Official Protocol Title:	A Phase-II, Randomized, Placebo-Controlled, Parallel-Group Clinical Trial to Study the Efficacy and Safety of MK-1029 in Adult Subjects with Persistent Asthma That is Uncontrolled While Receiving Montelukast
NCT number:	NCT02720081
Document Date:	03-Mar-2016

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TITLE:

A Phase-II, Randomized, Placebo-Controlled, Parallel-Group Clinical Trial to Study the Efficacy and Safety of MK-1029 in Adult Subjects with Persistent Asthma That is Uncontrolled While Receiving Montelukast.

IND NUMBER: 111,055
EudraCT NUMBER: 2015-005054-36

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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
1.0	Trial Summary	The duration of participation has been corrected to approximately 17 weeks as identified in the Trial Diagram and Trial Flow Chart. Clarified that subjects in either treatment group will take MK-1029 150 mg *or* matching-image placebo *and* that both treatment groups will be taking montelukast. Clarified that screening period is a total of up to 9 weeks.	Corrected error in summary.
2.1	Trial Design	Included text that this is a world-wide trial. Clarified that patients who undergo the 2 week Run-in period need approximately 3 weeks in "Pre-study" period to obey the "-5 weeks" rule from "Pre-study" to "Treatment" study period. Added "approximately" prior to Run-in, Treatment and Post-Treatment visit weeks to clarify that this time period will vary for subjects.	Clarified trial design study period, treatment groups and trial medication terminology.

		Clarified trial treatment during run-in and treatment periods. Clarified that "montelukast" and "montelukast sodium" may be used interchangeably.	
2.2	Trial Diagram	The timing for scheduled visits has been clarified in Section 2.2 Trial Diagram and Section 6.0 Flow Chart.	Provided as a correction of study visit weeks.
4.2.3.1	Efficacy Endpoints	Removed the description of Asthma Control Questionnaire (ACQ), Asthma Quality of Life Questionnaire (AQLQ), Asthma Disease Activity Score (ADAS)-6, and ADAS-4 from the endpoint discussion section.	Removed content description from the protocol.
5.1.2	Subject Inclusion Criteria	Inclusion Criteria #16 refers to Table 10 for investigators to check routine laboratory data. However, this should refer to Table 6, which correctly outlines the safety laboratory tests.	Corrected section reference.
5.1.3	Subject Exclusion Criteria	Corrected visit numbers regarding blood pressure measurements in Exclusion #16.	Corrected typographical error in blood pressure visit time points.

5.2.2, 7.1.1.8, 6.0 and 7.1.1.11.2	Trial Treatment, Trial Compliance and Witnessed Dosing	Added language to respective sections that single-blind dosing of study medication may be witnessed at Visit 3 as per site SOPs or local requirements. Clarified that witnessed dosing is required at Visit 4 to be consistent with Section 5.2.2, 6.0 and 7.1.1.11.2.	Added due to single-blind study design to maintain subject blind at Visit 3. Clarified double-blind trial medication witnessed dose at Visit 4.
6.0	Trial Flow Chart	Added study window for Visit 2 and updated week ranges for Visit 1 and Visit 2. Removed the study visit window for Visit 1 as this was an error. Corrected reference for Post-beta-agonist spirometry (FEV_1, FVC). Clarified spirometry timing for pre-beta-agonist spirometry.	Corrected and clarified study procedures and time frames.
7.1.2.2	Vital Signs	Corrected inconsistency with Section 6.0 flow chart to note that heart rate, sitting blood pressure and respiratory rate are to be collected as part of vitals.	Corrected vitals procedures to improve readability across multiple protocol sections.

7.1.5.2	Post-treatment Visit	Corrected discrepancy with Trial Flow Chart in Section 6.0 which had the correct window for the Post Treatment Visit of +4 days. Removed text relating to the Post-treatment Visit procedures *prior* to 14 days because the protocol does not allow for this visit to occur earlier than 14 days.	Corrected discrepancy in visit window for the Post Treatment Visit and aligned study window timeframe with Section 6.0 Flow Chart.
9.3	Clinical Supplies Disclosure	Disclosure envelopes will not be used. This global study is using the unblinding call center. Added a heading for blinded supplies to distinguish between open label and blinded clinical supplies disclosure.	Corrected emergency unblinding procedures for global study and clarified open label and blinded clinical supplies.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
4.2.1.2	Age Range	Included lower limit age range in this section.	Provided for clarity regarding age requirements.
4.2.2.1	Rationale for the use of Placebo	Re-arranged text to include rationale for placebo during run-in period first followed by rationale for placebo during treatment period. No content changes were made.	Placed text in chronological order of study phases.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
5.1.2	Subject Inclusion Criteria	"ACQ" and "ACQ-6" refer to the same questionnaire, but the terminology was not used consistently in Inclusion Criteria #13 and throughout the protocol. This has been corrected to use "ACQ-6" throughout the protocol.	Provided to add clarity regarding terminology of ACQ-6 questionnaire.
5.1.3	Subject Exclusion Criteria	Fixed error in Table 1 to note that creatinine is the specific lab test which will be drawn at Visit 1.	Edited table to be consistent with other table items.
5.2	Trial Treatment	Re-formatted Table 3 to clarify run-in and treatment trial medications. Used terminology of "matching-image placebo" and clarified that subjects will receive montelukast sodium 10 mg and MK- 1029 150 mg or MK-1029 matching-image placebo 150 mg throughout the section. Replaced "placebo-comparator" terminology with "experimental" for trial treatment use.	Clarified trial treatment medications during run-in and treatment periods, deleted text that was previously included in error and added a footnote relating to locally sourced trial medication.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
		Clarified that bottler order will not be labeled as such and thus removed "first" and "second" bottle text. Removed suggested text which was previously included in error because Merck GCS provides is providing clinical supplies. Included a footnote in the table that albuterol/salbutamol will be sourced locally.	
5.2.2, 5.2.3, 5.3, 8.1, 8.9, 8.11, 12.10	Timing of Dose Administration, Trial Blinding and Randomization or Treatment Allocation, Statistical Analysis Plan Summary, Power and Sample Size, Compliance (Medication Adherence) and Procedure for Tapering Controller Medications	Clarified treatment groups and included strength of montelukast. Clarified that placebo is matching-image 150 mg to MK 1029 150 mg.	Clarified treatment groups to increase readability across sections in the protocol.
5.5.2	Prior/Concomitant Inhaled Corticosteroid (ICS) Use	Clarified Visit 1 and medication criteria to progress to Visit 2 as well as the start point of Visit 3 ICS tapering.	Clarified study criteria and procedures relating to medication use.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
5.5.5.	Prohibited Medications	Removed conflicting information regarding post-treatment follow-up period.	Clarified discrepancy in text.
5.7.3	Contraception and Pregnancy Testing	Added language regarding pregnancy notification and trial medication discontinuation.	Clarified study procedures in the event of pregnancy between study visits.
5.8	Subject Withdrawal/Discontinuation Criteria	Reference provided for pregnancy and persistent elevations in ALT or AST discontinuation procedures.	Clarified discontinuation criteria.
7.1.1.2	Inclusion/Exclusion Criteria	Included the Section reference 5.1 for Entry Criteria.	Provided to increase readability across multiple protocol sections.
7.1.1.9.1	e-Diary	Moved e-Diary text which was previously incorrectly noted in section 7.1.2.6, which contained peak flow meter information. Clarified that e-Diary data will be entered twice.	Moved content to fall under the correct heading and clarified e-Diary data entry.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
7.1.1.9.4	Administrative Procedures	Section 7.1.1.9.4 regarding description of e-Diary questions and answer selections the protocol language indicates the e-Diary has a check box selection for "Call your doctor," however this is not a selection on the e-Diary screen and has been removed. Also clarified wording and order of choices as stated in the e-Diary screen.	Removed the check box since it does not impact e-Diary data analysis.
7.1.1.11.3	Double Blind Trial Medication + Montelukast Dispensed	Corrected error to reflect Trial Flow Chart in Section 6.0 schedule for dispensing of trial medication. Also clarified that only visit 4 will be a witnessed dose.	Corrected study medication dispensation discrepancy and clarified first witnessed dose visit in clinic.
7.1.1.11.4	Trial Medication Compliance	Moved paragraph regarding study staff instructions earlier in the section, there is no content change.	Increased readability of compliance check by site staff.
7.1.1.12	Review of Adverse Experiences	The protocol section reference regarding instructions on the reporting of SAEs to the sponsor is referred to Section 7.2.3; however, the correct reference is 7.2.3.1.	Corrected section reference to improve readability across multiple protocol sections.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
7.1.2.4	Asthma Control Questionnaire (ACQ-6) and Calculation of ACQ-6 score	Included the reference for Inclusion Criterion #13 related to ACQ-6 score eligibility.	Included section reference to improve readability across multiple protocol sections relating to ACQ-6 score eligibility.
7.1.2.5	Asthma Quality of Life Questionnaire (AQLQ(S))	Clarified that the questionnaire will be programmed in the e-Diary and the order of the e-Diary questionnaires which is also included in Section 7.1.2.4.	Clarified e-Diary questionnaire design.
7.1.2.6.1	PEF to Determine "Personal Best" and Alert Levels	The protocol section reference regarding deterioration of asthma is incorrectly referred to Appendix 12.7 and has been corrected to refer to Appendix 12.9.	Corrected section reference.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
7.1.2.7	Spirometry, also known as Pulmonary Function Testing (PFT)	Re-arranged content within section to increase readability. New content additions included adding a "Calibration" subheading and clarifying the timing of spirometry procedures. Additionally, corrected that NHANESIII and/or The Journal of The Japanese Respiratory Society guidelines (as applicable per local guidelines)reference ranges are to be used to determine percent predicted of both FEV_1 and FVC	Re-arranged structure and added section subtitle. Included timing reminder to improve readability across multiple protocol sections, corrected content of reference ranges and included new reference range.
7.1.2.7.1	Reversibility	The protocol section reference regarding asthma medications is referred to as Section 3.2.1.4 and has been corrected to refer to Section 5.5.1. Also added reference to Appendix 12.7 for reversibility testing. Corrected wording of Visit 2 to "pre-study" phase to align with study diagram and flow chart.	Corrected section reference, added additional reference and corrected study visit terminology.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
7.1.2.7.3	Post Beta-Agonist Spirometry (FEV_1, FVC)	The protocol section reference regarding post beta-agonist spirometry procedures is referred to as Appendix 12.8 and has been corrected to refer to Appendix 12.7.	Corrected section reference.
7.1.3.1	Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)	The laboratory evaluations incorrectly referred to Section 12.4 twice and has been corrected to refer to Table .1	Corrected section reference.
7.1.4.4	Calibration of Critical Equipment	The reference to Section 7.1.2.6 for detail on calibration of the spirometer is incorrect and has been corrected to refer to Section 7.1.2.7	Corrected section reference.
9.2	Packaging and Labeling Information	Clarified that supplies are for four weeks of dosing.	Clarified clinical supplies dispensation.
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.	To include trial registration and results posting obligations to the EMA
11.0	List of References	Deleted reference #17, #18 and #19 as related content moved to the supplemental statistical analysis plan, and updated subsequent numbering in the section and throughout the protocol.	Content will not be included in the protocol therefore the references are deleted.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
12.3	Appendix	Removed "Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff Pharmacogenetics Informational Brochure for IRBs/IECs & Investigational Site Staff" and replaced with "Pharmacogenetics Informational Brochure for IRBs/IECs & Investigational Site Staff."	Only the leftover extracted DNA would be stored for FBR therefore included the correct brochure.
12.4	Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Types	Clarified that Serum β-Human Chorionic Gonadotropin will be drawn at Visit 1 and for subsequent study visits if urine pregnancy test is positive.	Clarified parameter for testing to increase readability across protocol.
All	All	Minor editorial changes as needed	To ensure consistency through the document.

1.0 TRIAL SUMMARY

Abbreviated Title	Phase-II Study of MK-1029 added to Montelukast in Adults with Uncontrolled Asthma
Sponsor Product Identifiers	MK-1029 Montelukast
Trial Phase	Phase-II
Clinical Indication	Treatment of persistent asthma
Trial Type	Interventional
Type of control	Placebo
Route of administration	Oral
Trial Blinding	Double-blind
Treatment Groups	• MK-1029 150 mg and montelukast 10 mg • MK-1029 150 mg matching-image placebo and montelukast 10 mg
Number of trial subjects	Approximately 110 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 17 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject participates in the trial for up to about 17 weeks from the time of signing the Informed Consent Form (ICF) through the final contact. After a pre-screen, pre-study and run-in phase (total of up to 9 weeks), each subject receives assigned treatment for about 6 weeks. After the end of treatment, each subject is followed for 2 weeks.
Randomization Ratio	1:1

A list of abbreviations used in this document can be found in Section 12.6.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a world-wide randomized, double-blind placebo-controlled, parallel-group trial of MK-1029 in subjects with persistent asthma who remain uncontrolled while being maintained on montelukast (may be referred to and/or used interchangeably with montelukast sodium), to be conducted in conformance with Good Clinical Practices. The purpose of this trial is to examine the effects of adding MK-1029 to montelukast therapy, versus maintaining montelukast alone, in adults with persistent asthma who have a specific genetic marker for a clinical efficacy response to MK-1029. In brief, subjects with persistent asthma are evaluated for eligibility (including the ability to taper off any pre-study asthma controller therapy other than montelukast). Eligible subjects whose asthma is uncontrolled during the run-in period (while receiving single-blind MK-1029 150 mg matching image placebo and montelukast sodium 10 mg) enter a 6-week double-blind treatment period in which they are randomized to receive *either* MK-1029 150 mg and montelukast 10 mg or MK-1029 150 mg matching-

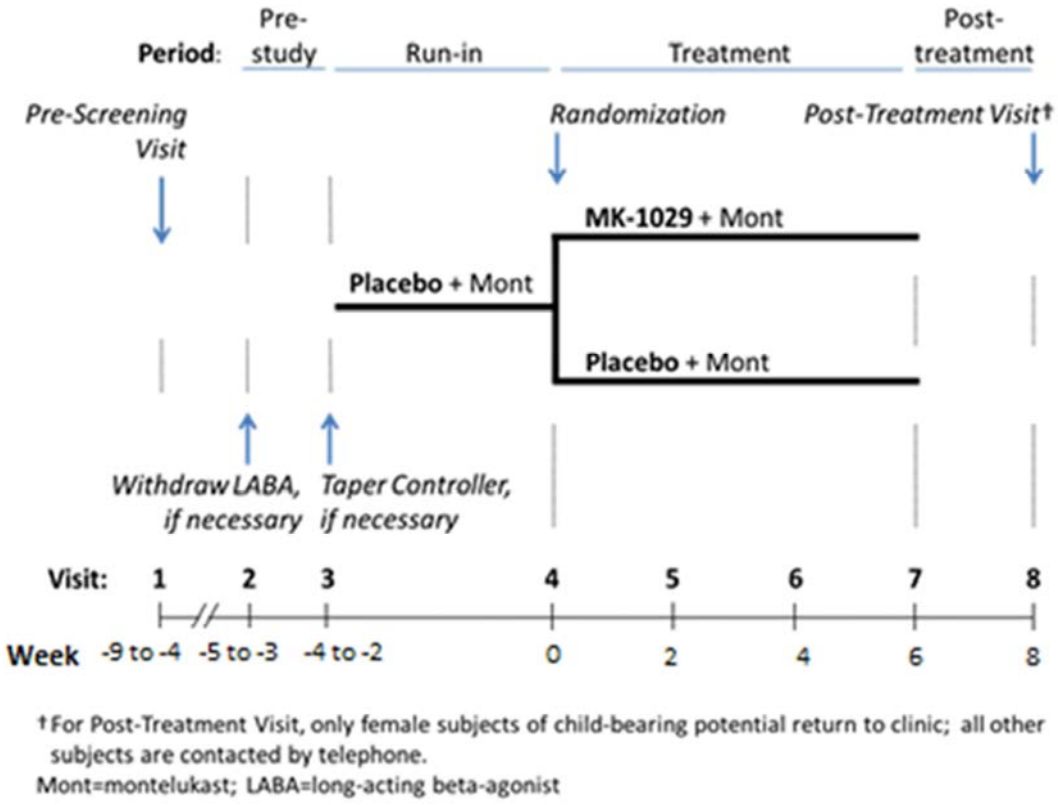
image placebo and montelukast 10 mg. Follow-up information is obtained approximately 2 weeks after completing the double-blind treatment period. The study is summarized as follows:

- **Pre-screening**: At this visit, a blood sample is collected to assess for the presence of a specific genetic marker for a robust clinical efficacy response to MK-1029 (see Section 4.2.1.1).
- **Pre-study** (approximately 1 to 3 weeks): Any eligible subjects receiving Long-acting Beta-Agonist (LABA) therapy must discontinue the LABA at the start of this period.
- **Run-in** (approximately 2 to 4 weeks): Subjects receive single-blind MK-1029 150 mg matching-image placebo and open-label montelukast 10 mg. Subjects taking asthma controller therapies prior to Visit 2 must discontinue or taper off these pre-study medications before randomization (according to a tightly specified approach) while receiving open-label montelukast 10 mg.
- **Treatment** (approximately 6 weeks): Subjects receive double-blind treatment of MK-1029 150 mg plus montelukast 10 mg; *or* MK-1029 150 mg matching-image placebo plus montelukast 10 mg.
- **Post-Treatment** (approximately 2 weeks): Follow-up is scheduled to occur after the last dose of trial medication. All female subjects of child-bearing potential are to return to the clinic for a follow-up visit that includes a urine pregnancy test. All other subjects will receive a telephone contact for post-treatment evaluation.

