acceptability and repeatability criteria should be obtained during every test session. The acceptability criteria must be applied before the repeatability criteria (Available from: http://www.thoracic.org/statements/). Unacceptable maneuvers must be discarded before applying the repeatability criteria. If a subject fails to provide repeatable maneuvers, an explanation should be recorded on the appropriate eCRF. At least two acceptable curves must be obtained.

The highest FEV_1 and the highest FVC values will be recorded after examining the data from all the acceptable curves, even if the values are not derived from the same curve. If two (or all three) spirometry efforts have identical FEV_1, the FEV_1 from the effort with the highest FVC will be recorded. The centralized spirometry vendor will perform readings of the PFTs from all sites to determine the selected measurements fulfill the ATS/ERS acceptability and repeatability criteria. These data values will be automatically reported from the central vendor's database once acceptability/repeatability criteria have been applied and agreed upon between the site and the central vendor. If the site and the central vendor cannot agree on the data value(s), the sponsor should be consulted.

In order to ensure timely receipt of the vendor's selected measurements, the PFT data should be transmitted, by the site, at the end of each testing day.

The spirometer must be calibrated according to ATS/ERS guidelines (i.e., with a 3-liter syringe), every day that a trial subject is seen and spirometry carried out, or at least weekly, that a trial subject is seen and spirometry carried out. The calibration records should be printed and kept in a reviewable log. It is preferred that the calibration syringe used to calibrate the spirometer also be subjected to a validated calibration according to the manufacturer's specifications.

Additional details regarding spirometry procedures and spirometer calibrations will be provided by the centralized spirometry vendor.

7.1.2.7 Airway Reversibility

At Visit 1 (Screening Visit), a test of airway reversibility will be administered following pulmonary function testing after asthma medications have been withheld for the appropriate intervals (Section 5.1.2 and Section 7.1.1.8). Reversibility (maximal post-bronchodilator spirometry) is defined as an increase in absolute FEV_1 of greater than or equal to 12% larger than the baseline value. Maximal post-bronchodilator spirometry must be performed as outlined in Appendix 12.8.

Note: Spacers **are** permitted for SABA administered for the purposes of demonstrating reversibility.

If the subject does not meet reversibility criteria at Visit 1, repeat assessments can be performed. At Visits where reversibility is performed, only a single series of (up to) 8 inhalations of SABA or 2 nebulizations of SABA is permitted to test for reversibility at that visit. If the subject meets reversibility at Visit 1, reversibility testing is not needed after Visit 1.

The subject must meet reversibility before Visit 3. The reversibility testing prior to Visit 3 must be performed at least two days prior to the Visit 3 due to the timeframe for the over-read of the spirometry report from the central vendor. (In order to have the final result in time to make a decision for subject inclusion in the trial, the latest timeframe reversibility should performed is 2 days prior to the randomization visit [V3].)

Note: The Investigator should consider the safety and well-being of the subject if reversibility is repeated more than once. In addition, the Investigator should have a clinical rationale for why reversibility should be repeated.

7.1.2.8 In-clinic witnessed dosing

At all in-clinic visits, the morning dose of trial medication will be given as a witnessed dose in the clinic (this includes the first dose of open-label trial medication and the first dose of double-blind trial medication). During Visits that include spirometry (Visit 1, [Visit 2 or an unscheduled visit, if reversibility is being assessed] and Visit 3 to Visit 7), the morning dose of trial medication will be given as a witnessed dose after pre-dose spirometry measurements are completed.

7.1.2.9 Pre- and post-dose spirometry

At Visits 3, 4, 5, 6, and 7 (as indicated in the Trial Flow Chart Section 6.0), serial spirometry measurements will be performed prior to administration of trial medication: at -30 minutes (before trial medication), then at 0 minutes (immediately prior to trial medication), and then during one hour following administration of trial medication (at 5, 15, 30, and 60 minutes after trial medication). At Visits 3 and 7 only, spirometry measurements also will be conducted at 2 hours and at 4 hours after trial medication. All post-dose evaluations will be performed after a witnessed dose in the clinic. The subject should refrain from using rescue medication for 1 hour after trial medication (and for 4 hours, at Visits 3 and 7). However, if a subject requires rescue medication during this time, he/she is allowed to receive SABA rescue medication, but then should not continue performing spirometry after receiving the rescue SABA.

7.1.2.10 eDiary (IVRS/IWRS) and Peak Flow Meter: Instructions

At the Screening Visit (Visit 1), each subject will be instructed on the use of an eDiary (IVRS/IWRS) and a PEF meter to use (with the assistance of a caregiver) for the duration of the trial.

The eDiary (IVRS/IWRS) records use of rescue medication and whether the subject took the trial medication. The Peak Expiratory Flow [PEF] measurements from the peak flow meter device used in this trial will also be recorded on the eDiary (IVRS/IWRS). Additional details (including setup/programming of the eDiary [IVRS/IWRS] and peak flow meter [if applicable]) will be provided by the central vendor(s).

After receiving training on both electronic diary systems (i.e., IVRS and IWRS) at Screening (Visit 1), subjects will select to use either the IVRS or the IWRS to collect daily trial assessments. The daily IVRS/IWRS assessments will begin the morning of the Screening Visit and continue through to the last in-clinic Visit (Visit 8). Daily assessment data must be reviewed by the investigator. Subjects who discontinue trial medication early should be encouraged to continue to complete the daily eDiary (IVRS/IWRS) assessments through the end of the trial.

The subject and the caregiver will be instructed in the proper collection of PEF and completion of the eDiary (IVRS/IWRS) at Visit 1. The subject and the caregiver should also be instructed to bring the peak flow meter to **all** visits to confirm that they are using it correctly and that it is working properly. Subjects must be able to demonstrate eDiary (IVRS/IWRS)/PEF meter use and must be able to perform spirometry maneuvers before beginning the Run-in Period (Visit 2).

The subject, with the assistance of their caregiver, should record diary entries twice daily. With the assistance of their caregiver, the subject will measure PEF first (once daily in the morning). After the subject has completed their PEF measurements, he/she will take the trial medication and record the trial medication administration in the eDiary (IVRS/IWRS). Then, he/she will complete the additional questions in the eDiary (IVRS/IWRS), which record any use of rescue medications (SABA, oral corticosteroids) since the last diary entry. Because the use of SABA as prevention for exercise-induced bronchospasm (EIB) is not considered rescue use, it should not be captured in the IVRS/IWRS system for the purpose of assessing asthma control. Use of SABA for prevention of EIB will be recorded in the concomitant medication module of the electronic case report form (eCRF).

Note: If SABA is used in response to asthma symptoms after exercise, this would be considered rescue use.

Specifically, regarding PEF:

- The subject should make 3 attempts to generate his/her best PEF on the peak flow meter. The best (i.e., highest) value of the 3 PEF attempts will be entered by the subject/caregiver in the eDiary (IVRS/IWRS).
- The subject should be asked to refrain from using their SABA 6 hours prior to performing the AM PEF measurements. If rescue medication is required within the 6 hours before measuring AM PEF, the subject will indicate this on the eDiary (IVRS/IWRS).

- Throughout the trial, the subject should be instructed to perform triplicate PEF measurements once daily, immediately before trial medication administration and/or rescue medication use (which is in the morning upon awakening).

The eDiary data will be downloaded/reviewed by the investigator or qualified designee. The review should include an assessment of:

- Peak Flow
- Daily rescue medication use
- Daily trial medication use
- Overall completeness and accuracy of all recorded entries

Deficiencies should be immediately discussed with the subject (and caregiver, as appropriate) in order to improve the quality of information subsequently recorded on the diaries.

Compliance with diary completion is essential. Any non-compliance noted by the Investigator or designee should result in documented consultation with the subject on corrective measures needed to ensure compliance.

Calculating the Stability Limits for Peak Flow to be Used for the Run-in and Double-blind Treatment Periods

The stability limits are calculated by the eDiary (IVRS/IWRS) based on the reported PEF data. (The best [i.e., highest of the three efforts] PEF value each day will be entered by the subject/caregiver in the eDiary [IVRS/IWRS]), in the morning when the assessment was completed.) The equation used to calculate a stability limit is as follows: the AM PEF values from the 7 days preceding Visit 2 are added, divided by the number of non-missing values, and multiplied by 0.70. **Note:** a minimum of 4 days of PEF data is required for the stability limit to be calculated.

See Table 6 for an example calculation of a stability limit.

Table 6 Example Calculation of the Stability Limit for Peak Flow

Trial Visit	Date	Trial Day	**AM PEF**
Pre Run-in (V2)	09-JUL	-14	-
	08- JUL	-15	280
	07- JUL	-16	290
	06- JUL	-17	270
	05- JUL	-18	290
	04- JUL	-19	280
	03- JUL	-20	270
	02- JUL	-21	280
		Total	1960
		Divide by 7	280
		Multiply by 0.70	**196**

During the Run-in Period and Double-blind Treatment period, the investigator must evaluate if the subject has a decrease in AM PEF below the stability limit on any 2 consecutive days. If yes, the investigator must determine if the subject can continue in the trial based on his/her clinical judgment; the decision should be clearly documented in the subject's trial files. Note that the subject/caregiver will also be monitoring daily PEF values according to their Personal Best PEF as recorded in the AAP (Section 7.1.2.12).

7.1.2.11 Obtain/Review eDiary (IVRS/IWRS) Data with Subject and Caregiver

At all trial visits from Visit 2 through the Final Visit (including follow-up telephone calls for subjects who have discontinued trial medication early), eDiary (IVRS/IWRS) data will be downloaded and reviewed with each subject and each caregiver by trial site personnel. The eDiary (IVRS/IWRS) data will be reviewed for missing or inconsistent information and missing doses of trial medication, and subjects and caregivers will be re-trained on the importance of complete diary information and diary procedures if there is missing data. The eDiary (IVRS/IWRS) data are available in a central database where the information should be reviewed by the investigator/designee.

Review/Record Short-Acting Beta-Agonist (SABA) Use

Twice daily, the subject, with the assistance of the caregiver, will document the number of SABA inhalations used for rescue (and will not include any SABA used specifically for prevention of EIB) during the time period since the last IVRS/IWRS session. The subject will also document (yes/no) whether SABA was used within the 6 hours prior to measuring their PEF in the morning.

The electronic record of SABA use will be used by the Investigator for assessments of asthma worsening/exacerbation. Daily IVRS/IWRS records of SABA use will also be used for determination of the secondary efficacy endpoint (total SABA use across the first 12 weeks of double-blind treatment).

NOTE: All use of SABA that is not provided to the subject by this trial (e.g., at an acute visit to the ER, hospital or other urgent-care facility) must be recorded at site visits and telephone contacts by the investigator/qualified designee. The reason for the use of this non-trial-provided SABA and the dose, route, start and stop dates should be recorded in the appropriate section of the eCRF. Chronic use of non-trial-provided SABA during the trial is not permitted and should be discontinued by the investigator upon notification by the subject/caregiver.

Review/Record Oral Corticosteroid (Prednisone/Prednisolone) Use

Twice daily, the subject, with the assistance of the caregiver, will document if oral prednisone/prednisolone was used as a rescue medication during the time period since the last evaluation. If the answer is "yes", oral prednisone/prednisolone use must be documented as a concomitant medication in the eCRF. If oral prednisone/prednisolone is used more than once for worsening asthma during the trial, the subject will be discontinued.

Subjects dispensed oral prednisone/prednisolone should be trained to use it only after the subject (or parent/legal guardian) calls the investigational site and after investigator approval, if possible. The subject will be advised not to take oral prednisone/prednisolone regularly or in anticipation of symptoms. Oral prednisone/prednisolone should only be used as emergency rescue medication at the discretion of the investigator in accordance with the subject's individualized written Asthma Action Plan (Appendix 12.10).

Review/Record Nebulized Treatment Usage

Twice daily, the subject, with the assistance of the caregiver, will document the number of nebulized albuterol/salbutamol treatments used during the time period since the last evaluation (one nebulized treatment is defined as 2.5 mg of albuterol/salbutamol).

Review/Record PEF Measurements

Once daily, the subject, with the assistance of the caregiver, will perform three PEF maneuvers in the AM upon rising. The best of the three efforts (i.e., the highest) will be recorded in the eDiary (IVRS/IWRS) in the morning when the assessment was completed.

7.1.2.12 Asthma Action Plan

At Visit 1, an individualized written Asthma Action Plan (see sample in Appendix 12.10) will be provided by the investigator to the subject and the caregiver to provide guidance on effectively managing the subject's asthma, as recommended by clinical practice guidelines. Additionally, the AAP will include a reminder for subjects to contact the investigational site immediately if they have experienced worsening asthma resulting in an ER/urgent-care visit

or hospitalization. (Note that in addition to the use of the AAP to help manage a subject's asthma, the IVRS/IWRS will be programmed to alert the investigators to contact the subject/caregiver if the subject has reported more than 8 inhalations of SABA for rescue on two consecutive days [one nebulized treatment is considered equivalent to 4 inhalations of the MDI in order to calculate if the subject has exceeded the equivalent of 8 inhalations in total SABA use for that day]).

For the AAP, three measurements of AM PEF, using the peak flow meter, will be obtained during Visit 1. The investigator will record the highest AM PEF (greatest value in 3 attempts) value and enter it as the "personal best" level on the Asthma Action Plan. This value will be used to determine the PEF range, along with changes in symptoms, which will guide the subject/caregiver in effectively managing the subject's symptoms as per the AAP. (Note that in addition, PEF measurements will be monitored by the Investigator according to the established stability limit, as described in Section 7.1.2.10).

The AAP will be reviewed with the subject/caregiver at all visits and should be updated by the investigator/qualified designee during the course of the trial, as needed. The AAP will be collected at the Final Visit and/or upon trial Discontinuation along with all trial-provided supplies.

7.1.2.13 Asthma Baseline Pediatric Profile

Subjects will also be asked to provide information on their asthma history and related conditions for completion of an Asthma Baseline Pediatric Profile (ABPP). The investigator or qualified designee will obtain medical history information about asthma to allow completion of an ABPP at Visit 1.

7.1.2.14 Dispense/Collect Trial medication Inhalers

Priming

All new inhalers dispensed should be primed (which means performing 4 actuations of the inhaler that are *not* to be inhaled by the subject) prior to first use. When inhalers for the trial medications are used as directed (i.e., two puffs taken in the morning and two puffs taken in the evening), each inhaler will be adequate to provide for the four actuations required for priming when the inhaler is dispensed, as well as 30 days of twice-daily dosing. Re-priming is required only if the inhaler is not used for more than 3 consecutive days. If a subject stops dosing for 3 days during the trial, the subject should be advised to contact the site for instruction on how to proceed with dosing.

Dispensing a backup inhaler

During the Double-blind Treatment period, a backup (i.e., second) MDI will be provided to the subject. For tracking purposes, the investigator or designee should fill in the "Do not use after ____" field on the inhaler used in the office at the dispensing visit. The date should correspond with 30 days of dosing for the MDI. Subjects should be advised that the second MDI will serve as a backup for prolonged visit schedules. If the backup needs to be used, subjects should be advised of the appropriate priming requirements of the MDI. At subsequent visits, additional new MDIs should be dispensed and the date field should be completed accordingly. From Visit 3 to Visit 8 of the Double-blind Treatment Period, subjects will be provided sufficient inhalers to cover the length of time between the visits as well as 1 additional inhaler as a backup.

Instructions for Dispensing

The subject and caregiver should be instructed to keep the inhaler in a secure, dry location at all times. Each inhaler will have enough medication for 30 days of dosing.

