Official Protocol Title:	A Phase III, Randomized, Placebo-Controlled Clinical Trial to Study the Efficacy and Safety of MK-3641, a Ragweed (Ambrosia artemisiifolia) Sublingual Immunotherapy Tablet, in Children With a History of Ragweed-Induced Rhinoconjunctivitis With or Without Asthma
NCT number:	NCT02478398
Document Date:	28-Jun-2018

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TITLE:

A Phase III, Randomized, Placebo-Controlled Clinical Trial to Study the Efficacy and Safety of MK-3641, a Ragweed (*Ambrosia artemisiifolia*) Sublingual Immunotherapy Tablet, in Children With a History of Ragweed-Induced Rhinoconjunctivitis With or Without Asthma

IND NUMBER: 12,970
EudraCT NUMBER: 2014-004341-27

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
5.8	Subject Withdrawal/ Discontinuation Criteria	Addition of "severe asthma exacerbation" to the list of discontinuation criteria.	This change was made based on an update to the Reference Safety Information in the Investigator's Brochure (Edition 13).

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
6.0	Trial Flow Chart	Removed the "X" for IVRS/ IWRS at the Telephone/ Follow-up, per the protocol clarification letter of 08-NOV-2016.	Typographical error.
7.1.1.15	Trial Compliance	Added text to clarify that calculation of compliance with study drug is between study visits.	To clarify how to calculate compliance with study drug.
7.1.2.10	Monitor Compliance with Study Medications	Revised text from "If not, the date(s) and reason for each deviation must be recorded." to "If not, the date(s) and reason for each dose variation must be recorded on the study medication (SM) eCRF."	To specify that dose variations must be recorded and where.
12.8	Anaphylaxis Emergency Action Plan	Added text stating that the Anaphylaxis Emergency Action Plan can also be modified in the United States, per the protocol clarification letter of 20-FEB-2017.	To clarify that the plan in the United States can be modified if necessary.

1.0 TRIAL SUMMARY

Abbreviated Title	MK-3641 Ragweed Pediatric Allergic Rhinoconjunctivitis Efficacy/Safety Study
Trial Phase	Phase III
Clinical Indication	Ragweed pollen-induced rhinoconjunctivitis with or without asthma
Trial Type	Interventional
Type of control	Placebo
Route of administration	Sublingual
Trial Blinding	Double-blind
Treatment Groups	MK-3641 (12 Amb a 1-U); Placebo
Number of trial subjects	Approximately 1000 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 3.5 years from the time the first subject signs the informed consent until the last subject's last visit.
Duration of Participation	Each subject will participate in the trial for up to approximately 20 months from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase of up to 12 months, each subject will be receiving assigned treatment for up to 28 weeks. After the end of treatment, each subject will be followed for 14 days.
Randomization Ratio	1:1

A list of abbreviations used in this document can be found in Section 12.13.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a randomized, placebo-controlled, parallel-group, multi-site, double-blind trial of MK-3641 in children with ragweed pollen-induced allergic rhinitis/rhinoconjunctivitis, with or without asthma, to be conducted in conformance with Good Clinical Practices. Approximately 1000 children ages 5 to 17 years will be randomized in a 1:1 ratio to receive either MK-3641, at a dose of 12 Amb a 1-U, or placebo once daily for a total of approximately 20 to 28 weeks. Subjects will be stratified by age to ensure an adequate number of subjects at younger ages are included. Subjects will also be stratified by asthma status. There may be multiple separate cohorts (approximately 2 to 3) recruited over consecutive ragweed seasons to complete the enrollment goal.

The trial consists of a screening period and a treatment period, which includes pre-seasonal and co-seasonal treatment. The screening period may last for up to approximately 12 months prior to randomization. Once randomized, subjects are treated with a minimum of approximately 12 weeks (up to approximately 20 weeks) of pre-seasonal treatment and approximately 8 weeks of co-seasonal treatment. There will be at least 7 clinic visits:

screening (Visit 1), randomization (Visit 2), Off-season (Visit 3), Off-season (Visit 4), Pre-season (Visit 6), In-season (Visit 7), and End-of-season (Visit 8 or Discontinuation Visit); Off-season (Visit 5) is only required if the time between Visit 4 and 6 is longer than 6-8 weeks. Subject compliance with study drug administration, rescue medication use, and daily e-dairy completion will be monitored. Compliance issues will prompt site retraining of subject/parent/guardian via telephone contacts as necessary. The End-of-season visit will be scheduled approximately 1 week after the end of the ragweed season. A final telephone contact will occur approximately 14 days after the End-of-season (or discontinuation) visit for the safety follow-up. Unscheduled visits are also permitted, if needed. The trial diagram is outlined in Section 2.2.

The first dose of MK-3641 must be administered in the clinic under the supervision of the investigator or qualified designee. The subject must be monitored for 30 minutes to allow for direct observation of any adverse events (AEs) that occur soon after study drug administration. Additionally, the supervised dose allows the investigator/qualified designee to ensure proper administration of study drug by the subject/parent/guardian. Details for the in-clinic dosing are in Section 5.2.2 – Timing of Dose Administration.

The investigator/qualified designee will provide instructions on proper administration of the tablet, as well as discuss expected immediate application site reactions and potential severe AEs requiring medical evaluation and/or treatment, prior to dispensing the study drug to the subject/parent/guardian for at-home administration. Doses of study drug subsequent to the first dose will be self-administered at home.

Open-label rescue medications for rhinoconjunctivitis symptoms will be supplied at Visit 6 for use throughout the ragweed season as required to treat allergic rhinoconjunctivitis symptoms.

The subject/parent/guardian will record allergic rhinitis/conjunctivitis and asthma symptoms in an electronic diary (e-diary) each day beginning at Visit 4. The study site and/or parent/guardian will determine whether the subject completes the e-diary him/herself or has assistance from a parent/guardian (e.g., based on the individual subject's abilities and maturity level to complete the e-diary). If the subject has assistance from a parent/guardian, the same parent/guardian should provide the assistance for the duration of the trial.

The subject/parent/guardian will also complete a side effect report card (called Sublingual Immunotherapy [SLIT] Report Card; Section 12.10) daily for the first ~28 days of study drug administration to record local side effects that occur within 60 minutes of study drug administration. The subject/parent/guardian will be provided a separate Comment Card to capture any AEs that occur and any medications used between scheduled clinic visits. During the first 28 days of study medication, local event occurring within the first 60 minutes of tablet administration should be collected on the SLIT Report Card and all other events should be collected on the Comment Card. Following the first 28 days, any AEs will be captured on the Comment Card.

An external Data Monitoring Committee (eDMC) will monitor the interim safety data from this trial (Section 7.3.3).

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

2.2 Trial Diagram

The trial design is depicted in Figure 1.

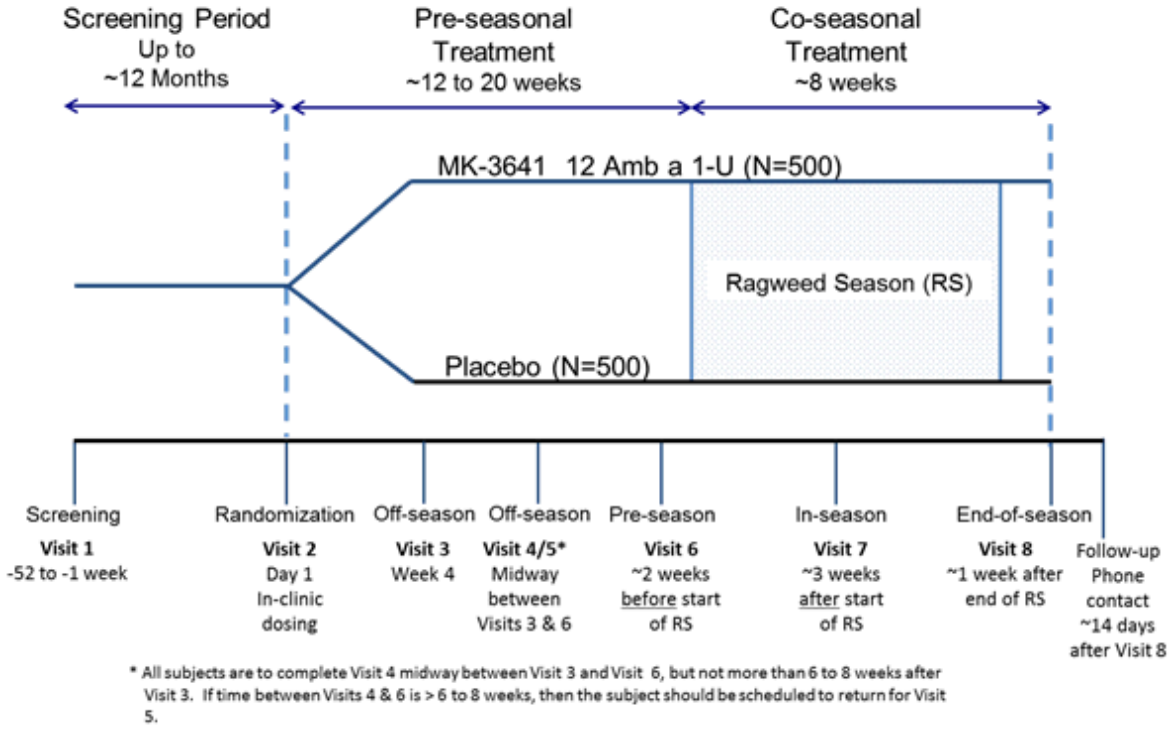

Figure 1 Trial Diagram

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

Objective: To evaluate the efficacy of MK-3641 sublingual immunotherapy tablet (12 Amb a 1-U) versus placebo in the treatment of children 5 to 17 years of age with ragweed-induced rhinoconjunctivitis, with or without asthma, based on the Total Combined Score (TCS) [sum of rhinoconjunctivitis daily symptom score (DSS) and rhinoconjunctivitis daily medication score (DMS)] averaged over the peak ragweed season (RS)[1].

Hypothesis: Administration of MK-3641 sublingual immunotherapy tablet (12 Amb a 1-U) to children 5 to 17 years of age, compared with placebo, will result in a significant reduction in TCS averaged over the peak RS.

3.2 Secondary Objective(s) & Hypothesis(es)

1) **Objective**: To compare the following between the MK-3641 (12 Amb a 1-U) and placebo groups:

    1. Average TCS during the entire RS[2];
    2. Average rhinoconjunctivitis DSS during the peak RS;
    3. Average rhinoconjunctivitis DMS during the peak RS.

    Hypotheses: Administration of MK-3641 (12 Amb a 1-U) in children 5 to 17 years of age, compared with placebo, will result in a significant score reduction on the following endpoints:

    1. Average TCS during the entire RS;
    2. Average rhinoconjunctivitis DSS during the peak RS;
    3. Average rhinoconjunctivitis DMS during the peak RS.

2) **Objective:** To assess the overall safety of MK-3641 (12 Amb a 1 U) in children 5 to 17 years of age with ragweed-induced rhinoconjunctivitis, with or without asthma.