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 diagram is depicted in Figure 1



†For Post-Treatment Visit, only female subjects of child-bearing potential return to clinic; all other subjects are contacted by telephone.
Mont=montelukast; LABA=long-acting beta-agonist

Figure 1 Trial Diagram

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

In adults who have persistent asthma that remains uncontrolled while receiving montelukast and who have a specific genetic marker for response to MK-1029:

Primary Objective: To demonstrate that MK-1029, compared with placebo, increases lung function when added to montelukast.

Hypothesis: When added to montelukast, treatment with MK-1029 is superior to placebo, as demonstrated by an increase in forced expiratory volume in one second (FEV_1), measured as the average change from baseline at the end of Week 4 and Week 6 of treatment.

3.2 Secondary Objective(s) & Hypothesis(es)

1) **Key Secondary Objective:** To demonstrate that MK-1029, compared with placebo, improves control of asthma when added to montelukast.

Hypothesis: When added to montelukast, treatment with MK-1029 is superior to placebo, as demonstrated by a decrease in the percent of days with worsening asthma (%d-WA), measured daily during Week 3 to Week 6 of treatment (inclusive).

2) **Objective**: To characterize the safety and tolerability of MK-1029, when added to montelukast, during 6 weeks of treatment.

3.3 Exploratory Objectives

1) **Objective**: To explore the relationship between pre-specified single-nucleotide polymorphisms (SNPs) and response to the treatment administered. Genetic variation will be analyzed for association with clinical data collected in this study.

2) **Objective**: To explore the relationship between genetic variation and response to the treatment administered. Variation across the human genome will be analyzed for association with clinical data collected in this study.

4.0 BACKGROUND & RATIONALE

4.1 Background

MK-1029 is a potent and selective Chemoattractant Receptor-homologous molecule on Th2 cells (CRTH2) receptor antagonist that is being developed as monotherapy and/or combination therapy with montelukast for chronic asthma. The availability of a novel, oral, potent antagonist of CRTH2, particularly in combination with montelukast, will offer asthmatic patients a treatment option that is both highly efficacious and convenient as an oral therapy, thus fostering better compliance and asthma control.

Refer to the Investigator's Brochure (IB) for detailed background information on MK-1029.

4.1.1 Pharmaceutical and Therapeutic Background

MK-1029 is a specific inhibitor of CRTH2 (also known as DP2), a G protein-coupled receptor for the inflammatory mediator prostaglandin D_2 (PGD_2). The major cellular source of PGD_2 in the human lung is the mast cell [1], which is recognized to be a major effector cell type in asthma. Cells that are known to express CRTH2 include eosinophils, T-helper cell type-2 (Th2) lymphocytes, basophils, and an innate lymphocyte thought to be the principal early producer of IL-13 [2]. In susceptible individuals, inhaled antigens interact with receptor-bound Immunoglobulin E (IgE) on the surface of mast cells, inducing clustering of IgE receptors. Clustered IgE receptors trigger the release of pro-inflammatory mediators including PGD_2, which activates CRTH2 on eosinophils, basophils, and Th2 cells. Accumulating evidence indicates that agents that target CRTH2 may be beneficial in asthma. In an animal model, inhalation of PGD_2 enhances eosinophilic and lymphocytic airway inflammation in a CRTH2-dependent fashion [3]. Additionally, over-expression of PGD synthase, an enzyme that catalyzes production of PGD_2, leads to increased allergic airway inflammation and Th2 cytokines in transgenic mice [4]. In humans, PGD_2 is found at high levels in bronchoalveolar lavage fluid of asthmatics [5]. Finally, recent clinical studies of other CRTH2 antagonists have suggested clinical efficacy in subjects with asthma [6]. In

contrast, clinical trials of compounds that antagonize the other recognized receptor of PGD_2, DP1, showed a lack of clinical efficacy, whether as a specific antagonist of DP1 [7], or as a dual antagonist of DP1 and CRTH2 [8]. Taken together, these findings are consistent with a potentially important role for PGD_2 and for inhibition of one of its two receptors, CRTH2, in the treatment of asthma.

Based on studies designed to assess the potential for drug-drug interactions (DDI), early data have suggested that exposure of MK-1029 and its glucuronide metabolite may be increased by inhibitors of the OATP1B1 and OATP1B3 proteins. MK-1029 is not expected to be an OATP1B1 inhibitor at the proposed clinical dose. Based on *in vitro* data, MK-1029 is not expected to be a "victim" of an interaction with the major human CYP or UGT isoforms at the target concentrations expected in this trial. Montelukast, at the clinically recommended dose, is not expected to inhibit the hepatic uptake of MK-1029 based on both *in vitro* and *in vivo* drug interaction data. Refer to the Investigator's Brochure (IB) for more detailed information.

4.1.2 Results from a Recently Completed Clinical Trial

Refer to the Investigator's Brochure (IB) for summaries of the primary results of all completed clinical trials data.

The primary efficacy results for Protocol 011 (P011), a 2-period crossover trial that assessed the addition of MK-1029 to montelukast in subjects with persistent asthma, are described in the IB: MK-1029 (versus placebo, when each was added to open-label montelukast) did not show significant efficacy in the primary analysis of lung function, measured as FEV_1, at the end of the 4-week treatment period, with an improvement of only 47mL (p=0.282).

Additional efficacy results have subsequently become available from P011, including from secondary pharmacogenetic analyses of the clinical efficacy data. The pharmacogenetic analyses assessed a set of approximately 70 SNPs that had been pre-specified for analysis in P011, based on available literature suggesting these SNPs could have a potential role in the biology of CRTH2 receptor antagonism for treatment of asthma. After P011 was unblinded, a closer examination of the data also revealed a baseline imbalance on efficacy measurements across treatment periods in one of the two crossover sequences in this study; therefore, a subsequent statistical adjustment for the baseline imbalance artifact was conducted. Finally, across the 70 pre-specified SNPs that were analyzed, a large treatment effect of MK-1029 was discovered in association with the presence of [redacted] at a SNP with the Reference SNP (rs) identifier number [redacted] In this pre-specified pharmacogenetic analysis, MK-1029 showed an improvement of 268mL in the 29 subjects in P011 who had a genotype [redacted]. This large treatment effect was significantly greater than the effect seen in the 74 subjects in P011 without this genotype, with a significant treatment-by-genotype interaction (including after Bonferroni adjustment), as shown in Figure 2.

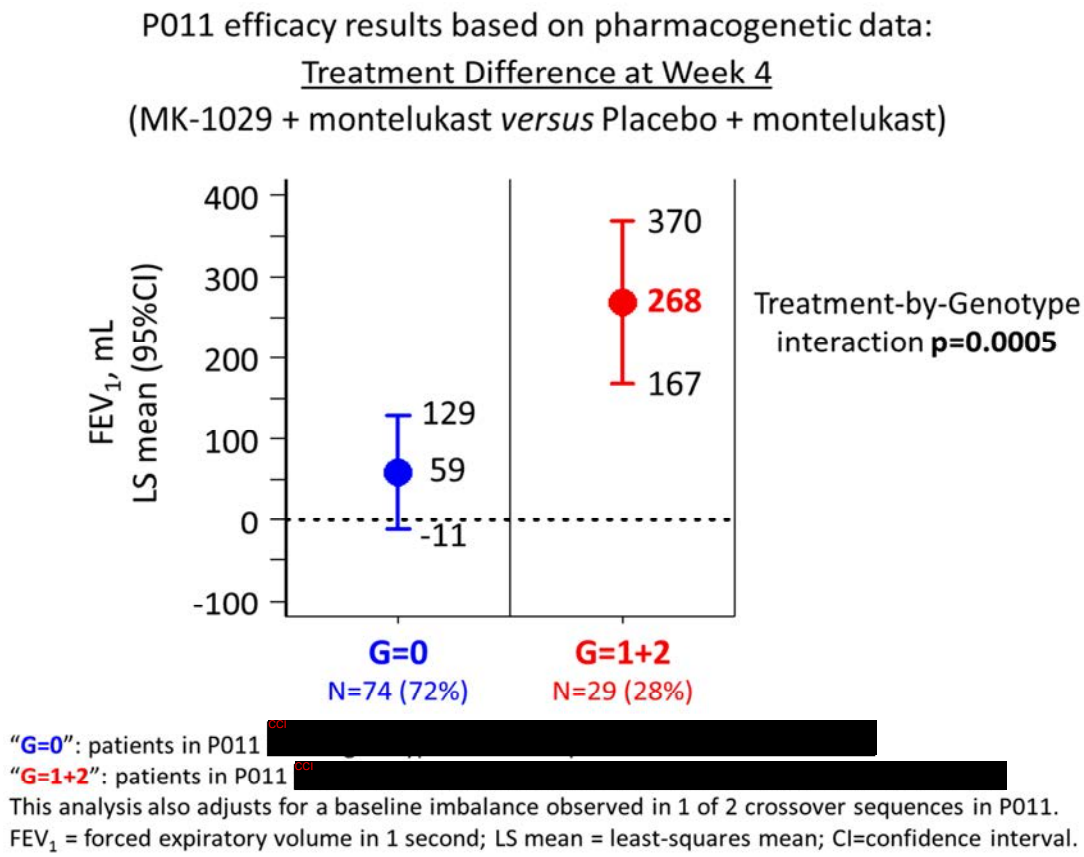


Figure 2 MK-1029 Effect (when Added to Montelukast) in a Pre-Specified Pharmacogenetic Analysis.

4.1.3 Background on Montelukast

Cysteinyl leukotrienes have been correlated with the pathophysiology of asthma and allergic rhinitis. Montelukast sodium is an antagonist of the cysteinyl leukotriene receptor type-1 ($CysLT_1$) receptor. It binds with high affinity and selectivity to the $CysLT_1$ receptor (in preference to other pharmacologically important airway receptors, such as the prostanoid, cholinergic, or beta-adrenergic receptor). Montelukast inhibits physiologic actions of cysteinyl leukotrienes at the $CysLT_1$ receptor without agonist activity. In adults, oral montelukast 10 mg once daily in the evening is approved for prophylaxis and treatment of chronic asthma.

Montelukast has been evaluated in randomized controlled clinical studies for treatment of asthma in approximately 2600 adult patients 15 years of age and older. In two similarly designed, 12-week placebo-controlled clinical studies, the only adverse experiences reported as drug related in ≥1% of patients treated with Montelukast and at a greater incidence than in patients treated with placebo were abdominal pain and headache. The incidences of these events were not significantly different in the two treatment groups. With prolonged treatment, the adverse experience profile did not change.

Co-administration of MK-1029+Montelukast

In a bioavailability study assessing the combination of MK-1029 and montelukast (this combination is referred to as MK-1029A), two probe fixed-dose combination (FDC) formulations were compared with co-administration of the individual components. In Protocol 013, 24 healthy adult subjects received 3 treatments in a crossover design: a single MK-1029A FDC tablet (MK-1029 150 mg with montelukast sodium 10 mg) as a monolithic-blend formulation, a single MK-1029A FDC tablet (MK-1029 150 mg with montelukast sodium 10 mg) as a bi-layer formulation, and co-administration of a single MK-1029 150 mg tablet with a montelukast sodium 10 mg tablet. The pharmacokinetic characteristics of each analyte (MK-1029 and montelukast) were very similar between the two test formulations. For MK-1029 and montelukast, the median T_{max} of the monolithic tablet, the bi-layer tablet, and co-administration was 2.00 hours. Also, montelukast and MK-1029 exposures observed in this study when co-administered were similar to exposures observed in a previous drug-drug interaction study. All treatments were deemed generally safe and were well tolerated by the subjects. There were no serious adverse experiences (SAEs) reported during this study and all adverse experiences (AEs) reported were mild and resolved prior to completion of the study. No subject was discontinued during the study due to adverse events. For all panels, there were no clinically important abnormalities in laboratory parameters, vital signs, and electrocardiogram (ECG) parameters. Refer to the Investigator's Brochure (IB) for more detailed information.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Asthma is a highly prevalent disease associated with significant morbidity and mortality, and accounting for high direct and indirect healthcare expenditures. World Health Organization (WHO) data currently estimate the prevalence of asthma to be 300 million individuals worldwide, with this number expected to increase to 400 million by 2025 [9]. This high disease burden is in part due to patients who are not well controlled on standard therapy [10]. In addition, compliance with standard inhaler therapy is relatively low. It is estimated that 44.2% and 51.5% of patients who begin a combination and concurrent inhalational therapy, respectively, do not renew their initial prescription during the first year [11]. Alternative options to inhalers include oral agents, such as montelukast and zileuton, as well as methylxanthines such as theophylline; however, these agents are recognized to be less potent than inhaled agents. Therefore, there is a need for a new, well-tolerated oral agent that effectively treats asthma, either alone or in combination with available therapies, such as oral montelukast.

4.2.1.1 SNP+ Population

Based on the presence of an identified genetic marker for the efficacy response to MK-1029 (when added to montelukast), the efficacy data in this trial may demonstrate the utility of a highly specific predictor of a robust clinical response to treatment with MK-1029 for asthma, an approach using genotypic data for patient selection that is sometimes referred to as "personalized medicine" or "precision medicine".

This trial will enroll subjects with a specific genetic marker for response to MK-1029, herein referred to as the SNP+ ("SNP positive") population. As defined for this trial (see also Section 4.1.2) SNP+ [redacted] SNP. Pre-screening in this trial uses pharmacogenetic testing to identify SNP+ patients. Only subjects who are SNP+ are eligible to continue into the pre-study period. Additionally, randomized allocation to treatment is stratified [redacted] (i.e., having [redacted] copies of the [redacted] SNP (see also Section 5.4).

4.2.1.2 Age Range

The age range (18 to 65 years, inclusive) for this study is consistent with many clinical trials of similar design. Analysis of a large cohort of asthmatics [12] suggests that late-onset asthmatics are more likely to demonstrate sputum neutrophilia and are likely to be phenotypically distinct from asthmatics whose onset of asthma is <45 yr [13]; therefore, we have established 65 years of age as the upper limit age range for recruited subjects in this trial.

4.2.1.3 Lung Function

The inclusion criterion specifying ranges of lung function (e.g., FEV_1 ≥55%-predicted and ≤85%-predicted for subjects not receiving controllers and ≥60%-predicted and ≤90%-predicted for subjects receiving controllers) is based on the following considerations: International treatment guidelines for asthma, including from the Global Initiative for Asthma (GINA), generally divide asthma treatments into one of two categories [9]: "Non-controllers" are asthma medications that provide bronchodilation without treating the underlying inflammation of asthma; these medications include $beta_2$-adrenergic agonists, both short-acting beta-agonists (SABAs) and long-acting beta-agonists (LABAs). "Controllers" are asthma medications that can treat the underlying inflammation of asthma; these medications include corticosteroids (inhaled, oral or injected), anti-leukotrienes, methylxanthines, anti-IgE and/or other biologic therapies. The lower FEV_1 limits in both controller and non-controller subjects were chosen to include subjects who are likeliest to conform to the target patient population for MK-1029. A slightly higher FEV_1 criterion for subjects on controllers was chosen, under the presumption that patients receiving controllers as pre-study therapy may have underlying asthma that is more difficult to manage.

4.2.2 Rationale for Dose Selection/Regimen

A sheep model was used, initially, to determine MK-1029 exposures that reduce inflammatory lung dysfunction after inhaled allergen challenge. Plasma levels of MK-1029 that inhibit a pharmacodynamic (PD) marker for MK-1029 activity (surface expression of cluster of differentiation molecule 11b [CD11b], as an activation marker on eosinophils, in an *ex-vivo* PGD2 stimulation assay) were determined first. The degree of inhibition of the PD marker after exposure to MK-1029 was then examined versus the level of lung dysfunction induced by allergen challenge in sheep after exposure to MK-1029. This same approach was then applied in Phase-1 human data; first, establishing the relationship between plasma levels of MK-1029 and the inhibition of *ex-vivo* expression of CD11b on eosinophils; and then, examining lung function and sputum eosinophil counts in response to inhaled allergen

challenge in a Phase-1b study of subjects with allergic asthma. In Protocol 03 (P003, as fully described in the IB), a lung allergen challenge model was used to assess the effects of MK-1029 60 mg and 500 mg. Both doses significantly inhibited the late bronchoconstrictive and inflammatory responses following inhaled allergen challenge. Maximal effects were seen at the 60 mg dose; i.e., no greater effects were seen with the 500 mg dose in this allergen challenge model. These clinical results were also examined versus the results for detailed pharmacokinetics (PK) assessment and for the CD11b PD marker. The available Phase-I data suggest that the 150 mg dose is at (or near) the plateau of the dose-response curve for efficacy, which supported selection of the 150 mg dose for use in P011 and Protocol 012 (P012, as fully described in the IB). The margin of safety established in Phase-I trials (with doses up to 1000 mg) and in Phase-II trials further supports use of the 150 mg dose. Specifically, no safety issues were identified with MK-1029 at doses of 150 mg (and lower) administered once daily in P011 and P012, as fully described in the IB. Therefore, 150 mg once daily was chosen as the dose of MK-1029 for this trial.