- At the Run-in Visit (Visit 2), the subject will be dispensed open-label MF MDI. Subjects will be switched from their previous asthma therapy to open-label MF MDI once laboratory results are found to be clinically acceptable by the investigator/sponsor, provided subjects continue to meet all inclusion criteria and none of the exclusion criteria. After appropriate priming, the first dose of open-label MF MDI will be administered to the subject in the office under the supervision of the investigator or qualified designee. This administration will be documented in the eDiary (IVRS/IWRS) and the source document.
- At Visit 2 and thereafter, subjects will be instructed to take 2 inhalations of trial medication upon rising and 2 at bedtime for the duration of the trial. After trial medication administration has been completed, the subject should also be advised to rinse their mouth with water or a suitable mouthwash and then spit it out. The subject should receive additional instruction on the proper completion of the eDiary (IVRS/IWRS) to reinforce the importance of accurately recording the date and time of trial medication dosing.
- At the Randomization Visit (Visit 3), the subject with the assistance of their caregiver should be initially dispensed one treatment kit as well as a back-up treatment kit. After appropriate priming, the first dose of blinded trial medication will be administered to the subject in the office under the supervision of the investigator or qualified designee. This administration will be documented in the eDiary (IVRS/IWRS) and the source document.

- At subsequent visits, IVRS will manage dispensing a variable number of inhalers depending on the time between visits, the need for additional backup inhalers and expiration of the product. The same process should be followed for site notations on the primary and backup inhalers. This will help ensure that the subjects use the correct inhalers, in the correct order, and have sufficient supply until their next visit.

Trial supplies are to be brought to each visit for inspection and evaluation. A new inhaler(s) will be dispensed when applicable. If a dispensed inhaler is found to be defective or non-operational, a replacement inhaler will be dispensed and primed at the discretion of the investigator or qualified designee.

All used and unused trial medication will be returned to the investigator or designee. All supplies should be accounted for, by the investigator or designee, at each visit and at the end of the trial.

7.1.2.15 Review Medication Compliance

The investigator or qualified designee will review trial medication usage with the subject from Visit 3 through the subject's Final Visit. To promote daily medication usage, the subject will be asked twice daily in their eDiary (IVRS/IWRS) whether they have taken their trial medication. The investigator or designee will train each subject, with the assistance of the caregiver, on the diary content and proper completion procedures. Any problems with medication usage should be addressed with the subject and their caregiver as soon as the investigator or designee becomes aware.

Subject must demonstrate at least 80% compliance with use of their trial medication during the 2-week Run-in Period to be eligible for randomization.

Throughout the trial, compliance will be determined by comparing the change in dose counter readings relative to the duration of treatment as entered on the eCRF.

7.1.2.16 Inhaler Use Training and Review

At Visit 1 the subject with the assistance of their caregiver will be instructed in the proper use of the MDI inhaler (Appendix 12.6). If the subject does not demonstrate proper use prior to the administration of Run-in medication, the subject should be excluded from the trial.

The investigator or qualified designee should observe the subject using the demonstration inhaler at every visit (throughout the Run-in and Double-blind Treatment period), as appropriate, in order to reinforce proper dosing technique. The investigator or qualified designee should make adjustments to the technique if necessary. These training supplies will remain at the site and are not to be dispensed to the subject to take home. Supplemental training should be provided, as needed, at all visits (with the exception of the final visit).

7.1.2.17 Rescue Medications

Dispense/Retrieve SABA Medication (as needed): All visits

SABA will be made available (as needed): Visit 1 until the end of the trial.

Albuterol 90 mcg/salbutamol 100 mcg HFA MDI (ex-actuator) (SABA) will be available to all sites as rescue medication for the acute relief of asthma symptoms.

- Spacers are only permitted for SABA used as rescue medication (as well as for SABA administered for the purposes of demonstrating reversibility [Section 7.1.2.7]).
- The subject will be instructed to return all used and unused SABA at each visit.
- Use of SABA as a prevention for exercise-induced bronchospasm (EIB) is permitted if previously taken in this manner and should be discussed with the investigator at the Screening Visit. Use of SABA for prevention of EIB will be recorded in the concomitant medication module of the eCRFs and not on the eDiary.
- Subjects who discontinue trial medication early will have the option to continue to receive SABA, to be used on an as-needed basis.

Dispense/Retrieve Oral Prednisone/Prednisolone Medication (as needed): All visits

Prednisone/prednisolone tablets/syrup will also be made available as rescue medication, which will be administered according to the Asthma Action Plan (Appendix 12.10). Prednisolone will be provided in countries where prednisone is not available. Per GINA 2012 guidelines, the recommended dose for an acute asthma exacerbation, for self-administration at home, is 1-2 mg/kg/day (maximum dose 60 mg), but the dosage prescribed (the course of steroid treatment will be determined by the prescribing health care provider) is at the investigator's discretion. The subject should be instructed to contact the investigator urgently (immediately) for instructions before initiating treatment, and if the investigator is not immediately available, the subject should start oral prednisone/prednisolone as indicated on the subject's individualized Asthma Action Plan. Any subject with PEF <60% of personal best, or as defined by the subject's Asthma Action Plan, must proceed to the emergency room immediately after taking the prescribed prednisone/prednisolone.

7.1.2.18 PK Sub-trial

At a subset of trial sites, subjects who have signed a specific consent form to participate in the main trial will also have the option to sign a separate informed consent to participate in the Pharmacokinetic (PK) sub-trial. See Appendix 12.5 for details of the PK sub-trial, including objective, design, procedures etc.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in Section 12.4.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 7.

Female subjects of child bearing potential will be required at all visits to perform a urine pregnancy test with a dipstick as well as HCG urine testing. Sites will submit HCG urine testing to the central lab regardless of the outcome from the site performed dipstick testing.

Table 7 Laboratory Tests

Hematology	Chemistry	Urinalysis
Red blood cells (RBCs) Hematocrit Hemoglobin Platelet count WBC (total and differential) Eosinophils Neutrophils Lymphocytes Monocytes Basophils	Albumin Alkaline phosphatase Aspartate aminotransferase (AST; SGOT) Alanine aminotransferase (ALT; SGPT) Bicarbonate Lactate dehydrogenase Calcium Chloride Creatinine Glucose Inorganic Phosphorus Potassium Sodium Total Bilirubin Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal Total protein Blood Urea Nitrogen (BUN) Cholesterol Serum β-Human Chorionic Gonadotropin (β-hCG [if needed to confirm a positive urine pregnancy test])	pH Specific Gravity Protein Glucose Ketones Blood Microscopic exam Urine pregnancy test (beta hCG) (for girls of childbearing potential)

7.1.3.2 Pharmacokinetic/Pharmacodynamics Evaluations

See detail of PK Sub-trial in Appendix 12.5 for PK evaluations. No PK/PD evaluations are planned.

7.1.3.3 Blood Collection for Plasma MK-0887A

Sample collection, storage and shipment instructions for plasma samples for MF are provided in Appendix 12.5 for the PK Sub-trial.

7.1.3.4 Future Biomedical Research

The following specimens are to be obtained as part of Future Biomedical Research:

- Buccal swabs for genomics use.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

Subjects who discontinue/withdraw from treatment prior to completion of the treatment regimen should continue to be monitored in the trial.

When a subject discontinues and withdraws consent from participation in the trial, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Thus, if a subject discontinues from participation in the trial (i.e., withdraws consent) after being given trial medication, a Discontinuation Visit will be performed, if possible, as soon as feasible and any related worksheets will be completed. These worksheets will be completed whether the discontinuation occurs during a regularly scheduled visit, shortly before, or shortly after such a visit. Every attempt should be made to schedule a Discontinuation Visit as soon as possible once a decision to discontinue participation in the trial has been made. A clear evaluation of the patient's condition must be made.

7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com), and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

7.1.4.2 Lost to Follow-up

If a subject fails to return to the clinic for a required study visit and/or if the site is unable to contact the subject, the following procedures are to be performed:

- The site must attempt to contact the subject and reschedule the missed visit. If the subject is contacted, the subject should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the subject at each missed visit (e.g. phone calls and/or a certified letter to the subject's last known mailing address or locally equivalent methods). These contact attempts should be documented in the subject's medical record.
- Note: A subject is not considered lost to follow up until the last scheduled visit for the individual subject. The amount of missing data for the subject will be managed via the pre-specified data handling and analysis guidelines.

7.1.4.3 Blinding/Unblinding

When the investigator or sub-investigator needs to identify the drug used by a subject and the dosage administered in case of emergency e.g., the occurrence of serious adverse experiences, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or sub-investigator the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the sponsor. The emergency unblinding call center will make a record promptly however, the investigator or sub-investigator must enter the intensity of the adverse experiences observed, their relation to study drug, the reason thereof, etc., in the medical chart etc., before unblinding is performed. Subjects whose treatment assignment has been unblinded must be discontinued from study drug, but should continue to be monitored in the trial.

Additionally, the investigator must go into the IVRS system and perform the unblind in the IVRS system to update drug disposition. In the event that the emergency unblinding call center is not available for a given site in this trial, IVRS/IWRS should be used for emergency unblinding in the event that this is required for subject safety.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date and reason) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded.

7.1.4.4 Domiciling

The trial will be conducted in an outpatient clinic setting. Subjects will report to the clinic on the morning of the scheduled visit days, during which trial drug is administered. Following trial drug administration, subjects will continue with additional testing. At the discretion of the investigator, subject may be requested to remain in the clinic longer. See Appendix 12.5 for domiciling requirements for subjects participating in the PK Sub- trial.

7.1.4.5 Calibration of Critical Equipment

The investigator or qualified designee has the responsibility to ensure that any critical device or instrument used for a clinical evaluation/test during a clinical trial that provides important information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained with the study documentation as source documentation at the trial site.

Critical Equipment for this trial includes:

- Spirometer

Please refer to Section 7.1.2.6 for detail on calibration of the spirometer.

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Re- Screening

Approximately 1 week prior to the Run-in Visit, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Screening procedures may be repeated after consultation with the Sponsor.

A subject who has at least one trial procedure performed in addition to signing an informed consent form and is assigned a subject identifier but does not meet one or more criteria required for participation in the trial is classified as a "screen failure". The Interactive Voice/Web Response System (IVRS/IWRS) system used to track trial enrollment must be notified. At a minimum, the following information on subjects who are not randomized must be collected in the eCRF:

- Date screened
- Subject screening number
- Demography (race, age, and gender)
- Reason subject failed screening
- Any Serious Adverse Event (SAE) related to trial procedures or concomitant medications that occurred after signing the informed consent/assent

Per the judgment of the investigator, a subject who is classified as a screen failure may be re-screened once if they do not meet inclusion/exclusion criteria at Visit 1 or Visit 2. A subject may not be rescreened after they have entered the open-label Run-in Period in the trial.

To be dispensed Run-in trial medication, subjects must meet all the relevant entry criteria as of Visit 2. The Sponsor must be notified when subjects who do not meet the entry criteria are incorrectly started on Run-in treatment.

7.1.5.2 Discontinued Subjects Continuing to be Monitored in the Trial

It is intended that all subjects should be followed through completion of the trial, regardless of premature discontinuation of treatment, unless the subject's caregiver withdraws consent. Thus, subjects who discontinue from trial medication prior to completion of the trial should continue to be monitored through the end of the trial, by use of follow-up phone calls, to obtain relevant information. Follow-up phone calls should be made in a timeframe that corresponds to each remaining clinic visit. Such telephone contacts will allow collection of follow-up information, including if any adverse events have occurred, any concomitant medication have been used, and will allow assessment of daily eDiary (IVRS/IWRS) entries, as applicable.

For these subjects who have discontinued trial medication early, sites will be instructed to exert diligent efforts to continue to contact these subjects (and their caregivers). To enable sites to reach subjects/caregivers, the caregivers should provide primary and secondary contact information (e.g., home phone, work phone, mobile phone). Sites must document the outcome of the telephone contact(s), to demonstrate diligent efforts have been made. If a subject/caregiver does not agree to be contacted by phone for follow-up for each of the remaining visits, the subject/caregiver should be encouraged to accept a telephone contact at least at the final visit date (Week 24).

Subjects/caregivers should be asked (and sites must document) the preferred method of follow-up:

- *No on-site trial visits, but **agree to be contacted by telephone**, for **each** remaining clinic visit, **through** **Week 24:*** Investigators may continue to collect trial-related information from available sources, such as medical records.
- *No on-site trial visits and **no telephone contacts** for each remaining clinic visit, **but agree to be contacted at Week 24 only:*** Investigators may continue to collect trial-related information from available sources, such as medical records.
- *No on-site trial visits and **no longer wishes to be contacted:*** No further trial-related contacts will occur. No further data collection will occur. (This final choice should only pertain when the subject's caregiver withdraws consent for further trial participation.)

Additionally, the informed consent form will explain the importance of continued data collection from subjects, including the use of continued contact by phone.

7.1.5.3 Post-Trial

Approximately 14 days after the last regularly scheduled dose of blinded trial therapy or trial end/discontinuation, female subjects of child-bearing potential will be scheduled for a post-trial visit (Visit 9) and will return to the clinic in 14 (±3) days. All male subjects and those female subjects who are not of child-bearing potential will receive a telephone contact for post-trial evaluation.

If the post-trial visit occurs less than 14 days after the last dose of trial drug, a subsequent follow-up phone call should be made at 14 days after the last dose of trial drug to determine if any adverse events have occurred since the post-trial clinic visit.

7.2 Assessing and Recording Adverse Events and Patient/Device Events

An adverse event is defined as 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. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through 14 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Device and/or patient events include all untoward events related to the use of the device or device-like features of a drug delivery system. Device events include any malfunction or deterioration in the characteristics and/or performance of the device, as well as any inadequacy in the labeling or the instructions for use, that led to or could have led to an untoward event for the user or any person. Patient events are adverse events experienced by the subject caused by or suspected to be caused by the device or device-like features of a drug delivery system.

All device or patient events that occur after the consent form is signed but before allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of allocation/randomization through 14 days following cessation of treatment, all device or patient events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all non-serious device or subject events for outcome.

Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

In this trial, an overdose is any dose higher than the dose specified in Section 5.2 of this protocol.

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 14 days following cessation of Sponsor's product must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.3 Immediate Reporting of Adverse Events and Incidents to the Sponsor

7.2.3.1 Serious Adverse Events and Incidents

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a cancer;
- Is associated with an overdose.

Refer to Table 8 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

All subjects with serious adverse events must be followed up for outcome.

An incident is any malfunction or deterioration in the characteristics and/or performance of the device, as well as any inadequacy in the labeling or the instructions for use that, directly or indirectly, led to or could have led to, the death of a subject or user, or of other persons, or to a serious deterioration in their state of health.

A serious deterioration in the state of health can include:

1. Life-threatening illness;
2. Permanent impairment of a body function or permanent damage to a body structure;
3. A condition necessitating medical or surgical intervention to prevent 1 or 2;
4. A condition that requires hospitalization or significant prolongation of existing hospitalization; or
5. Fetal distress, fetal death or any congenital abnormalities or birth defects.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any incident, including follow up to an incident, including death due to any cause, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any incident, or follow-up to an incident, whether or not related to the device, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any incident considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time outside of the time period specified above also must be reported immediately to the Sponsor.

All subjects involved with incidents must be followed up for outcome.

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

3. an asthma exacerbation that results in emergency care (an emergency room visit or hospitalization due to asthma) or treatment with oral corticosteroid use.

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 8. The investigator's assessment of causality is required for each adverse event. Refer to Table 8 for instructions in evaluating adverse events.