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[1] Peak ragweed season is defined as the 15 consecutive recorded days within the entire ragweed season with the highest 15-day moving average pollen count for each study site.

[2] Entire ragweed season is defined as starting from the first day of 3 consecutive recorded days with pollen counts ≥10 grains/m^3 through the last day of the last occurrence of 3 consecutive days with pollen counts ≥10 grains/m^3.

3.3 Other Objectives

3.3.1 Tertiary Objectives

1) **Objective:** To compare the average rhinoconjunctivitis DSS during the entire RS between the MK-3641 (12 Amb a 1-U) and placebo groups.

2) **Objective:** To assess and compare the following immunologic parameters between the MK-3641 and placebo groups at specified time points before and during treatment:

   1. Immunoglobulin E (IgE) level against *Ambrosia artemisiifolia;*
   2. Immunoglobulin G_4 (IgG_4) level against *Ambrosia artemisiifolia*.

3.3.2 Exploratory Objective

Objective: To explore the effect of MK-3641 versus placebo on asthma endpoints in those subjects with asthma and those without asthma.

4.0 BACKGROUND & RATIONALE

4.1 Background

Allergic rhinitis/rhinoconjunctivitis (AR/ARC) affects between 10% to 30% of adults and up to 40% of children in the US [1]. Ragweed pollen is one of the most common inhalant allergens in North America, and for many patients ragweed pollen is a cause of their rhinoconjunctivitis symptoms [2]. Until recently, ragweed was predominantly a problem in North America, however, higher rates of ragweed allergy prevalence and sensitization are now seen in some European countries [3].

Allergen-specific immunotherapy consists of administering allergens to an allergic patient in order to induce immunological tolerance to the natural allergen. Subcutaneous immunotherapy (SCIT) has been the main approach for the application of this type of therapy [4]. However, these treatments are associated with risk of severe systemic reactions and must be administered by trained health care personnel at the physician's office. The administration of an oral allergen formulation, such as sublingual immunotherapy tablets, also reduces immediate reactivity to specific IgE antibody and is associated with a favorable safety profile that, in contrast to SCIT, permits self-administration by the patient after the first dose has been shown to be tolerable under physician observation. The predominant adverse reactions when administering allergen sublingually include local allergic events such as oral pruritus, itching of the throat, or swelling under the tongue, which will generally resolve with continuous treatment over the following weeks.

MK-3641 (RAGWITEK®[3]) is a sublingual immunotherapy (SLIT) tablet approved for use in the United States (US) and Canada for the treatment of short ragweed pollen-induced allergic rhinitis, with or without conjunctivitis, in adults 18 through 65 years of age. It is self-administered at home after the first dose is administered under supervision by a health care professional. To date, MK-3641 has not been studied in children. However, a similar tablet formulation containing Timothy grass (MK-7243) has been shown to be efficacious and safe for children down to 5 years of age. MK-7243 is approved in North America and Europe under the trade names of GRASTEK®[4] and GRAZAX®[5], respectively, for the treatment of allergic rhinitis and conjunctivitis in patients 5 to 65 years of age.

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3641.

4.1.1 Pharmaceutical and Therapeutic Background

MK-3641 is a freeze-dried, rapidly (within seconds) dissolving SLIT tablet containing *Ambrosia artemisiifolia* (short ragweed) extract, specifically 12 Amb a 1-U of the major short ragweed allergen Amb a 1. The effect of MK-3641 on alleviating the symptoms of ragweed pollen-induced allergic rhinoconjunctivitis is thought to be mediated via immunization of oral Langerhans cells inducing immunologic responses within the oral mucosa or local lymph nodes after sublingual allergen exposure and potential uptake into local tissues [5].

The placebo tablet is indistinguishable from the active tablet in appearance but contains no ragweed allergen.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

MK-3641 has been demonstrated to be efficacious for ragweed-allergic adults in reducing the symptoms of rhinoconjunctivitis and has an acceptable tolerability profile with few reported serious AEs (SAEs), of which none were assessed as related to the SLIT tablet. MK-3641 has yet to be studied in subjects <18 years old.

The prevalence rate of ragweed allergy in children ages 5 to 11 years and 12 to 17 years in the general population is not yet established. However, in one survey of children with asthma seen in an allergy specialty clinic, sensitization to short ragweed was 14% in young children (ages 3 to 11 years) and 25% in adolescents (ages 12 to 18 years) [6]. This study

[3] RAGWITEK® (MK-3641) is a registered trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A.

[4] GRASTEK® (MK-7243) is a registered trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A.

[5] GRAZAX® is a registered trademark of ALK-Abelló A/S, Hørsholm, Denmark.

will be the first trial to evaluate the efficacy and safety of MK-3641 in children 5 to 17 years of age (inclusive).

There is no reason to first perform dose-escalation safety and tolerability studies of MK-3641 in the pediatric population when a safety and tolerable dose has been established for adults as the general dosing principal of immunotherapy treatment is the same regardless of age. This is in accordance with current allergen immunotherapy practice guidelines that recommend initiating the same dose across ages and do not recommend specific dose adjustments for children [7]. This is supported by data from similar SLIT tablet formulations (MK-7243 Timothy grass tablet and MK-8237 house dust mite tablet) that have been studied in dose-escalation and Phase 3 studies in adults and children 5 years of age and older, and the data show a similar safety profile of the same maintenance dose across age ranges [8]. The study will be stratified by age and will endeavor to enroll approximately 35% of subjects 5 to 11 years of age; this distribution is to ensure an adequate number of subjects in the younger age group are included in the study.

As subjects with severe or uncontrolled asthma could be considered at higher risk of a potential systemic allergic reaction becoming severe, only those subjects with controlled asthma may be eligible for participation in this study. Those subjects on long-acting inhaled beta$_2$-agonists (LABAs) are not eligible for the study. Provided that their asthma is controlled on the regimen, subjects with asthma may use short-acting beta$_2$-agonists (SABAs) and/or low or medium daily doses of inhaled corticosteroids (ICS) as defined by the National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma (Table 1) [9]. If a subject with asthma is controlled on an ICS that is delivered by a method or modality other than those specified in the NAEPP Guidelines [10], the dose that the subject is receiving should be clinically equivalent to those noted in Table 1 in order to be allowed entry into this study. The assessment of asthma control will be determined per individual physician judgment at the time of screening and randomization, and at each clinic visit. This study will also be stratified by subject asthma status (yes/no).

Table 1 Low or Medium Daily Dose Corticosteroids as Defined by the NAEPP Guidelines

Inhaled Corticosteroid Medication	Low or Medium Daily Dose	
	5 to 11 Years of Age	≥12 Years of Age
Beclomethasone HFA	≤320 mcg	≤480 mcg
Budesonide DPI	≤800 mcg	≤1200 mcg
Flunisolide	≤1250 mcg	≤2000 mcg
Flunisolide HFA	≤320 mcg	≤640 mcg
Fluticasone DPI	≤400 mcg	≤500 mcg
Fluticasone HFA/MDI	≤352 mcg	≤440 mcg
Mometasone furoate	<440 mcg[a]	≤440 mcg[a]
Triamcinolone acetonide	≤900 mcg	≤1500 mcg
Ciclesonide HFA	≤160 mcg[a]	≤320 mcg[a]

DPI = dry-powder inhaler; GINA = Global Initiative for Asthma; HFA = hydrofluoroalkane; MDI = metered-dose inhaler; NAEPP = National Asthma Education and Prevention Program.
Dose delivery by method or modality other than those noted above should be clinically equivalent.

[a] Per GINA guidelines [11].

Potential trial subjects will be recruited from clinics with experience in the diagnosis and treatment of allergy and endemic areas with high ragweed pollen exposure such as the US, Canada, and Eastern Europe, where there is minimal overlap from other pollen/mold/dust mite seasons.

The primary endpoint of this study, the Total Combined Score (TCS), is a combination of (sum of) the rhinoconjunctivitis daily symptom score (DSS) and the rhinoconjunctivitis daily medication score (DMS) averaged over the peak ragweed season. The effectiveness of the treatment will depend on how well the rhinoconjunctivitis symptoms are relieved. A lower symptom score on active treatment indicates effectiveness compared with placebo. However, the use of rescue medications by a subject will result in a lower symptom score and will, therefore, be a confounding variable. As a result, basing the efficacy of the treatment on the symptom score alone may not reflect the treatment's true efficacy potential. Additionally, more subjects on the placebo group are likely to use rescue medications than those in the active treatment group, indicating the need to account for the use of rescue medications.

The combined symptom and medication score, which reflects the use of rescue medications, is an appropriate indicator of the efficacy potential of the treatment. This is consistent with current global regulatory positions on appropriate reporting of results from specific immunotherapy trials. The European Medicines Agency (EMA) has stated in their guidance on specific immunotherapy that the primary endpoint for trials should be reflective of both severity of symptoms and the intake of rescue medications [12]. In addition, the World Allergy Organization (WAO) has stated that symptoms and rescue medication utilization are interdependent variables. Therefore, in assessing the effect of allergen immunotherapy, a single predefined combined daily symptom and medication score more accurately reflects the clinical benefit experienced by the subject [13]. The TCS during the peak ragweed season is the same endpoint that has been used in the adult studies and was the basis for health authority approval. By focusing on the peak season, the treatment effect of MK-3641 will be evaluated during the time when pollen exposure is highest, least variable, and when symptoms are more likely to be most severe.

4.2.2 Rationale for Dose Selection/Regimen

The basic principle for allergen immunotherapy dose selection is to use the highest tolerable and safe dose. The highest tolerable/safe and effective dose of MK-3641 has been shown to be 12 Amb a 1-U in adults. The safety and efficacy profile of the same dose of sublingual tablet immunotherapy has been shown to be similar in adults and children [7] [14] [15] [16]. Also, the practice guidelines do not recommend dose adjustment in children as allergens act on the immune system, and are neither systemically absorbed nor metabolized by the liver and kidneys. Therefore, the MK-3641 dose of 12 Amb a 1-U approved for use in adults will also be used in children in this study, in line with the clinical practice of using the same dosage of immunotherapy in adults and children. This approach was utilized for a similar tablet-based SLIT product, MK-7243 (GRASTEK®/ GRAZAX®), approved for treatment of allergic rhinitis and conjunctivitis in patients 5 to 65 years of age. A comparable efficacy and safety profile in the adult and pediatric grass allergic subjects was demonstrated with the same 2800 BAU/75,000 SQ-U dose of the Timothy grass tablet (MK-7243).

4.2.2.1 Rationale for the Use of Placebo

A placebo arm will be used as a comparator to MK-3641. A placebo arm is considered ethically justifiable since subjects will be allowed to use rescue medications to treat their allergic rhinoconjunctivitis symptoms during the ragweed season. In addition, subjects will be medically monitored during the study and be provided appropriate treatment as needed. Subjects can also discontinue from the study at any time if they find the treatment intolerable.