4.2.2.1 Rationale for the use of Placebo

Placebo during the Run-in Period

This study targets a population of subjects who have asthma that is inadequately controlled while receiving montelukast. Both to ensure that this population is correctly identified and to maintain blinding of randomized therapy during the treatment period, the trial medication administered during the run-in period is (single-blind) placebo for MK-1029 added to open-label montelukast. As stated above, the risks of placebo treatment (during the run-in) are minimized by allowing subjects to continue their use of "as-needed" inhaled albuterol/salbutamol in addition to open-label treatment with montelukast and by providing subjects an action plan for deteriorating asthma (Appendix 12.9).

Placebo during the treatment period

To date, efficacy of MK-1029 has not been definitively established in asthmatics; therefore, a placebo comparison is necessary to ensure the validity of this study. The risks of placebo treatment are minimized by allowing all subjects to continue their use of "as-needed" inhaled albuterol/salbutamol in addition to open-label treatment with the asthma controller montelukast and by providing subjects an action plan for deteriorating asthma (Appendix 12.9). In addition, should subjects demonstrate evidence of deterioration in their level of asthma such that they require more than one oral steroid rescue during the treatment period, they will be discontinued from the trial medication.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

The primary efficacy endpoint in this trial is a measure of lung function that is considered standard in asthma clinical trials, FEV_1, which is known to have excellent measurement characteristics in various lung diseases and has been used as the basis for the product registrations of almost all asthma treatments now in wide clinical use. The key secondary efficacy endpoint, %d-WA, is a composite measure that combines subjective components

(e.g., symptoms scores reported by subjects in a daily e-Diary) and objective components (e.g., lung function measured daily as peak expiratory flow) into a single endpoint that provides a daily quantitative assessment of asthma control. The definition of %d-WA used in this trial has been used in a number of asthma studies previously performed by Merck and published in the peer-reviewed literature (Note: in these older publications, this endpoint was referred to as "percent of days with asthma exacerbations") [12,14,15,16].

The primary time period for evaluation of efficacy is during the final 4 weeks of the 6-week double-blind treatment period. Prior experience in P011 suggests that subjects begin to benefit from MK-1029 as early as 2 weeks from initiation of treatment. But, it is not expected that the treatment effect will plateau at the end of Week 2. Therefore, the primary efficacy assessment period for this trial begins at the start of Week 3 (i.e., after subjects have been exposed to treatment for a full 2 weeks) and proceeds through the end of Week 6. In this way, the primary and secondary objectives both evaluate the effect of the final 4 weeks of treatment.

- Primary – FEV_1: Spirometry is performed at visits scheduled every 2 weeks during the 6-week treatment period. Therefore, FEV_1 data obtained at the last 2 visits during this period (i.e., at the end of Week 4 and Week 6, respectively) measure the cumulative effect over the last 4 weeks of treatment, and the endpoint is calculated based on the measurements at Week 4 and Week 6.
- Key Secondary – %d-WA: This measure of asthma control is obtained daily. Therefore, this key secondary endpoint is calculated based on daily measurements obtained from the start of Week 3 through the end of Week 6, to measure the effect over the final 4 weeks of treatment.

4.2.3.2 Safety Endpoints

- Clinical and laboratory adverse experiences reported during each period of the trial.
- Change from baseline in vital signs parameters and change or percent change (as appropriate) from baseline in laboratory safety parameters at the end of treatment.

4.2.3.3 Planned Exploratory Biomarker Research

As described in Section 4.2.1.1, analysis of the SNP [redacted] SNP will be used as a key factor to define the groups being studied, in order to understand if this SNP is associated with efficacy of MK-1029 in this trial. SNP [redacted] was initially selected for pre-specified analysis in P011 [redacted] The [redacted] SNP was determined to be an expression SNP (eSNP), meaning that it was shown to associate with gene expression levels, in multiple different data sets. Published eSNP data [redacted] Also, this SNP is located in a Deoxyribonucleic acid (DNA) loop that is highly transcribed in mast cells. Like basophils, mast cells are inflammatory cells that are known to be associated with asthma and to generate large amounts of inflammatory mediators in asthma, such as Prostaglandin D_2 (which is

blocked by MK-1029) and Leukotriene D_4 (which is blocked by montelukast). Based on all of these available data, [redacted] defines "SNP+" status.

[redacted], is associated with long-term decline over time in the ratio of FEV_1/ forced vital capacity (FVC) in asthmatic patients, but not in non-asthmatic patients; this result [redacted] was both genome-wide significant and replicated. Of interest, [redacted] Additional fine-mapping analyses in the region of the [redacted] SNP have been performed, using data from P011. From these post-hoc analyses, two other SNPs have been identified that are in linkage disequilibrium [redacted] and are associated with a large FEV_1 effect in P011, similar to that seen [redacted] (Section 4.1.2, Figure 2); these SNPs are identified as [redacted] Because these three SNPs [redacted] are considered secondary to [redacted] they are not part of the definition of "SNP+" status in this trial.

Planned Genetic Analysis

Understanding genetic determinants of drug response is an important endeavor during medical research. This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or adverse events, the data might inform optimal use of therapies in the patient population. This research contributes to understanding genetic determinants of efficacy and safety associated with the treatments in this study.

In addition to evaluating variation across the human genome, SNPs [redacted] also of specific interest and so have been pre-specified for planned genetic analysis in this trial.

4.2.3.4 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on DNA specimens collected for future biomedical research 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. 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.

Some subjects in the trial may show a modest deterioration of asthma 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 bronchodilator rescue medication to be used as-needed. Instructions on when to use rescue medications will be provided to the subject. Trial subjects will use their peak expiratory flow (PEF) meter (a lung function measurement device) as a self-monitoring tool, as guided by the Action Plan for Deterioration of Asthma (Appendix 12.9), 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 action plan containing very specific instructions on actions to take if symptoms are increased and/or PEF is decreased. 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 round-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

Male/Female subjects with persistent asthma between the ages of 18 and 65 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 able to provide written informed consent for the trial and may also provide consent for Future Biomedical Research. However, the subject may participate in the trial without participating in Future Biomedical Research.
2. Be female or male between 18 and 65 years of age, inclusive.
3. Have a consistent clinical history, for at least one year, of symptoms of persistent asthma that may include, but are not limited to, dyspnea, wheezing, chest tightness, cough, and/or sputum production.
4. Must be willing to provide blood sample for SNP testing at Visit 1.
5. Must have documented SNP+ test result prior to Visit 2.

Contraception

6. Not be pregnant (as evidenced by negative serum pregnancy test for subjects of childbearing potential) or breastfeeding and does not plan to become pregnant for the duration of the trial and post-treatment follow-up period.

7. If of reproductive potential: Agree to remain abstinent or to use (and/or have their partner use) 2 acceptable methods of birth control within the projected duration of the trial. Accepted methods of birth control are: intrauterine device (IUD), diaphragm with spermicide, contraceptive sponge, condom, vasectomy, hormonal contraceptives.

   A female subject who is not of reproductive potential is eligible without requiring the use of contraception. A female subject who is not of reproductive potential is defined as one who has either 1) reached natural menopause (defined as 6 months of spontaneous amenorrhea with serum follicle stimulating hormone (FSH) levels in the postmenopausal range as determined by the laboratory, or 12 months of spontaneous amenorrhea), 2) 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, or 3) bilateral tubal ligation.

   A male subject who is not of reproductive potential is eligible without requiring the use of contraception. A male subject who is not of reproductive potential is defined as: one who has undergone a successful vasectomy. A successful vasectomy is defined as: (1) microscopic documentation of azoospermia, or (2) a vasectomy more than 2 years ago with no resultant pregnancy despite sexual activity post-vasectomy.

   Note: If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

Pulmonary function test (PFT)

8. Have acceptable lung function at Visit 2 and Visit 4:

   8.1 FEV_1 ≥55% and ≤85% of the predicted value (or, ≥60% and ≤90% of the predicted value if subject is receiving controllers) at Visit 2, after withholding inhaled beta-agonist bronchodilators prior to spirometry (see section 5.5.1); AND

   8.2 FEV_1 ≥50% and ≤85% of the predicted value at Visit 4, after withholding inhaled beta-agonist bronchodilators prior to spirometry (see section 5.5.1).

9. Have evidence of reversibility of airway obstruction, defined as an increase in FEV_1 of at least 12% and at least 200mL when measured 10 to 30 minutes following short-acting beta-agonist (SABA) administration, after withholding inhaled beta-agonist bronchodilators prior to spirometry (see section 5.5.1).

   NOTE: For subjects who are not on controllers at Visit 2, reversibility is documented once during Visit 2 or Visit 3; for subjects who are on controllers at Visit 2, reversibility is documented once during Visit 2 or Visit 4.

Asthma Medications Use

10. Have a history of asthma treatment, prior to Visit 1, that is in one of two categories (see section 4.2.1.3):

    10.1 Controllers: Receiving stable doses of low- or medium-dose ICS, combination ICS/LABA, and/or other asthma controller medications; and (based on investigator's judgment) can tolerate tapering of these controllers (e.g., ICS) or discontinuing these controllers (i.e., non-ICS) while receiving montelukast 10mg once daily (QD) starting at Visit 3; OR

    10.2 Non-controllers: Not receiving asthma controller medications, and using only "as-needed" inhaled SABAs, for ≥4 weeks prior to Visit 1.

11. Agree at Visit 3 to discontinue controllers (e.g., leukotriene antagonists other than montelukast), or taper them (e.g., ICS) over 2-4 weeks (as described in Appendix 12.10). Also, agree at Visit 3 to begin montelukast 10 mg QD.

12. Have a daytime and nocturnal SABA administration average ≥1 puff per day, as recorded on the subject's e-Diary for the last 7 days prior to Visit 4.

13. Have an ACQ-6 score meeting the following requirements.

    13.1 Non-controllers: At Visit 2, must have an ACQ-6 score ≥1.5 and a score between 1 and 6 for Question #6. At Visit 4, must have an ACQ-6 score ≥1.5.

    13.2 Controllers: Visit 4 must have an ACQ-6 score ≥1.5.

Trial-specific criteria

14. Be a non-smoker or is a non-smoker for at least 1 year, with a smoking history of no more than 10 pack-years (i.e., 1 pack [20 cigarettes] per day for 10 years) as evaluated at Visit 2.

15. Have a Body Mass Index (BMI) between 15 and 40 kg/m^2 inclusive (BMI =weight in kg/[height in meters]^2) (Appendix 12.5).

16. Be judged to be in stable health (except for his/her asthma) on the basis of medical history, physical examination, and routine laboratory data (see Table 6), and appears able to successfully complete this trial.

17. Demonstrate at least 80% compliance with self-administration of trial medication and at least 80% compliance with completion of the e-Diary (to record symptoms, SABA use, and PEF) between Visit 3 and Visit 4.

5.1.3 Subject Exclusion Criteria

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

1. Is, in the opinion of the investigator, mentally or legally incapacitated preventing informed consent from being obtained, unable to read or comprehend written material, or unable to comply with the study procedures or protocol.

2. Intends to move or anticipates missing any clinic visit days.

3. Has participated in a clinical trial involving an investigational drug within the 4 weeks prior to Visit 1.

Spirometry, also known as Pulmonary function test (PFT)

4. Is unable to perform acceptable, repeatable spirometry.
5. Has evidence of another clinically significant, active pulmonary disorder, such as bronchiectasis or COPD, documented by history, physical examination, or chest x-ray.
6. Has been treated in an emergency room for asthma within 4 weeks of Visit 1 or has been hospitalized for asthma or respiratory condition within 2 months prior to Visit 1.
7. Has had an upper respiratory tract infection (viral or bacterial) within 1 month prior to Visit 1.
8. Has evidence of active, clinically significant sinus disease within 2 weeks prior to Visit 1.
9. Experiences a clinically significant deterioration of asthma between Visit 2 and Visit 4. A significant deterioration of asthma is defined as one or more of the following:
    9.1 Decrease in absolute FEV_1 (in L) by 20% or more from the FEV_1 at Visit 2;
    9.2 Decrease in %-predicted FEV_1 to less than 50% of the predicted value;
    9.3 Clinical asthma exacerbation requiring emergency treatment, hospital admission (serious AE), or treatment with additional asthma medication (other than SABAs).

General Medical

10. Has a recent history (within 3 months of Visit 1) of myocardial infarction, congestive heart failure, or uncontrolled cardiac arrhythmia; or of a clinically significant psychiatric disorder, other than stable depression.
11. Is currently a regular user or a recent past abuser (within the past 5 years) of alcohol (>14 drinks/week) or illicit drugs, as evaluated at Visit 2.
12. Has undergone any major surgical procedure within 4 weeks prior to Visit 1.
13. Has donated a unit of blood within 2 weeks prior to Visit 1 or intends to donate a unit of blood at any time during the course of this study.
14. Has a history of HIV.
15. Is hypersensitive or intolerant to inhaled beta-agonists, leukotriene antagonists, leukotriene synthesis inhibitors, or any of their formulation components, including lactose and its metabolite, galactose.
16. Has evidence of uncontrolled hypertension, defined as systolic >160 mmHg and/or diastolic >100 mmHg, during at least 2 of the 3 study visits (Visit 2, Visit 3, and Visit 4).
17. Has a clinically unstable disease of the ophthalmologic, neurological, hepatic, renal, connective tissue, genitourinary, gastrointestinal, cardiovascular or hematologic systems.
18. Has a history of any illness that would require treatment with an excluded medication, could be immediately life threatening (e.g., ventricular arrhythmia, neoplasia, incompletely cured or treated in the last 3 months], poorly-controlled diabetes mellitus),

would pose a restriction on participation or successful completion of the trial, or would pose an additional risk to the subject on administration of trial medication.

19. Has a history of malignancy ≤5 years prior to signing informed consent except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer.

20. Has any of the following abnormalities on Visit 1 laboratory studies:

Table 1 Abnormal Lab Results at Visit 1

Lab Result	**Exclusion Value**
Creatinine	≥1.5 mg/dL
Hemoglobin	<11 g/dL
WBC count	<3000/mm^3
Platelet count	<100,000/mm^3
Alanine aminotransferase (ALT) †	>1.5 times the upper limits of normal (ULN)
Aspartate aminotransferase (AST) †	>1.5 times the upper limits of normal (ULN)
†Note: For the ALT and/or AST parameters, one retest will be allowed for subjects at Visit 1, if values are >1.5 x ULN and ≤2 x ULN.	

21. Has had an electrocardiogram (ECG), obtained at screening or at any point prior to randomization at Visit 4, which demonstrates a clinically significant or unexplained abnormality that requires further diagnostic evaluation or intervention (e.g., new clinically significant arrhythmia or a conduction disturbance).

22. Has taken or is taking any of the below prohibited medications:

Table 2 Prohibited Medications

Medication	**Timing of Last Dose**
SABAs other than albuterol/salbutamol	Throughout the study
Initiation of immunotherapy ("allergy shots" or sublingual immunotherapy)	At least 6 months prior to Visit 2
ICS high dose	At least 6 months prior to Visit 2
Omalizumab or other biological agents	At least 4 weeks prior to Visit 2
Systemic corticosteroids (e.g., oral, intravenous, intramuscular, intra-articular or rectal)	At least 4 weeks prior to Visit 2
Digoxin, digitoxin	At least 2 weeks prior to Visit 2
Inhibitors or substrates of OATP1B1 and OATP1B3: atazanavir, bosentan, clarithromycin, cyclosporine, gemfibrozil, lopinavir, methotrexate, paclitaxel, rifampin (Please see Table 4: OATP1B1/OATP1B3 inhibitors/substrates that are permitted)	At least 2 weeks prior to Visit 2
Inhaled long- or short-acting anticholinergic agents	At least 2 weeks prior to Visit 2
LABA (see also Section 5.5.1)	At least 12 hours prior to Visit 2
Oral controllers (e.g., theophylline)	After Visit 3
ICS low/medium dose	Between Visit 3 and Visit 4 (following controller tapering)

Specific medications, although not listed individually, are excluded if they are used to treat conditions that are excluded by the protocol. However, if a patient received an excluded therapy after being randomized that is not explicitly excluded in the protocol, the investigator will determine based on his/her clinical judgment if the patient may continue in the study.

23. Is known to be sensitive to or has not had previous exposure to aspirin or non-steroidal anti-inflammatory drugs.
24. Has previously been randomized in a study and received MK-1029.
25. 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.

Table 3 Trial Treatment

Trial Medication	Dose/Potency	Dose Frequency	Route of Administration	Treatment Period	Use
MK-1029 Matching-image Placebo	Placebo for 150 mg	QD	Oral	Run-in	Experimental
Montelukast sodium	10 mg	QD	Oral	Run-in	Standard of care
MK-1029	150 mg	QD	Oral	Treatment	Experimental
MK-1029 Matching-image Placebo	Placebo for 150 mg	QD	Oral	Treatment	Experimental
Montelukast sodium	10 mg	QD	Oral	Treatment	Standard of care
Albuterol/ Salbutamol†	90 µg – 100 µg per inhalation	1 or 2 inhalations QID PRN	Inhaled	Run-in & Treatment	Rescue medication
† Will be sourced locally, all other supplies will be provided by Sponsor.					