Table 8 Evaluating Adverse Events

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities)
Seriousness	A serious adverse event (AE) is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred [Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.]; or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect (**in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a cancer (although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is associated with an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information The following components are to be used to assess the relationship between the Sponsor's product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the Sponsor's product and the AE: (continued)**	
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Sponsor's product in this trial? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following:	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).**	
Yes, there is a reasonable possibility of Sponsor's product relationship.	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.	
No, there is not a reasonable possibility of Sponsor's product relationship	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)	

7.2.5 Sponsor Responsibility for Reporting Adverse Events and Patient/Device Events and Incidents

All Adverse Events and Patient/Device Events and Incidents will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Scientific Advisory Committee

This trial was developed in collaboration with a Scientific Advisory Committee (SAC). The SAC comprises both Sponsor and non-Sponsor scientific experts who provide input with respect to trial design, interpretation of trial results and subsequent peer-reviewed scientific publications.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the trial. If, after the trial has begun, but prior to any unblinding, changes made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the trial. Post hoc exploratory analyses will be clearly identified in the CSR.

8.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Full detail is in the Statistical Analysis Plan (SAP) (Section 8.2).

Table 9 Summary of the Statistical Analysis Plan

Study Design Overview	A phase III, randomized, active-controlled, parallel-group clinical trial to study the efficacy and long-term safety of mometasone furoate / formoterol fumarate (MF/F, MK-0887A [SCH418131]), compared with mometasone furoate (MF, MK-0887 [SCH032088]), in children with persistent asthma
Treatment Assignment	Subjects will be randomized, in a 1:1 ratio, to MF/F 100/10 mcg twice daily or MF 100 mcg twice daily. Randomization will be stratified according to the following factors: Age and Region.

Analysis Populations	Efficacy: Full Analysis Set (FAS) Safety: All Subjects as Treated (ASaT)
Primary Endpoint	AM Post-dose %-predicted FEV_1 (measured during 60 minutes post-dose) averaged across Day 1, Week 1, Week 4, Week 8 and Week 12 of treatment.
Key Secondary Endpoint	Change from baseline (pre-dose on Day 1) in AM post-dose %predicted FEV_1 at 4 and 2 hours, 60, 30, 15, and 5 minutes on Day 1
Statistical Methods for Key Efficacy Analyses	The Primary Hypothesis will be evaluated by comparing MF/F 100/10 mcg twice daily to MF 100 mcg twice daily using a constrained LDA method proposed by Liang and Zeger [6], adjusting for treatment, time, treatment-by-time interaction, age strata (5-to-7 or 8-to-11 years of age, inclusive) and region, after applying a control-based multiple imputation proposed by Ratitch and O'Kelly [7]. MF/F 100/10 mcg twice daily will be considered superior to MF 100 mcg twice daily if the MF/F 100/10 treatment is superior to MF 100 with an observed two-sided p-value ≤ 0.050, which will determine the success of the trial.
Statistical Methods for Key Safety Analyses	Pre-specified Tier-1 AEs include headache, tremor, and tachycardia. Tier-2 AEs include any Asthma Exacerbations; Treatment-Emergent AE, any SAE, any Drug-Related AE, any Serious and Drug-Related AE, any Discontinuations due to AE; and any Specific AEs with incidence $\geq$4 subjects in one of the treatment groups. Tier-1 AEs will be evaluated with p-values and 95% confidence intervals (CI) for between-treatment differences in the percentage of subjects with events using the Miettinen and Nurminen method [8]. Tier-2 AEs will also be evaluated using the Miettinen and Nurminen method, but will only be evaluated with 95% confidence intervals for between-treatment differences in the percentage of subjects.
Interim Analyses	No interim analysis will be performed in this trial.
Multiplicity	The Type-I error rate over the primary and key secondary endpoints will be controlled by a sequential testing procedure.
Sample Size and Power	The planned sample size is 160 subjects for the primary endpoint. The trial has between 77% and 82% power to demonstrate that MF/F 100/10 mcg twice daily is superior to MF 100 mcg twice daily at an overall two-sided 5% alpha-level, if the underlying treatment difference is 4.2 percentage-points. The range of power is a reflection of the potential impact of a control-based imputation applied to the analysis dataset prior to analysis.

8.2 Statistical Analysis Plan

The statistical analysis of the data obtained from this trial will be the responsibility of the designee/ Clinical Biostatistics department of the SPONSOR.

This trial will be conducted as a double-blind trial under in-house blinding procedures.

8.2.1 Hypothesis/Estimation

Objectives and hypotheses of the trial are stated in Section 3.0.

8.2.2 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and/or between-treatment differences are summarized in Section 8.1.

8.2.2.1 Derivations of Efficacy Endpoints

Evaluations of the primary endpoint, AM post-dose %-predicted FEV_1 as measured during 60 minutes post-dose, are scheduled at Day 1, Week 1, Week 4, Week 8 and Week 12. Assignment of scheduled evaluations will use visit windows as: Week 1 evaluation, ± 3 days; Week 4, ± 1 week; and Week 8 and 12 evaluations, ± 2 weeks.

The primary endpoint will be derived at each visit by first calculating an AUC using the trapezoid rule. Trapezoids will be derived and summed across 0-5, 5-15, 15-30, and 30-60 minute time intervals. To preserve the units for analysis, the AUC will be divided by the total time interval: 60 minutes for subjects with a complete 60-minute evaluation, and less than 60 minutes for those who discontinue the evaluation series early. This will ensure the post-dose %-predicted FEV1 is standardized to the same percentage units as the baseline pre-dose evaluation. Interim missing serial evaluations will be imputed using linear interpolation prior to the calculation of the AUC. Derivation of the post-dose %-predicted FEV1 when measured during 4 hours post-dose at Day 1 and Week 12 will be performed in a similar manner.

For the calculation of baseline for the primary endpoint, the mean of two pre-dose measures of %-predicted FEV1 (at -30 minutes and 0 minutes pre-dose) will be calculated. If one of the two evaluations is missing, baseline will consist of the remaining non-missing evaluation. For visit endpoints, if a subject discontinues early and the final visit evaluation is performed outside of a visit window, that evaluation will be carried forward into the next scheduled visit window.

Total daily short-acting beta-agonist (SABA) usage (as needed by the subject) will be collected across the 24-week Double-blind Treatment Period. Data collected during the first 12 weeks will be analyzed as a secondary efficacy endpoint, while data collected during the second 12 weeks are to be used by the investigator to help assess safety. There are two sources of SABA inhalation: 1) a handheld MDI and 2) a nebulizer. For computing the daily totals, one nebulizer administration is equivalent to 4 inhalations (“puffs”) of a handheld MDI.

8.2.2.2 Derivations of Safety Endpoints

For vital sign parameters, changes are based on subtracting the most recent pre-treatment value from the on-treatment value.

8.2.3 Analysis Populations

8.2.3.1 Efficacy Analysis Population

The Full Analysis Set (FAS) will be used for the efficacy analysis. This population includes all subjects that are as close as possible to the ideal implied by the intention-to-treat principle. This set is derived from the set of all subjects that received randomized treatment assignment by minimal and justified exclusion of subjects. For this trial, the FAS includes subjects who have received at least one dose of randomized trial medication with at least one primary efficacy evaluation across the 12-week efficacy period.

8.2.3.2 Safety Analysis Population

All Subjects as Treated (ASaT) population will be used for assessments of safety and tolerability. The ASaT population consists of all randomized subjects who receive at least one dose of trial medication. For the analysis of safety data using the ASaT population, subjects will be included in the treatment group corresponding to the trial medication they actually received. For most subjects, this will be the treatment group to which they are randomized. Subjects who take incorrect trial medication for the entire treatment period will be included in the treatment group corresponding to the trial medication actually received.

8.2.4 Statistical Methods

Statistical methods for the analysis of efficacy endpoints are provided in Section 8.2.4.1. Statistical testing and inference for safety analyses are described in Section 8.2.4.3. Efficacy results that will be considered to be statistically significant after consideration of the strategy for controlling the Type I error are described in Section 8.2.5. Nominal p-values will be computed for other efficacy analyses as a measure of strength of association between the endpoint and the treatment effect, rather than as formal tests of hypotheses (i.e., these nominal p-values are not controlled for multiplicity). Unless otherwise stated, all statistical tests will be conducted at the overall two-sided 5% alpha-level.

8.2.4.1 Statistical Methods for Efficacy Analysis

The primary efficacy variable is the AM post-dose %-predicted FEV_1 as measured during 60 minutes post-dose, analyzed as the change from AM pre-dose %-predicted FEV_1, and averaged across Day 1, Week 1, Week 4, Week 8 and Week 12 of treatment for the comparison of the MF/F 100/10 twice daily with MF 100 twice daily. For subjects in the MF/F group who are missing the %-predicted FEV_1 data, the missing data will be imputed based on the MF group data. For subjects in the MF group, missing data will be imputed using the MAR assumption. See below for details of imputations.

8.2.4.1.1 Applying a Control-based Multiple Imputation

Prior to analysis, a control-based multiple-imputation will be applied to the analysis dataset of the primary efficacy variable. This imputation method includes implementation of a pattern mixture model approach using PROC MI in SAS® with a control-based pattern multiple imputation proposed by Ratitch and O'Kelly [7]. Given the visit schedule, the analysis dataset is expected to have a non-monotone missing-data pattern. Some subjects will have missing FEV1 evaluations at intermediate visits with data available at subsequent visits, other subjects will have all data missing subsequent to dropout (a monotone missing-data pattern), and still other subjects will have a combination of these two missing-data patterns. Therefore, missing-data imputation will be performed in two steps.

- First, interim visits will be imputed using the Monte Carlo Markov Chain (MCMC) method assuming a multivariate normal distribution, under the assumption of missing at random (MAR). This method is justified by the fact that those subjects with missing data who return to the clinic for subsequent FEV1 evaluations are most likely not missing data due to lack of efficacy, so their interim missing data are independent of the unobserved values, after accounting for the observed values in the imputation. Multiple monotone missing datasets are generated under this first step.
- Next, each of the monotone missing datasets will be imputed step-wise by missing visit. Imputation will only consider all subjects in the MF (control) arm, and those subjects in the MF/F treatment arm who have missing observations in that visit. This approach assumes all subjects who drop out follow a pattern of treatment response similar to MF, as such subjects are assumed to not respond to the additive effect of F in the MF/F treatment arm, supporting a zero treatment difference assumption between MF and MF/F. To assign the subjects included in each step, MF/F treatment subjects will be partitioned into cohorts based on the timing of their dropout, and combined with all the subjects in the MF treatment at each step. Therefore, imputations will be performed in five steps; one step for each missing data visit: Day 1, Week 1, Week 4, Week 8, and Week 12. At each step, after the MF/F treatment subject missing data is imputed, those MF/F subjects excluded from the imputation step are added to the imputed subjects for a complete subject dataset. This complete subject dataset is considered for the next step.

Once all visits are imputed, each completely imputed dataset will be analyzed using a constrained longitudinal data analysis (cLDA) method proposed by Liang and Zeger [6]. This method assumes a common mean across treatment groups at baseline and a different mean for each treatment at each of the post-baseline time points. Time is treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. In the model, the response vector consists of baseline and the values observed at each post-baseline time point. The analysis model will adjust for treatment, time, treatment-by-time interaction, age stratum (5- to-7 or 8-to-11 years of age, inclusive) and region (US, ex-US). An unstructured covariance matrix will be used to model the correlation among repeated measurements. Although the baseline measurement is included in the response

vector, it is independent of treatment, and hence, the baseline means are constrained to be the same for different treatment groups.

The results of the cLDA for each completely imputed dataset will be combined into an overall result by applying the MIANALYZE procedure.

The same method of analysis, using the cLDA with control-based multiple-imputation, will be applied to the key secondary endpoint (i.e., serial FEV_1 data on Day 1). Analyses of other efficacy endpoints will be based on the cLDA approach without imputation. Table 9 summarizes the efficacy analyses.

Table 10 Summary of Efficacy Analyses

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoint			
Change from baseline AM post-dose %-predicted FEV_1 as measured during 60 minutes post-dose, averaged across Day 1, Week 1, Week 4, Week 8 and Week 12 of treatment	cLDA† with Multiple Imputation	FAS	Control-based Imputation‡
Key Secondary Endpoint			
Change from baseline AM post-dose %-predicted FEV_1 at 4 and 2 hours, 60, 30, 15 and 5 minutes post-dose on Day 1 of treatment	cLDA† with Multiple Imputation	FAS	Control-based Imputation‡
Other Secondary Endpoints			
Change from baseline AM post-dose %-predicted FEV_1 as measured during 4 hour post-dose, at Day 1 and Week 12 of treatment	cLDA†	FAS	Model-based (MAR)
Change from baseline in AM pre-dose %-predicted FEV_1 averaged across Week 4, Week 8 and Week 12 of treatment	cLDA†	FAS	Model-based (MAR)
Change from baseline in total daily SABA use across the first 12-weeks of treatment	cLDA†	FAS	Model-based (MAR)
Characterize the plasma PK profile of MF	cLDA†	FAS	Model-based (MAR)

† Constrained Longitudinal Data Analysis model with terms for treatment, time, treatment-by-time interaction, age stratum (5-to-7 or 8-to-11 years of age, inclusive) and region
‡Pattern Mixture Model proposed by Ratitch and O'Kelly

8.2.4.1.2 Missing-Data Sensitivity Analyses

The primary analysis incorporates imputations of missing data. Additional, sensitivity analyses will be performed to further examine the impact of missing data on study results using imputation methods other than that used in primary analysis. The description of these sensitivity analyses is as follows:

Constrained Longitudinal Data Analysis without Multiple Imputation

This analysis will be performed using a constrained longitudinal data analysis (cLDA) method proposed by Liang and Zeger [6] without multiple imputation, and thus will rely on the model for handling of missing data. The cLDA model will adjust for the same covariates as those applied to the control-based imputation datasets in the primary analysis. Given this model relies on the missing-at-random assumption (MAR), the results of this sensitivity analysis can be compared to the control-based imputation primary and key secondary analyses to assess the impact of early dropouts. Details of the model specification, assumptions, and SAS implementation codes are given in Appendix 12.12.

Tipping-point Multiple-imputation Analysis

Sensitivity analysis using a pattern-mixture model, and based on the tipping-point approach, will be used to assess the robustness of the control-based imputation primary approach. For a given constant, c, the tipping-point analysis is conducted in a fashion similar to that used in standard multiple imputation, whereby m complete datasets are randomly generated using the original observed dataset [9]; [10]; [11]. These m complete datasets are subsequently analyzed using the primary model, and the results of those analyses are then combined. This procedure will be repeated (using the same m imputed datasets) until the smallest c is found such that the significant result turns non-significant (i.e., $p \geq 0.050$). This tipping-point value c provides a measure of robustness of the primary result. A relatively large value of c implies better robustness of the primary analysis against the impact of missing data in the trial. It is noted that when $c=0$, the tipping-point analysis described above corresponds to an analysis conducted under the assumption that the missing data are MAR. For values of c larger than 0, the tipping point analyses do not assume that the missing values follow a MAR mechanism. In fact, the analysis is based on a special MNAR mechanism in which all missing data in the MF/F treatment arm are assumed to have a worse response by a constant amount of c than the values would have had under MAR, while the missing data in the MF control arm are assumed to be the same as that obtained under MAR. The search for tipping point will be performed separately over a grid of varying shift values in the MF control arm. Note that this grid will include negative and positive values in order to allow both worsenings and improvements in the control arm. Note also that the search for tipping point will include cases where dropouts in the MF/F treatment arm have worse outcomes than those in the MF control arm.

Additional Imputation Analyses

To further evaluate the robustness of the primary results, additional sensitivity analyses will be performed to reflect different reasons for discontinuation, and possibly treatment groups, as factors in the imputation steps, ensuring that lack of efficacy is not imputed as treatment success in these algorithms.

Additional computational details of sensitivity analyses to address missing data will be provided in the supplemental SAP (sSAP).

8.2.4.2 Other Analysis

Analysis of the PK Sub-trial is provided in Appendix 12.5.

8.2.4.3 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, Asthma Exacerbations and vital signs measurements. Tier 1 and Tier 2 safety summaries will be provided, in addition, the number and percentage of subjects will be reported for AEs, SAEs, drug-related AEs, and discontinuations due to AEs.