4.2.2.2 Rationale for Dose Interval and Trial Design

Continuous exposure to the allergen is essential to induce allergen-specific tolerance and disease-modifying treatment effects from immunotherapy.

Results from previous adult/pediatric (ages 5 to 65 years) grass SLIT trials (MK-7243) and adult ragweed SLIT trials (MK-3641) have indicated that subjects receiving at least 12 weeks of pre-seasonal treatment demonstrate a higher treatment effect compared to subjects with shorter pre-seasonal treatment periods. In addition, the RAGWITEK label (approved for use in adults) indicates that treatment should be initiated at least 12 weeks before the expected onset of ragweed pollen season and continued throughout the season. Thus, subjects in the current study will receive approximately 12 weeks (and up to approximately 20 weeks) of pre-seasonal treatment with MK-3641 and continue through the ragweed season with approximately 8 weeks of co-seasonal treatment.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

4.2.3.1.1 Rhinoconjunctivitis Endpoints

The components that contribute to the rhinoconjunctivitis endpoints of TCS, rhinoconjunctivitis DSS, and rhinoconjunctivitis DMS are collected in an e-diary completed by the subject/parent/guardian. These rhinoconjunctivitis endpoints were agreed to by regulatory authorities (e.g., US Food and Drug Administration [FDA]) and were used as primary or key secondary endpoints in the adult RAGWITEK (ages 18 to 65 years) and adult/pediatric GRASTEK® (ages 5 to 65 years) programs. One change is that prednisone is not included in the rhinoconjunctivitis DMS for this pediatric ragweed trial. Few subjects in the previous studies used prednisone, with no difference in the efficacy analyses between the full analysis set (included subjects who used prednisone) and a sensitivity analysis that excluded subjects who used prednisone. It is anticipated that even fewer children will use prednisone than was seen with the previous studies in which the majority of subjects were adults.

4.2.3.1.1.1 Total Combined Score (TCS)

The TCS is the sum of the rhinoconjunctivitis daily symptom score (DSS) and the rhinoconjunctivitis daily medication score (DMS).

4.2.3.1.1.2 Rhinoconjunctivitis Daily Symptom Score (DSS)

The rhinoconjunctivitis DSS consists of a total of 6 allergic symptoms: 4 rhinitis symptoms and 2 conjunctivitis symptoms, and will be measured on a scale from 0 to 3 as follows:

0: **No** symptoms; (i.e., no sign/symptom evident);

1: **Mild** symptoms (i.e., sign/symptom clearly present, but minimal awareness; easily tolerated);

2: **Moderate** symptoms (i.e., definite awareness of sign/symptom that is bothersome but tolerable);

3: **Severe** symptoms (i.e., sign/symptom that is hard to tolerate; may cause interference with activities of daily living and/or sleeping).

The 6 allergic symptoms are classified in 2 groups as follows:

- Rhinitis:
  - Runny nose;
  - Stuffy nose;
  - Sneezing;
  - Itchy nose.
- Conjunctivitis:
  - Itchy eyes;
  - Watery eyes.

The maximum daily symptoms score is 18 points if a subject experiences all six symptoms with an intensity of 3 for each symptom.

4.2.3.1.1.3 Rhinoconjunctivitis Daily Medication Score (DMS)

The rhinoconjunctivitis DMS consists of rhinoconjunctivitis symptomatic rescue medication scores. To transform the amount of symptomatic medications used into medication scores, the scoring principles detailed in Table 2 are applied.

Table 2 Scoring of Symptomatic Rescue Medication Use

RHINOCONJUNCTIVITIS				
Step	**Rescue Medication[a]**	**Subject Dosing Instructions**	**Score/ Dose Unit**	**Maximum Daily Score**
1	Loratadine syrup, 1 mg/mL	5 years old: 5 mL once daily	6 per 5 mL	6
	or	6 to 17 years old: 10 mL once daily	6 per 10 mL	
	Loratadine oral tablet, 5 mg or 10 mg	5 years old: 5 mg tablet (1 tablet) once daily 6 to 17 years old: 10 mg tablet (1 tablet) once daily	6 per tablet	
1b	Olopatadine hydrochloride ophthalmic solution, 0.1%	1 drop in each affected eye twice daily	1.5 per drop	6
2	Mometasone furoate monohydrate nasal spray, 50 mcg	5 to 11 years old: 1 spray in each nostril once daily	4 per spray	8
		12 to 17 years old: 2 sprays in each nostril once daily	2 per spray	
Maximum rhinoconjunctivitis daily medication score (DMS)				**20**

[a] In countries where a rescue medication is not available, a similar medication will be dispensed in a clinically equivalent dosage.

4.2.3.1.2 Asthma Endpoints

All of the asthma endpoints will be collected in the e-diary completed by the subject/parent/guardian. The asthma daily symptom score (aDSS) has been used in the previous adult RAGWITEK program (ages 18 to 65 years), as well as the adult/pediatric GRASTEK® program (ages 5 to 65 years). The beta$_2$-agonist use and nocturnal awakenings endpoints have been used extensively in previous adult and pediatric asthma studies as key secondary and other endpoints, respectively.

4.2.3.1.2.1 Asthma Daily Symptom Score (aDSS)

The aDSS consists of a total of 3 asthma symptoms: cough, wheeze, and chest tightness/dyspnea. Each symptom is measured on the same scale as the rhinoconjunctivitis DSS. The aDSS will be completed daily beginning with Visit 4 by all subjects in the study.

4.2.3.1.2.2 Beta$_2$-agonist Use

Only those subjects with asthma will record on the e-diary the number of puffs of as-needed SABA (albuterol/salbutamol) used each day for asthma symptoms. Any use of SABA for prophylaxis, such as for exercise-induced asthma, will not be included.

4.2.3.1.2.3 Nocturnal Awakenings

Only those subjects with asthma will record on the e-diary whether they woke up at night due to asthma symptoms requiring SABA (albuterol/salbutamol) use (yes/no).

4.2.3.2 Safety Endpoints

The safety endpoints for this trial have been selected based on previous studies in subjects with grass (adult/pediatric subjects 5 to 65 years of age), ragweed (adult subjects), and/or house-dust mite (adult/pediatric subjects 5 years of age and older) allergies treated with grass (MK-7243), ragweed (MK-3641), or house-dust mite (MK-8237) SLIT tablets, respectively. By assessing the severity and frequency of commonly occurring local AEs, in addition to overall AEs and drug-related AEs, safety and tolerability can be assessed.

In addition, the SLIT Report Card (Section 12.10) will be completed by the subject/parent/guardian, daily for the first ~28 days of dosing, to collect information on local side effects of SLIT that occur within the first 60 minutes after each daily study drug intake. An exploratory review of severity grading will be conducted for identified local AEs as graded programmatically and as assessed by the investigator.

4.2.3.3 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens collected for future biomedical research during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. For instance, exploratory pharmacogenetic (PGt) studies may be performed if significant Pharmacokinetic/Pharmacodynamic (PK/PD) relationships are observed or adverse events are identified. Genomic markers of disease may also be investigated. Such retrospective pharmacogenetic studies will be conducted with appropriate biostatistical design and analysis and compared to PK/PD results or clinical outcomes. Any significant PGt relationships to outcome would require validation in future clinical trials. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 - Collection and Management of Specimens for Future Biomedical Research. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

4.3 Benefit/Risk

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

MK-3641 provides an alternative formulation and mode of administration of immunotherapy that expands the treatment options for children suffering from ragweed-induced allergic rhinoconjunctivitis. MK-3641 is an effective treatment for adult patients for whom immunotherapy is indicated and has an acceptable safety profile in this population. In contrast to subcutaneous immunotherapy treatments, MK-3641 allows for a short induction period with a simple dosing form that does not require up- or down-titration and allows for at-home dosing after administration of the first dose in a health care setting under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases. Based on the efficacy/safety studies of MK-3641 in adults and those of a grass SLIT tablet (MK-7243) in both adults and children (ages 5 to 65 years), the benefit/risk assessment for conducting this pediatric trial of MK-3641 is favorable. Risks in this trial are manageable when the first tablet is administered under physician supervision and with appropriate education of the subject and parent/guardian about symptoms and signs of severe allergic reactions. There is no expectation of an increased safety risk for children enrolled in this trial compared with that observed in the adult ragweed trials and adult/pediatric grass trials.

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 a history of ragweed pollen-induced allergic rhinoconjunctivitis, with or without asthma, between the ages of 4 and 17 years (inclusive) 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. Have a legal representative who provides written informed consent for the trial on the subject's behalf after understanding the study procedures, alternative treatments available, risks involved with the study, and voluntarily agreeing to allow the subject to participate. The legal representative may also provide consent for Future Biomedical Research on the subject's behalf. However, the subject may participate in the main trial without participating in Future Biomedical Research. The subject, depending on their age and ability to understand the nature and intent of the study, must also assent to participate in the study main trial and to Future Biomedical Research.

2. Be ≥4 to ≤17 years of age on the day informed consent is obtained from the legal representative, however, the subject must be ≥5 years old at the Randomization Visit. The subject may be of either gender and any race/ethnicity.
3. Have a clinical history of significant ragweed pollen-induced allergic rhinitis/rhinoconjunctivitis of ≥1 year (at least 1 season for ages 4 to 6 years) or ≥2 years (at least 2 seasons for ages 7 to 17 years) duration diagnosed by a physician (with or without asthma) and have received treatment for the condition during the previous ragweed season.

   Note: If medical records are not available, verbal history from subject/parent/legal guardian may be elicited at the Screening Visit and can be used to fulfill this criterion if documented in the subject study file by the investigator.
4. Have a positive skin prick test response (average wheal diameter ≥5 mm larger than the saline control after 15 to 20 minutes) to *Ambrosia artemisiifolia* at the Screening Visit.

   Note: The test can have been performed up to 1 year before the Screening Visit if the skin prick test reagents and prick devices used are the same as provided for this trial.
5. Have a specific IgE against *Ambrosia artemisiifolia* ≥ IgE Class 2 (0.7 kU/L) at the Screening Visit.
6. Have a forced expiratory volume in 1 second (FEV_1) ≥80% of predicted value at the Screening and Randomization Visits (following at least a 6-hour washout of short-acting $beta_2$-agonists, 12-hour washout of twice daily long-acting $beta_2$-agonists, or 24-hour washout of once daily long-acting $beta_2$-agonists).

   Note: Long-acting inhaled $beta_2$-agonists are prohibited within 30 days prior to randomization and for the duration of the study.

   Note: A subject who is ≤7 years old and cannot perform reproducible FEV_1 maneuvers, despite coaching, does not need to meet this criterion.
7. Have safety laboratory tests and vital signs conducted at the Screening Visit be within normal limits or are clinically acceptable to the investigator/Sponsor.
8. Be able to adhere to dose and visit schedules.
9. Be able to read, understand, and complete the questionnaires and diaries (or can have help from the parent/guardian).
10. Have a negative urine pregnancy test at the Screening and Randomization Visits (if female of reproductive potential). A female subject who is not of reproductive potential is defined as: one who 1) has not reached menarche, 2) is 6 weeks post-surgical documented total hysterectomy and/or bilateral salpingo-oophorectomy, or 3) has had bilateral tubal ligation.