A subject who meets all eligibility criteria enters the placebo run-in period to receive MK-1029 150 mg matching-image placebo (in a single-blind fashion) and open-label montelukast 10 mg. Although the investigator is aware that the study drug during this period is placebo, "single-blind" requires that the subject is NOT told that the content of the study drug during this period is placebo.

The first dose of double-blind trial treatment is administered at the trial site at Visit 4.

Trial medication supplies are packaged in 2 bottles. One bottle contains open-label montelukast sodium 10 mg. The other bottle contains MK-1029 150 mg or matching-image placebo tablets.

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

5.2.1.1 Dose Selection (Preparation)

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

Subjects will be instructed to take 1 tablet from each bottle once daily in the evening at bedtime with or without food, throughout the duration of the run-in and treatment period of the study, with the exception of Visit 3 and Visit 4.

At Visit 3, dosing of trial medication may be witnessed as per site standard operating procedures (SOPs) or local requirements in the morning at the clinic. No evening dose will be administered on the day of Visit 3.

At Visit 4, dosing of trial medication will be administered as a witnessed dose in the morning at the clinic. No evening dose will be administered on the day of Visit 4.

All subsequent trial medication doses by the subject (i.e. unsupervised at home) will be administered once daily in the evening at bedtime with or without food

5.2.3 Trial Blinding

Prior to randomization, patients will receive MK-1029 150 mg matching-image placebo. A single-blinding technique will be used. The single-blind technique is specific to the period between Visit 3 and Visit 4. MK-1029 150 mg matching-image placebo will be packaged so that blinding is maintained. The subject will not know the treatment they are administered; however, the investigator and Sponsor personnel or delegate(s) who are involved in the treatment or clinical evaluation of the subjects will be aware of the group assignments.

A double-blinding technique with in-house blinding will be used. MK-1029 150 mg and the MK-1029 150 mg matching-image placebo will be packaged identically so that blinding 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.

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

Treatment allocation/randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 treatment arms. Subjects will be assigned randomly in a 1:1 ratio to *either* MK-1029 150 mg plus

montelukast sodium 10 mg *or* MK-1029 150 mg matching-image placebo plus montelukast sodium 10 mg.

5.4 Stratification

Treatment allocation/randomization will be stratified according to the number [redacted], yielding two strata:

1. [redacted]
2. [redacted]

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject.

5.5.1 Prior/Concomitant Beta-Agonist Bronchodilator Use

Inhaled bronchodilator medications must be restricted prior to clinic visits, as follows:

1. Inhaled SABA, such as albuterol/salbutamol, for at least 6 hours before any clinic visit;
2. Inhaled LABA administered twice daily, such as salmeterol or formoterol, for at least 12 hours before Visit 2;
3. Inhaled LABA administered once daily, such as vilanterol or indacaterol, for at least 24 hours before Visit 2.

If any of the above inhaled beta-agonist medications are required within the specified time prior to a visit, the subject should notify the investigator and the visit should be rescheduled. Compliance with respect to the withholding of medications will be noted on the case report form or electronic case report form.

Use of any inhaled SABA other than albuterol/salbutamol is prohibited during this study. Use of any beta-agonist bronchodilator other than by the inhaled route is also prohibited. It is expected that after Visit 2, subjects will no longer be using any LABA therapies.

5.5.2 Prior/Concomitant Inhaled Corticosteroid (ICS) Use

A subject, who has successfully met the criteria for Visit 1 and has been on a stable dose of low or medium ICS or combination ICS/LABA (any dose) for at least 4 weeks prior to Visit 2 can be screened to determine eligibility. For subjects taking combination ICS/LABA prior to Visit 2, they will be required to discontinue the LABA component at Visit 2 while continuing to receive an ICS component (until ICS tapering begins at Visit 3). If eligible at

Visit 3, these subjects must be able to tolerate tapering off ICS while taking montelukast 10 mg QD.

Maximal permitted daily doses* of ICS at screening are as follows:

- 1000 µg beclomethasone CFC
- 500 µg beclomethasone HFA
- 800 µg budesonide
- 2000 µg flunisolide
- 500 µg fluticasone propionate
- 100 µg fluticasone furoate
- <800 µg mometasone furoate
- 2000 µg triamcinolone acetonide
- 320 µg ciclesonide

*Note: These doses correspond to the approximate doses delivered to the lung, rather than the actuated doses.

Study subjects may not use ICS or combination ICS/LABA, at any dose, after they are randomized into the study at Visit 4.

5.5.3 Allowed Asthma Therapy

Subjects are permitted to use inhaled albuterol/salbutamol throughout the study on an "as-needed" basis for relief of asthma symptoms. Subjects are encouraged to decrease their use of albuterol/salbutamol if their asthma has improved.

In the event of significant deterioration of asthma, an action plan for treatment and continuation of subjects in the study is outlined in Appendix 12.9.

5.5.4 Allowed Allergic Rhinitis and Immunotherapy Medications

Intranasal corticosteroids will be allowed, if the patient has been on a stable dose for at least 4 weeks prior to Visit 2. The dose must remain constant throughout the study. Intranasal cromolyn or nedocromil will be permitted as needed during the study.

Non-sedating systemic antihistamines with low anticholinergic effects will be allowed throughout the study, as will oral or nasal decongestants.

Immunotherapy (e.g., allergy shots or sublingual immunotherapy), will be allowed if the subject has been on a stable dose of immunotherapy for at least 6 months prior to Visit 2.

5.5.5 Prohibited Medications

Specific medications, although not listed individually, are excluded if they are used to treat conditions that are excluded by the protocol. However, if a patient received an excluded therapy after being randomized that is not explicitly excluded in the protocol, the investigator will determine based on his/her clinical judgment if the patient may continue in the study.

1. The following inhibitors or substrates of OATP1B1 and OATP1B3 are prohibited at any dose: atazanavir, bosentan, clarithromycin, cyclosporine, gemfibrozil, lopinavir, methotrexate, paclitaxel, rifampin.
2. The following OATP1B1/OATP1B3 inhibitors or substrates are permitted, provided that the daily dose (alone, or as part of a fixed-dose combination) is less than or equal to the indicated dose. Because this list is not comprehensive, the investigator should use his/her medical judgment when a subject presents with an OATP1B1/OATP1B3 inhibitor or substrate not described in Table 4, or call the Sponsor Clinical Monitor for clarification:

Table 4 OATP1B1/OATP1B3 Inhibitors/Substrates that are Permitted

Drug	Maximum Allowed Daily Dose
atorvastatin	40 mg
cefoperazone	2 g
enalapril	20 mg
erythromycin	1 g
olmesartan	20 mg
pitavastatin	2 mg
pravastatin	20 mg
rosuvastatin	20 mg
simvastatin	20 mg
telmisartan	40 mg
valsartan	160 mg
caspofungin	70 mg by mouth
glyburide	20 mg
repaglinide	16 mg
torasemide	200 mg

3. Beta-adrenergic receptor blocking agents in individuals known to be sensitive to these compounds or who have not had previous exposure.
4. Aspirin and nonsteroidal anti-inflammatory medication in subjects known to be sensitive or subjects who have not had previous exposure to these compounds.

Subjects who, in the assessment by the investigator and after consultation with the Sponsor, require the use of any of the aforementioned treatments for clinical management should be removed from the trial.

There are no prohibited therapies during the post-treatment follow-up period.

5.6 Rescue Medications & Supportive Care

Throughout the trial, each subject will have access to a supply of bronchodilator rescue medication (to be purchased locally by the site) for use on an as-needed basis. Short-Acting Beta-Agonist (SABA) via metered-dose inhaler (MDI), as albuterol/salbutamol 90 or 100 µg

per inhalation, will be provided by sites to subjects for potential use at home as a rescue medication. The SABA is to be used in accordance with the product labeling.

- The subject should be advised to take SABA on a rescue/as-needed basis *only*, and *not* on a regular basis in absence 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 Pre-study visit. Because the use of SABA when taken as prevention for EIB is not considered rescue use, it should *not* be captured/recorded by subjects in the e-Diary for the purpose of assessing daily 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 the Pre-study visit (Visit 2), 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.
- Use of SABA in powder form (in lieu of the MDI provided) is prohibited.

5.7 Diet/Activity/Other Considerations

5.7.1 Diet/Activity/Awake/Sleep Cycle

Subjects will be allowed to consume their usual diet throughout the study and engage in their usual level of exercise throughout the study. However, it is recommended that subjects refrain from strenuous exercise for at least 72 hours prior to clinic visits during which blood samples will be collected (Appendix 12.4).

It is recommended that subjects maintain a constant day/night, awake/sleep cycle in order to reduce the diurnal variation that can be seen in pulmonary function testing.

5.7.2 Caffeine

Subjects are asked not to change their usual consumption of caffeine once enrolled in the study. It is recommended that subjects refrain from the use of caffeinated beverages or food for at least 8 hours prior to each clinic visit in order to reduce a potential confounding effect on pulmonary function testing.

5.7.3 Contraception and Pregnancy Testing

A subject who is of reproductive potential agrees to remain abstinent or use (and/or have their partner use) 2 acceptable methods of birth control within the projected duration of the study. Acceptable methods of birth control are: intrauterine device (IUD), diaphragm with spermicide, contraceptive sponge, condom, vasectomy, hormonal contraceptives.

A female subject who is not of reproductive potential is eligible without requiring the use of contraception. A female subject who is not of reproductive potential is defined as: one who

has either 1) reached natural menopause (defined as 6 months of spontaneous amenorrhea with serum FSH levels in the postmenopausal range as determined by the laboratory, or 12 months of spontaneous amenorrhea), 2) 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, or 3) bilateral tubal ligation.

A male subject who is not of reproductive potential is eligible without requiring the use of contraception. A male subject who is not of reproductive potential is defined as: one who has undergone a successful vasectomy. A successful vasectomy is defined as: (1) microscopic documentation of azoospermia, or (2) a vasectomy more than 2 years ago with no resultant pregnancy despite sexual activity post-vasectomy.

If there is any question that a subject will not be reliable in the use of these contraceptive methods, he/she should not be entered into the study.

Subjects must be completely informed of the unknown risks of pregnancy and agree not to become pregnant during the time they are participating in this study. In the case of a positive pregnancy test, study drug will be stopped immediately, and the patient will be discontinued. The site will contact the subject at least monthly and document the patient's status until the pregnancy has been terminated or completed. The outcome of the pregnancy will be reported to the Merck Clinical Monitor without delay.

All females participating in the study will have a serum beta-human chorionic gonadotropin (β-hCG) or urine pregnancy test at each study visit as indicated in the Study Flow Chart, beginning at entry with Visit 1 and ending with the Post-treatment Visit (Visit8). All females who discontinue before completion of the Treatment period will return 14 days after the Discontinuation Visit for a urine pregnancy test. Subjects who become aware they are pregnant between study visits should contact the site immediately and stop trial medication.

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures; including specific details regarding withdrawal from Future Biomedical Research, are provided in Section 7.1.4 – Other Procedures.

Table 5 provides reasons why a subject must be discontinued from treatment but may continue to be monitored in the trial, as well as reasons why a subject must be discontinued from treatment and the trial.

Table 5 Discontinuation Scenarios

Reason for Discontinuation Scenario	Action
The subject or legal representative (such as a parent or legal guardian) withdraws consent.	Discontinue from Treatment and Trial
The subject's treatment assignment has been unblinded by the investigator, Merck subsidiary or through the emergency unblinding call center.	Discontinue from Treatment and Trial
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 participation in the trial or does not allow the subject to adhere to the requirements of the protocol.	Discontinue from Treatment and Trial
The subject has a confirmed positive serum pregnancy test (Refer to Section 7.2.2 for procedures).	Discontinue from Treatment (may continue to monitor in the trial)
The subject develops persistent elevations in ALT or AST (2 consecutive measurements) ≥3 times ULN (Refer to Section 7.2.3.2).	Discontinue from Treatment (may continue to monitor in the trial)
Significant deterioration of asthma that **requires** discontinuation from trial medication based on one or more of the following: • decrease in %-predicted FEV_1 to less than 50% of predicted normal; • decrease in absolute FEV_1 (L) of ≥20% from baseline (at randomization, Visit 4).	Discontinue from Treatment (may continue to monitor in the trial)
The subject requires therapy with any excluded medication (including parenteral corticosteroids).	Discontinue from Treatment (may continue to monitor in the trial)
The subject has received any rescue therapy other than that outlined in Appendix 12.9.	Discontinue from Treatment (may continue to monitor in the trial)
Discontinuation due to asthma exacerbation that does not respond to the Action Plan for Deterioration of Asthma.	Discontinue from Treatment (may continue to monitor in the trial)

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

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:		Pre-study	Run-in	Treatment				Post-treatment	
Visit Number: Title:	**1** Pre-screening	**2** Pre-study	**3** Run-in	**4** Treatment	**5** Treatment	**6** Treatment	**7** Treatment	Discon-tinuation[1]	**8** Post-treatment[2]
Scheduled Week:	**-9 to -4**	**-5 to -3**	**-4 to -2**	**0**	**2**	**4**	**6**		**8**
Scheduling Visit Window (days):		±3	±3	±3	±3	±3	±3		+4
Administrative Procedures									
Informed Consent[3]	X								
Informed Consent for Future Biomedical Research		X							
Inclusion/Exclusion Criteria	X	X	X	X					
Subject Identification Card Dispensed		X							
Subject Identification Card Returned							X	X	
Medical History		X							
Complete Asthma Baseline Profile		X							
Review prior and/or concomitant therapy		X	X	X	X	X	X	X	X
Assign screening number	X								
Assign randomization number				X					
Review Study procedures reviewed with subject: e-Diary, rescue beta-agonist use, PEF, study medication		X	X	X	X	X			
Review Action Plan for Deterioration of Asthma with subject (see Appendix12.9)		X	X	X	X	X			
Dispense Subject e-Diary/PEF meter dispensed		X							
Review Subject e-Diary/PEF meter responses/data			X	X	X	X	X	X	
Return Subject e-Diary/PEF meter							X	X	
Schedule next visit[2]		X	X	X	X	X	X		
Review laboratory safety results (blood, urine pregnancy test)		X			X				X

Trial Period:		Pre-study	Run-in	Treatment				Post-treatment	
Visit Number: Title:	**1** Pre-screening	**2** Pre-study	**3** Run-in	**4** Treatment	**5** Treatment	**6** Treatment	**7** Treatment	Discon-tinuation[1]	**8** Post-treatment[2]
Scheduled Week:	**-9 to -4**	**-5 to -3**	**-4 to -2**	**0**	**2**	**4**	**6**		**8**
Scheduling Visit Window (days):		±3	±3	±3	±3	±3	±3		+4
Dispense/assess Rescue beta-agonist supplies assessed/dispensed[4]		X	X	X	X	X			
Single-blind trial medication and montelukast dispensed[5]			X						
Double-blind trial medication: Witnessed dosing[5]				X					
Double-blind trial medication and montelukast dispensed				X		X			
Trial medication compliance checked/inspected				X	X	X	X	X	
Trial medication returned				X		X	X	X	
Review of adverse experiences		X	X	X	X	X	X	X	X
Review of subject questionnaires		X		X		X	X	X	
Clinical Procedures/Assessments									
Focused Physical Exam (including height, weight)		X[6]					X	X	
Full Physical Exam			X						
Vital Signs (heart rate, sitting blood pressure, respiratory rate) [7]		X	X	X	X	X	X	X	
Electrocardiogram (ECG) 12-lead[7]			X						
Asthma Control Questionnaire (ACQ-6)		X[8]		X		X	X	X	
Calculate ACQ-6 score		X[8]		X					
Asthma Quality of Life Questionnaire (AQLQ(S))				X		X	X	X	
PEF to determine "personal best" and alert levels		X	X[9]	X					
Pre-beta-agonist spirometry (FEV_1, FVC) [10]		X	X	X	X	X	X	X	
Post-beta-agonist spirometry (FEV_1, FVC) [11]		X	X	X					
Calculate overall rescue beta-agonist use				X					

Trial Period:		Pre-study	Run-in	Treatment				Post-treatment	
Visit Number: Title:	**1** Pre-screening	**2** Pre-study	**3** Run-in	**4** Treatment	**5** Treatment	**6** Treatment	**7** Treatment	Discon-tinuation[1]	**8** Post-treatment[2]
Scheduled Week:	**-9 to -4**	**-5 to -3**	**-4 to -2**	**0**	**2**	**4**	**6**		**8**
Scheduling Visit Window (days):		±3	±3	±3	±3	±3	±3		+4
Laboratory Procedures/Assessments									
Laboratory safety tests (blood, urine) [12]	X			X			X	X	
Serum β-hCG test or FSH – if applicable[13]	X								
Urine Pregnancy Test – if applicable[14]		X	X	X	X	X	X	X	X
Blood for SNP testing[15]	X								
Blood for Genetic Analysis [16]				X					

[1] Discontinuation Visit is for subjects who are discontinued after randomization, but prior to completion of Visit 7.
[2] Female subjects of child-bearing potential must come to the clinic for a urine pregnancy test. All other subjects are expected to complete the post-treatment follow-up visit via telephone.
[3] Informed consent must be obtained prior to any Visit 1 procedures.
[4] The investigator will be responsible for providing and ensuring subjects have adequate supplies of inhaled SABA (albuterol/salbutamol).
[5] Trial medication will be witnessed in the clinic the morning of Visit 4 and *may* be witnessed in the clinic per site SOPs or local requirements the morning of Visit 3; no evening dose will be administered on these visit days. Subjects will be instructed to administer all subsequent doses, outside of the clinic, in the evening at bedtime with or without food.
[6] Height should only be measured once (at Visit 2 only).
[7] Vital signs and ECG should be obtained prior to administration of albuterol/salbutamol (reversibility).
[8] Only performed on non-controller subjects at Visit 2.
[9] Only to be performed at Visit 3 for subjects who discontinued LABA at Visit 2
[10] Spirometry testing should be initiated between 6 AM and 10 AM. Spirometry measurements for a given subject should occur at about the same time during each visit
[11] Spirometry measurements for a given subject should occur at about the same time during each visit. Post beta-agonist spirometry will be determined by administering 4 puffs of albuterol/salbutamol through a spacer device, then measuring spirometry 10 to 30 minutes after albuterol/salbutamol administration (Appendix12.7). Subjects who meet pre-defined reversibility criteria at one visit need not repeat reversibility testing at a later visit.
[12] Laboratory safety blood test samples should be collected between 6 AM and 10 AM at each visit. Safety blood test samples for a given subject should occur about the same time during each visit.
[13] A negative pregnancy test (serum β-hCG) at Visit 1 (and prior to Visit 4) must be confirmed for all female subjects of child-bearing potential.
[14] If urine pregnancy test is positive at any point during the trial, a serum β-hCG test is required for confirmation.
[15] The blood sample is drawn for genotyping [redacted].
[16] This sample will be drawn for [redacted] genotyping and for planned analysis of the association between genetic variants in DNA and drug response. Data analysis will be limited to [redacted] genotyping if the IRB/IEC does not approve of, or if there is a documented law or regulation prohibiting, the planned analysis of the association between DNA variations and drug response. Leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent.