Continuous measures such as changes from baseline (or percent change from baseline as appropriate) in vital signs will be summarized in table format by treatment group/arm, and as a pooled group for measurements upon completion of the trial or early discontinuation of the trial. For subjects who discontinue trial medication early, their off-treatment safety data will be summarized separately. Baseline for vital signs will be defined based on the last available measurement prior to randomization.

The analysis of safety results will follow a tiered approach (Table 10). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse experiences of special interest that are identified *a priori* constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance, with p-values and 95% confidence intervals provided for between-group comparisons.

Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates, with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

Adverse experiences (specific terms as well as system organ class terms) and predefined limits of change in vital signs that are not pre-specified as Tier-1 endpoints will be classified as belonging to either "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least 4 subjects in any treatment group exhibit the event; all other AEs and predefined limits of change (PDLC) will belong to Tier 3. The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences.

Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse experiences and predefined limits of change.

Continuous measures, such as changes from baseline in vital signs that are not pre-specified as Tier-1 endpoints, will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

P-values (Tier 1 only) and 95% confidence intervals (Tier 1 and Tier 2) will be provided for between-treatment differences in the percentage of subjects with events; these analyses will be performed using the Miettinen and Nurminen method (1985) [8], an unconditional, asymptotic method. If events do not meet minimum frequency criteria, as determined by the commonly occurring event definition, only point estimates will be provided. The analysis strategy for safety parameters is provided in Table 10

Table 11 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint†	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	Headache	X	X	X
	Tremor	X	X	X
	Tachycardia	X	X	X
Tier 2	Any Treatment Emergent AE		X	X
	Any SAE		X	X
	Any Drug-Related AE		X	X
	Any Serious and Drug-Related AE		X	X
	Discontinuation due to AE		X	X
	Specific AEs‡ (incidence ≥4 subjects in one of the treatment groups)		X	X
	Asthma Exacerbations		X	X
Tier 3	Specific AEs‡ (incidence <4 subjects in all of the treatment groups)			X
	Change from Baseline Results (Vital Signs)			X

†Adverse Experience references refer to both Clinical and Laboratory AEs.
‡Includes only those endpoints not pre-specified as Tier 1 or not already pre-specified as Tier-2 endpoints.
SOC=System Organ Class; X = results will be provided.

8.2.4.4 Summaries of Baseline Characteristics and Demographics

Demographic variables (sex, race, age, weight, height, etc., and other baseline characteristics such as asthma, previous asthma therapy, reversibility, and %-predicted FEV_1) will be summarized by treatment group. No inferential analysis of these data is planned.

8.2.5 Multiplicity

The step-down approach for multiplicity will be applied to the primary and key secondary endpoint. If success of the primary endpoint is met (i.e., MF/F 100/10 mcg twice daily is superior to MF 100 mcg twice daily with an observed two-sided p-value ≤0.050), then the success of the key secondary endpoint will be tested. The key secondary endpoint will be assessed sequentially for the comparison of MF/F 100/10 mcg twice daily to MF 100 mcg twice daily in the following order: 4 hours, 2 hours, followed by 60, 30, 15, and 5 minutes. Using this sequential approach, the onset of action of MF/F will be determined as the earliest time point with a two-sided p-value ≤0.050..

Other secondary endpoints are supportive in nature and are not controlled for multiplicity. Therefore, observed p-values are nominal, as discussed in Section 8.2.4.

8.2.6 Justification of Sample Size

8.2.6.1 Sample-size Calculation for the Primary Analysis (using Multiple Imputation)

Power/sample size was calculated under two scenarios: the primary analysis (using control-based imputation), and the sensitivity analysis (under the MAR assumption).

The resulting power for the primary analysis was estimated to be approximately 77% under the worst-case 5% reduction in the mean treatment difference, given a sample size of 160, with 80 subjects in each arm. Therefore, depending on the impact of missing data in this trial, power is expected to range from 82% down to 77% under the control-based multiple imputation primary analysis method. Details of power calculation are provided below.

To estimate the sample size and power for this trial, the following process was adopted:

- First, in order to assess the magnitude of reduction in the mean treatment difference from a missing-at-random based cLDA approach (without multiple imputation, see Section 8.2.6.2) to the control-based imputation cLDA approach, the primary analysis method using control- based multiple imputation was applied to each of four previous MF/F adult studies. The four studies included asthma studies (P04073 and P04334), and COPD studies (P04229 and P04230), which were selected for this estimation exercise based on similarities to this trial in visit scheduling and FEV_1 endpoints, as well as the available comparison of MF/F versus MF at the same dose of MF. Two endpoints were considered in the evaluation across a multiple- evaluation visit schedule: FEV_1 AUC and pre-dose FEV_1. Across the four studies and the two endpoints, the reduction in treatment difference did not exceed ~5% of the missing-at- random cLDA treatment difference.

- Next, the sample size for this trial was calculated under the missing-at-random cLDA analysis (without multiple-imputation) assuming, among other parameters, the effect size of 4.2% of predicted FEV_1, resulting in ~82% power at the two-sided 5% level of significance (discussed in Section 8.2.6.2 below).
- Finally, taking into consideration a reduction of treatment difference in this trial similar to that noted in the four adult trials, the power was recalculated under the same assumptions for all other parameters. Sample-size Calculation for the cLDA Analysis (without Multiple Imputation)

Approximately 355 subjects will be screened (assuming a screen-failure rate of 55%) in order to randomize 80 subjects into the MF/F arm and 80 subjects into the MF arm. With at least 160 total randomized subjects in the analysis, assuming a pooled standard deviation of 9.0% derived from an unstructured covariance matrix for the efficacy evaluations repeated across the visit schedule, a true mean treatment difference of 4.2 percentage-point difference (MF/F compared with MF) in AM post-dose %-predicted FEV_1 measured during 60 minutes post-dose will be detectable with a power of ~82% and two-sided 5% level of significance. The following pattern of discontinuation was assumed in the calculation of the total sample size for estimating the power: 0, 2%, 10%, 15%, and 20% for each of the two treatment arms at Day 1, Week 1, Week 4, Week 8 and Week 12, respectively.

The target effect size of 4.2 percentage-point difference is supported by the results of a previous pediatric trial P06476 (a Phase II single-dose trial to evaluate spacer use), in which MF/F 100/10 mcg, F 10 mcg, and placebo were evaluated over 12 hours on Day 1 of dosing. An average across the first hour of this evaluation in P06476 was derived to match the primary endpoint in this current trial. An effect size of 4.5 percentage points for the AM %-predicted FEV_1 measured during 60 minutes post-dose was observed for the comparison of MF/F 100/10 mcg to placebo (in change from baseline) in P06476. This effect size can be used to estimate the comparison of MF/F to MF on Day 1 because the effect of MF is expected to be none to minimal after only one day of dosing, and the current trial includes a run-in on MF prior to randomization. Given the pediatric trial was only 1 day in duration and used a cross-over design, data from a similarly designed adolescent and adult 12-week trial (P04073) was used to generate an adjusted covariance matrix to match the estimate of 9.0% for the pooled standard deviation across a 12- week evaluation period. This pooled standard deviation was observed in a previous 12-week pediatric trial (C98005) comparing MF 100 mcg to placebo in AM pre-dose %-predicted FEV_1, and is expected to be similar to the pooled standard deviation of the AM %-predicted FEV_1 measured during 60 minutes post-dose to be evaluated in this current trial, based on comparing pooled standard deviations between these two FEV_1 endpoints in P04073 (i.e., comparing MF/F 100/10 mcg to MF). Assumptions for the pattern of discontinuations over time are based on examining the drop-out patterns observed in the two 12-week trials; C98005 in the pediatric subjects and P04073 in the adolescent and adult subjects. Finally, the magnitude of the effect size is expected to be similar across visits, given the bronchodilator effect of F is expected to reach maximal efficacy after 1 hour with a

sustained effect throughout the 12-week treatment period.

Due to the inherent variability of FEV_1 evaluations across asthma populations, there is no universally accepted clinically meaningful difference. However, effect sizes of ~5 percentage- point difference have been accepted as evidence of efficacy in regulatory submissions, and have been observed in both pediatric trials P06476 (as a 12-hour evaluation comparing MF/F to placebo on Day 1 for the bronchodilator effect), and in C98005 (as AM pre-dose evaluation comparing MF to placebo at Week 12 for the steroid effect). Therefore, a target effect size of 4.2 percentage points is reasonable since the comparison of MF/F is to MF (not placebo), and since the one hour duration for the primary endpoint does not include later evaluations (2 and 4 hours) which have larger formoterol effects than the effects prior to 1 hour evaluation.

8.2.7 Subgroup Analyses and Effect of Baseline Factors

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoint will be estimated and plotted within each category of the following classification variables. (The primary method of analysis, control-based imputation, will be used for calculating the treatment effects and CI's across subgroups.) :

- Age category (5 to 7 years vs. 8 to 11 years)
- Sex (female, male)
- Race (white, non-white)
- Region

Subgroup plots may exclude categories which accrue <15% of the FAS subjects (i.e. < 24 out of 160 subjects) as the exploration of such small sample sizes are considered to be non-informative in nature.

8.2.8 Interim Analyses

No interim analyses are planned for this trial.

8.2.9 Compliance (Medication Adherence)

In this trial, as part of the routine recording of the amount of trial treatment taken by each subject, the number of inhalations ("puffs") of trial medication will be reviewed and recorded at regular intervals. These results will be used to calculate subject compliance.

A subject will be considered 100% compliant only if usage of exactly 4 puffs of trial medication per day is recorded on the eCRF. Therefore, the rate of compliance will be a function of the total number of puffs while on therapy, to be calculated using the following formula:

> Percent Compliance = 100 x the recorded number of puffs of trial medication while on therapy, divided by the expected number of puffs while on therapy.

The days on therapy includes the interval of days from randomization to the last day of dose of trial medication, whether the subject completes the full scheduled trial regimen or discontinues early. Days of follow-up after discontinuation of trial treatment are not included in the compliance calculation (e.g., follow-up on pregnancy).

Summary statistics will be provided on percent-compliance by treatment group for the FAS population.

8.2.10 Extent of Exposure

Duration of subject exposure to randomized treatment will be summarized, by treatment group, across intervals of time through the last observed exposure weekly interval; In addition, summary statistics (n, median, minimum and maximum) for duration (in days) will be provided.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by the Sponsor as summarized in Table 12.

Table 12 Product Descriptions

Product Name & Potency	Dosage Form
Mometasone furoate 50 mcg	Metered Dose Inhaler (MDI)
Mometasone furoate / formoterol fumarate 50/5 mcg	Metered Dose Inhaler (MDI)
MDI Placebo (Trainer)	Metered Dose Inhaler (MDI)

All other supplies not indicated in Table 12 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the trial site, subsidiary or designee every attempt will be made to source these supplies from a single lot/batch number. The trial site will be responsible for recording the lot number, manufacturer and expiry date of any locally purchased product.

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Supplies will be packaged as kits where each kit will contain 1 inhaler. At the Run-in visit, each patient will be dispensed an open label kit of mometasone furoate 50 mcg MDI. Blinded, monthly kits will be provided to all randomized subjects during the treatment period. Subjects will be dispensed sufficient kits to support their visit interval plus back-up inhalers as required.

9.3 Clinical Supplies Disclosure

The emergency unblinding call center will use the randomization schedule for the trial to unblind subjects and to unmask treatment. In the event that the emergency unblinding call center is not available for a given site in this trial, the central electronic randomization system (IVRS/IWRS) should be used in order to unblind subjects and to unmask treatment/vaccine identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies to the emergency unblinding call center.

Treatment identification information is to be unmasked ONLY if necessary for the welfare of the subject. Every effort should be made not to unblind the subject unless necessary.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date and reason) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded to treatment assignment. Subjects whose treatment assignment has been unblinded (by the investigator, Merck subsidiary, or through the emergency unblinding call center) must be discontinued from study drug, but should continue to be monitored in the trial.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

9.6 Standard Policies

Trial site personnel will have access to a central electronic randomization system (IVRS/IWRS system) to allocate subjects, to assign treatment to subjects and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;
2. hospital or clinic address and telephone number;
3. curriculum vitae or other summary of qualifications and credentials; and
4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC member that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor or through a secure password-protected electronic portal provided by the

Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last

approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this trial or its results to those registries

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees

to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

11.0 LIST OF REFERENCES

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate subjects, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC review

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect subject safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck will approve the subject informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck does not pay incentives to enroll subjects in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The DNA specimen(s) collected in the current trial will be used to study various causes for how subjects may respond to a drug/vaccine. The DNA specimen(s) will be stored to provide a resource for future trials conducted by Merck focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by Merck or designees and research will be monitored and reviewed by a committee of our scientists and clinicians.

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

All subjects enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-trial.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons. Information contained on the consent form alone cannot be traced to any specimens, test results, or medical information once the specimens have been rendered de-identified.

Subjects are not required to participate in the Future Biomedical Research sub-trial in order to participate in the main trial. Subjects who decline to sign the Future Biomedical Research informed consent will not have the specimen collected nor will they be discontinued from the main trial.

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository. Each consent will be assessed for appropriate specimen permissions.

Each informed consent approved by an ethics committee is assigned a unique tracking number. The tracking number on this document will be used to assign specimen permissions for each specimen into the Entrusted Keyholder's Specimen Database.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of both consent and acquisition of Future Biomedical Research specimens will be captured in the electronic Case Report Forms (eCRFs). Reconciliation of both forms will be performed to assure that only appropriately-consented specimens are used for this sub-trial's research purposes. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen Collections

Buccal swab specimens for DNA isolation will be obtained at a time when the subject is having other trial procedures conducted. Specimens like tissue and bone marrow will usually be obtained at a time when the subject is having such a procedure for clinical purposes.

Specimens will be collected and sent to the laboratory designated for the trial where they will be processed (e.g., DNA or RNA extraction, etc) following the Merck approved policies and procedures for specimen handling and preparation.

If specimens are collected for a specific genotype or expression analysis as an objective to the main trial, this analysis is detailed in the main body of this protocol (**Section 8.0 – Statistical Analysis Plan**). These specimens will be processed, analyzed, and the remainder of the specimen will be destroyed. The results of these analyses will be reported along with the other trial results. A separate specimen will be obtained from properly-consented subjects in this protocol for storage in the biorepository for Future Biomedical Research.

4. Confidential Subject Information for Future Biomedical Research

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing subject characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, Merck has developed secure policies and procedures. All specimens will be de-identified as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens for transfer to the storage facility. This first code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between subject identifiers and this first unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

This first code will be replaced with a second code at a Merck designated storage/lab facility. The second code is linked to the first code via a second key. The specimen is now double coded. Specimens with the second code are sometimes referred to as de-identified specimens. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code. Access to both keys would be needed to link any data or specimens back to the subject's identification.

The second code is stored separately from the first code and all associated personal specimen identifiers. A secure link, the second key, will be utilized to match the second code to the first code to allow clinical information collected during the course of the trial to be associated with the specimen. This second key will be transferred under secure procedures by the Merck designated facility to an Entrusted Keyholder at Merck. The second code will be logged into the primary biorepository database at Merck and, in this database, this identifier will not have identifying demographic data or identifying clinical information (i.e., race, sex, age, diagnosis, lab values) associated with it. The specimen will be stored in a designated biorepository site with secure policies and procedures for specimen storage and usage.

The second key can be utilized to reconstruct the link between the results of future biomedical research and the clinical information, at the time of analysis. This linkage would not be possible for the scientist conducting the analysis, but can only be done by the Merck Entrusted Keyholder under strict security policies and procedures. The Merck Entrusted Keyholder will link the information and then issue a de-identified data set for analysis. The only other circumstance by which future biomedical research data would be directly linked to the full clinical data set would be those situations mandated by regulatory authorities (e.g., EMEA, FDA), whereby this information would be directly transferred to the regulatory authority.