11. If female, agree to remain abstinent or use (or have their partner use) an acceptable method of birth control within the projected duration of the study. Abstinence is defined as true abstinence, when this is in line with the usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Acceptable methods of birth control are intrauterine device (IUD), hormonal contraception, diaphragm with spermicide, contraceptive sponge, condom, vasectomy, as per local regulations or guidelines. A female subject who is not of reproductive potential is eligible without requiring the use of contraception.

5.1.3 Subject Exclusion Criteria

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

1. Has a clinical history of symptomatic seasonal allergic rhinitis (and/or asthma) due to another allergen, which has required regular medication during, or potentially overlapping, the ragweed season.
2. Has a clinical history of significant symptomatic perennial allergic rhinitis and/or asthma due to an allergen to which the subject is regularly exposed during the ragweed season which would interfere with assessment of the treatment effect.
3. Has any nasal condition that could confound the efficacy or safety assessments (e.g., nasal polyposis).
4. Has asthma requiring high daily doses of inhaled corticosteroids within the 6 months prior to the Screening Visit.
5. Is one of the following:
   - >7 years old and cannot perform reproducible FEV_1 maneuvers despite coaching;
   - ≤7 years old who cannot perform reproducible FEV_1 maneuvers despite coaching and has current symptoms of asthma characterized by recurrent episodes of wheezing, or episodes of cough, wheeze, difficulty in breathing, or chest tightness [17].
6. Has severe, unstable, or uncontrolled asthma, as judged by the clinical investigator, or has experienced a life-threatening asthma attack or an occurrence of any clinical deterioration of asthma that resulted in emergency treatment, hospitalization due to asthma, or treatment with systemic corticosteroids (but allowing short-acting beta-agonists) at any time within the last 3 months prior to the Screening or Randomization Visits.
7. Has a history of anaphylaxis with cardiorespiratory symptoms with prior immunotherapy, unknown cause, or inhalant allergen.
8. Has a diagnosis of eosinophilic esophagitis.
9. Has a history of chronic urticaria and/or chronic angioedema.
10. Has a clinical history of chronic sinusitis during the 2 years prior to the Screening or Randomization Visits.

11. Has current severe atopic dermatitis.
12. Has a history of allergy, hypersensitivity, or intolerance to the ingredients of the investigational medicinal products (except for *Ambrosia artemisiifolia*), rescue medications, or self-injectable epinephrine.
13. Has any clinically significant condition or situation, other than the condition being studied that, in the opinion of the investigator, would interfere with the study evaluations or optimal participation in the study. Specific examples include, but are not limited to, hypertension being treated with beta blockers, arrhythmia, ocular conditions requiring topical beta blockers, any condition requiring the use of beta blockers, and systemic disease affecting the immune system, i.e., autoimmune diseases, immune complex diseases, or immune deficiency diseases.
14. Is female and is breast-feeding at randomization, pregnant, or intending to become pregnant within the projected duration of the study.
15. Has previously received MK-3641.
16. Is unable to meet medication washout requirements as listed in Table 3.

Table 3 Prohibited Medications Prior to Randomization

Prohibited Medication(s)[a]	**Washout Period Prior to Randomization**
Anti-IgE treatment (e.g., Xolair)	At any time
Maintenance doses of ragweed immunotherapy[b]	5 years
High daily doses of inhaled corticosteroids[c]	6 months
Immunosuppressive therapy (except steroids for allergic and asthma symptoms)	90 days
Investigational drugs	30 days
Long-acting inhaled $beta_2$-agonists	30 days
Tricyclic antidepressant medications with antihistaminic effects (e.g., doxepin, mianserin)	14 days
Monoamine oxidase inhibitors	14 days
Beta blockers, regardless of route of administration	7 days
Antipsychotic medications with antihistaminic effects (e.g., chlorpromazine, levomepromazine, clozapine, olanzapine, thioridazine)	7 days

ICS = inhaled corticosteroid.

[a] Although medications in Table 5 (Section 5.5) are not specifically prohibited prior to randomization, please consider whether a subject is able to wash out of the listed medications prior to Visit 6 (e.g., leukotriene antagonist use for allergic rhinitis could be washed out; however, subjects using a leukotriene antagonist for asthma should not be enrolled in this trial unless it is used as short-term treatment outside of the ragweed season (e.g., during winter season, tree pollen season).

[b] Allowed within the last 5 years if duration of ragweed immunotherapy from initiation <1 month.

[c] Subjects maintained on a low- or medium-dose ICS will be allowed to continue on his/ her medication during the trial. A subject must have been using a low or medium daily dose of ICS for at least 12 weeks before screening and/or randomization and must have been on a stable regimen (daily dose unchanged) for at least 2 weeks before Screening (Visit 1) and/or 4 weeks before Randomization (Visit 2). Low or medium daily doses of ICS can be found in Section 4.2.1 Table 1; Note: Dose delivery by method or modality other than described in Table 1 should be clinically equivalent.

17. Is unable to or will not comply with the use of self-injectable epinephrine administration (in countries where epinephrine is a regulatory requirement).
18. May be at greater risk of developing adverse reactions after epinephrine administration.
19. Has a clinically significant abnormal vital sign or laboratory value that, in the opinion of the investigator, would preclude participation in the study, or has a laboratory value that does not meet the Algorithm for Assessing Out-of-Range Laboratory Values (see Section 12.5).

    Note: A maximum of one re-draw is permitted for re-evaluation of out-of-range safety laboratory values. The investigator is encouraged to ensure prompt follow-up of all subjects with a potentially life threatening laboratory abnormality, as per investigator's clinical judgment.
20. Is unlikely to be able to complete the trial, for any reason, or likely to travel for extended periods of time during the ragweed season, which in the opinion of the investigator will compromise the data.
21. Has previously been randomized into this study.
22. Is participating in the study at another investigational site.
23. Is participating in any other clinical study or plans to participate in another clinical study during the duration of this study.
24. Has a history or current evidence of any condition, therapy, lab abnormality or other circumstance that might expose the subject to risk by participating in the trial, confound the results of the trial, or interfere with the subject's participation for the full duration of the trial.
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 4.

Table 4 Trial Treatments

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
MK-3641	12 Amb a 1-U	Once daily	Sublingual	Up to ~28 weeks	Experimental
Placebo	Not applicable	Once daily	Sublingual	Up to ~28 weeks	Placebo comparator
Self-injectable epinephrine[a, b]	Suggested doses = 15-30 kg (33-66 pounds): 0.15 mg ≥30 kg (≥66 pounds): 0.3 mg	As needed	Intramuscular	-	Rescue medication dispensed at Randomization (Visit 2), when applicable
Albuterol/ Salbutamol[c]	90 mcg/puff[d]	As needed	Inhalation	-	Rescue medication dispensed at Randomization (Visit 2)
Loratadine[b, e]	5 years old: 5 mg (1 mg/mL syrup or 5 mg tablet) 6 to 17 years old: 10 mg (1 mg/mL syrup or 10 mg tablet)	-	Oral	-	Rescue medication dispensed at Pre-Season Visit (Visit 6)
Olopatadine hydrochloride[b, e]	1 drop (0.1%) per affected eye	-	Ophthalmic	-	Rescue medication dispensed at Pre-Season Visit (Visit 6)
Mometasone furoate monohydrate[b, e]	5 to 11 years old: 1 spray (50 mcg/ spray) per nostril 12 to 17 years old: 2 sprays (50 mcg/spray) per nostril	-	Intranasal	-	Rescue medication dispensed at Pre-Season Visit (Visit 6)

[a] Provided in countries where epinephrine is a regulatory requirement.
[b] In countries where a rescue medication is not available, a similar medication will be dispensed in a clinically equivalent dosage.
[c] Provided to those subjects with asthma.
[d] Albuterol metered-dose inhaler (MDI) 90 mcg/puff; salbutamol MDI 100 mcg/puff.
[e] See Table 2 for dosing instructions.

The first dose of trial treatment will be administered at the trial site at Visit 2. Subsequent dosing will be performed once daily by the subject (i.e., unsupervised at his/her home) at approximately the same time each day.

All supplies indicated in Table 4 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

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

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, usage and disposal 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

The first dose of study drug will be administered under supervision at the study site at Visit 2. Subsequent dosing will be performed once daily at home by the subject/parent/guardian at approximately the same time each day for up to approximately 28 weeks and should occur at a time of the day that would allow the parent/guardian to keep the subject under observation for AEs for approximately 30 minutes after administration.

5.2.2.1 In-Clinic Dosing at Visit 2

At Visit 2, the first dose of study drug will be administered under supervision at the study site, and then the subject will be required to stay at the study site for an observation period of approximately 30 minutes to assess any AEs. Prior to administration of the first dose of study drug, the investigator should discuss well-known immediate application site reactions and severe AEs requiring medical evaluation and/or the use of rescue emergency medications (such as antihistamines, epinephrine, etc.) with the subject/parent/guardian. The site should record the duration of AEs (in minutes) following the first administration of the study drug at the randomization visit. If any significant AE such as wheezing, dyspnea, severe oral swelling, or signs of generalized anaphylactic reaction is observed or reported, the investigator or medically qualified sub-investigator must evaluate the subject to determine whether treatment of the adverse reaction should be initiated. In such cases, the observation period should be extended for at least an additional 30 minutes. When the subject/parent/guardian leave the study site, instructions should be given to contact the study site immediately if the reaction reoccurs or a new reaction appears. If the investigator determines that a subject cannot leave the study site but needs further attention not otherwise

available at the study site, the subject will be transferred to an appropriate facility such as an emergency room.

Subjects not experiencing clinically significant reactions may leave the study site approximately 30 minutes after the first dose of study drug has been given. The subject/parent/guardian should be instructed to contact the study site immediately if any reaction occurs after leaving the study site.

5.2.2.2 At-home Dosing

Following the first supervised dose of study drug, the subject/parent/guardian will be dispensed the study drug for at-home administration for subsequent dosing. The subject/parent/guardian will be instructed on how to open the blister pack and administer the tablet. In addition, the subject/parent/guardian will be provided with a written description of the procedure (Section 12.7). The tablet is to be placed under the tongue and allowed to remain there for a few seconds until it has dissolved. The subject should be advised not to swallow during the first minute. The subject also should be advised not to eat or drink for approximately 5 minutes after tablet administration. The subject/parent/guardian will be instructed to contact the study site for any AEs that the subject/parent/guardian considers significant or if the subject/parent/guardian considers treatment for the AE necessary. The subject/parent/guardian will be instructed on and provided with an Anaphylaxis Emergency Action Plan[6] (Section 7.1.1.10; Section 12.8) for any potential anaphylactic reactions. In addition, those subjects in countries where self-injectable epinephrine is a regulatory requirement will be provided with self-injectable epinephrine (Section 5.6.3; Section 7.1.1.11). The subject should only take 1 tablet of study drug each day. If the subject misses a dose of study drug, they should resume taking study drug the following day. At each clinic visit, any missed doses should be reported.