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 to ensure that the subject qualifies for the trial (Section 5.1).

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. This will include a full medical history for the 5 years prior to Visit 1.

7.1.1.4.1 Asthma Baseline Profile

Subjects will also be asked to provide information on their asthma history and related conditions for completion of an Asthma Baseline Profile. The investigator or qualified designee will obtain medical history information about asthma to allow completion of an Asthma Baseline Profile at Visit 2.

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 4 weeks or longer as appropriate prior to Visit 2. Any prior medications are to be recorded on the electronic Case Report Form (eCRF).

Section 5.1.3 provides a list of medications prohibited prior to Visit 2.

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.

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 treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened more than once 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 7.1.5.1.

7.1.1.7 Assignment of Treatment/Randomization Number

All eligible subjects will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the subject for all procedures occurring after treatment allocation/randomization. Once a treatment/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 treatment/randomization number.

7.1.1.8 Trial Compliance

Interruptions from the protocol specified study medication for compliance ≤80% require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

Administration of trial medication may be witnessed by the investigator and/or trial staff at Visit 3 per site SOPs or local requirements for single-blind trial medication and will be witnessed at the Treatment Visit 4 for double-blind trial medication.

7.1.1.9 Study Procedures to be Reviewed with Subject

In the performance of this trial, there are a number of procedures that must be discussed with subjects, to ensure correct performance of procedures and appropriate collection of trial data. These include e-Diary use (for collection of data on SABA use, PEF, asthma symptoms, additional measures to manage deterioration of asthma , as well as triggering of alerts), appropriate use of medications during the trial, and collection of data regarding adverse experiences and other patient-reported outcomes.

7.1.1.9.1 e-Diary

The e-Diary will be used to collect asthma symptoms (daytime and nighttime), inhaled SABA (albuterol/salbutamol) use (daytime and nighttime), AM and PM PEF, and additional

measures to manage deterioration of asthma (i.e., oral steroids, unscheduled physician visits, emergency department visits or hospitalizations) throughout the study. The subject will complete all data fields in the electronic diary every morning and evening. The subject should be instructed to bring the e-Diary to all visits to confirm that the devices are used correctly and are working properly. The importance of maintaining a current and accurate e-Diary will be reinforced by the study staff.

All subjects must demonstrate proper use of the e-Diary, including adequate compliance. At Visit 2, the subject will be given an e-Diary to be completed twice daily and returned at the next visit. Before giving the e-Diary to the subject, the study coordinator is responsible for explaining to the subject the e-Diary questions and the proper method for entering data into the e-Diary twice daily. Subjects should be instructed to bring the e-Diary to the clinic at each visit. At each visit (Visit 3 through Visit 7 and/or discontinuation), the study coordinator must carefully review the e-Diary entries with the subject to ensure there is adequate comprehension of the questions/responses and adequate compliance with data entry.

Competence with the e-Diary will be assessed. The subject should demonstrate competence, including at least 80% compliance with recording e-Diary data between Visit 3 and Visit 4, in the opinion of the investigator and/or study site staff.

To ensure ongoing subject compliance with e-Diary reporting throughout the study, sites are requested to carefully monitor e-Diary data at least weekly using the study internet site. Sites should retrain subjects who are not compliant and should ascertain problems with non-compliance to ensure that subjects experiencing difficulties are re-trained.

The e-Diary data, including PEF readings, will be obtained and reviewed for each subject. The e-Diary will record information to a central database and/or a printed version of all e-Diary information will be provided to the investigator or qualified designee. The e-Diary information should be reviewed for completeness of entries and subjects should be re-educated in their correct use, if deemed necessary.

7.1.1.9.2 Rescue Short-acting Beta-agonist (SABA) use

Subjects should be carefully instructed to use inhaled SABAs on an "as-needed" basis only. Routine (habitual) use of inhaled SABAs in the absence of symptoms should be discouraged. Investigators will provide all subjects with inhaled SABAs (as albuterol/salbutamol only).

Twice daily (upon arising and before going to sleep), the subject will record in the e-Diary the total number of inhalations ("puffs") of SABA used. The number of SABA puffs to be recorded is the number of actuations of the canister. For example, when SABA use is required and 3 actuations are inhaled, this should be recorded as 3.

If the subject administered salbutamol immediately before going to bed these puffs must be recorded under total salbutamol puffs since arising. The puffs recorded under total albuterol/salbutamol puffs since bedtime must reflect the amount of salbutamol used since getting into bed and before arising at the normal time in the morning.

Subjects will also record the number of nebulizer treatments used, if any. If the subject should require short-acting beta-agonist by nebulization during the study, by convention one administration should be recorded as three puffs on the e-Diary.

Although habitual use of inhaled SABAs in the absence of symptoms should be discouraged, the 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 Pre-study visit. Because use of SABA when taken as prevention for EIB is not considered "as needed" rescue use; it should not be captured/recorded by subjects in the e-Diary.

The puffs of salbutamol used during a clinical visit to assess airway reversibility also are not considered "as needed" use, and will not be recorded on the e-Diary.

For trial eligibility: The subject must have a daytime and nocturnal beta-agonist administration average ≥1 puff per day, as recorded on the subject's e-Diary between Visits 3 and 4. This value will be calculated by the e-Diary at Visit 4. The average number of SABA puffs is the sum of puffs recorded in the morning e-Diary for the 7 days prior to Visit 4 (including the morning of the study visit) and in the evening e-Diary for the 7 days prior to Visit 4, divided by 7. If the patient did not record SABA puffs in any e-Diary for those 7 days, a value of 0 should be used for the estimated number of puffs.

7.1.1.9.2.1 Short-Acting Beta-Agonist Supplies Assessed/Dispensed

Albuterol/salbutamol, will be supplied by the investigative site as needed. The investigator or designee will record the lot number, expiration date, and drug dispensed.

7.1.1.9.2.2 Calculate Overall Rescue Short-Acting Beta-Agonist Use

This will be collected in the e-Diary and is the sum of daytime and nighttime number of puffs of SABA use for each day.

7.1.1.9.3 Asthma Symptoms

In the evening just before going to bed, the subject scores his/her symptoms for the period since arising. Symptoms to be considered by the subject in determining the daily symptom score are symptoms of asthma that might include, but are not limited to, chest discomfort (tightness), wheezing, shortness of breath (breathlessness), and cough.

Each of 4 questions is evaluated using a 7-point scale, as follows:

1) How often did you experience asthma symptoms today?

0	1	2	3	4	5	6
None of the time						All of the time

2) How much did your asthma symptoms bother you?

0	1	2	3	4	5	6
Not at all bothered						Severely bothered

3) How much activity could you do today?

0	1	2	3	4	5	6
More than usual activity						Less than usual activity

4) How often did your asthma affect your activities today?

0	1	2	3	4	5	6
None of the time						All of the time

7.1.1.9.4 Additional Measures to Manage Deterioration of Asthma

On the e-Diary, subjects will answer the following question regarding healthcare resource utilization and management of a deterioration of their asthma:

In the past 24 hours, did worsening asthma symptoms cause you to?

If yes, check all that apply:

- ❑ None
- ❑ Take oral steroids (e.g., prednisone)
- ❑ Make an unplanned visit to a physician's office or urgent care clinic
- ❑ Go to the emergency room
- ❑ Stay in the hospital overnight

If the subject answers "yes" to this question, the study coordinator should verify that any new medication or medication change is listed in the corresponding Concomitant Medication (CM) electronic case report form, that any procedures that occurred during a doctor's visit, hospitalization, or emergency room visit are listed in the Procedure (PROC) electronic case report form (only if related to the adverse experience), and that "asthma exacerbation" should be listed in the corresponding Adverse Events electronic case report form. Note that some of these events may require either consideration for, or mandatory, discontinuation, as outlined in Section 5.8.

7.1.1.10 Action Plan for Deterioration of Asthma

Subjects will be instructed to monitor their asthma symptoms and PEF levels and to telephone the study site in the event of deterioration of asthma. The investigator will review with each subject the procedures to be followed in the event of deterioration of asthma (Appendix 12.9). Note that any deterioration of asthma documented by the investigator should be considered an AE and should be evaluated and reported according to the procedures outlined in Section 7.2.

Note: Subjects who require rescue therapy (with prednisone) will be asked to return to the clinic (for an unscheduled visit) to perform spirometry measurements **before** prednisone therapy is initiated, whenever possible. The spirometry measurements obtained at these unscheduled visits will be used in the efficacy analysis for this study.

7.1.1.11 Trial Medication

7.1.1.11.1 Single-Blind Trial Medication + Montelukast Dispensed

Study medication will be dispensed at Visit 3 for 'at home administration' during the run-in period. All doses are to be taken in the evening, at approximately the same time of day.

7.1.1.11.2 Witnessed Dosing

During Visit 3, the first dose of trial medication may be witnessed in the presence of site staff as per site SOPs or local requirements. During Visit 4, the first dose of trial medication will be given as a witnessed dose in the clinic.

7.1.1.11.3 Double Blind Trial Medication + Montelukast Dispensed

Study medication will be dispensed for 'at home administration' at Visits 4 and 6. The first dose, at Visit 4 will be administrated at the site as a witnessed dose in the presence of site staff after all Visit 4 study procedures have been completed. All doses (except Visit 4 witnessed dose) are to be taken in the evening, at approximately the same time of day.

Unused study medication will be collected at specific study visits during the treatment period, as outlined in Section 6.0.

7.1.1.11.4 Trial Medication Compliance

The investigator or designee will review trial medication compliance with the subject. Any problems with medication usage should be addressed with the subject as soon as the investigator or designee becomes aware.

Study staff will instruct each subject to bring all study drug and rescue medications to each visit. The study drug and rescue medications (empty, partially used, and unused) will be inspected at all protocol-specified visits.

Subject must demonstrate at least 80% compliance with use of their trial medication between Visits 3 and 4 to be eligible for randomization. Throughout the trial, sites will determine

compliance by assessing if subjects have any missed doses or any overdoses of trial medication (which will be entered in the eCRF).

7.1.1.12 Review of Adverse Experiences

The investigator or designee will question the subject about all AEs and intercurrent illnesses since the last visit (as applicable) and will record the pertinent information on the eCRF.

See Section 7.2.3.1, for instructions on the reporting of SAEs to the sponsor and Section 7.2.4 for instructions on the assessment of AEs.

7.1.1.13 Review of Subject Questionnaires

The following questionnaires will be reviewed with the patient as indicated in the study flow chart (Section 6.0):

- Asthma Control Questionnaire (ACQ-6)
- Asthma Quality of Life Questionnaire (AQLQ(S))

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Physical Exam

A complete physical examination will be performed at Visit 3, and a focused physical examination will be performed at Visit 2 and Visit 7 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 focused physical examination as part of the discontinuation procedures.

A focused physical exam will include the following: assessment of appearance, throat and nasal examination, and auscultation of heart and lungs, height and weight measures. Other body systems may be examined as clinically indicated. Any abnormal physical findings (from visits other than Visit 2) should be recorded in the adverse event section of the eCRF.

7.1.2.2 Vital Signs

Vital signs including heart rate, sitting blood pressure, and respiratory rate should be assessed as indicated in the study flow chart (Section 6.0). Subjects should be resting in a semi-recumbent position for at least 10 minutes prior to having vital sign measurements obtained.

Vital signs should be obtained prior to administration of albuterol/salbutamol (e.g., for reversibility testing).

7.1.2.3 Electrocardiogram (ECG) 12-lead

A local 12-Lead ECG should also be performed at Visit 3, as indicated in the study flow chart (Section 6.0), and any abnormalities should be documented. Results must be available prior to the subject receiving study medication. Subjects should be resting in a semi-recumbent position for at least 10 minutes prior to having ECG readings obtained. Clinically

significant findings from the Visit 3 ECG must be documented in the subject's chart and captured on the medical history eCRF.

If an ECG is performed for any medical reason while the patient is on the study treatment or during the follow-up period, any clinically significant changes compared with the Visit 3 ECG must be captured as AEs on the eCRF and documented in the subject's chart.

The ECG should be obtained prior to administration of albuterol/salbutamol (e.g., for reversibility testing).

7.1.2.4 Asthma Control Questionnaire (ACQ-6) and Calculation of ACQ-6 score

The investigator or qualified designee will administer the 6 patient-reported items of the ACQ-6 to the subject at the visits indicated in the Study Flow Chart and upon study discontinuation. The ACQ-6 is a validated 6-item measure of asthma control that was developed for use in clinical trials to evaluate asthma control both at a single point in time and to assess change in asthma control over time in response to therapy.

The individual responsible for administering the questionnaire must review the standards for administration of the ACQ-6 and follow the procedures described below. The subject must complete the ACQ-6 independently. In order to mitigate any potential bias, every effort should be made to have the same individual administer the questionnaire at approximately the same time at each visit. The ACQ-6 administrator should explain to the subject that the ACQ-6 assesses how well their asthma is controlled. Ensure that the subject has a private, quiet place in which to complete the questionnaire. The subject should be reminded that all questions should be answered, that responses should be focused on asthma and not on other problems. Remind the subject of the recall period of the "last week." The ACQ-6 administrator will review the completed questionnaire with the subject (and the subject's legal representative, as appropriate) to ensure that all questions have been completed, and ask the subject to complete missing items. Completion of the ACQ-6 is estimated to take approximately 5 minutes. The ACQ-6 should be completed immediately after the AQLQ(S) is completed.

The ACQ-6 is scored as the mean of the responses to the 6 items. The score, therefore, is between 0 (totally controlled) and 6 (extremely poorly controlled). The developer does not have a specific standard for missing data but generally recommends no more than 10% missing data in a single questionnaire. Therefore, if more than one item is missing, then the score will not be calculated. Please note, at Visit 2 for subjects not receiving controllers, and at Visit 4 for all subjects, subjects will be required to respond to all 6 ACQ questions to determine eligibility in the study. The ACQ-6 administrator will confirm that complete responses are provided at these visits as needed, and that the subject meets the inclusion criteria (see Section 5.1.2 inclusion criterion #13) before a subject is randomized.

The ACQ-6 will be programmed into the e-Diary unit and will be completed at the visits specified in the Study Flow Chart. Instructions on the administration of the ACQ-6 questionnaire using the e-Diary unit will be provided by the vendor developing and supplying the e-Diary. SABA inhalation data reflecting rescue use, collected for the ACQ-6, will not be reconciled with the total SABA usage recorded in the e-Diary. In addition, no effort will be made to reconcile other individual components of the ACQ-6 (symptoms, activity limitation, or awakenings) with e-Diary data.

7.1.2.5 Asthma Quality of Life Questionnaire (AQLQ(S))

This is a self-administered validated questionnaire that will be programmed in the e-Diary .

The AQLQ(S) will be performed as indicated in the Study Flow Chart. The subject should complete the AQLQ(S) independently. The AQLQ(S) is to be completed before the ACQ-6.

Instructions on the administration of the AQLQ(S) using the e-Diary unit will be provided by the vendor developing and supplying the e-Diary.

7.1.2.6 Peak Flow Meter (PEF)

The peak flow meter will be provided to all study subjects for measurement of PEF at home (Appendix 12.8). The peak flow meter device used in this study measures and saves all relevant expiratory parameters, (i.e., PEF). Additional details (including setup/programming of the peak flow meter) will be provided by the vendor.

At the Pre-study (Visit 2), the subject will be provided with verbal and written instructions on the proper use of the e-Diary and the PEF meter. These instructions will be reviewed at each subsequent visit. In addition, the user will be guided through the entire process by clear and easy-to-read instructions on a screen. Visual indicators allow for an immediate assessment of the measurement. The Flow-Volume sensor complies with current American Thoracic Society / European Respiratory Society (ATS/ERS) standards and produces repeatable and accurate measurement results. The date and time will automatically be recorded.