5. Biorepository Specimen Usage

Specimens obtained for the Merck Biorepository will be used for analyses using good scientific practices. However, exploratory analyses will not be conducted under the highly validated conditions usually associated with regulatory approval of diagnostics. The scope of research performed on these specimens is limited to the investigation of the variability in biomarkers that may correlate with a clinical phenotype in subjects.

Analyses utilizing the Future Biomedical Research specimens may be performed by Merck, or an additional third party (e.g., a university investigator) designated by Merck. The investigator conducting the analysis will be provided with double coded specimens. Re-association of analysis results with corresponding clinical data will only be conducted by the Merck Entrusted Keyholder. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-trial. Future Biomedical Research specimens remaining with the third party after the specific analysis is performed will be returned to the sponsor or destroyed and documentation of destruction will be reported to Merck.

6. Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact Merck using the designated mailbox (clinical.specimen.management@merck.com) and a form will be provided by Merck to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from Merck to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction can not be processed.

7. Retention of Specimens

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from acquisition. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Merck designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Merck policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Separate databases for specimen information and for results from the Future Biomedical Research sub-trial will be maintained by Merck. This is done to separate the future exploratory test results (which include genetic data) from the clinical trial database thereby maintaining a separation of subject number and these results. The separate databases are accessible only to the authorized Sponsor and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based in international standards (e.g., ISO17799) to protect against unauthorized access. The Merck Entrusted Keyholder maintains control over access to all specimen data. These data are collected for future biomedical research purposes only as specified in this sub-trial will not be used for any other purpose.

9. Reporting of Future Biomedical Research Data to Subjects

There is no definitive requirement in either authoritative ethical guidelines or in relevant laws/regulations globally that research results have to be, in all circumstances, returned to the trial participant. Some guidelines advocate a proactive return of data in certain instances. No information obtained from exploratory laboratory studies will be reported to the subject or family, and this information will not be entered into the clinical database maintained by Merck on subjects. Principle reasons not to inform or return results to the subject include: lack of relevance to subject health, limitations of predictive capability, concerns of misinterpretation and absence of good clinical practice standards in exploratory research typically used for diagnostic testing.

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information as to how to offer clinical diagnostic testing (paid for by Merck) to subjects enrolled and will be advised that counseling should be made available for all who choose to participate in this diagnostic testing.

If any exploratory results are definitively associated with clinical significance after completion of a clinical trial, Merck will publish the results without revealing specific subject information, inform all trial sites who participated in the Merck clinical trial and post anonymized results on our website or other accredited website(s) that allow for public access (e.g., disease societies who have primary interest in the results) in order that physicians and patients may pursue clinical diagnostic testing if they wish to do so.

10. Gender, Ethnicity and Minorities

Although many diagnoses differ in terms of frequency by ethnic population and gender, every effort will be made to recruit all subjects diagnosed and treated on Merck clinical trials for future biomedical research. When trials with specimens are conducted and subjects identified to serve as controls, every effort will be made to group specimens from subjects and controls to represent the ethnic and gender population representative of the disease under current investigation.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. Buccal swab specimens will be collected inside the cheek with no associated venipuncture to obtain the specimen. Therefore, there will not be an additional risk for the subject.

Merck has developed strict security, policies and procedures to address subject data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

It is necessary for subject-related data (i.e., ethnicity, diagnosis, drug therapy and dosage, age, toxicities, etc.) to be re-associated to double coded specimens at the time of data analysis. These subject data will be kept in a separate, secure Merck database, and all specimens will be stripped of subject identifiers. No information concerning results obtained from future biomedical research will be entered into clinical records, nor will it be released to outside persons or agencies, in any way that could be tied to an individual subject.

12. Self-Reported Ethnicity

Subjects who participate in future biomedical research will be asked to provide self-reported ethnicity. Subjects who do not wish to provide this data may still participate in future biomedical research.

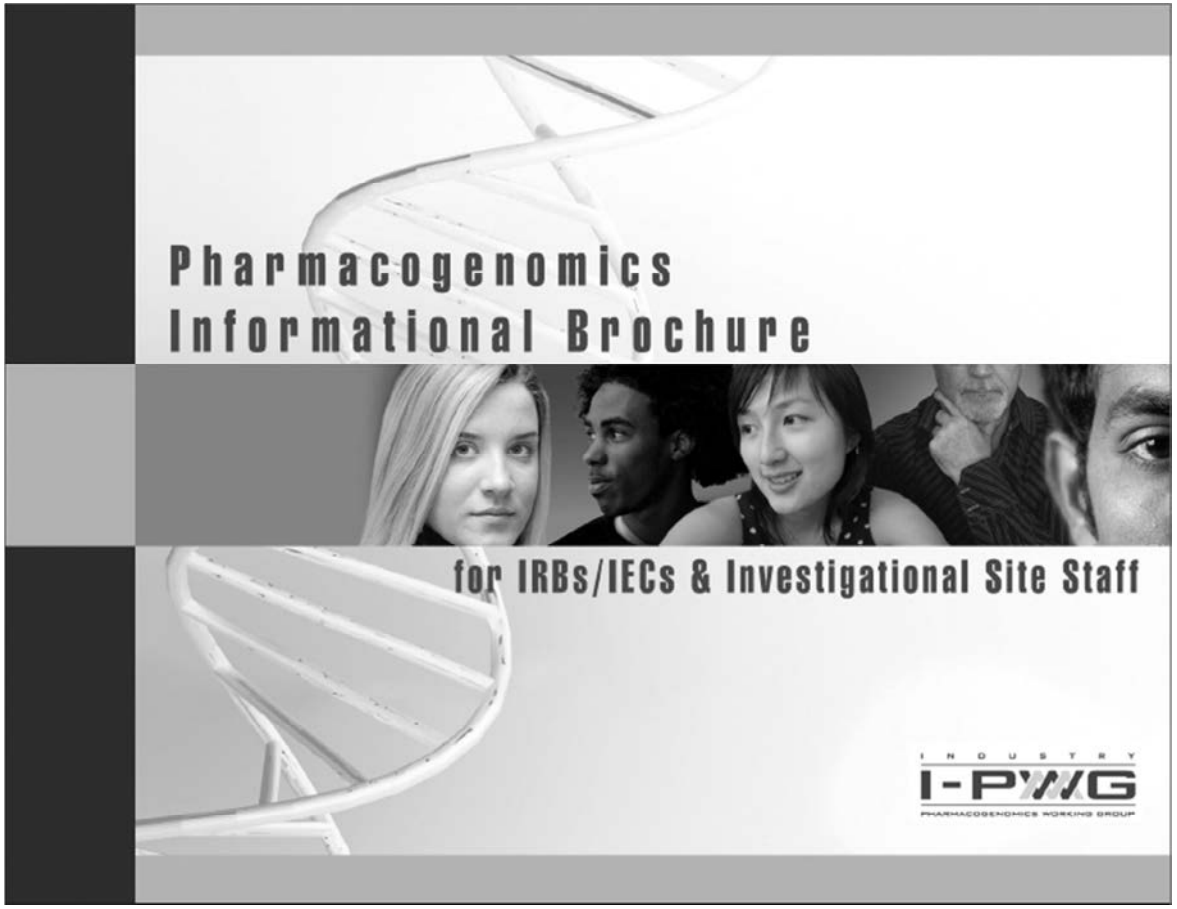
13. Questions

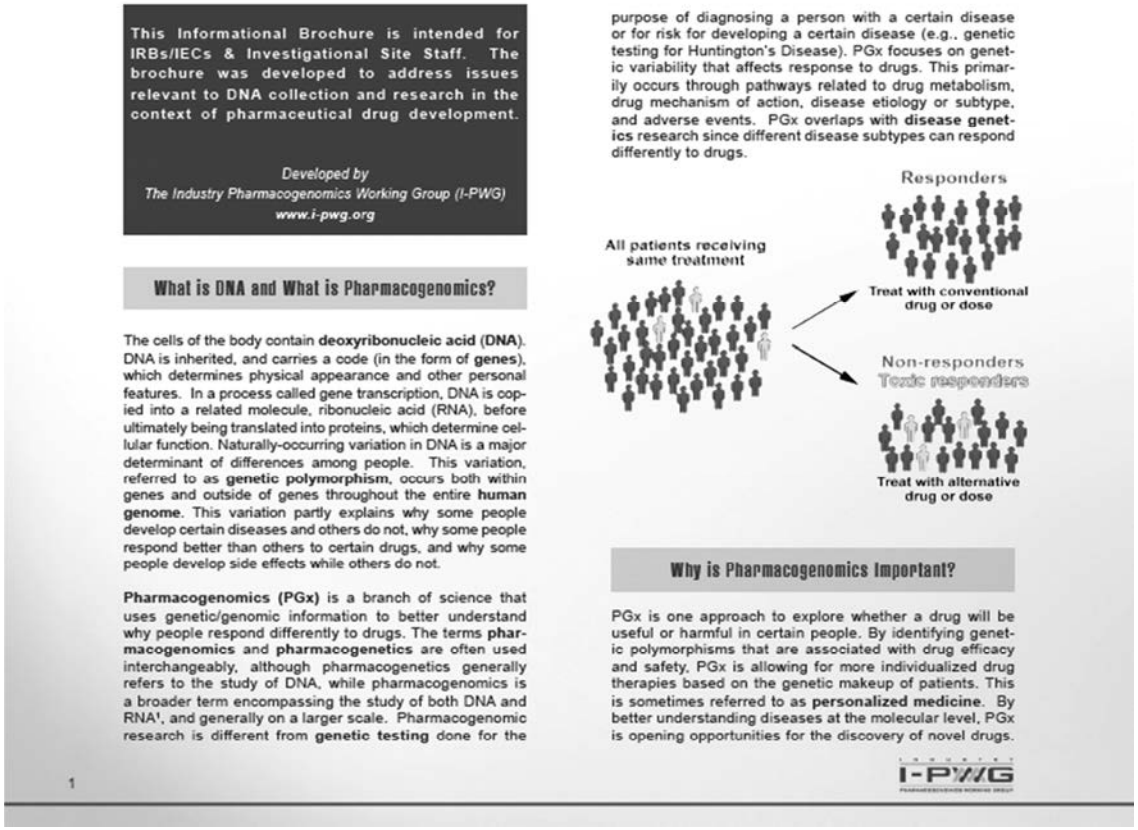
Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

14. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf

12.3 Pharmacogenetics Informational Brochure for IRBs/IECs & Investigational Site Staff





This Informational Brochure is intended for IRBs/IECs & Investigational Site Staff. The brochure was developed to address issues relevant to DNA collection and research in the context of pharmaceutical drug development.

Developed by
The Industry Pharmacogenomics Working Group (I-PWG)
www.i-pwg.org

What is DNA and What is Pharmacogenomics?

The cells of the body contain **deoxyribonucleic acid** (**DNA**). DNA is inherited, and carries a code (in the form of **genes**), which determines physical appearance and other personal features. In a process called gene transcription, DNA is copied into a related molecule, ribonucleic acid (RNA), before ultimately being translated into proteins, which determine cellular function. Naturally-occurring variation in DNA is a major determinant of differences among people. This variation, referred to as **genetic polymorphism**, occurs both within genes and outside of genes throughout the entire **human genome**. This variation partly explains why some people develop certain diseases and others do not, why some people respond better than others to certain drugs, and why some people develop side effects while others do not.

Pharmacogenomics (PGx) is a branch of science that uses genetic/genomic information to better understand why people respond differently to drugs. The terms **pharmacogenomics** and **pharmacogenetics** are often used interchangeably, although pharmacogenetics generally refers to the study of DNA, while pharmacogenomics is a broader term encompassing the study of both DNA and RNA[1], and generally on a larger scale. Pharmacogenomic research is different from **genetic testing** done for the purpose of diagnosing a person with a certain disease or for risk for developing a certain disease (e.g., genetic testing for Huntington's Disease). PGx focuses on genetic variability that affects response to drugs. This primarily occurs through pathways related to drug metabolism, drug mechanism of action, disease etiology or subtype, and adverse events. PGx overlaps with **disease genetics** research since different disease subtypes can respond differently to drugs.

Why is Pharmacogenomics Important?

PGx is one approach to explore whether a drug will be useful or harmful in certain people. By identifying genetic polymorphisms that are associated with drug efficacy and safety, PGx is allowing for more individualized drug therapies based on the genetic makeup of patients. This is sometimes referred to as **personalized medicine**. By better understanding diseases at the molecular level, PGx is opening opportunities for the discovery of novel drugs.

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PGx has the overarching goal of developing safer, more effective drugs, and ensuring that patients receive the correct dose of the correct drug at the correct time.

How is Pharmacogenomics Being Used in Drug Development?

PGx is increasingly becoming a core component of drug development programs. By using PGx to determine how drugs work differently in subgroups of patients, drug developers are making better decisions about which drugs to develop and how best to develop them. Technologies are now available to simultaneously analyze over 1 million genetic polymorphisms in the human genome. This is allowing for the identification of novel genetic markers of drug response and of disease in absence of pre-existing knowledge of the involvement of specific pathways.

PGx research is currently being used in drug development to:

- Explain variability in response among subjects in clinical trials
- Address emerging clinical issues, such as unexpected adverse events
- Determine eligibility for clinical trials (pre-screening) to optimize trial design
- Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of adverse events
- Better understand the mechanism of action or metabolism of new and existing drugs
- Provide better understanding of disease mechanisms
- Allow physicians to prescribe the right drugs at the optimal dose for individual patients

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Pharmacogenomics Already a Reality in Drug Labels

A number of drugs now have instructions on their labels either recommending or requiring a PGx test when prescribing a drug or when making dosing decisions. A well-known example is the anti-coagulant drug *warfarin*. The drug label for warfarin now includes a recommended PGx test to minimize the risk of excessive bleeding (US label). There are currently three categories of PGx information in drug labels according to the FDA:

i) tests **required** for prescribing

ii) tests **recommended** when prescribing

iii) PGx information **for information only**.

For a current list of examples of how PGx is impacting drug labeling see:

www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

DNA Samples from Clinical Trials An Invaluable Resource

Adequate sample sizes and high-quality clinical data are key to advancements in the field of PGx. Drug development programs are therefore an invaluable resource and a unique opportunity for highly productive research in PGx. Although PGx is a rapidly evolving branch of science, the complexities of the genetic code are only beginning to be understood. As scientific discoveries continue to be made, samples collected today will become a valuable resource

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for future research. This may lead to the future development of new drugs that are better targeted to certain individuals and to disease subtypes.

For these reasons, it is vital to systematically collect DNA samples across all centers recruiting subjects into clinical trials that include a PGx component (where local regulations permit). Consent for storage of samples for future research should also be obtained if maximum benefit is to be derived from DNA samples donated by subjects. The scope of the research that may be performed both during the trial and in the future should be clearly defined in the informed consent form.

Informed Consent

Policies and regulations for legally effective informed consent vary on national, state, and local levels. There currently are no internationally recognized regulations that dictate the basic elements of informed consent for PGx research. The I-PWG has published an article on the elements of informed consent to be considered in PGx research studies[2]. These elements build upon existing basic elements of informed consent for clinical research on human subjects[3].

Return of Genomic Research Results to Study Subjects

Policies for the return of genomic results to study subjects vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of PGx research results to study subjects. These include i) the conditions under which genomic results were generated (i.e., research laboratory environment versus accredited diagnostic laboratory), ii) whether the results will have an impact on patient medical care, iii) whether genetic counseling is necessary, and iv) international, national, and local guidelines, policies, legislation, and regulations regarding subjects' rights to access data generated on them. These considerations are addressed in detail in Renegar et al. 2006[4].