Study drug administration should occur at approximately the same time each day and should occur at a time of the day that would allow the parent/guardian to keep the subject under observation for AEs for approximately 30 minutes after administration.

[6] The Anaphylaxis Emergency Action Plan can be modified outside the US to meet local standards for the use (or type) of epinephrine dispensed, and for calls to 911 or alternative local emergency services.

5.2.2.3 Temporary Study Drug Interruptions

Treatment with study drug should be temporarily stopped for up to 7 days under the following conditions:

1. In case of oral surgery (including dental extraction), oral injury or other oral conditions affecting the integrity of the oral mucosa to allow healing of the oral cavity (not including loss of deciduous teeth);

2. Other reasons as deemed necessary by the investigator or designee.

If a subject has a treatment interruption due to a worsening AE related to the study drug, then the subject should be re-evaluated by the investigator, or designee, prior to reinitiating the study drug.

5.2.3 Trial Blinding/Masking

A double-blind/masking technique will be used. MK-3641 and placebo will be packaged identically so that blind/masking is maintained. The subject/parent/guardian, the investigator and Sponsor personnel or delegate(s) who are involved in the treatment administration 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

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 MK-3641 and placebo, respectively.

5.4 Stratification

Randomization will be stratified according to the following factors:

1. Age (5 to 11 years, 12 to 17 years);
2. Asthma status (asthma, non-asthma) of the subjects.

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.

Restrictions for concomitant therapy beginning prior to the start of the ragweed season (with the listed washout requirements) and continuing for the duration of the study (with the exception of study-provided rescue medications) are listed in Table 5. Those medications listed in Table 3 are prohibited beginning with the washout periods prior to randomization and continuing for the duration of the study.

Table 5 Prohibited Medications Beginning Prior to Pre-Season Visit 6 and for Duration of Trial

Prohibited Medication(s)	Washout Period Prior to Pre-Season Visit 6
Long-acting parenteral (intramuscular, intra-articular) corticosteroids	90 days
Oral corticosteroids	60 days
Nasal corticosteroids	30 days
Short-acting parenteral corticosteroids	30 days
Leukotriene antagonists/synthase inhibitors	30 days
Corticosteroid eye drops	30 days
Inhaled, topical, or oral nedocromil or cromolyn sodium	14 days
Oral or topical antihistamines[a]	7 days
Nasal or ocular decongestants	7 days

[a] Pre-treatment with medications (e.g., antihistamines) to treat potential AEs will not be permitted; this is to avoid masking or delayed reactions.

Medications or vaccines that are not restricted by the protocol (Table 3 and Table 5) and that would not be expected to interfere with the conduct of the study are allowed. Chronic medications should be dosed on a stable regimen. All concomitant medications must be appropriately documented on the electronic case report form (eCRF). The use of any concomitant medication must relate to the documented medical history, prophylaxis, or an AE of the subject.

5.6 Rescue Medications & Supportive Care

5.6.1 Allergy Rescue Medications for Rhinoconjunctivitis Symptoms

Subjects may experience allergy symptoms that require additional treatment. Thus, rescue medications for rhinitis/conjunctivitis symptoms will be provided (beginning at Visit 6) according to the following steps (for dosage instructions, see Table 2; for subject instructions, see Section 12.6):

1. Step 1: Loratadine syrup, 1 mg/mL or loratadine oral tablet, 5 mg (5 years old) or 10 mg (≥6 years old)
2. Step 1b: Olopatadine hydrochloride ophthalmic solution, 0.1%
3. Step 2: Mometasone furoate monohydrate nasal spray, 50 mcg.

5.6.2 Medications for Asthma Symptoms

Short-acting inhaled beta$_2$-agonist (i.e., albuterol/salbutamol metered-dose inhaler) will be provided to those subjects with asthma. Other medications for asthma will not be provided. Subjects who are taking low or medium daily dose inhaled corticosteroids for asthma management will be allowed to continue with the same medications during the study. A subject must have been using a low or medium daily dose of ICS for at least 12 weeks before screening and/or randomization and must have been on a stable regimen (daily dose unchanged) for at least 2 weeks before Screening (Visit 1) and/or 4 weeks before Randomization (Visit 2). Low and medium daily doses of inhaled corticosteroids are defined in Table 1 (Section 4.2.1).

If a subject requires additional asthma medications, the subject should follow recommendations regarding medication adjustments provided by his/her physician. Medication use should be recorded on the eCRF.

5.6.3 Rescue Medication for Severe Allergic Reactions (Self-Injectable Epinephrine)

Self-injectable epinephrine will be provided to each subject/parent/guardian at the randomization visit (Visit 2) in countries where it is a regulatory requirement, and should be available around the time that the tablets are administered at home.

Self-injectable epinephrine is intended for immediate self-administration for an anaphylactic reaction, including symptoms/signs of upper airway obstruction. Anaphylaxis is likely when multiple organ systems are adversely affected following exposure to an allergen. A list of symptoms that may be present during anaphylaxis include flushing, apprehension, syncope, tachycardia, thread or unobtainable pulse associated with a fall in blood pressure, vomiting, diarrhea and abdominal cramps, wheezing, dyspnea due to laryngeal spasm, lower airway obstruction, pruritus, rashes (such as urticaria), or angioedema. Self-injectable epinephrine should be administered promptly (in countries where it is part of usual care) when significant respiratory and/or cardiovascular symptoms accompany an allergic reaction.

If eligible for enrollment after completing all of the screening procedures, the subject/parent/guardian in countries where epinephrine is a regulatory requirement will be provided with self-injectable epinephrine at the Randomization Visit (Visit 2). The investigator or designee will instruct the subject/parent/guardian on how to administer the self-injectable epinephrine and have it available when tablet(s) are administered. The investigator or designee will provide and explain to the subject/parent/guardian written instructions, and will review when to administer the self-injectable epinephrine. The investigator/designee will complete an Anaphylaxis Emergency Action Plan[7] for each

[7] The Anaphylaxis Emergency Action Plan can be modified outside the US to meet local standards for the use (or type) of epinephrine dispensed, and for calls to 911 or alternative local emergency services.

subject, provide a copy to the subject/parent/guardian, and keep a copy for the site's records (Section 12.8).

In the event that self-injectable epinephrine is used, the subject/parent/guardian must immediately call the local emergency number and the 24-hour investigational site emergency number indicated in the informed consent and on the subject identification card. An unscheduled visit will be arranged to further evaluate the subject. The investigator or designee must notify the Sponsor within 1 working day of first becoming aware of the use of self-injectable epinephrine. The symptoms and/or circumstances that triggered the use of self-injectable epinephrine must be clearly recorded on the eCRF.

5.7 Diet/Activity/Other Considerations

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

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.

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

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- The subject experiences an SAE (not including those only associated with an overdose) which is considered treatment related, OR a causal association cannot be ruled out, OR the cause of the SAE is unknown.
- The subject experiences persistent and escalating adverse reactions in the mouth or throat.
- The subject experiences severe or persistent symptoms of esophagitis.
- The subject experiences an anaphylactic reaction with severe symptoms associated with the investigational treatment.
- The subject experiences a severe asthma exacerbation (such as requiring hospitalization or oral corticosteroid use) or the subject's asthma becomes difficult to control.
- The subject experiences other persistent, intolerable AEs considered to be due to the study treatment, as determined by the investigator or the subject/parent/guardian.

- 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.
- The subject is unable to tolerate the study medication, as perceived by the investigator or subject.
- The subject fails to comply with the dosing (see Sec 7.1.1.15), evaluations, or requirements of the study, despite documentation at the site of repeated efforts to reinforce compliance.
- The subject has a confirmed positive serum pregnancy test.
- The subject becomes pregnant.

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

Early trial termination will be the result of the criteria specified below:

1. Treatment-related death of an individual;
2. Treatment-related anaphylactic shock in at least 2 subjects*.

* The criterion for 2 events is based on prior trial experience where it has been observed that events of severe anaphylactic reactions unrelated to investigational medicinal product (IMP) may occur in allergic trial subjects even with a temporal relationship to tablet administration.

Study drug intake may only be resumed after the information has been presented to health authorities, and health authorities concur with continued drug intake. In case of complete premature termination of the trial, participating investigators/subjects/parent/guardian, the IRB/ERC, and the relevant health authorities must be promptly informed of the termination.

6.0 TRIAL FLOW CHART

Trial Period:	Screening	Treatment						Post-treatment
Visit Number:	1	2	3	4/5 [a]	6	7	8	--
Visit Title:	Screening	Randomization	Off-Season	Off-Season	Pre-Season	In-Season	End-of-Season/ Discontinuation	Telephone/ Follow-up
Scheduled Day/Week:	Weeks -52 to -1[b]	Day 1	Week 4[c]	Midway between Visits 3 & 6	~2 weeks before start of RS	~3 weeks after start of RS[d]	~1 week after end of RS	Post 14 days
Scheduling Window (Days):	-	-	+7 days		± 7 days		± 7 days	± 5 days
Administrative Procedures								
Informed Consent[e]	X							
Informed Consent for Future BiomedicalResearch[f]	X							
IVRS/IWRS	X	X	X	X	X	X	X	
Inclusion/Exclusion Criteria	X	X						
Demography	X							
Medical History	X	X						
Allergic Rhinitis Baseline Profile and Family History of Atopy	X	X						
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X
Issue/Update Subject Identification Card	X	X[g]						
Issue/Instruct in the use of e-diary				X				
Review e-diary data and instructions for use					X	X		
Activate Medication section of e-diary					X			
Discontinue/Collect e-diaries							X	
Dispense/Review Anaphylaxis Emergency Action Plan[h]		X	X	X	X	X		
Provide Self-Injectable Epinephrine and Educational Information, Instruct in its use[i]		X						

Trial Period:	Screening	Treatment						Post-treatment
Visit Number:	1	2	3	4/5 [a]	6	7	8	--
Visit Title:	Screening	Randomization	Off-Season	Off-Season	Pre-Season	In-Season	End-of-Season/ Discontinuation	Telephone/ Follow-up
Scheduled Day/Week:	Weeks -52 to -1 [b]	Day 1	Week 4 [c]	Midway between Visits 3 & 6	~2 weeks before start of RS	~3 weeks after start of RS [d]	~1 week after end of RS	Post 14 days
Scheduling Window (Days):	-	-	+7 days		± 7 days		± 7 days	± 5 days
Provide albuterol/salbutamol to subjects with asthma [j]		X	X [j]	X [j]	X [j]	X [j]		
Issue/Instruct in the use of SLIT Report Card		X						
Collect/Review SLIT Report Card			X					
Issue/Instruct in the use of Comment Card		X	X	X	X	X		
Collect/Review Comment Card			X	X	X	X	X	
Clinical Procedures/Assessments								
Vital Signs (Temperature, Blood Pressure, Pulse, Respiration Rate) [k]	X	X	X	X	X	X	X	
Body Height and Weight [k]	X	X						
Physical Examination	X						X [k]	
Oropharyngeal Examination [l]	X	X [l]	X	X	X	X	X	
Pulmonary Function Tests [m]	X	X			X	X	X	
Beta$_2$-agonist reversibility [n]		X						
Skin Prick Test	X							
Adverse Events Monitoring		X	X	X	X	X	X	X
On-site Dosing of Study Medication		X						
Dispense Study Medication		X	X	X	X	X		
Verify Subject has Self-Injectable Epinephrine and Review Instructions for use			X	X	X	X		
Verify subjects with history of asthma have albuterol/salbutamol			X	X	X	X		
Check/Collect Study Medication			X	X	X	X	X	