The subject should be instructed to bring the peak flow meters to all visits to confirm that the devices are used correctly and are working properly. The subject should be instructed to perform triplicate PEF measurements twice daily (BID), in the AM upon rising and in the PM, immediately before study drug administration, at bedtime. All three values will be recorded and the best measurement will be determined through the e-Diary. The subject should be asked to refrain from using SABA within the 6 hours prior to performing the PEF measurements. If the subject should use SABA within 6 hours of his/her regular bedtime, the subject should measure the PEF *before using* the SABA. If it is more than 6 hours until bedtime, the subject will use SABA and wait until the regular bedtime to measure PEF. After the subject has completed their PEF measurements, he/she will be instructed to complete their e-Diary questions every morning and evening.

An alarm will be triggered if the subject hasn't made any measurements that AM or PM. It is very important that the subject use the peak flow meter and e-Diary twice a day.

At each study visit, after Visit 2, the investigator or qualified designee will review the PEF readings and any findings will be discussed with the subject and clinical relevance determined. The e-Diary data, including PEF readings, will be obtained (downloaded) and reviewed for each subject. The e-Diary will download all recorded information to a central database and/or a printed version of all e-Diary information will be provided to the investigator or qualified designee. The e-Diary information should be reviewed for completeness of entries and subjects should be re-educated in their correct use, if deemed necessary.

7.1.2.6.1 PEF to Determine "Personal Best" and Alert Levels

Three measurements of PEF will be obtained during the clinic visits and the "personal best" level (greatest value in 3 attempts) determined for the subject. An alert level at 60% of the personal best is calculated and programmed in the subject e-Diary as a reference level. The subject should be instructed to measure their PEF immediately upon rising in the morning and immediately before going to bed in the evening (prior to taking study drug, and before using any SABA [albuterol/salbutamol]), and to call the study site if their PEF level falls below the 60% alert range. In this situation, the subject's asthma status will be assessed by the site and an action plan for deterioration of asthma will be instituted, if appropriate (Appendix12.9).

Competence with the PEF meter will be assessed. The subject should demonstrate competence, including at least 80% compliance with recording PEF completion, in the opinion of the investigator and/or study site staff.

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

A standard spirometer will be provided for this study.

Spirometry should be performed in accordance with guidelines established by the American Thoracic Society/European Respiratory Society (ATS/ERS) Standardization of Lung Function Testing: Standardization of Spirometry; 2005.

At all visits, PFTs should be performed in the morning, between 6 AM to 10 AM. Spirometry measurements for a given subject should occur at about the same time during each visit.

Every attempt must be made to use one spirometer consistently on each subject. 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 study.

The subject should refrain from using SABA 6 hours prior to PFT initiation unless the PEF falls below the stability limit. After albuterol/salbutamol has been withheld for the appropriate interval, tests will be performed to measure FEV_1 and FVC. Reference ranges are to be used to determine percent predicted include NHANESIII and/or The Journal of The Japanese Respiratory Society guidelines, whichever is applicable per local requirements.

Three measurements will be performed at each visit. The largest FEV_1 and the largest FVC should be recorded after the data are examined from all of the acceptable curves, even if they do not come from the same curve. Automated best efforts, which combine FEV_1 and FVC, are not acceptable.

Calibration

The spirometer must be calibrated following the principles of the ATS/ERS Guidelines (i.e., with a 3-liter syringe) every day that a study subject is seen and spirometry is performed. The calibration records should be kept in a reviewable log. It is preferred that the calibration equipment (i.e., a 3-liter syringe) that is used to calibrate the spirometer be subjected to a validated calibration according to the manufacturer's specifications.

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

7.1.2.7.1 Reversibility

At Visit 2, a reversibility test will be administered following pulmonary function testing after asthma medications have been withheld for the appropriate intervals (Section 5.5.1). Subjects will receive four puffs of albuterol/salbutamol from a primed MDI (Appendix 12.7). Reversibility, which is defined as an increase in absolute FEV_1 of greater than or equal to 12%, and at least 200 mL, over the Baseline value, should be demonstrated within 30 minutes of bronchodilator administration.

If the subject meets reversibility criteria at Visit 2, post SABA PFTs are not needed after Visit 2.

If the subject does not meet the reversibility criterion at Visit 2, and the subject is not receiving controllers, reversibility testing will be performed at Visit 3. A subject who is not receiving controllers at Visit 2, must demonstrate reversibility once during Visit 2 or Visit 3.

For subjects who were receiving controllers during the pre-study period between Visits 2 and 3 and did not demonstrate reversibility at Visit 2, as defined above, reversibility testing can be repeated at Visit 4. Reversibility must be documented once during Visit 2 or Visit 4.

7.1.2.7.2 Pre-Beta-Agonist Spirometry (FEV_1, FVC)

Spirometry testing should be initiated between 6 AM and 10 AM, and measurements should occur at about the same time during each visit for each subject.

7.1.2.7.3 Post-Beta-Agonist Spirometry (FEV_1, FVC)

Post beta-agonist spirometry will be determined by administering 4 puffs of albuterol/salbutamol through a spacer device and then measuring spirometry 10 to 30 minutes after albuterol/salbutamol administration (Appendix 12.7).

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 6.

Laboratory evaluations will be performed at a central laboratory chosen by the Sponsor. If all of the laboratory values are within the normal reference range at Pre-Screening Visit 1, the subject may continue to be evaluated for study entry. If one or more values fall outside of the normal range, the investigator may either exclude the subject from the study or investigate further to determine clinical relevance (Table 1). The investigation will include a careful evaluation of the potential subject's complete medical history and current physical examination in the context of the abnormal laboratory value(s). If the investigator does not

identify any medical condition or disease that could result in the observed laboratory abnormality, the abnormal laboratory value may be considered not clinically relevant by the investigator and will be documented as such on the laboratory results form. Any questionable laboratory results should be reviewed with the Sponsor prior to randomization (Table 1). Repeat laboratory testing, at the discretion of the investigator and/or Sponsor, is permitted and should be indicated as such. If there is any clinical uncertainty regarding the significance of an abnormal value(s), the subject will be excluded from the study.

All laboratory results must be found clinically acceptable to the investigator, and Sponsor, where appropriate, prior to study medication administration.

Table 6 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit Hemoglobin WBC[a] Platelets	Albumin BUN Creatinine Total bilirubin AST ALT Alkaline phosphate Glucose Sodium Potassium Chloride Bicarbonate Calcium Cholesterol Uric acid	Glucose pH Protein Microscopic: WBCs, RBCs Urine pregnancy test[c]	Blood for SNP testing Blood for Genetic Analysis Follicle Stimulating Hormone (FSH)[b] Serum Beta-human chorionic gonadotropin (β-hCG)

a. Total and differential (neutrophil, lymphocyte, atypical lymphocyte, monocyte, eosinophil, basophil)
b. For postmenopausal women at screening only
c. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

7.1.3.2 Blood for SNP testing

This sample will be drawn for genotyping SNP [redacted]. The result of this testing is required in order to proceed to Visit 2 of the study.

7.1.3.3 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the operations/laboratory manual.

7.1.3.4 Future Biomedical Research Sample Collection

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

-- DNA for future research.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

Subjects who discontinue/withdraw from treatment prior to completion of the treatment should be encouraged to continue to be followed for all remaining study visits.

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the Discontinuation 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.

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 PPD 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 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.

Section 5.8 outlines the criteria for allowing subjects who are discontinued from treatment to 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, reason and person performing the unblinding) 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. 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.

7.1.4.3 Domiciling

Not applicable

7.1.4.4 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 as source documentation at the trial site.

Critical Equipment for this trial includes:

- Spirometer

Please refer to Section 7.1.2.7 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 Rescreening

Per the judgment of the investigator, a subject who is classified as a screen failure may be re-screened once due to not meeting all inclusion/exclusion criteria at either Visit 1 or Visit 2. A subject may not be re-screened after entering the open-label Run-in Period of the trial.

7.1.5.2 Post-treatment Visit

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 Treatment Visit and will return to the clinic in 14 (+4) days. All male subjects and those female subjects who are not of child-bearing potential will receive a telephone contact for post-trial evaluation.

7.2 Assessing and Recording Adverse 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 Electronic Data Capture (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 for MK-1029 is any dose higher than 1 tablet a day. An overdose for montelukast is a dose more than 10 mg a day, consistent with its approved use. An overdose of as-needed SABA (albuterol/salbutamol) is administration of greater than 16 puffs per day on two consecutive days.

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 to the Sponsor

7.2.3.1 Serious Adverse Events

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 7 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.

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).

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

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 7 . The investigator's assessment of causality is required for each adverse event. Refer to Table 7 for instructions in evaluating adverse events.

Table 7 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

All Adverse Events 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.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any final database lock, 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 final database lock, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. Separate analysis plans (i.e., separate documents from the sSAP) will be developed to detail other planned analyses (i.e., those specific to the analysis of future biomedical research).

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan (SAP) are summarized below; the comprehensive plan is provided in Sections 8.2-8.12.

Study Design Overview	A randomized, double-blind placebo-controlled, parallel-group trial of MK-1029 in subjects with persistent asthma who remain uncontrolled while being maintained on montelukast.
Treatment Assignment	Subjects will be randomized in 1:1 ratio to *either* MK-1029 150 mg plus montelukast 10 mg *or* MK-1029 150 mg matching-image placebo plus montelukast 10 mg, stratified by the number [redacted] Double-blind assignment with in-house blinding will be implemented.
Analysis Populations	Efficacy: Full Analysis Set (FAS). The FAS approach includes all randomized subjects who receive at least one dose of trial treatment. Subjects will be included in the treatment group to which they are randomized. Safety: All Subjects as Treated (ASaT). The ASaT population consists of all randomized subjects who received at least one dose of trial treatment. Subjects will be included in the treatment group corresponding to the trial treatment they actually received.
Primary Endpoint	Average change from baseline in forced expiratory volume in 1 second (FEV_1) measured at the end of Week 4 and Week 6 of treatment
Key Secondary Endpoint	Percent of days with worsening asthma measured daily during Week 3 to Week 6 of treatment (inclusive)
Statistical Methods for Key Efficacy Analyses	The primary hypothesis will be evaluated by comparing MK-1029 to placebo, when added to montelukast, on the average change from baseline in FEV_1 using a constrained longitudinal data analysis model. The key secondary hypothesis will be evaluated by comparing MK-1029 to placebo, when added to montelukast, on the %d-WA using an analysis of variance model.
Statistical Methods for Key Safety Analyses	No Tier 1 safety endpoint is specified for this trial. For Tier 2 endpoints, between-group comparisons will be assessed via point estimates with 95% confidence intervals provided using the stratified Miettinen and Nurminen method.
Interim Analyses	No interim analysis is planned in this trial.
Multiplicity	The primary and key secondary endpoints will be tested in a stepwise procedure, where statistical conclusions will be made on the key secondary efficacy endpoint only if statistical significance is demonstrated in the primary efficacy endpoint.
Sample Size and Power	The planned sample size is 110 subjects in total. For the average change from baseline in FEV_1 measured at the end of Week 4 and Week 6 of treatment, the trial has approximately 92% power to demonstrate that MK-1029 is superior to placebo at an overall two-sided 5% alpha-level, if the underlying treatment difference in mean changes from baseline in FEV_1 is 180ml. For the %d-WA measured during Week 3 to Week 6 of treatment, the trial has approximately 80% power to demonstrate that MK-1029 is superior to placebo at an overall two-sided 10% alpha-level, if the underlying treatment difference in %d-WA is -10.0%.

8.2 Responsibility for Analyses/in-house Blinding

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

This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study treatment assignment. Randomization will be implemented in an interactive voice response system (IVRS).

8.3 Hypotheses/Estimation

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

8.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and/or between-treatment differences are listed below, followed by the descriptions of the derivations of selected endpoints.

8.4.1 Efficacy Endpoints

The descriptions of the efficacy measurements and time points at which they are measured are described in Section 4.2.3.1.

Primary Efficacy Endpoint

- Average change from baseline in FEV_1 as measured at the end of Week 4 and Week 6 of treatment

Key Secondary Efficacy Endpoint

- Percent of days with worsening asthma (%d-WA) as measured daily during Week 3 to Week 6 (inclusive) of treatment

8.4.2 Safety Analysis

- Percentage of subjects with adverse experience
- Clinical and laboratory adverse experiences reported during the treatment period
- Change from baseline in vital signs parameters and change or percent change (as appropriate) from baseline in laboratory safety parameters at the end of the trial

8.4.3 Derivations of Efficacy Endpoints

This section provides the descriptions of the primary and key secondary efficacy endpoints. Descriptions of the exploratory endpoints are provided in the sSAP.

FEV_1

For FEV_1, baseline value (Visit 4) and measurements at the end of Weeks 2, 4, and 6 will be included in the analysis model. Assignment of an FEV_1 measurement to a specific week will be based on the relative day at which the measurement is obtained. If more than 1 FEV_1 measurement is obtained within or assigned to a week, the FEV_1 associated with the last relative day within that specific week is kept for the analysis. An FEV_1 measurement obtained up to 1 week from the last day of an asthma (systemic corticosteroid) rescue-therapy episode will not be used in any analysis. The start of an asthma rescue episode is defined as the first day the subject's asthma symptoms require treatment with steroids as indicated on the subject diary and/or concomitant medication case report form. The episode ends on the last day of a period with steroid use.

Day with Worsening Asthma

For this trial, a day with worsening asthma (d-WA) is defined based on e-Diary entries, as any day during which any of the following occurs:

- a decrease from baseline in AM PEF of more than 20%
- AM PEF less than 180 L/min
- an increase in beta-agonist use of more than 70% (and a minimum increase of at least 2 puffs)
- an increase from baseline in daytime asthma symptom score of more than 50%
- overnight asthma symptom of: Awake "all night"
- an asthma attack, as defined by any day when one or more of the following events due to asthma has occurred: corticosteroid use (systemic); unscheduled visit to the doctor or urgent care clinic; unscheduled visit to the emergency department; and/or hospitalization.

The percentage days with worsening asthma, as well as other diary-derived endpoints, will be calculated using the e-Diary values collected from the beginning of Week 3 to the end of Week 6 (or discontinuation). No e-Diary measurement obtained up to 1 week from the last day of an asthma rescue-therapy episode will be included for the endpoint derivation. It is required that at least 80% of the expected diary data from the beginning of Week 3 to the end of Week 6 (or discontinuation) should be available to compute the diary-derived endpoints.

Baseline

For the primary efficacy endpoint of FEV_1, the pre-dose baseline value is defined as the last measurement obtained on or before Visit 4 prior to randomization.

8.4.4 Derivations of Safety Endpoints

For laboratory, and vital sign parameters, baseline is defined as the last measurement taken prior to the first dose of double-blind trial treatment, which is typically taken at the day of randomization. Change from baseline in laboratory, and vital signs parameters is calculated as on-treatment value minus the baseline value.

8.5 Analysis Populations

8.5.1 Efficacy Analysis Populations

A full analysis set (FAS) approach will be used for efficacy analyses. The FAS approach includes all randomized subjects who receive at least one dose of trial treatment.

A supportive analysis using the Per-Protocol (PP) population will be performed for the primary efficacy endpoint if the number of protocol violators is more than 10% of the FAS population in either treatment group. The PP population excludes subjects due to important deviations from the protocol based on a set of pre-specified criteria (e.g., dropouts, noncompliant of trial procedure, etc.). The final determination on major protocol deviations, and thereby the composition of the Per-Protocol population, will be made prior to the final unblinding of the database and will be documented in a separate memo.

Subjects will be included in the treatment group to which they are randomized for the analysis of efficacy data using both the FAS and PP populations. If an endpoint analysis involves baseline, a baseline measurements is required for the subject to be included in that analysis. Details on the approach to handling missing data are provided in Section 8.6 – Statistical Methods.

8.5.2 Safety Analysis Population

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this trial. The ASaT population consists of all randomized subjects who received at least one dose of trial treatment. Subjects will be included in the treatment group corresponding to the trial treatment they actually received for the analysis of safety data using the ASaT population. If a subject takes incorrect trial treatment for the entire treatment period, the subject will be included in the treatment group corresponding to the trial treatment actually received. Otherwise, subjects will be included in the treatment group to which they are randomized.

At least one laboratory or vital sign measurement obtained subsequent to at least one dose of trial treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

Details on the approach to handling missing data for safety analyses are provided in Section 8.6 – Statistical Methods.

8.6 Statistical Methods

Statistical testing and inference for safety analyses are described in 8.6.2. Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 8.8, Multiplicity. Nominal p-values may be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity, sample size, etc. Unless otherwise stated, all statistical tests will be conducted at the α=0.05 (2-sided) level.

8.6.1 Statistical Methods for Efficacy Analysis

This section describes the statistical methods that address the primary and key secondary objectives. Methods related to exploratory objectives will be described in the sSAP.