Privacy, Confidentiality, and Patient Rights

An issue that is generally perceived to be of relevance to clinical genetic research is the risk associated with inadvertent or intentional disclosure and misuse of genetic data. Although coded specimens generally have been considered adequate to protect patient privacy in most clinical development, companies and other institutions involved in PGx research have historically applied a variety of additional safeguards that can be used alone, or in combination, to further minimize the potential risk of disclosure and misuse of genetic data. These include:

i) Sample Labeling

DNA samples and corresponding clinical data can be labeled in several ways to achieve different levels of patient privacy and confidentiality. Definitions of labeling methods are provided in the glossary and are described in greater detail in the ICH Guidance E15[1]. It is important to recognize that there is a trade-off between the level of patient privacy protection and the ability to perform actions related to withdrawal of consent, data return, clinical monitoring, subject follow-up, and addition of new data (see Table 1)[1]. The *Identified* and *Anonymous* labeling categories described in the table are generally not applicable to pharmaceutical clinical trials.

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Table adapted from ICH Guidance E15

Sample Coding Category		Link Between Subject's Personal Identifiers and Genomic Biomarker Data	Traceability back to the Subject (Actions Possible, Including e.g., Sample Withdrawal or Return of Individual Genomic Results at Subject's Request	Ability to Perform Clinical Monitoring, Subject Follow-up, or Addition of New Data	Extent of Subject's Confidentiality and Privacy Protection
Identified		Yes (Direct) Allows for Subjects to be Identified	Yes	Yes	Similar to General Healthcare Confidentiality and Privacy
Coded	Single	Yes (Indirectly) Allows for Subjects to be Identified (via Single, Specific Coding Key)	Yes	Yes	Standard for Clinical Research
	Double	Yes (Very Indirectly) Allows for Subjects to be Identified (via the Two Specific Coding Keys)	Yes	Yes	Added Privacy and Confidentiality Protection over Single Code
Anonymized		No Does not Allow Subject to be Re-Identified as the Coding-Key(s) Have Been Deleted	No	No	Genomic Data and Samples no Longer Linked to Subject as Coding Key(s) have been Deleted
Anonymous		No – Identifiers Never Collected and Coding Keys Never Applied. Does not Allow for Subjects to be Identified	No	No	Genomic Data and Samples Never Linked to Subject

ii) Separation of Data and Restricted Access

- Maintaining PGx-related documentation separate from other medical records.
- Restricting access to data and samples by means of password-protected databases and locked sample storage facilities.

PGx studies in pharmaceutical development are generally conducted in research laboratories that are not accredited diagnostic laboratories. Therefore, PGx research data usually cannot be used to make clinically meaningful or reliable decisions about a subject's health or health risks. Furthermore, confidentiality protections described above serve to guard against inappropriate disclosure of these data. For these reasons, the potential risk to a subject's employment or health/life insurance is considered to be minimal. The measures taken to protect subjects against reasonably foreseeable risks should be addressed in the informed consent form[2].

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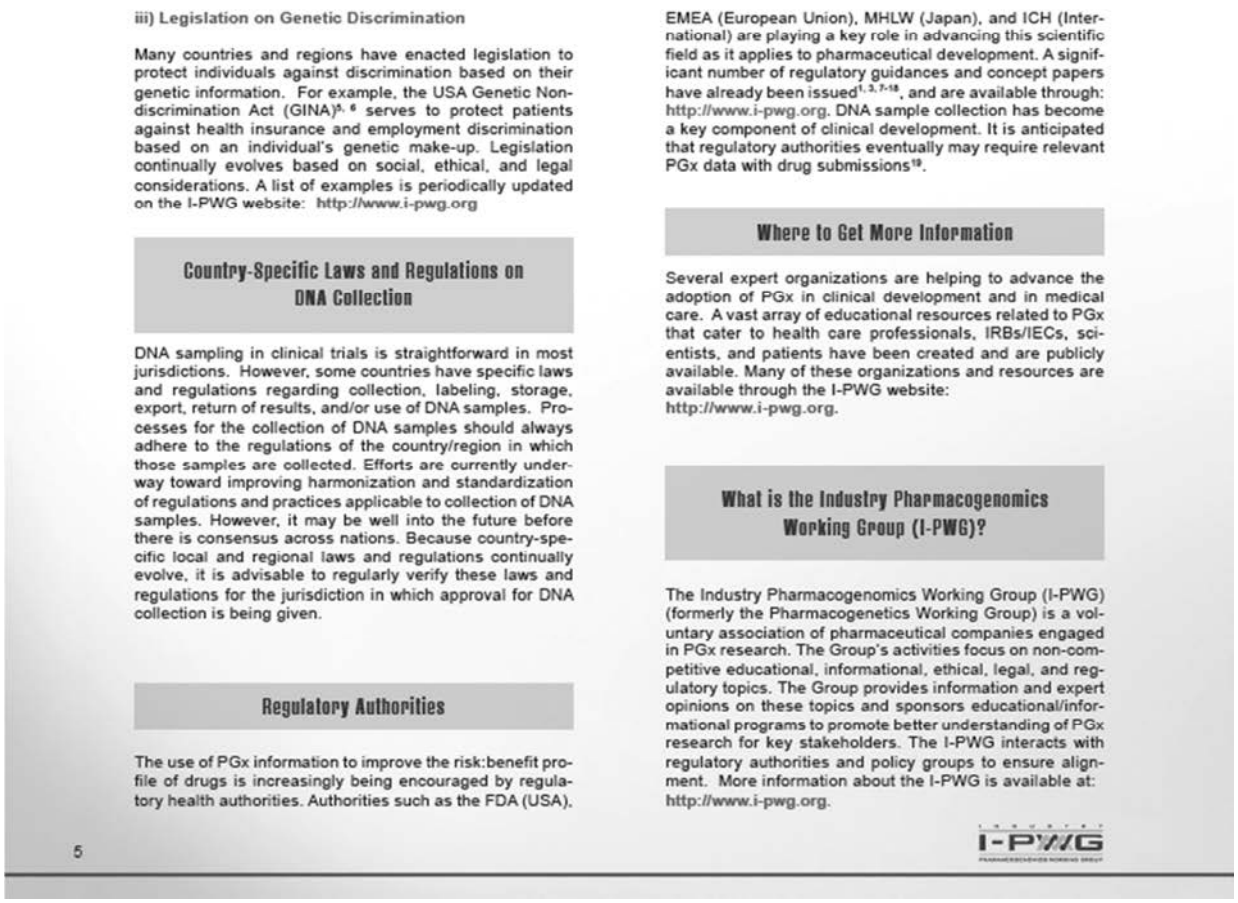

iii) Legislation on Genetic Discrimination

Many countries and regions have enacted legislation to protect individuals against discrimination based on their genetic information. For example, the USA Genetic Non-discrimination Act (GINA)[5, 6] serves to protect patients against health insurance and employment discrimination based on an individual's genetic make-up. Legislation continually evolves based on social, ethical, and legal considerations. A list of examples is periodically updated on the I-PWG website: http://www.i-pwg.org

Country-Specific Laws and Regulations on DNA Collection

DNA sampling in clinical trials is straightforward in most jurisdictions. However, some countries have specific laws and regulations regarding collection, labeling, storage, export, return of results, and/or use of DNA samples. Processes for the collection of DNA samples should always adhere to the regulations of the country/region in which those samples are collected. Efforts are currently underway toward improving harmonization and standardization of regulations and practices applicable to collection of DNA samples. However, it may be well into the future before there is consensus across nations. Because country-specific local and regional laws and regulations continually evolve, it is advisable to regularly verify these laws and regulations for the jurisdiction in which approval for DNA collection is being given.

Regulatory Authorities

The use of PGx information to improve the risk:benefit profile of drugs is increasingly being encouraged by regulatory health authorities. Authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development. A significant number of regulatory guidances and concept papers have already been issued[1, 3, 7-18], and are available through: http://www.i-pwg.org. DNA sample collection has become a key component of clinical development. It is anticipated that regulatory authorities eventually may require relevant PGx data with drug submissions[19].

Where to Get More Information

Several expert organizations are helping to advance the adoption of PGx in clinical development and in medical care. A vast array of educational resources related to PGx that cater to health care professionals, IRBs/IECs, scientists, and patients have been created and are publicly available. Many of these organizations and resources are available through the I-PWG website: http://www.i-pwg.org.

What is the Industry Pharmacogenomics Working Group (I-PWG)?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in PGx research. The Group's activities focus on non-competitive educational, informational, ethical, legal, and regulatory topics. The Group provides information and expert opinions on these topics and sponsors educational/informational programs to promote better understanding of PGx research for key stakeholders. The I-PWG interacts with regulatory authorities and policy groups to ensure alignment. More information about the I-PWG is available at: http://www.i-pwg.org.

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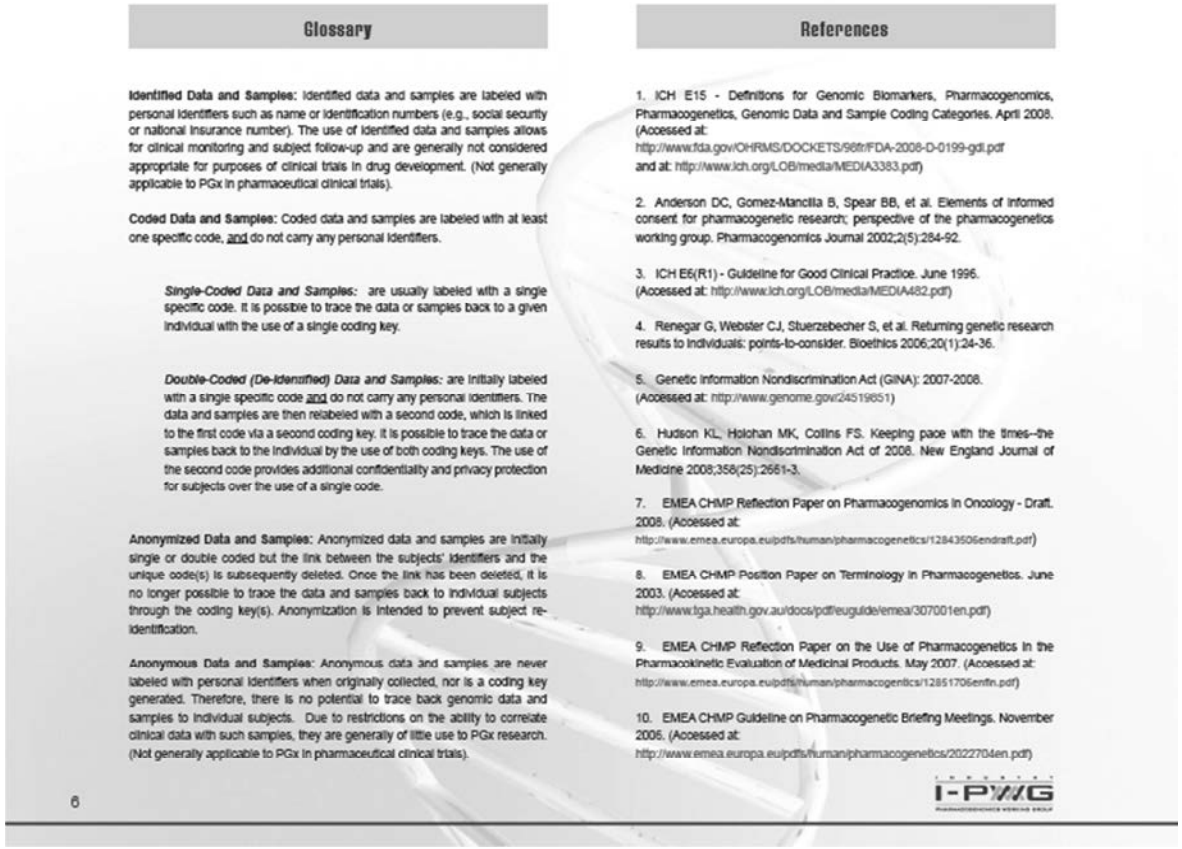

Glossary

Identified Data and Samples: Identified data and samples are labeled with personal identifiers such as name or identification numbers (e.g., social security or national insurance number). The use of identified data and samples allows for clinical monitoring and subject follow-up and are generally not considered appropriate for purposes of clinical trials in drug development. (Not generally applicable to PGx in pharmaceutical clinical trials).

Coded Data and Samples: Coded data and samples are labeled with at least one specific code, and do not carry any personal identifiers.

Single-Coded Data and Samples: are usually labeled with a single specific code. It is possible to trace the data or samples back to a given individual with the use of a single coding key.

Double-Coded (De-identified) Data and Samples: are initially labeled with a single specific code and do not carry any personal identifiers. The data and samples are then relabeled with a second code, which is linked to the first code via a second coding key. It is possible to trace the data or samples back to the individual by the use of both coding keys. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code.

Anonymized Data and Samples: Anonymized data and samples are initially single or double coded but the link between the subjects' identifiers and the unique code(s) is subsequently deleted. Once the link has been deleted, it is no longer possible to trace the data and samples back to individual subjects through the coding key(s). Anonymization is intended to prevent subject re-identification.

Anonymous Data and Samples: Anonymous data and samples are never labeled with personal identifiers when originally collected, nor is a coding key generated. Therefore, there is no potential to trace back genomic data and samples to individual subjects. Due to restrictions on the ability to correlate clinical data with such samples, they are generally of little use to PGx research. (Not generally applicable to PGx in pharmaceutical clinical trials).

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12.4 Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Types

Trial Visit/Cycle/etc.	Screening Visit 1	Treatment Visit 3	Treatment Visit 4	Treatment Visits 5-7	Post-Treatment
Blood Parameter[†]	**Approximate Blood Volume (mL)**				
Hematology	2 mL	NA	NA	NA	NA
Serum/Plasma Chemistry	6 mL	NA	NA	NA	NA
Expected Total (mL)	8.5 mL			NA	NA
[†] Refer to Appendix 12.5 for PK collection blood volumes					

12.5 Pharmacokinetic Sub-Trial: MK-0887A Protocol 087

A. BACKGROUND AND RATIONALE

This pharmacokinetic (PK) sub-trial is intended to characterize the plasma concentration-time profile and the key PK parameters for mometasone furoate (MF) following multiple oral inhalations of MF/F or MF from a metered-dose inhaler, when administered to approximately steady-state in children ages 5–11 years old with persistent asthma.

To minimize discomfort and avoid multiple venipunctures, subjects may be housed overnight for trial-related activities during the PK Visit. Blood samples collected at the time points specified in the protocol may be obtained via an indwelling catheter. The total amount of blood collected during the 12-hour period will be within the limitation of most guidelines suggested; i.e., no more than 5% of Total Blood Volume (TBV).

B. OBJECTIVE

- To characterize the plasma pharmacokinetics (PK) profile of MF and to determine the PK parameters (e.g., $AUC_{0\text{-}12h}$, $AUC_{0\text{-}last}$, C_{max}, and T_{max}) at steady state after multiple oral inhalations via MDI device in children ages 5-11 years old with persistent asthma.
- **Estimation:** The plasma PK parameters of MF (e.g., $AUC_{0\text{-}12h}$, $AUC_{0\text{-}last}$, C_{max}, and T_{max}) at steady state after multiple oral inhalations in children ages 5-11 years old with persistent asthma.

C. SUBJECT DEFINITION

1. Inclusion Criteria

1. Subject is actively participating in the main trial (Protocol 087).
2. Subject is willing to give written informed assent, in accordance with local regulations, and the subject's legal representative to give written informed consent for the trial.
3. Subject has a body weight ≥18 kg.
4. Subject has both normal hemoglobin and normal hematocrit at the Visit 1 laboratory safety measurements.