Trial Period:	Screening	Treatment						Post-treatment
Visit Number:	1	2	3	4/5 [a]	6	7	8	--
Visit Title:	Screening	Randomization	Off-Season	Off-Season	Pre-Season	In-Season	End-of-Season/ Discontinuation	Telephone/ Follow-up
Scheduled Day/Week:	Weeks -52 to -1 [b]	Day 1	Week 4 [c]	Midway between Visits 3 & 6	~2 weeks before start of RS	~3 weeks after start of RS [d]	~1 week after end of RS	Post 14 days
Scheduling Window (Days):	-	-	+7 days		± 7 days		± 7 days	± 5 days
Dispense/Review Need for Allergy Rescue Medication					X	X		
Record Use of Allergy Rescue Medication (e-diary)					X	X	X	
Collect Rescue Medication/Self-Injectable Epinephrine							X	
Monitor compliance with Study Medication			X	X	X	X	X	
Monitor Compliance with e-dairy completion				X	X	X	X	
Laboratory Procedures/Assessments								
Serum specific IgE to a panel of allergens	X							
Hematology, Chemistry, Urinalysis	X							
Urine Pregnancy Test – if applicable [o]	X	X	X	X	X	X	X	
Immunologic sample (IgE, IgG_4) [p]		X			X		X	
Saliva (DNA) for Future Biomedical Research [q]		X						

DNA = deoxyribonucleic acid; e-diary = electronic diary; FBR = future biomedical research; FEV_1 = forced expiratory volume in 1 second; IgE = immunoglobulin E; IgG_4 = immunoglobulin G_4; IVRS/IWRS = Interactive Voice/Web Response System; PFT = pulmonary function test; RS = ragweed season; SLIT= sublingual immunotherapy; US = United States.

a. All subjects are to complete Visit 4 midway between Visit 3 and Visit 6, but not more than 6 to 8 weeks after Visit 3. If time between Visits 4 & 6 is > 6 to 8 weeks, then subject should be scheduled to return for Visit 5 approximately midway between Visits 4 and 6; study drug is not dispensed at Visit 5 (see Section 9.2 for the visits when study drug is dispensed).

b. During the first season of screening, subjects may be in screening up to approximately 9 months (-39 to -1 week). During subsequent season(s) of screening, subjects may be in screening up to approximately 12 months (-52 to -1 week).

c. Visit 3 should be scheduled on Day 28 (+7 days) to allow the subject to complete the SLIT Report Card for ~28 days.

d. It is preferable that Visit 7 be scheduled approximately 3 weeks after the start of the ragweed season.

e. Informed consent/assent must be obtained before any trial-related procedures are performed.

f. Informed consent for future biomedical research samples (optional) must be obtained before the saliva for DNA sample.

g. Update Subject Identification Card with randomization number.

h. The Anaphylaxis Emergency Action Plan can be modified outside the US to meet local standards for the use (or type) of epinephrine dispensed, and for calls to 911 or alternative local emergency services.

Trial Period:	Screening	Treatment						Post-treatment
Visit Number:	1	2	3	4/5 [a]	6	7	8	--
Visit Title:	Screening	Randomization	Off-Season	Off-Season	Pre-Season	In-Season	End-of-Season/ Discontinuation	Telephone/ Follow-up
Scheduled Day/Week:	Weeks -52 to -1[b]	Day 1	Week 4[c]	Midway between Visits 3 & 6	~2 weeks before start of RS	~3 weeks after start of RS[d]	~1 week after end of RS	Post 14 days
Scheduling Window (Days):	-	-	+7 days		± 7 days		± 7 days	± 5 days

i. Self-injectable epinephrine is provided only in those countries where it is a regulatory requirement.

j. Albuterol/salbutamol should also be dispensed to subjects diagnosed with asthma during the trial as needed.

k. Vital Signs (axillary temperature, blood pressure, pulse, respiration rate) in a seated position, height, and weight should be performed prior to performing pulmonary function tests. At the End-of-season/Discontinuation visit a limited physical exam will be performed.

l. Oropharyngeal examinations will be performed before and after study drug administration at Visit 2. Targeted physical examinations may be conducted at visits that do not already include a physical exam, if deemed necessary by the investigator, due to signs/symptoms.

m. FEV_1 results should be available and reviewed by investigator or designee prior to administration of first dose of study medication to ensure results meet inclusion criteria. Following randomization, PFTs are required only for subjects with asthma at the subsequent visits identified in the trial flow chart, unless the investigator feels a PFT is warranted for a subject without asthma. Note: PFTs are not required for those subjects ≤7 years of age who cannot perform reproducible FEV_1 maneuvers despite coaching; those subjects ≤7 years of age who can perform reproducible FEV_1 maneuvers, including those who initially could not at the Screening Visit, must complete the PFTs.

n. $Beta_2$-agonist reversibility (Section 12.9) will be performed at Visit 2 for all subjects performing PFTs (i.e., all subjects >7 years of age and all subjects ≤7 years of age who can perform reproducible FEV_1 maneuvers).

o. If a urine test result is positive, confirm with a serum β-hCG test.

p. Immunologic samples will only be collected at selected sites. The Visit 2 sample should be collected prior to administration of the first dose of study drug. Leftover main study serum samples will be stored for future biomedical research if the subject consents to future biomedical research.

q. Saliva (DNA) for FBR should be the last procedure performed at Visit 2. If not obtained at Visit 2, can be obtained at a subsequent visit once the informed consent for FBR is obtained.

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.

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 at Visits 1 and 2 by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Interactive Voice Response System (IVRS) / Interactive Web Response System (IWRS)

The investigator or designee will call into IVRS/IWRS following each subject's Screening Visit. Upon confirmation of a subject's eligibility at Visit 2, the investigator or designee will call back into IVRS/IWRS to randomize the subject. Subjects who do not continue to meet the eligibility criteria at Visit 2 will be screen-failed via IVRS/IWRS. For all randomized subjects, the investigator or designee will continue to call into IVRS/IWRS as per the Trial Flow Chart (Section 6.0). The investigator or designee will make the final call into IVRS/IWRS following completion of each randomized subject's final visit at the end of the study.

7.1.1.4 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.

7.1.1.5 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. Subjects will be asked to provide information on allergic rhinitis history and related conditions, as well as family history of atopy.

Those subjects suspected of having asthma must meet at least one of the following 3 minimum criteria to be considered as having a diagnosis of asthma (and documented as such in the appropriate eCRF):

- At least one episode of wheeze, cough, shortness of breath or chest tightness and a change in $FEV_1 \geq 12\%$ after $beta_2$-agonist administration;

- Recurrent wheeze with or without prolonged phase of forced exhalation observed at physical examination and an intake of asthma medication which resulted in a clinically relevant effect;
- Wheezing with or without prolonged phase of forced exhalation observed at physical examination and a change in $FEV_1 \geq 12\%$ after $beta_2$-agonist administration.

Subjects who do not have asthma at randomization (Visit 2) and are subsequently diagnosed with asthma during the study should have asthma listed on the AE eCRF; also, the Asthma Diagnosis (ASDX) eCRF should be completed.

As the screening period can be up to 1 year in duration, medical history, including allergic rhinitis history and family history, should be reviewed at Visit 2 for any new information, with the appropriate eCRF(s) updated accordingly.

7.1.1.6 Demography

All subjects will have their demographic information collected.

7.1.1.7 Prior and Concomitant Medications Review

7.1.1.7.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 30 days (or longer if appropriate) before starting the trial. Medications will be recorded on the eCRF as per data entry guidelines.

7.1.1.7.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial.

7.1.1.8 Dispense Electronic Diary (e-diary)

Electronic diaries will be dispensed and instructions reviewed for use.

7.1.1.9 Dispense Sublingual Immunotherapy (SLIT) Report Card

The investigator or designee will train the subject/parent/guardian on the use of the SLIT Report Card (Section 12.10) prior to dispensing study medication to the subject at randomization (Visit 2). The SLIT Report Card will be completed daily for the first ~28 days of study drug administration. The SLIT Report Card will be reviewed at the next scheduled clinic visit (Visit 3) and stored in the subject's source document file. Any AE data from the SLIT Report Card will be entered into the eCRF with appropriate assessments made by the investigator.

7.1.1.10 Dispense Comment Card

The investigator or designee will train the subject/parent/guardian on the use of the Comment Card prior to dispensing study medication to the subject at randomization (Visit 2). The Comment Card will be dispensed at Visits 2 through 7, reviewed at the next scheduled clinic visit (Visits 3 through 8), and stored in the subject's source document file. Any AE data from the Comment Card will be entered into the eCRF with appropriate assessments made by the investigator. Any concomitant therapy data from the Comment Card will be entered as appropriate into the eCRF.

7.1.1.11 Anaphylaxis Emergency Action Plan

The subject/parent/guardian will be provided with educational information regarding symptoms of anaphylaxis and treatment, including a written Anaphylaxis Emergency Action Plan (Section 12.8) at Visit 2. The Anaphylaxis Emergency Action Plan can be modified outside the US to meet local standards for the type of epinephrine dispensed (or local standard of care if it does not include the use of epinephrine) and for calls to 911 or alternative local emergency services.

7.1.1.12 Self-Injectable Epinephrine

In countries where self-injectable epinephrine is a regulatory requirement, the investigator or designee will dispense self-injectable epinephrine, instruct in its use, and provide the subject/parent/guardian with educational information, including a written Anaphylaxis Emergency Action Plan[8] (Section 12.8) at Visit 2. At each subsequent visit following the dispensing, the investigator or designee will verify the subject has self-injectable epinephrine and will review instructions for use. Unused rescue self-injectable epinephrine will be collected at Visit 8.

7.1.1.13 Assignment of Screening Number

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

Given the long screening period (up to one year), re-screening may be permitted up to 1 time, but only if prior to randomization and upon Sponsor consultation. Any subject who is re-screened will retain the original screening number assigned at the initial screening visit.

[8] The Anaphylaxis Emergency Action Plan can be modified outside the US to meet local standards for the use (or type) of epinephrine dispensed, and for calls to 911 or alternative local emergency services.