Primary Endpoint

For the analysis of the average change from baseline in FEV_1 at the end of Week 4 and Week 6, a constrained longitudinal data (cLDA) method proposed by Liang and Zeger [20] will be used. This model assumes a common mean across treatment groups at baseline and a different mean for each treatment at each post-baseline time points. In this model, the response vector consists of the baseline FEV_1 and the FEV_1 observed at each post-baseline time points (up to Week 6). Time is treated as categorical variable so no restriction is imposed on the trajectory of the means over time. The analysis model will adjust for treatment, visit, the treatment-by-visit interaction, number of C alleles at the rs'961 SNP (1 copy / 2 copies), and prior inhaled corticosteroids (ICS) use (Yes/No). An unstructured covariance matrix will be used to model the correlation among repeated measurement. The Kenward-Roger adjustment will be used with residual maximum likelihood (REML) to make proper statistical inference. The treatment difference in terms of the average change from baseline in FEV_1 at the end of Week 4 and Week 6 will be estimated and tested from the cLDA model.

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. Of note, in the event that there are no missing data, the estimated treatment difference from the above cLDA model will be identical to that from a traditional longitudinal Analysis of covariance (ANCOVA) model which uses the baseline value as a covariate. However, unlike longitudinal ANCOVA, the cLDA model accounts for variability in the baseline values, thus providing more accurate standard errors and confidence intervals for individual treatment effects. Moreover, this model allows the inclusion of subjects who are missing either the baseline or post-baseline measurements, thereby increasing efficiency. Details of the model specification, assumptions, and SAS implementation codes will be provided in the sSAP.

The cLDA method assumes that data are missing at random (MAR). Based on the experience in previous Phase-II trials for MK-1029, typical reasons for discontinuation from the trial include clinical or laboratory adverse experiences, protocol deviations/non-compliance, physician decision, and/or lack of efficacy. It is expected that in this trial, Missing at Random and Missing Completely at Random (MAR/MCAR) mechanisms will underlie most of the missingness, combined with the assumed dropout rate of 10%, the proportion of data missing not at random (MNAR), driven solely by unobserved values of the study endpoints, will be small.

Supportive Analysis for the Primary Endpoint

Supportive analyses based on the Per Protocol (PP) population will be conducted using the same cLDA model described above. The PP population contains all subjects in the FAS who do not meet the protocol violation criteria.

In addition, the Jump-to-Reference (J2R) multiple-imputation and the tipping-point analysis will be performed, as supportive analyses for the primary endpoint, to evaluate the MAR/MCAR assumptions and the impact of missing data.

- The J2R approach assumes that subjects who dropout during the trial have the same response profile as those in the control group at time points after discontinuation, had they remained in the trial. Under the J2R approach, missing data from all subjects after

dropout will be imputed using the profile from the control group (i.e., placebo plus montelukast).

- In the tipping-point analysis, missing data are first imputed for all time points under the MAR assumption, and then the worsening/shift is applied. This procedure is repeated with increasing the delta-shift (worsening) until the result is no longer statistically significant.

Further details of these two analyses are provided in the sSAP.

Key Secondary Endpoint

The key secondary endpoint of %d-WA will be analyzed using an analysis of variance (ANOVA) model with fixed effects of treatment, [redacted] and prior ICS use (Yes/No). The ANOVA model will be based on the FAS and subjects will be evaluable for this analysis if they have non-missing endpoint value.

The primary analysis approach for the %d-WA will be based on non-missing values only, that is, the percentage will be calculated as:

The supportive analysis approach for the %d-WA will be based on a worse-neighbor imputation approach. That is, for each component of d-WA, missing value on any given day (consecutive days) will be imputed by the worse of the non-missing value immediately before and after the missing one(s). Worsening of asthma will then be evaluated based on the imputed value(s). The percentage of days with worsening asthma based on the worse-neighbor approach is calculated as:

Table 8 summarizes the primary and key secondary efficacy analyses.

Table 8 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach[†]	Statistical Method[‡]	Analysis Population	Missing Data Approach
Primary Endpoint				
Average change from baseline in FEV_1 at the end of Week 4 and Week 6	P	cLDA[§]	FAS	Model-based
	S		PP	Model-based
	S	ANCOVA[#]	FAS	Jump-to-Reference multiple imputation
	S			Tipping-point analysis
Secondary Endpoints/Hypotheses				
Key Secondary Endpoint				
Percent of days with worsening asthma during Week 3 to Week 6 of treatment	P	ANOVA[%]	FAS	Average of non-missing values, no missing data will be imputed
	S			Worse-neighbor imputation

[†] P=Primary approach; S=Supportive approach.
[‡] Statistical models are described in further detail below:
[§] constrained longitudinal data analysis model with terms for treatment, time, and the interaction of time by treatment, [redacted] and prior inhaled corticosteroids use (Yes/No).
[#] ANCOVA model with terms for treatment, [redacted] and prior inhaled corticosteroids use (Yes/No) as fixed effects and baseline as a covariate.
[%] ANOVA model with terms for treatment, [redacted] and prior inhaled corticosteroids use (Yes/No).
FEV_1 = Forced expiratory volume in 1 second; FAS=Full analysis set; PP=per-protocol analysis

8.6.2 Statistical Methods for Safety Analysis

Safety and tolerability will be assessed by a clinical review of all relevant parameters, including adverse experiences (AEs), laboratory safety parameters, and vital signs.

The analysis of safety results will follow a tiered approach (Table 9). 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 laboratory, vital signs, and ECG parameters that are not pre-specified as Tier-1 endpoints will be classified as belonging to "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 adverse experiences and predefined limits of change 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.

Table 9 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint†	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	(none)		
Tier 2	Any AE	X	X
	Any Serious AE	X	X
	Any Drug-Related AE	X	X
	Any Serious and Drug-Related AE	X	X
	Discontinuation due to AE	X	X
	Specific AEs, SOCs, or PDLCs‡ (incidence ≥4 of subjects in one of the treatment groups)	X	X
Tier 3	Specific AEs, SOCs or PDLCs‡ (incidence <4 of subjects in all of the treatment groups)		X
	Change from Baseline Results (Labs, 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.
Note:
(1) CI = Confidence Interval; SOC=System Organ Class; PDLC=Pre-Defined Limit of Change; X = results will be provided.
(2) PDLC criteria for laboratory parameters are provided in Table 10.

For this trial, no adverse experiences have been identified as Tier 1 events. The broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, a drug related AE, a serious AE, an AE which is both drug-related and serious, and who discontinued due to an AE will be considered Tier 2 endpoints. For Tier 2 events, point estimates with 95% confidence intervals will be provided for between-treatment differences in the percentage of subjects with events, using the Miettinen and Nurminen method stratified [redacted]

Continuous measures such as changes from baseline in laboratory, and vital signs parameters that are not pre-specified as Tier 1 endpoints will be considered as Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format. Table 10 summarizes the predefined limits of change for laboratory parameters:

Table 10 Predefined Limits of Change

Laboratory Test	Predefined Limit of Change
Hematocrit (%)	Decrease ≥20% and <LLN Increase ≥20% and >ULN
WBC count (1000/mm^3)	Decrease ≥20% and <LLN Increase ≥20% and >ULN
Platelet count (1000/mm^3)	Decrease ≥25% and <LLN Increase ≥50% and >ULN
Bilirubin (mg/dL)	Increase ≥100% and >ULN ≥ 50% increase and >1.5X ULN ≥ 50% increase and >2X ULN >3X ULN >5X ULN
AST (IU/L)	Increase ≥100% and >ULN ≥ 50% increase and >1.5X ULN ≥ 50% increase and >2X ULN >3X ULN >5X ULN
ALT (IU/L)	Increase ≥100% and >ULN ≥ 50% increase and >1.5X ULN ≥ 50% increase and >2X ULN >3X ULN >5X ULN
ALP (IU/L)	Increase ≥100% and >ULN ≥ 50% increase and >1.5X ULN ≥ 50% increase and >2X ULN >3X ULN >5X ULN
Neutrophil (1000/mm^3)	Decrease ≥20% and <LLN Increase ≥20% and >ULN
BUN(mg/dL)	Increase ≥ 50% Increase ≥ 20% and BLN>ULN
Serum creatinine(mg/dL)	Increase ≥ 50% Increase ≥ 20% and BLN>ULN
WBC = White Blood Cell; AST = Aspartate transaminase; ALT = Alanine transaminase; ALP = Alkaline phosphatase; LLN = Lower limit of normal range; ULN = Upper limit of normal range.	

8.6.3 Summaries of Baseline Characteristics, and Demographics

The comparability of the treatment group for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (including age, gender, race, weight, height, and body mass index), baseline characteristics (including duration of asthma, age diagnosed of asthma, asthma controller pre-trial, ICS use, blood eosinophil count, baseline ACQ-6, and smoking history), primary and secondary diagnoses, prior and concomitant therapies, [redacted]

[redacted] will be summarized by treatment either by descriptive statistics or categorical tables.

8.7 Interim Analysis

No formal efficacy interim analysis is planned for this trial. Safety data will be continuously monitored in a blinded fashion by the study team.

8.8 Multiplicity

The primary and key secondary endpoints will be tested in a stepwise procedure, where statistical conclusion will be made on the key secondary efficacy endpoint only if statistical significance is demonstrated in the primary efficacy endpoint. No multiplicity adjustment will be implemented among the exploratory endpoints.

8.9 Power and Sample Size

Subjects will be randomized in a 1:1 ratio to *either* MK-1029 150 mg plus montelukast 10 mg *or* MK 1029 150 mg matching-image placebo montelukast 10 mg. Assuming a 10% drop out rate, a total of 55 subjects per treatment group will be randomized.

With approximately 55 randomized subjects per group, the study has about 92% power to demonstrate the superiority of MK-1029 over placebo, when added to montelukast at an overall two-sided 5% alpha-level, if the underlying treatment difference in average change from baseline FEV_1 is 180mL. The sample size is based on the following assumptions: 1) an approximately 10% cumulative overall dropout rate over the 6-week treatment, 2) an unconditional correlation matrix of compound symmetry structure with correlation coefficient of 0.9, and 3) an unconditional standard deviation of 705ml on FEV_1 at each time point. The calculation is based on Inverse Probability Weighted Complete Cases Approach by Lu, Mehrotra and Liu (2008) [21] with 55 subjects in each treatment group expected to be included in the analysis and is carried out using SAS v9.3. In addition, there is approximately 80% power to detect (at 2-sided α=0.10) a difference of -10.0 percentage points in %d-WA between MK-1029 and placebo, assuming a standard deviation (SD) of 19.6 percentage points. The assumptions for treatment difference and SD for the primary and key secondary endpoints, and the dropout rate are based on Phase-II trials already conducted for MK-1029.

8.10 Subgroup Analysis 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 each subgroup. The following are examples of classification variables:

- Age groups (≤/> median)
- Gender (female, male)
- Race (Asian, White, Black or African American, and Other)

- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Region (Americas, Europe/Africa, Asia/Pacific)
- FEV_1 %-predicted at baseline (≤/> median)
- Baseline ACQ-6 (≤/> median)
- Age Diagnosed of Asthma (≤/> 12 yrs.)
- Blood eosinophilia (yes/no), with eosinophilia defined based on blood eosinophil count ≥0.30 × 10^6/L at Visit 4
- [redacted]

The consistency of the treatment effect will be assessed descriptively via summary statistics by category for the classification variables listed above.

8.11 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 tablets remaining in trial packaging will be counted, reviewed, and recorded at regular intervals. These results will be used to calculate subject compliance.

A day within the trial will be considered an "On-Therapy" day if the subject takes all the required number of tablets of each type (MK-1029 150 mg or matching-image placebo and montelukast 10 mg) as noted in Section 5.2.

For a subject who is followed for the entire treatment period, the "Number of Days Should be on Therapy" is the total number of days from randomization to the last scheduled day for treatment administration for that subject. For a subject who discontinued from the trial permanently, the "Number of Days Should be on Therapy" is the total number of days from randomization to the earlier of

- the date of the last dose of trial medication.
- the date the subject discontinued from the trial.

For each subject, percent compliance will then be calculated using the following formula:

$$\text{Percent Compliance} = \frac{\text{Number of Days on Therapy}}{\text{Number of Days Should be on Therapy}} \times 100.$$

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

8.12 Extent of Exposure

The Extent of Exposure to study treatment will be evaluated by summary statistics (N, mean, median, and standard deviation) and frequencies (< 2 weeks, 2 to < 4 weeks, 4 to 6 weeks, and > 6 weeks) for the "Number of Days on Therapy" by treatment group.

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 11.
Clinical supplies will be packaged to support enrollment and replacement subjects as required. When a replacement subject is required, the Sponsor or designee needs to be contacted prior to dosing the replacement supplies.

Table 11 Product Descriptions

Product Name & Potency	Dosage Form
Montelukast sodium 10 mg	Tablet
MK-1029 150 mg or matching-image placebo	Tablet

All placebos were created by the Sponsor to match the active product.

9.2 Packaging and Labeling Information

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

Subjects will receive per dispensing visit, one open label bottle of montelukast sodium 10 mg and one blinded bottle of either MK-1029 150 mg or MK-1029 150mg matching-image placebo to support four weeks of dosing.

No kitting is required.

9.3 Clinical Supplies Disclosure

Open label montelukast sodium: The montelukast sodium in this trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded. Montelukast sodium 10 mg (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

Blinded Supplies: MK 1029 150 mg or matching-image placebo

The emergency unblinding call center will use the treatment/randomization schedule for the trial to unblind subjects and to unmask treatment identity. In the event that the emergency unblinding call center is not available for a given site in this trial, the central electronic treatment allocation/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.

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, reason and person performing the unblinding) 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.

Section 5.8 outlines the criteria for allowing subjects who are discontinued from treatment to 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 treatment allocation/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 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. 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 specimens collected in this trial as outlined in Section 7.1.3.4 – Future Biomedical Research Sample Collection will be used to study various causes for how subjects may respond to a drug/vaccine. Future biomedical research specimen(s) will be stored to provide a resource for future trials conducted by the Sponsor 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 the Sponsor or those working for or with the Sponsor.

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.

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.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of subject consent for Future Biomedical Research will be captured in the electronic Case Report Forms (eCRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen Collections

Collection of specimens for Future Biomedical Research will be performed as outlined in the trial flow chart. In general, if additional blood specimens are being collected for Future Biomedical Research, these will usually be obtained at a time when the subject is having blood drawn for other trial purposes.

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, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines 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.

5. Biorepository Specimen Usage

Specimens obtained for the Merck Biorepository will be used for analyses using good scientific practices. Analyses utilizing the Future Biomedical Research specimens may be performed by the Sponsor, or an additional third party (e.g., a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. 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 specific analysis is performed will be reported to the Sponsor.

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 the Sponsor using the designated

mailbox PPD and a form will be provided to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. Documentation will be sent 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 the end of the main study. 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 Sponsor-designated biorepository. If a central laboratory is not utilized in a particular trial, the trial site will ship directly to the Sponsor-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 Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives 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 on international standards (e.g., ISO17799) to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Subjects

No information obtained from exploratory laboratory studies will be reported to the subject, family, or physicians. Principle reasons not to inform or return results to the subject include: Lack of relevance to subject health, limitations of predictive capability, and concerns regarding misinterpretation.

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. After the clinical trial has completed, if any exploratory results are definitively associated with clinical significance, the Sponsor will endeavor to make such results available

through appropriate mechanisms (e.g., scientific publications and/or presentations). Subjects will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all subjects diagnosed and treated on Sponsor clinical trials for Future Biomedical Research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. No additional risks to the subject have been identified as no additional specimens are being collected for Future Biomedical Research (i.e., only leftover samples are being retained).

The Sponsor 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.

12. Questions

Any questions related to the future biomedical research should be e-mailed directly to PPD .