2. Exclusion Criteria

1. In the opinion of the investigator, the subject suffers from any physical, psychological or other condition(s) that might prevent participation in the pharmacokinetic sub-trial.
2. On the day of the PK Visit (Visit 7), the subject has a body weight <18 kg.

D. TRIAL DESIGN

1. Summary of Sub-Trial Design/Procedures

At a prespecified subset of trial sites, subjects who have been randomized to the main trial for Protocol 087 will have the option to participate in a PK sub-trial. There will be specific consent/assent forms for the PK sub-trial (i.e., the consent/assent forms for the pharmacokinetic sub-trial will be distinct from the consent/assent forms for the main trial). Participation in the PK sub-trial will require the subject's legal representative to give written informed consent for the sub-trial and subjects to give written informed assent, in accordance with local regulations, on or before Visit 7.

Approximately 20 subjects (from either the MF/F arm or the MF arm) who have consented to participate in the sub-trial, and have met the criteria for both the main trial and sub-trial, will participate in the PK sub-trial. Attempts will be made to ensure that subjects who complete the PK sub-trial adequately represent the targeted population (ages 5 to 11 years). Because the inter-subject coefficient of variation (CV) ranged from approximately 35 to 70% for C_{max} and AUC values following multiple-dose administration of MF/F MDI to asthmatic adults (Refer to Investigator's Brochure for details), it is anticipated that approximately 20 subjects is appropriate to characterize the pharmacokinetics of MF with adequate precision in the targeted pediatric population [12]. On the other hand, to respect the special needs of children, a higher number of participants in this PK sub-trial, as well as a higher number of venipunctures, is not desirable.

In addition to the procedures outlined in the main trial, at Visit 7 (Week 12 of treatment), subjects who agree to participate in this sub-trial will have pharmacokinetic samples obtained at specified time points shown in the table.

Dosing and Pharmacokinetic Sampling Time Points

Procedure	Times Obtained (Hours)
Dosing	0 (8 AM ± 1 hour)
Blood samples for pharmacokinetics[†]	0 hour (predose), 0.75, 1.5, 3, 8, 12 hours postdose
[†]Samples (3-mL each) will be collected into tubes containing pre-chilled K3-EDTA. PK samples should be taken as close to the nominal time as possible. PK blood collection is to take precedence over all other trial procedures (including those in the main trial) with the exception of spirometry measurements. Record the actual time the PK sample was obtained in the electronic case report form.	

Procedures for the sub-trial are detailed below.

At Visit 7, subjects participating in the sub-trial will report to the trial site at 8 am ± 1 hour. At the investigator's discretion, subjects may be admitted to the trial site on the evening prior to Visit 7. Peripheral intravenous access may be established for the purpose of obtaining pharmacokinetic samples. Blood sampling may also be accomplished by repeated venipuncture at the discretion of the investigator. Topical anesthetics are permitted for the purposes of establishing peripheral venous access and/or venipuncture. Blood samples will be collected at specified time points.

Pharmacokinetic samples for the sub-trial should be obtained as close to the scheduled time as possible. Pharmacokinetic blood collections take precedence over all other procedures (including those of the main trial) at any given time point with the exception of spirometry measurements. The exact time at which the in-clinic witnessed dosing takes place and the time at which a pharmacokinetic sample is obtained must be recorded on the electronic case report forms.

The total volume of blood required from each patient will not be of physiological significance in these non-anemic subjects. Since subjects are required to have a body weight of ≥18 kg, the total amount of blood collected (18 mL) for pharmacokinetic samples over the 12-hour collection period will be well below the limitation of most guidelines suggested; i.e., no more than 5% of Total Blood Volume.

Throughout the PK sub-trial, water may be administered ad libitum. Subjects may be provided meals (breakfast, lunch, and/or dinner) and snacks while at the trial site for the PK sub-trial. Food may be administered up to 1 hour prior to and as soon as 1 hour after trial drug administration. Grapefruit and grapefruit juice should be avoided. There are no other specific food restrictions prior to or after dosing, with the exception of ensuring a reasonable degree of consistency of any meals/snacks (with respect to content) and ensuring that meals/snacks do not interfere with clinical procedures during the trial.

Subjects will be discharged from the trial site after completion of the 12-hour post-dose blood sample and removal of the venous access (as applicable). At the investigator's discretion, subjects may be remain overnight at the trial center on the evening prior to Visit 7 and be discharged from the clinic after completing serial spirometry and the 12 hours PK procedure at Visit 7.

Sample processing and shipping is described below.

2. Treatment

Except as directly related to the sub-trial, subjects enrolled in the sub-trial will follow the same treatment plan, special handling requirements, prior and concomitant medications/treatments, and diet/activity/other described in the main trial (Protocol 087). Please refer to the main trial protocol for details.

E. TRIAL PROCEDURES

1. Allocation Scheme

Subjects enrolled in the sub-trial will use the same allocation number assigned in the main trial.

2. Protocol Outline

Subjects enrolled in the sub-trial will complete procedures as listed in the main trial (Protocol 087). Please refer to the main trial protocol for details.

3. General Sub-trial Procedures

General protocol procedures listed in the main trial apply for the sub-trial. Please refer to the main trial protocol for details. Additional procedures unique to the sub-trial are listed below.

F. PROCESSING OF PHARMACOKINETIC SAMPLES

1. Blood Samples for Plasma Mometasone Furoate Determination

- Careful attention to collection, handling and storage is essential to reduce pharmacokinetic variability.
- Collect 3 mL of whole blood at each specified time point into pre-chilled tubes containing K3-EDTA for determination of drug concentrations.
- Keep samples on wet ice until centrifuged, then frozen.
- Place blood sample into a centrifuge, and centrifuge 15 minutes at 1,500*g*.
- Collect plasma and dispense into Corning 2 mL polypropylene cryotubes (Corning Part No. 430659; self-standing, externally threaded, orange-capped vials).
- Samples ***must be stored frozen at -20 °C (or colder) until*** transferred to the analytical site on dry ice.
- Samples must be transferred to the analytical site on dry ice.

The assay will be conducted at a contract laboratory.

2. Packaging Samples for Shipment

It is the responsibility of the primary investigator to ensure that all staff personnel who will be handling, packaging, and/or shipping clinical specimens act in conformance with International Air Transport Association (IATA) regulations relating to the handling and shipping of hazardous goods.

1. All shipments will be made in freezer boxes containing adequate amount of DRY ICE to keep samples frozen for at least 72 hours.
2. Please include a sample inventory with each shipment.

3. Samples should be sent at intervals to be determined by the SPONSOR and the investigator. Shipments should be sent on MONDAY or TUESDAY to assure receipt by Friday.

3. Shipment Information

Shipment information is provided separately in the laboratory procedures manual.

G. CRITERIA FOR SUBJECT DISCONTINUATION FROM PK SUB-TRIAL

The subject must be discontinued from further participation in the sub-trial if any of the discontinuation criteria for the main trial are met or if the subject and legal guardian withdraw consent/assent.

Note: Discontinuation from the PK sub-trial does not mean that the subject must be discontinued from the main trial; see Section 5.8 for criteria for discontinuation from the main trial.

H. PHARMACOKINETIC MEASUREMENTS

Blood samples will be collected for the determination of PK parameters for MF at steady state such as area under the concentration-time curve from 0 to 12 hours ($AUC_{0\text{-}12h}$), area under the curve from 0 to last concentration observed ($AUC_{0\text{-}last}$), maximum plasma concentration (C_{max}), and time to C_{max} (T_{max}).

PK parameters for formoterol will not be determined in this trial.

Samples will be assayed by a LC-MS/MS (Liquid Chromatography–Mass Spectrometry / Mass Spectrometry) assay method.

I. SAFETY MEASUREMENTS

Safety measurements for subjects participating in the PK sub-trial will be presented within the main trial report (Protocol 087); safety data from the sub-trial will not be reported separately.

J. DATA ANALYSIS

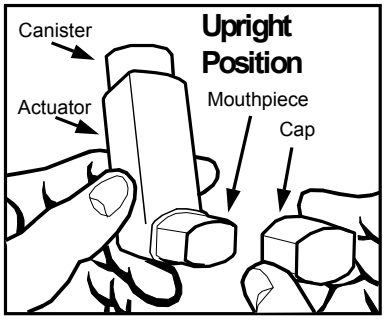
Main efficacy data for subjects participating in the PK sub-trial will be analyzed within the main trial report (Protocol 087) and will not be reported separately. Additional data analyses unique to the sub-trial are presented below.

Individual values will be listed for plasma concentrations and each derived pharmacokinetic parameters ($AUC_{0\text{-}12h}$, $AUC_{0\text{-}last}$, C_{max}, and T_{max}) for mometasone furoate and summarized by treatment groups and combined across treatments and the following descriptive statistics will be provided by treatments as well as combined across treatment groups: N (number of subjects with non-missing data), arithmetic mean, standard deviation, arithmetic coefficient of variation (calculated as 100x standard deviation/arithmetic mean), geometric mean, geometric coefficient of variation (calculated as 100 x sqrt(exp(s2) - 1), where s2 is the observed variance on the natural log-scale), minimum, median and maximum.

12.6 General Instructions for Use of the MDI

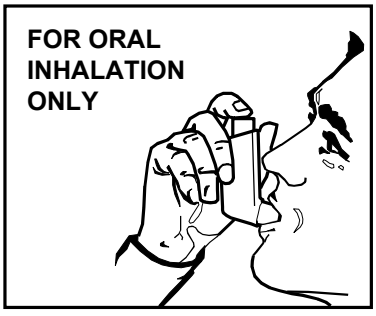
1. REMOVE THE CAP FROM THE MOUTHPIECE (Figure 1). Check mouthpiece for foreign objects prior to use. Make sure the canister is fully inserted into the actuator.

Figure 1



2. SHAKE THE INHALER **WELL** immediately before each use.
3. BREATHE OUT FULLY THROUGH THE MOUTH expelling as much air from your lungs as possible. Place the mouthpiece fully into the mouth holding the inhaler in its upright position (Figure 1) and closing the lips around it.
4. WHILE BREATHING IN DEEPLY AND SLOWLY THROUGH THE MOUTH, FULLY DEPRESS THE TOP OF THE METAL CANISTER with your index finger (Figure 2). Release your finger from the canister.

Figure 2



5. HOLD YOUR BREATH AS LONG AS POSSIBLE, up to 10 seconds. Then remove the inhaler from your mouth and breathe out through your nose, while keeping the lips closed.
6. For administration of the second puff, wait **at least half a minute**, shake the inhaler again and repeat Steps 2 through 5.
7. Replace the cap immediately after use.

For best results, MDIs should always be used at room temperature. The product should not be exposed to extreme heat or cold.

After you have finished taking your dose, rinse your mouth with water or a mouthwash solution and then spit this out. This will help you prevent thrush.

Cleaning Instructions:

Keeping the plastic mouthpiece clean is extremely important to prevent medication build-up. The mouthpiece should be cleaned using a dry wipe after every 7 days of use.

For cleaning do not remove the unit from the actuator. Wipe the internal and external surfaces of the actuator mouthpiece with a clean, dry tissue. Do not wash or put any part of the inhaler in water.

Never immerse the metal canister in water.

12.7 Stoughton-Cornell Scale

POTENCY RANKING OF SOME COMMONLY USED BRAND NAME CORTICOSTEROID[a]				
Potency	Group	Preparation		
Super Potent	1	Temovate cream	0.05%	(a)
		Temovate ointment	0.05%	(a)
		Diprolene cream	0.05%	(b)
		Diprolene ointment	0.05%	(b)
		Psorcon ointment	0.05%	(c)
Potent	2	Cyclocort ointment	0.1%	(d)
		Diprolene cream AF	0.05%	(b)
		Diprosone ointment	0.05%	(e)
		Elocon ointment	0.1%	(f)
		Florone ointment	0.05%	(g)
		Halog cream	0.1%	(h)
		Lidex cream	0.05%	(I)
		Lidex gel	0.05%	(I)
		Lidex ointment	0.05%	(I)
		Maxiflor ointment	0.05%	(g)
		Topicort cream	0.25%	(j)
		Topicort gel	0.05%	(j)
		Topicort ointment	0.25%	(j)
	3	Aristocort A ointment	0.1%	(k)
		Cyclocort cream	0.1%	(d)
		Cyclocort lotion	0.1%	(d)
		Diprosone cream	0.05%	(e)
		Florone cream	0.05%	(g)
		Lidex E cream	0.05%	(I)
		Halog ointment	0.1%	(h)
		Maxiflor cream	0.05%	(g)
		Valisone ointment	0.1%	(l)
Mid-Strength	4	Cordran ointment	0.05%	(m)
		Elocon cream	0.1%	(f)
		Kenalog cream	0.1%	(k)
		Synalar ointment	0.025%	(n)
		Westcort ointment	0.2%	(o)
	5	Cordran cream	0.05%	(m)
		Diprosone lotion	0.05%	(e)
		Kenalog lotion	0.1%	(k)
		Locoid cream	0.1%	(p)
		Synalar cream	0.025%	(n)
		Valisone cream	0.1%	(l)

POTENCY RANKING OF SOME COMMONLY USED BRAND NAME CORTICOSTEROID[a]				
Potency	Group	Preparation		
Mild	6	Westcort cream	0.2%	(o)
		Alclovate cream	0.05%	(q)
		Alclovate ointment	0.05%	(q)
		Aristocort cream	0.1%	(k)
		DesOwen cream	0.05%	(r)
		Synalar solution	0.01%	(n)
		Tridesilone cream	0.05%	(r)
		Valisone lotion	0.05%	(l)
	7	Topicals w/hydrocortisone, dexamethasone, flumethalone, prednisolone and methylprednisone		

a: Group 1 is the super-potent category; potency descends with each group to Group 7, which is least potent (2, 3 -- potent steroids; 4, 5 -- mid-strength steroids; 6, 7 -- mild steroids). There is no significant difference between agents **within** Groups 2 through 7; the compounds are simply arranged alphabetically. However, within Group 1, Temovate cream or ointment is more potent than Diprolene cream or ointment and Psorcon ointment.

(a) Clobetasol propionate
(b) Betamethasone dipropionate (optimized vehicle)
(c) Diflorasone diacetate (optimized vehicle)
(d) Amcinonide
(e) Betamethasone dipropionate
(f) Mometasone furoate
(g) Diflorasone diacetate
(h) Halcinonide
(I) Fluocinonide
(j) Desoximetasone
(k) Triamcinolone acetonide
(l) Betamethasone valerate
(m) Flurandrenolide
(n) Fluocinolone acetonide
(o) Hydrocortisone valerate
(p) Hydrocortisone dipropionate
(q) Alclometasone dipropionate
(r) Desonide

12.8 Method for Administering Short-Acting Beta-Agonist (SABA) During Postbronchodilator testing for Airway Reversibility

In assessing β-agonist response in the clinic, four to eight inhalations ("puffs") of SABA (albuterol/salbutamol) or one to two nebulizations of SABA will be administered.

If nebulizations of SABA will be used during the reversibility procedure, please refer to guidance directly after the procedure for 'puffs' of SABA.

Note: Spacers **are** permitted for SABA administered for the purposes of demonstrating reversibility.