7.1.1.14 Assignment of Randomization Number

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

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

7.1.1.15 Trial Compliance

The subject will be asked whether he/she has taken study medication as instructed at each visit, during telephone contacts, and at unscheduled visits.

Interruptions from the protocol specified treatment plan (compliance ≤75% between study visits) require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

Administration of the first dose of study drug will be witnessed by the investigator and/or trial staff (see Section 7.1.2.8—In-Clinic Dosing of Study Drug for further details).

7.1.1.16 Pollen Counts

Each study site will obtain pollen count data an average of 5 days per week.

Each study site will obtain daily pollen count data locally, regionally, or through a professional provider (e.g., National Allergy Bureau) for ragweed and other pollen, including tree, grass, and other weeds, as appropriate. Daily pollen counts will be recorded on a pollen count log for approximately 2-4 weeks prior to the expected ragweed season and 2-4 weeks after the end of the expected ragweed season, which will reflect the pollen present in the area of the study site. The counts for ragweed, expressed as counts per meter cubed air, will be tabulated for each site and used to determine the ragweed pollen season for the efficacy analyses. All other counts will be expressed as absent, low, medium, high, or very high. Rain days should be noted on the pollen count logs.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Vital Signs (Temperature, Blood Pressure, Pulse, Respiration)

Vital signs will be recorded as noted on the Trial Flow Chart (Section 6.0). For in-clinic dosing visits, vital signs will be performed prior to the administration of study drug. Vital signs will include axillary temperature, blood pressure (mmHg), pulse rate (beats/minute), and respiratory rate (breaths/minute), measured while in a seated position after ≥3 minutes of seated inactivity.

7.1.2.2 Body Height and Weight

The subject's body height and weight will be recorded as noted on the Trial Flow Chart (Section 6.0).

7.1.2.3 Physical Examination

All subjects will undergo a full physical examination at Screening. A targeted physical exam may be performed at any clinic visit that does not already include a physical exam if deemed necessary by the investigator due to signs/symptoms. A physical exam (full or limited, based on investigator judgment) can be performed at any unscheduled visit if deemed necessary by the investigator.

Physical findings at Screening will be recorded on the medical history page of the eCRF. Abnormal findings from other visits will be recorded on the AE section of the eCRF.

The full examination should be based on the following body systems: general appearance, head (oral inspection, ears, eyes, nose, and throat), respiratory (auscultation/stethoscopy examination of the lungs), heart (auscultation/stethoscopy examination of the heart), abdomen, musculoskeletal, neurological, lymph nodes, and skin. Subjects with evidence of current, clinically significant, intercurrent illness (e.g., significant cold or flu) may be rescheduled for rescreening on resolution of their illness.

For the following body systems, questioning regarding symptoms may be sufficient: abdomen, urogenital, musculoskeletal, and neurological. If deemed necessary by the investigator, a physical examination of these body systems will be performed.

At the End-of-Season/ Discontinuation visit, a limited physical exam will be performed. The exam will be directed based on investigator judgment.

7.1.2.4 Oropharyngeal Examination

The oral cavity will be inspected for signs of mouth irritation, edema, and any other abnormalities according to the schedule noted on the Trial Flow Chart (Section 6.0). Abnormal findings at Visit 1 should be recorded on the medical history. Abnormal findings after Visit 1 considered AEs must be recorded on the AE module of the eCRF. Oropharyngeal examinations preformed at Visit 2 will take place **before and after** investigational study drug administration.

7.1.2.5 Pulmonary Function Tests

Pulmonary function tests (PFTs) will include measurements of FEV_1, FEV_1 percent predicted, forced vital capacity (FVC), and FVC percent predicted for all subjects at Visits 1 and 2 (exception: those subjects ≤7 years of age who cannot perform reproducible PFT maneuvers despite coaching). PFTs will continue to be performed as noted on the Trial Flow Chart (Section 6.0) for those subjects with asthma (exception: those subjects ≤7 years of age who cannot perform reproducible PFT maneuvers despite coaching). For those subjects ≤7 years of age who could not perform reproducible PFT maneuvers at Visit 1, it is expected that sites will try to obtain reproducible PFT maneuvers at subsequent visits (Visit 2 for all subjects and subsequent visits for those with asthma). PFTs may also be performed at a

subsequent visit for those subjects without asthma at baseline if the investigator or designee considers a PFT is warranted.

Beta2-agonist reversibility (Section 12.9) will be performed at Visit 2 for all subjects performing PFTs (i.e., all subjects >7 years of age and all subjects ≤7 years of age who can perform reproducible FEV1 maneuvers); beta2-agonist reversibility is not an entry criterion for this study.

7.1.2.6 Skin Prick Test

Skin prick testing will be performed to confirm hypersensitivity to the ragweed allergen extract *(Ambrosia artemisiifolia)* (2 tests). Investigators/designees should follow standard office procedures with respect to wash-out requirements of antihistamines prior to skin testing. Skin test solutions will be applied to the inner forearm in duplicate. A histamine positive control (1 test) and saline negative control (1 test) will also be applied to the inner forearm. For each of the two wheals produced by the ragweed allergen extract (*Ambrosia artemisiifolia*), the wheal size will be determined by averaging the horizontal and vertical diameters 15 to 20 minutes after application. To record the skin testing, each wheal should be outlined on the skin with a ball point pen. Tape should be adhered to the skin and then removed. The pen outlines of the wheal should have transferred to the tape, and this record of the wheal size should then be adhered to the source documents and measured. Additional detailed information regarding skin prick testing will be provided separately.

Subjects should wait an appropriate amount of time before departing from the study site following the test and should be counseled to call the study site if any untoward symptoms occur.

Skin prick test reagents and prick test devices will be provided by the Sponsor or designee.

7.1.2.7 Adverse Event Monitoring

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

If a subject has a treatment interruption due to a worsening AE related to the study drug, then the subject should be re-evaluated by the investigator, or designee, prior to reinitiating the study drug.

See Section 7.2.3 for instructions on the reporting of SAEs to the sponsor and Section 7.2.4 for instructions on the assessment of SAEs.

7.1.2.7.1 Assess and Record Duration of Local Adverse Events of Interest

Pre-specified local AEs that occur on Day 1, including the date, time, and duration (in minutes) will be monitored by site personnel, recorded in source documents, and entered into the eCRF based on the data entry guidelines, which will be provided to the sites by the Sponsor.

During all in-clinic visits, the site will also collect information regarding pre-specified local AEs [date(s) and duration (if less than 24 hours)] by questioning the subject (including

review of the SLIT Report Card at Visit 3), and this will be recorded in the source documents and entered into the eCRF.

7.1.2.7.2 Alternate Local Adverse Event Severity Grading

The SLIT Report Card (Section 12.10) will be employed as an alternate method to capture adverse experience information in real time on a daily basis from the subject. The SLIT Report Card is to be completed by the subject/parent/guardian to collect information on AEs identified as local effects of sublingual immunotherapy that occur within the first 60 minutes after study drug intake.

Subjects will be trained on the proper method to complete the SLIT Report Card by completing a practice SLIT Report Card (paper format) at Visit 2. The subject will be provided the SLIT Report Card at Visit 2 to complete daily for approximately 28 days of treatment and document the presence of any pre-specified local side effects of SLIT during the first 60 minutes after dosing on the SLIT Report Card. The SLIT Report Card data will be reviewed at the next scheduled clinic visit (Visit 3) and any AEs will be recorded on the eCRF. If Visit 3 is less than 28 days after Visit 2, then the subject should take the SLIT Report Card back and continue completing the SLIT Report Card until Day 28 of study medication administration.

7.1.2.8 In-Clinic Dosing of Study Drug

A subject who meets the eligibility criteria will have the first dose of study medication taken at the study site at Visit 2. The subject will remain at the site for approximately 30 minutes following the first dose of study medication. The duration in minutes of the pre-specified local adverse events will be recorded during the first supervised dose of study medication.

7.1.2.9 Dispense/Review/Collect Study Medications (Study Drug, Self-Injectable Epinephrine, Beta$_2$-agonist and Allergy Rescue Medication)

Study drug will be dispensed for 'at home administration' at Visit 2, following the first on-site administration of study medication and the subsequent observation period. All doses are to be taken at approximately the same time of day. Unused study medication will be collected at each study visit during the treatment period.

Self-injectable epinephrine (in countries where it is a regulatory requirement) and beta$_2$-agonist (for subjects with asthma) will be dispensed at Visit 2 and subsequent visits (including unscheduled visits) as necessary. Allergy rescue medications will be dispensed at Visit 6. The investigator or designee will provide instructions (see Table 2 and Section 12.6) and demonstrate proper technique in the use of each medication. The subject's use and requirement for rescue medications should be reviewed by the investigator or designee at each visit during the ragweed season. Unused rescue medications will be collected at Visit 8.

7.1.2.10 Monitor Compliance with Study Medications

The subject must take the first dose of study drug at the study site under the supervision of the investigator or designee. At all protocol-specified visits, the investigator or qualified designee is to note in the appropriate section of the eCRF whether study drug had been taken

per protocol in the preceding interval. If not, the date(s) and reason for each dose variation must be recorded on the study medication (SM) eCRF.

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.

Compliance with the e-diary and rescue medication usage is essential. The subject should record daily the intake of any rescue medications (beta$_2$-agonist from Visit 4 to Visit 8 and allergy rescue medication from Visit 6 to Visit 8) in the e-diary. Any rescue medication taken prior to dispensing of the e-diary should be reported on the Concomitant Medications eCRF. Any noncompliance noted upon review will result in documented consultation with the subject on corrective measures needed to ensure compliance.

7.1.2.11 Complete/Review Daily Symptoms in e-Diary

The subject/parent/guardian will be required to record allergy and asthma symptoms in an e-diary once daily, preferably in the evening before bedtime, from Visit 4 to Visit 8. Subjects should be instructed to record the worst severity rating for each symptom during the 24-hour recall period. For example, if the subject experienced severe itchy eyes for only 10 minutes during the past 24 hours and mild itchy eyes for the rest of the past 24-hour period, the subject should record 'Severe Symptoms' on the e-diary for the day. In the rare case that the subject/parent/guardian cannot complete the e-diary at their regular time, they will be allowed to complete the daily e-diary up to 9 am the following morning. An e-diary will be issued at Visit 4 and collected at Visit 8. Instructions on how to complete entries and e-diary findings will be reviewed with the subject/parent/guardian at all visits.

A total of nine symptoms, six rhinoconjunctivitis symptoms (runny nose, stuffy nose, sneezing, itchy nose, itchy eyes, and watery eyes) and three asthma symptoms (cough, wheeze, chest tightness/shortness of breath [dyspnea]) will be measured on a scale of 0 to 3 as follows:

0 = no symptoms	No sign/symptom evident
1 = mild symptoms	Sign/symptom is clearly present but minimal awareness; easily tolerated
2 = moderate symptoms	Definite awareness of sign/symptom, which is bothersome but tolerable
3 = severe symptoms	Sign/symptom is hard to tolerate; may cause interference with activities of daily living and/or sleeping

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 to be drawn over the course of the trial (from pre-trial to post-trial visits), including approximate blood volumes drawn by visit and by sample type per subject can be found in Section 12.4.