13. References

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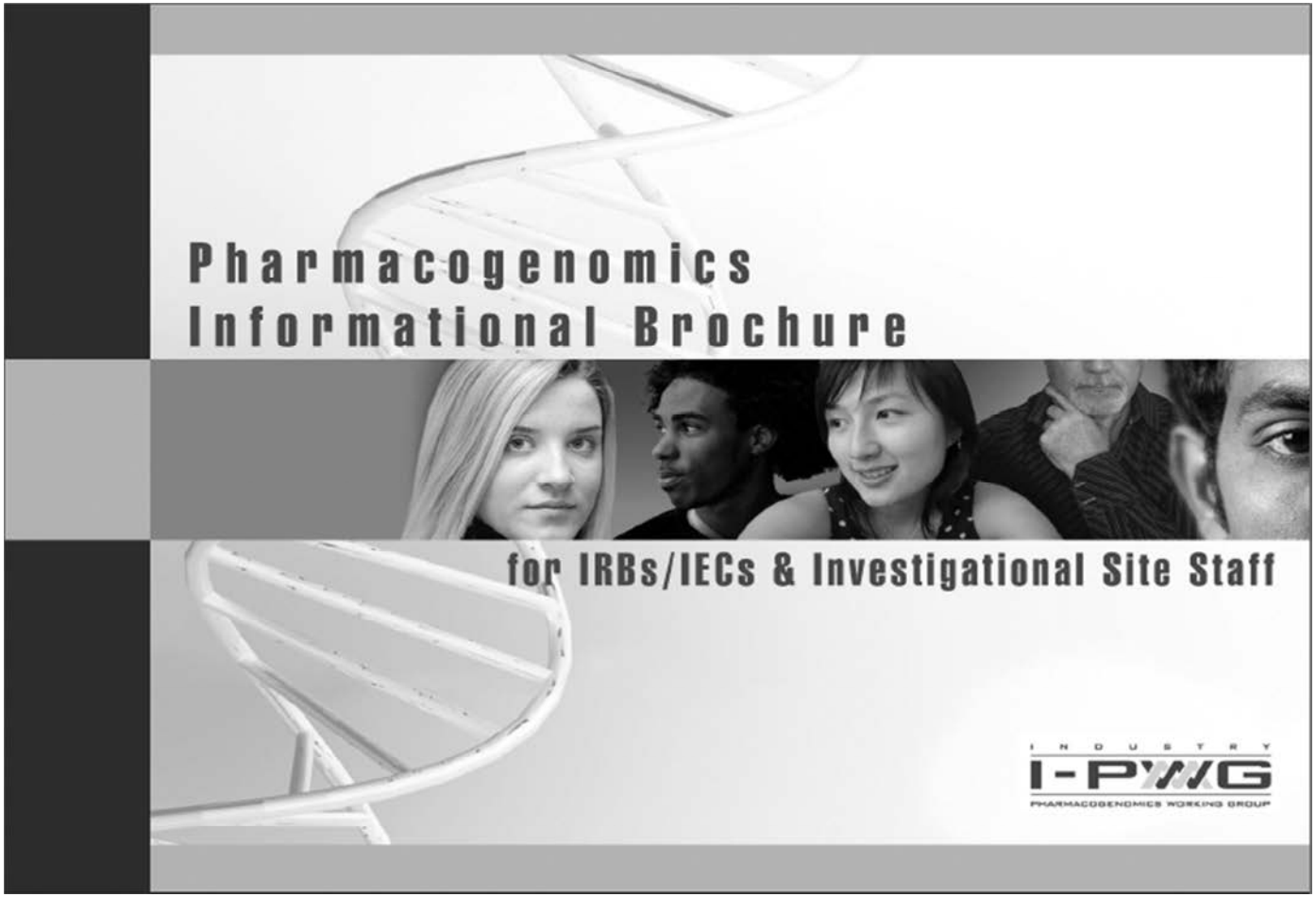
12.3 Pharmacogenetics Information Brochure for IRB/IECs & Investigational Site Staff



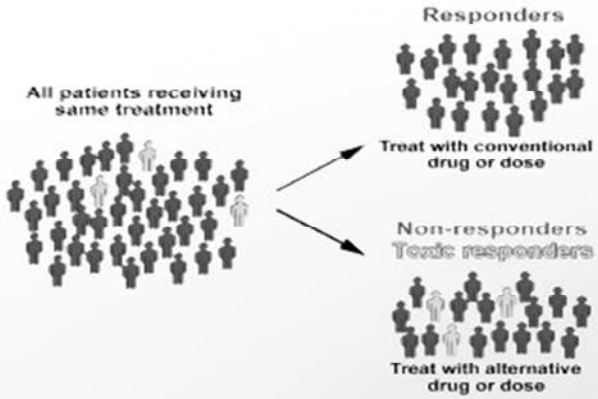
This Informational Brochure is intended for IRBs/IECs & Investigational Site Staff. The brochure was developed to address issues relevant to DNA collection and research in the context of pharmaceutical drug development.

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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http://www.i-pwg.org

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

	Pre-screening Visit 1	Treatment Visit 4	Treatment Visit 5-6	Treatment Visit 7	Post-Treatment
Blood Parameter	**Approximate Blood Volume (mL)**				
Hematology	2 mL	2 mL		2 mL	
Serum/Plasma Chemistry	2 mL	2 mL		2 mL	
Serum β-Human Chorionic Gonadotropin (β-hCG)[a]	1 mL				
Serum Follicle Stimulating Hormone (FSH)[b]	1 mL				
Blood for Planned Genetic Analysis [c]		8.5 mL			
Blood for SNP testing	4 mL				
Expected Total (mL)	**10 mL**	**12.5 mL**		**4 mL**	

a. For female subjects of child bearing potential only drawn at visit 1. If the urine pregnancy test is positive at subsequent visits, β-hCG sample will be drawn to confirm.
b. If applicable
c. No additional specimens are being collected for Future Biomedical Research (i.e., only leftover samples from the blood for planned genomic analyses are being retained for future biomedical research)

12.5 Body Mass Index

BMI equals a person's weight in kilograms divided by height in meters squared. (BMI=kg/m^2). To use the table, find the appropriate weight in the left-hand column. Move across the row to the given height. The number at the intersection is the BMI for that height and weight.

BMI	Height(cm)																									
Weight kg.	**150**	**152**	**154**	**156**	**158**	**160**	**162**	**164**	**166**	**168**	**170**	**172**	**174**	**176**	**178**	**180**	**182**	**184**	**186**	**188**	**190**	**192**	**194**	**196**	**198**	**200**
60	27	26	25	24	24	23	23	22	22	21	21	20	20	19	19	18	18	17	17	17	16	16	16	15	15	15
62	28	27	26	26	25	24	24	23	22	22	21	21	20	20	19	19	19	18	18	17	17	16	16	16	16	15
64	28	28	27	26	26	25	24	24	23	22	22	22	21	21	20	19	19	19	18	18	17	17	17	16	16	16
66	29	29	28	27	26	26	25	24	24	23	23	22	22	21	21	20	20	19	19	18	18	17	17	17	17	16
68	30	30	29	28	27	26	26	25	25	24	23	23	22	22	21	21	20	20	19	19	19	18	18	17	17	17
70	31	30	30	29	28	27	27	26	25	25	24	24	23	23	22	21	21	20	20	20	19	18	18	18	18	17
72	32	31	30	30	29	28	27	27	26	25	25	24	24	23	23	22	22	21	20	20	20	19	19	18	18	18
74	33	32	31	30	30	29	28	27	27	26	26	25	24	24	23	23	22	22	21	21	20	20	20	19	19	19
76	34	33	32	31	30	30	29	28	27	27	26	26	25	24	24	23	23	22	22	21	21	20	20	20	19	19
78	35	34	33	32	31	30	30	29	28	27	27	26	26	25	24	24	23	23	22	22	21	21	21	20	20	19
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82	36	36	35	34	33	32	31	30	30	29	28	27	27	26	26	25	25	24	23	23	22	22	22	21	21	20
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86	38	37	36	35	34	34	33	32	31	30	30	29	28	28	27	26	26	25	25	24	23	23	23	22	22	21
88	39	38	37	36	35	34	33	33	32	31	30	30	29	28	28	27	27	26	25	25	24	24	23	23	22	22

BMI	Height(cm)																									
Weight kg.	**150**	**152**	**154**	**156**	**158**	**160**	**162**	**164**	**166**	**168**	**170**	**172**	**174**	**176**	**178**	**180**	**182**	**184**	**186**	**188**	**190**	**192**	**194**	**196**	**198**	**200**
90	**40**	**39**	**38**	**37**	**36**	**35**	**34**	**33**	**33**	**32**	**31**	**30**	**30**	**29**	**28**	**28**	**27**	**26**	**26**	**25**	**25**	**24**	**24**	**23**	**23**	**22**
92	**41**	**40**	**39**	**38**	**37**	**36**	**35**	**34**	**33**	**33**	**32**	**31**	**30**	**30**	**29**	**28**	**28**	**27**	**26**	**26**	**25**	**25**	**24**	**24**	**23**	**23**
94	**42**	**41**	**40**	**39**	**38**	**37**	**36**	**35**	**34**	**33**	**32**	**32**	**31**	**30**	**30**	**29**	**28**	**28**	**27**	**26**	**26**	**25**	**25**	**24**	**24**	**23**
96	**43**	**42**	**41**	**40**	**38**	**38**	**37**	**36**	**35**	**34**	**33**	**32**	**32**	**31**	**30**	**30**	**29**	**28**	**28**	**27**	**26**	**26**	**25**	**25**	**24**	**24**
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108	48	47	46	44	43	42	41	40	39	38	37	36	36	35	34	33	33	32	31	31	30	29	29	28	28	27
110	49	48	46	45	44	43	42	41	40	39	38	37	36	35	35	34	33	32	32	31	31	30	29	29	28	28

12.6 List of Abbreviations

ACQ-6	Asthma Control questionnaire- 6 items
AE	Adverse experience
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
AN	Allocation number
ANCOVA	Analysis of covariance
AQLQ	Asthma Quality of Life Questionnaire
AQLQ(S)	Asthma Quality of Life Questionnaire (Standardised Activities)
AST	Aspartate aminotransferase
ATS/ERS	American Thoracic Society/European Respiratory Society
BMI	Body Mass Index
CD11b	Cluster of differentiation molecule 11b
CFC	Chlorofluorocarbon
cLDA	Constrained longitudinal data
CI	Confidence interval
C_{max}	Maximum concentration
CRTH2	Chemoattractactant Receptor-homologous molecule on Th2 cells
CSR	Clinical study report
CysLT1	Cysteinyl leukotriene receptor type-1
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECI	Event of clinical interest
eCRF	Electronic case report form
eSNP	Expression SNP
FAS	Full Analysis Set
FEV_1	Forced expiratory volume in 1 second
FSH	Follicle stimulating hormone
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
hCG	Human chorionic gonadotropin
HFA	Hydrofluoroalkane
HIV	Human immunodeficiency virus
IB	Investigator's brochure
ICS	Inhaled corticosteroids
IEC	Institutional ethics committee
IgE	Immunoglobulin E
IRB	Institutional Review Board
IUD	Intrauterine device
IVRS	Interactive voice response system
LABA	Long-acting (inhaled) β_2-adrenergic agonist
LLN	Lower limits of normal

MDI	Metered-dose inhaler
mg	Milligrams
mL	Milliliter
mRNA	Messenger ribonucleic acid
PD	Pharmacodynamic
PDLC	Predefined limits of change
PEF	Peak expiratory flow
PFT	Pulmonary Function Test
PGD_2	Prostaglandin D_2
PK	Pharmacokinetics
QD	Once daily
rs	Reference SNP (identifier)
SABA	Short-acting β_2-adrenergic agonist
SAE	Serious adverse experience
SAP	Statistical analysis plan
SD	Standard deviation
SNP	Single nucleotide polymorphism
sSAP	Supplemental statistical analysis plan
Th2	T-helper cell type 2
ULN	Upper limit of normal
µg	Microgram

12.7 Method for Administering Short-Acting Beta-Agonist (SABA) during Postbronchodilator Testing

In assessing β-agonist response in the clinic, spacer devices will be used to administer medication. Four puffs of SABA (albuterol/salbutamol) will be administered.

Procedure

1. Shake the metered-dose inhaler and insert into spacer device.
2. Tilt the head back slightly and breathe out.
3. Place spacer device in mouth.
4. Press down on inhaler to release medication into spacer device.
5. Breathe in slowly (3 to 5 seconds) to total lung capacity.
6. Hold breath for 10 seconds.
7. Wait 1 minute between each puff and repeat the same sequence 3 additional times.

12.8 Method for Performing Peak Flow Measurements

A peak flow meter will be provided to each patient and should be used throughout the study by all patients. Patients should demonstrate adequate performance of the peak flow procedure.

Procedure

1. Place the indicator at the base of the numbered scale.
2. Stand up.
3. Take a deep breath to total lung capacity.
4. Place the meter in the mouth and close lips around the mouthpiece. Hold the meter such that fingers will not interfere with the movement of the indicator.
5. Blow out as hard and fast as possible. A prolonged expiration is necessary when performing spirometry, but not in PEF.
6. Write down the achieved measurement or value.
7. Repeat the process 2 more times.
8. Record the highest of the 3 numbers achieved.

The peak flow measurement is to be obtained in the early morning, upon rising, and at bedtime prior to taking study drug. All peak flow measurements should be obtained at least 6 hours after the last SABA (albuterol/salbutamol) dose. If SABA is needed within the 6 hours before going to bed in the evening, then the peak flow should be done before the administration of SABA.

Otherwise, AM peak flow should be performed immediately upon arising out of bed. PM peak flow should be performed immediately before going to bed in the evening prior to taking study drug, and before using any SABA.

12.9 Action Plan for Deterioration of Asthma

A. If the PEF decreases below the predefined alert level (60%) compared to baseline
OR

If the subject believes that there is significant worsening of asthma symptoms necessitating an increase in usual medications:

1. The subject should call the investigator immediately.
2. The investigator will make a clinical evaluation of the patient.
3. If additional treatment is required, the use of nebulized β-adrenergic agents should be the first treatment and the patient should be brought in for an unscheduled visit as soon as possible.
4. If other therapy is deemed necessary:
   - Perform spirometry as soon as possible after subject notes worsening of asthma symptoms.
   - Begin oral corticosteroid therapy (equivalent of prednisone) 20 to 60 mg daily.
5. If the subject is stabilized within 5 days (return to clinical state before exacerbation), the subject can be continued in the study.
   Note: Whenever possible, the patient will be asked to return to the clinic for interim spirometry measurements before rescue therapy is initiated.

B. If stabilization does not occur within 5 days with the above action plan, the subject will be discontinued from further study after consultation with the clinical monitor.

C. A subject should be discontinued from further study if any corticosteroid therapy other than the single oral corticosteroid rescue therapy is required (e.g., inhaled corticosteroid therapy is initiated), or if theophylline (oral or intravenous) is required for an asthma attack.

D. Once stable, every attempt should be made to taper the oral corticosteroid dose to zero within 14 days. If the subject must be maintained on oral corticosteroid therapy for greater than 14 days in order to achieve stability, then the subject should be considered to be discontinued from the study.

E. If the subject receives more than one rescue after randomization, then the patient should be discontinued from the study.

F. If the subject receives one rescue between Visits 2 and 4, then the subject should be discontinued from the study.

12.10 Procedure for Tapering Controller Medications

Any subject receiving asthma controller medication(s) prior to Visit 2 is required to undergo controller reduction, using a tightly specified approach, between Visit 2 and Visit 4. Short-acting Beta-Agonist (SABA), for rescue use as needed, will be provided to all subjects. While tapering off controllers, the subject completes the e-Diary for twice-daily monitoring of symptoms and PEF, which helps ensure subject safety.

1. Pre-study Period from Visit 2 to Visit 3 (about 1 week in duration):

   1.1 Subjects receiving LABA discontinue it at Visit 2. Subjects continue to receive their usual dose of ICS.*

   *Note: In some cases, substitution of the subject's ICS with a different but comparable ICS is permissible if local regulations or reimbursement policies make it difficult for the subject to continue a specific ICS.

   1.2 Subjects not receiving LABA continue their pre-study controller regimen.

2. Single-blind Run-in Period from Visit 3 to Visit 4 (about 2 to 4 weeks in duration):

   - During this period, all subjects receive open-label montelukast (supplied by this study), plus MK-1029 150 mg matching-image placebo, which are taken together once daily in the evening (QD PM). Subjects should *not* be told that placebo is administered specifically during this period.

   Tapering: Patients receiving asthma controller therapy will taper off that therapy during this period.

   2.1 Subjects receiving leukotriene antagonists, xanthines (e.g., theophylline), or other oral controllers will discontinue them.

   → If the subject does not meet Tapering Exclusion Criteria (defined below) during ≥14 days of receiving only open-label montelukast plus MK-1029 150 mg matching-image placebo, then the subject returns to the site for Visit 4.

   2.2 Subjects receiving ICS will reduce the total daily ICS dose by approximately 50%. This could be accomplished by decreasing the number of puffs/day (e.g., 2 puffs BID decreases to 1 puff BID; or, 1 puff [of the lowest strength of ICS] BID decreases to 1 puff QD PM) *or* by decreasing the ICS strength (e.g., fluticasone propionate 250 µg BID decreases to 100 µg BID).

   → If the subject does not meet Tapering Exclusion Criteria (defined below) during ≥14 days of reduced ICS therapy, then the ICS is discontinued. *THEN*...

   → If the subject does not meet Tapering Exclusion Criteria (defined below) during ≥14 days of receiving only open-label montelukast 10 mg plus MK-1029 150 mg matching-image placebo, then the subject returns to the site for Visit 4.

Tapering Exclusion Criteria

At the discretion of the Investigator, subjects **may** be excluded from the study if one or more of the following occur:

1. use of >12 puffs of SABA and/or >2 treatments with nebulized SABA on any two consecutive days;
2. a decrease in AM or PM peak flow below the "60% PEF alert" value (established at Visit 2) on two consecutive days;
3 the investigator believes the subject cannot tolerate tapering of asthma controller therapy.

A subject who experiences a clinically significant deterioration of asthma between Visit 2 and Visit 4 **must** be excluded from the study. The criteria for a significant deterioration of asthma that **requires** exclusion are one or more of the following, *if* observed:

1. a decrease in FEV_1 to less than 50% of predicted normal;
2. an absolute decrease in FEV_1 of 20% or greater from baseline at Visit 2;
3. a clinical asthma exacerbation requiring emergency treatment, hospital admission (serious AE) or treatment with additional asthma medication (other than SABA).

Summary of Procedure for Tapering Controller Medications

Visit 2:

- In subjects receiving LABA/ICS, discontinue the LABA and maintain the ICS (at equivalent strength/dose) for about 1 week .

Visit 3:

- In subjects receiving oral controllers, discontinue them for ≥14 days.
- In subjects receiving ICS, reduce the dose by 50% for ≥14 days;

About 2 weeks following Visit 3:

- In subjects receiving reduced-dose ICS, discontinue ICS for ≥14 days.

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 – TRIAL PROCEDURES (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	