Procedure - 'Puffs' of SABA

1. Perform Pre-Bronchodilator spirometry (baseline FEV_1)

2. Shake the metered-dose inhaler

3. Tilt the head back slightly and breathe out

4. Place device in mouth

5. Press down on inhaler to release medication

6. Breathe in slowly (3 to 5 seconds) to total lung capacity

7. Hold breath for 10 seconds

8. Wait 30 seconds between each inhalation ("puff") and repeat the same sequence 3 additional times

9. After 4 inhalations of SABA, wait approximately 10 minutes and then perform spirometry. Compare results with baseline spirometry

- If there is a $< 12\%$ change in FEV_1, continue to Step 10
- If there is a $\geq 12\%$ change in absolute FEV_1, then end procedure – patient has met inclusion criteria

10. Repeat steps to administer an additional 2 inhalations of SABA with approximately 30 seconds between inhalations

11. Wait approximately 10 minutes, perform spirometry, and compare with baseline FEV_1

- If there is a < 12% change in FEV_1, continue to Step 12
- If there is a ≥ 12% change in absolute FEV_1, then end procedure – patient has met inclusion criteria

12. Repeat steps to administer an additional 2 inhalations of SABA with approximately 30 seconds between inhalations

13. Wait approximately 10 minutes, perform spirometry, compare with baseline FEV_1

- If there is a < 12 % change in absolute FEV_1, the subject has not met the inclusion criterion for reversibility
- If there is a ≥ 12 % change in absolute FEV_1, the subject has met the inclusion criterion for reversibility

Procedure - 'Nebulization' of SABA

Nebulization treatments of 2.5 mg albuterol/salbutamol per treatment can be used to demonstrate reversibility. The reversibility procedure for using nebulized treatments is described below:

1. Perform Pre-Bronchodilator spirometry (baseline FEV_1)

2. After 1 nebulized treatment, wait approximately 10 minutes and then perform spirometry. Compare results with baseline spirometry

- If there is a < 12% change in FEV_1, continue to the next step
- If there is a ≥ 12% change in absolute FEV_1, then end procedure – patient has met inclusion criteria

3. Repeat step to administer 1 additional nebulized treatment

4. Wait approximately 10 minutes, perform spirometry, and compare with baseline FEV_1

- If there is a < 12% change in FEV_1, continue to the next step
- If there is a ≥ 12% change in absolute FEV_1, then end procedure – patient has met inclusion criteria

5. You may wait an additional 10 minutes (approximately) and attempt only spirometry again (without any further use of nebulization of SABA)

12.9 Standardization of Spirometry

American Thoracic Society. ATS Documents: Statements, Guidelines & Reports: ATS/ERS standardisation of lung functioning testing: Standardisation of spirometry, 2005. http://www.thoracic.org/statements/

Also refer to the detailed instructions provided by the Central Vendor.

12.10 Asthma Action Plan

MK-0887A Protocol 087

GUIDE TO PERCENTAGE CALCULATIONS (ASTHMA ACTION PLAN)

(This guide is to be completed and included for the subject's study files. Please remove this guide prior to providing the Asthma Action Plan to the subject and Parent/Caregiver)

The Asthma Action Plan must first be completed with the subject's peak expiratory flow (PEF) ranges. However, for some subjects the PEF is of limited value and change of symptoms may be of greater importance. This should be explained to the subject and Parent/Caregiver. The Investigator will indicate on the form below, the adequate rescue medication to use, depending on the PEF range and symptoms. The Asthma Action Plan will help the subject and their parent/caregiver to effectively manage his/her/the subject's symptoms.

Measure the subject's highest peak expiratory flow (PEF).
This should be the highest PEF from three attempts.
Enter the subject's highest PEF onto the Asthma Action Plan.
Calculate the percentage ranges as follows:

CALCULATE ONE PERCENT OF THE SUBJECT'S BEST PEF:

1% = PEF ÷ 100

THEN USE THE FOLLOWING TO CALCULATE THE RANGES:

100% = 1% x 100 (this is equal to PEF)
80% = 1% x 80
79% = 1% x 79
70% = 1% x 70
60% = 1% x 60

Enter these ranges (80-100%, 60-79%, <60%) onto the asthma action plan.
.

EXAMPLE

A subject has three attempts at PEF and records 325, 270, 300. The subject's highest PEF is 325.

CALCULATE 1% of 325: 325 ÷ 100 = 3.25

CALCULATE THE RANGES:

80% TO 100% = 3.25 x 80 to 3.25 x 100
= 260 to 325

Range (80% to 100%) = 260 to 325

60% TO 79% = 3.25 x 60 to 3.25 x 79
= 195 to 256.75

Range (60% to 79%) = 195 to 256.75

<60% See 60% calculation above

Range (less than 60%) = calculation above.

Asthma Action Plan

MK-0887A Protocol 087

Subject ID: _____ Date: _____

Highest (Personal Best) Peak Expiratory Flow (PEF) (Please record the highest of 3 attempts): _____

Investigator's Name: _____ Investigator's Phone Number: _____

GREEN: Subject is doing well.

IF → Subject is well and has no asthma symptoms, even during active play

Peak Flow Number _____ To _____ (80%-100% of Personal Best)

USE TRIAL MEDICATION:

MEDICATION	HOW MUCH TO TAKE	WHEN TO TAKE IT	SPECIAL INSTRUCTIONS

YELLOW: Caution! Asthma Getting Worse: Do not leave subject alone.

IF → Subject is not well and has asthma symptoms or a cold that may include:

- Coughing
- Wheezing
- Runny nose and other cold symptoms
- Difficulty breathing (breathing harder and faster)
- Nighttime awakenings due to coughing, difficulty breathing, or other asthma symptoms
- Playing less than usual
- Other

Peak Flow Number _____ To _____ (60%-79% of Personal Best)

TAKE RESCUE MEDICATION:

MEDICATION	HOW MUCH TO TAKE	WHEN TO TAKE IT	SPECIAL INSTRUCTIONS

RED: Caution! Severe Asthma Symptoms: Do not leave subject alone.

Call the investigator immediately or seek immediate medical care (call 911 or go to the EMERGENCY ROOM) now!

IF → Subject feels very bad! Warning signs may include:

- Subject's wheeze, cough, or difficulty breathing continues to worsen, even after giving above medications
  - No response to short acting β agonist (SABA)/albuterol (rescue medication)
- Subject is breathing so hard that he/she is having trouble walking/talking/eating/playing
- Subject is drowsy or less alert than normal
- Subject's skin is sucked in around the neck and ribs, lips and/or fingernails are grey, or blue
- Subject doesn't respond to you

Peak Flow is less than _____ (≤60% of Personal Best)

TAKE THESE MEDICINES UNTIL YOU TALK WITH THE INVESTIGATOR OR UNTIL YOU GET OTHER MEDICAL HELP

MEDICATION	HOW MUCH TO TAKE	WHEN TO TAKE IT	SPECIAL INSTRUCTIONS

12.11 Asthma eDiary (IVRS/IWRS) Questions

The eDiary (IVRS/IWRS) is to be used daily to capture the subject's use of trial medication and use of rescue medication(s). Because the use of SABA as prevention for exercise-induced bronchospasm (EIB) is not considered rescue use, it should not be captured in the IVRS/IWRS system for the purpose of assessing asthma control. Use of SABA for prevention of EIB will be recorded in the concomitant medication module of the electronic case report form (eCRF).

A sample listing of the asthma eDiary (IVRS/IWRS) questions is provided below. Additional details (including set-up/programming of the eDiary) will be provided by the central vendor. At the Screening Visit, the subject and parent/legal guardian will be provided with verbal and written instructions on the proper use of the eDiary (IVRS/IWRS) and PEF meter. In addition, the user will be guided by clear and easy-to-read instructions on the eDiary (IVRS/IWRS).

Morning Questionnaire:

The subject, with the assistance of the parent/legal guardian, will answer the following questions in the morning upon rising and after completing their PEF measurements, and taking their trial medication and/or SABA (albuterol/salbutamol) (Section 5.2). **SABA taken as pre-treatment for prevention of exercise-induced bronchospasm (EIB) is *not* considered as rescue use and should *not* be recorded on the asthma eDiary (IVRS/IWRS).**

During the Screening Period (between Visit 1 and Visit 2), "trial medication" in Question 1 refers to the subjects pre-trial ICS/LABA combination therapy. Also, as Visit 1 will be the first trial visit, Questions 2 through 7 of the Morning Questionnaire will not apply for that visit.

For subjects who discontinue/withdraw from trial medication prior to completion of the trial, Question 1 will not apply.

Question	Response(s)
1. Have you taken your trial medication this morning?	Yes/No
2. Did you take any puffs of albuterol/salbutamol since your last eDiary session?	Yes/No
3. How many puffs of albuterol/salbutamol have you taken since your last eDiary session?	0 – X puff(s)
4. Did you take any albuterol/salbutamol nebulizations since your last eDiary session?	Yes/No
5. How many nebulizations of albuterol/salbutamol have you taken since your last eDiary session?	0 – X neb(s)
6. Did you take albuterol/salbutamol (puffs or nebulizations) within last 6 hrs. of this morning PEF Reading?	Yes/No
7. Did you take oral prednisone/prednisolone since your last eDiary session?	Yes/No

Evening Questionnaire:

The subject, with the assistance of the parent/legal guardian, will answer the following questions in the evening at bedtime and after taking their trial medication and/or SABA (albuterol/salbutamol) (Section 5.2). SABA taken as pre-treatment for prevention of exercise-induced bronchospasm (EIB) is *not* considered as rescue use and should *not* be recorded on the asthma eDiary (IVRS/IWRS).

During the Screening Period (between Visit 1 and Visit 2), "trial medication" in Question 1 refers to the subjects pre-trial ICS/LABA combination therapy.

For subjects who discontinue/withdraw from trial medication prior to completion of the trial, Question 1 will not apply.

Question	Response(s)
1. Have you taken your trial medication this evening?	Yes/No
2. Did you take any puffs of albuterol/salbutamol since your last eDiary session?	Yes/No
3. How many puffs of albuterol/salbutamol have you taken since your last eDiary session?	0 – X puff(s)
4. Did you take any albuterol/salbutamol nebulizations since your last eDiary session?	Yes/No
5. How many nebulizations of albuterol/salbutamol have you taken since your last eDiary session?	0 – X neb(s)
6. Have you taken oral prednisone/prednisolone since your last eDiary session?	Yes/No

12.12 Statistical Methodology

Constrained Longitudinal Data Analysis (cLDA) Method (with Adjustment for Baseline Values) – Technical Details for Model Specification, Assumptions, and SAS Implementation Codes

Model

Let Y_{ijt} be the response for subject *i,* with treatment assignment *j*, at time *t*. The marginal mean responses of the cLDA model can be formulated as

$$E(Y_{ij0}) = \gamma_0, \quad t = 0,$$

and

$$E(Y_{ijt}) = \gamma_0 + \gamma_{jt}, \quad j = 0,1, \quad t = 1,2,..., T.$$

The mean response γ_0 at t =0 is constrained to be the same for all treatment groups due to randomization. The effect γ_{jt} denotes the change from baseline for treatment *j* at time *t*. The cLDA model assumes that baseline and post-baseline values have a joint multivariate normal distribution. An unstructured covariance matrix can be specified in the mixed model to account for within subject correlation at times $t \geq 0$ (including baseline).

The treatment difference for the mean change from baseline at time point *t*, $t = 1,2,...,T$ is defined as:

$$\eta_t = \gamma_{1t} - \gamma_{0t}.$$

At each time point *t*, $t = 1,2,...,T$, the mean change from baseline (LSMEANS) for test drug and control are γ_{1t} and γ_{0t}, respectively, as defined in the cLDA model above.

This longitudinal model provides valid statistical inference in the presence of possible missing data if the missing data mechanism is ignorable (or more specifically, missing at random [MAR] or missing completely at random [MCAR]). This missing data mechanism requires that the probability of a data point being missing does not depend on the missing data after adjusting for the observed data. For reasons discussed in Section 8.2 of the protocol, it is expected that MAR/MCAR mechanisms will underlie most of the missingness and the proportion of data missing not at random [MNAR], driven solely by unobserved values of the trial endpoints, will be small.

Model Convergence

If the unstructured covariance model fails to converge with the default algorithm, then Fisher scoring algorithm or other appropriate methods can be used to provide initial values of the covariance parameters. In the rare event that none of the above methods yield convergence, a structured covariance such as Toeplitz can be used to model the correlation among repeated measurements. In this case, the empirical option will be used because the sandwich variance estimator is asymptotically unbiased.

SAS Codes

SAS codes for fitting the full likelihood cLDA model are provided below.

```
*--- SAS Coding assumes the dataset is already structured for analysis ---;

*--- Model effects decodes and explanation of options ---

        age=age strata (5<=age<=7 ,8<=age<=11)
        region=geographical region
        trt=treatment (MF/F 100/10 mcg twice daily, MF 100 mcg )
        time=week of scheduled visit (0, 1,4, 8,12 weeks)
        kr=the kenwardroger option performing degrees of freedom calculations based on
            Kenward and Roger (1997).
        om=assures weighing of categorical covariates but requires an equal number of
            records per subject (i.e. include a records of missing evaluations in database)

*---- Constrain the Baseline as a single estimate across treatments ---;
data a; set a; if time=0 then trt='x';

*---- Estimate statements are provided for the Day1 post dose treatment difference,

          and the Day 1 post dose, Weeks 1,4,8,12 average treatment difference (MF/F
versus MF) ----;

proc sort data=a;  by time;

proc mixed data=a;
class subjnbr time trt age region;
model y = age region trt*time/noint ddfm=kr;
repeated time/subject=subjnbr type=un;
lsmeans trt*time/cl pdiff om;
estimate ‘Day 1 diff ' trt*time 0  -1   1  0  0  0  0  0  0  0  0  / cl;
estimate ‘Weeks diff ' trt*time 0  -1/5   1/5  -1/5  1/5  -1/5  1/5  -1/5  1/5  -1/5  1/5  / cl;
```

output will be programmed to extract those estimates relevant for the remaining pre-specified analyses in the protocol, such as treatment differences at each time point.

12.13 List of Abbreviations

AAP	Asthma Action Plan
ABPP	Asthma Baseline Pediatric Profile
AE	Adverse experience
ANCOVA	Analysis of covariance
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATS/ERS	American Thoracic Society/European Respiratory Society
AUC_{0-12h}	Area under the concentration-time curve from 0 to 12 hours
AUC_{0-last}	Area under the curve from 0 to last concentration observed
β-hCG	β-Human Chorionic Gonadotropin
BID	Twice daily
CI	Confidence interval
CI (Protocol)	Principal Coordinator / Coordinating Investigator
cLDA	Constrained longitudinal data analysis
C_{max}	Maximum concentration
CSR	Clinical Study Report
CV	Coefficient of Variation
DILI	Drug-induced liver injury
DPI	Dry-powder inhaler
ECI	Event of clinical interest
eCRF	Electronic Case Report Form
EIB	Exercise-induced bronchospasm
ERC	Ethics Review Committee
EU	European Union
F	Formoterol Fumarate
FAS	Full analysis set
FDC	Fixed Dose Combination
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
GCP	Good Clinical Practice
Ht	Height
IB	Investigator's Brochure
ICF	Informed consent form
ICS	Inhaled corticosteroids

IEC	Institutional ethics committee
IRB	Institutional Review Board
IVRS	Interactive voice-response system
IWRS	Integrated web-response system
Kg	Kilograms
LABA	Long-acting beta-agonist
LC-MS/MS	Liquid Chromatography–Mass Spectrometry / Mass Spectrometry
LDA	Longitudinal data analysis
MAR	Missing at Random
MCAR	Missing Completely at Random
mcg	Micrograms
MDI	Metered-dose inhaler
Mg	Milligrams
MF	Mometasone Furoate
NHIS	National Center for Health Statistics
NSAE	Non-serious adverse experience
OTC	Over the counter
PD	Pharmacodynamics
PDLC	Predefined limits of change
PEF	Peak expiratory flow
PFT	Pulmonary Function Test
PGt	Pharmacogenetic
PK	Pharmacokinetics
PRN	When necessary
QD	Once daily
SABA	Short-acting beta-agonist
SAE	Serious adverse experience
SAP	Statistical analysis plan
SD	Standard deviation
T_{max}	Time to Cmax
US	United States
Wt	Weight

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – Assessing and Recording Adverse Events. I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	