7.1.3.1 Serum-specific IgE

Blood samples will be collected at screening (Visit 1) for determination of serum-specific IgE against ragweed (*Ambrosia artemisiifolia*), other weeds (dependent upon region), grasses (dependent upon region), oak and other trees (dependent upon region), cat, dog, alternaira, cladosporium, dust mites, mugwort, and other allergens considered clinically relevant for a particular locale.

A subject must have a specific IgE against *Ambrosia artemisiifolia* of ≥0.7 kU/L at screening to be included in the trial.

7.1.3.2 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 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 (Section 12.5). 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 results 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 (Section 12.5). 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	Albumin	Blood	
Hemoglobin	Alkaline phosphatase	Glucose	Serum β-human chorionic gonadotropin (β-hCG)[a]
Platelet count	Alanine aminotransferase (ALT)	Protein	
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	
	Bicarbonate	Microscopic exam, if abnormal results are noted	
	Blood Urea Nitrogen		
	Calcium		
	Chloride		

Hematology	Chemistry	Urinalysis	Other
	Creatinine		
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
[a] Only performed if urine pregnancy test is positive.			

7.1.3.3 Urine Pregnancy Test

A female subject of childbearing potential must have a negative urine pregnancy test at Visits 1 and 2 to be eligible to participate in the study. A positive urine pregnancy test should be followed up with a serum pregnancy test (β-hCG). Pregnancy tests should be repeated as per the Trial Flow Chart (Section 6.0).

7.1.3.4 Pharmacodynamic Evaluations

Blood samples for the immunologic assessment will be collected for a subset of subjects at selected sites per the study flow chart (Section 6.0). The serum samples for analyses of specific IgE and IgG_4 will be submitted to ALK-Abelló for measurement.

7.1.3.5 Future Biomedical Research

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

- Saliva for future research,
- Leftover main study serum from immunologic samples (IgE, IgG_4) stored for future research.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial

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

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

7.1.4.2 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.

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

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

7.1.4.3 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

  The spirometer must be calibrated according to American Thoracic Society guidelines. Calibration checks should be performed (i.e., with a 3-liter syringe) at a minimum of each day that a trial subject performs a spirometry assessment. The calibration check records should be printed and kept in a reviewable log. It is preferred that the calibration syringe used to check calibration of the spirometer also be subjected to a validated calibration according to the manufacturer's specifications.

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.

7.2 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 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 randomization through 14 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in Section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

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

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

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

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

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

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

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

Pregnancies and lactations that occur after the consent form is signed but before 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 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 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 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 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 randomization through 14 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

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

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).
3. Anaphylactic reactions, anaphylaxis and/or systemic allergic reactions.
4. Events treated with epinephrine.
5. Severe local swelling or edema of the mouth and/or throat.
6. Severe drug-related asthma exacerbations.
7. Eosinophilic esophagitis.

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.

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Scientific Advisory Committee

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

7.3.2 Executive Oversight Committee

The Executive Oversight Committee (EOC) comprises members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the Data Monitoring Committee (DMC) regarding the trial.

7.3.3 Data Monitoring Committee

To supplement the routine trial monitoring outlined in this protocol, an external Data Monitoring Committee (DMC) will monitor the interim data from this trial. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the trial in any other way (e.g., they cannot be trial investigators) and must have no competing interests that could affect their roles with respect to the trial.

The DMC will make recommendations to the EOC regarding steps to ensure both subject safety and the continued ethical integrity of the trial. Also, the DMC will review interim trial results, consider the overall risk and benefit to trial participants (see Section 8.1.4 - Interim Analyses) and recommend to the EOC if the trial should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the trial governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is reviewed and approved by the DMC. The DMC will monitor the trial at an appropriate frequency, as described in the detailed DMC charter. The DMC will also make recommendations to the Sponsor protocol team regarding steps to ensure both subject safety and the continued ethical integrity of the trial.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

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

8.1.1 Efficacy Analyses

Primary Efficacy Analysis

The primary analysis will be conducted on the Full Analysis Set (FAS) population. The FAS population includes all subjects who receive at least one dose of study treatment. Subjects will be analyzed according to the treatment group to which they are randomized.

The primary efficacy endpoint for the current trial is the average TCS during the peak ragweed season. It will be analyzed using the analysis of variance (ANOVA) model, which includes fixed effects of treatment, baseline asthma status (yes, no), age group (5 to 11 years, 12 to 17 years), pollen season, and pollen region nested within pollen season. Pollen region will be defined based on pollen station, and may include several sites within an acceptable distance between the pollen counters and corresponding sites.

Two-sided 95% confidence interval (CI) of the treatment difference in adjusted means will be presented. Also, the treatment difference in adjusted means relative to the adjusted mean of the placebo group will be presented as a percentage with corresponding 2-sided 95% CI derived using the bootstrap method. No missing data will be imputed.

The normality assumption of the ANOVA model will be checked using the Shapiro-Wilk test and inspection of the Q-Q plot. If a severe violation is observed, the primary analysis will be based on Wilcoxon Rank Sum test; the p-value will be reported together with the associated Hodges-Lehmann estimate of the treatment difference and its 2-sided 95% CI. Also, the difference in the treatment group medians relative to the median of the placebo group will be presented as a percentage with the corresponding 2-sided 95% CI derived using the bootstrap method.

A Per Protocol (PP) analysis will be conducted for the primary efficacy endpoint, where the same ANOVA model and missing data approach will be used. See Section 8.2.5.1 for further sensitivity analyses of the primary efficacy endpoint.

Key Secondary Efficacy Analyses

The key secondary efficacy endpoints for the current trial include:

- Average TCS during the entire RS;
- Average rhinoconjunctivitis DSS during the peak RS;
- Average rhinoconjunctivitis DMS during the peak RS.

These endpoints will be analyzed based on the FAS population using the same ANOVA model as the primary efficacy endpoint. A fixed sequence procedure will be applied to

control multiplicity, where the primary efficacy endpoint will be tested first, and then the key secondary efficacy endpoints will be tested in the order stated above.

In a situation when there are more than 30% of the daily rhinoconjunctivitis DMS equal to zero, the zero-inflated lognormal model [18] will be used as the primary analysis method for rhinoconjunctivitis DMS as appropriate; this model takes the average rhinoconjunctivitis DMS during the peak RS as response and adjusts for the same terms as in the ANOVA model.

Table 8 summarizes the key analysis strategy for the primary and key secondary efficacy endpoints.

Table 8 Analysis Strategy for Key Efficacy Endpoints

Endpoint	Statistical Method[a]	Analysis Population	Missing Data Approach
Primary Efficacy Endpoint			
Average TCS during the peak RS	ANOVA	FAS	Observed data only
			LOCF
			Multiple Imputation[b]
		PP	Observed data only
	Wilcoxon Rank Sum Test; Hodges-Lehmann estimate of treatment difference[c]	FAS	Observed data only
	Longitudinal Data Analysis	FAS	Model based
Key Secondary Efficacy Endpoints			
Average TCS during the entire RS	ANOVA	FAS	Observed data only
Average rhinoconjunctivitis DSS during the peak RS	ANOVA	FAS	
Average rhinoconjunctivitis DMS during the peak RS	ANOVA	FAS	
	Zero-inflated log-normal[c]		

TCS = Total Combined Score; DSS = Daily Symptom Score; DMS = Daily Medication Score; RS = Ragweed Season.
ANOVA = Analysis of Variance; LOCF = Last non-missing observation carried forward.
FAS = Full Analysis set; PP = Per Protocol.
[a] Details of the statistical models are described in Section 8.2.5.
[b] Missing data from both treatment groups will be imputed using the sample distribution of TCS observed from the placebo group.
[c] This method will be applied if excessive zeros are observed in the data.

8.1.2 Safety Analyses

An All-Subjects-as-Treated (ASaT) population will be used for safety analyses. The ASaT population includes all subjects who receive at least one dose of study treatment. Subjects will be included in the treatment group corresponding to the study treatment they actually receive during the trial.

The analysis of safety endpoints will follow a tiered approach. For this study, Tier 1 safety endpoints include:

- Proportion of subjects reporting pre-specified local application site reactions (including adverse events related to lip swelling/edema, mouth swelling/edema, palatal swelling/edema, swollen tongue/edema, oropharyngeal swelling/edema, pharyngeal edema/throat tightness, oral pruritus, throat irritation, tongue pruritus, and ear pruritus);
- Proportion of subjects reporting anaphylaxis and/or systemic allergic reactions;
- Proportion of subjects treated with epinephrine.

Tier 1 safety endpoints will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals provided for between-group comparisons. They will be analyzed using the stratified Miettinen and Nurminen method [1985] with baseline asthma status and age group as stratification factors.

8.1.3 Power and Sample Size

A total of approximately 1000 subjects will be randomized in a 1:1 ratio to either MK-3641 or placebo. Assuming a 15% dropout rate, this gives approximately 425 evaluable subjects per treatment group.

With 425 subjects per arm, the study will have:

- approximately 90% power (2-sided, $\alpha = 0.05$) to have the upper bound of the 95% CI for relative difference below -10%, and
- more than 90% power (2-sided, $\alpha = 0.05$) to have an estimated relative difference below -15%.

See Section 8.2.7 for further details of sample size calculation.

8.1.4 Interim Analyses

No efficacy interim analysis is planned for this trial. Safety data will be reviewed by an external Data Monitoring Committee (eDMC) (see Section 7.3.3).

8.2 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 unblinding, changes are 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.

8.2.1 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the designee 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 violators have been identified, and data have been declared final and complete.

The randomized allocation schedule will be generated by the sponsor, and implemented by the vendor of the study interactive voice response system (IVRS).

Safety will be monitored by the external Data Monitoring Committee (eDMC) on an ongoing basis and the eDMC will make recommendations to the sponsor as appropriate.

8.2.2 Hypotheses

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

8.2.3 Analyses Endpoints

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

8.2.3.1 Efficacy Endpoints

Primary Efficacy Endpoint

- Average TCS during the peak RS.

Key Secondary Efficacy Endpoints

- Average TCS during the entire RS;
- Average rhinoconjunctivitis DSS during the peak RS;
- Average rhinoconjunctivitis DMS during the peak RS.

Tertiary Efficacy/Immunologic Endpoints

- Average rhinoconjunctivitis DSS during the entire RS
- Change from baseline in IgE level against *Ambrosia artemisiifolia* at Visit 6 and at Visit 8;
- Change from baseline in IgG_4 level against *Ambrosia artemisiifolia* at Visit 6 and at Visit 8.

Exploratory Efficacy Endpoints

- Average Asthma DSS during the peak RS and the entire RS;Average daily number of puffs of as-needed SABA used during the peak RS and the entire RS;

- Average weekly number of nights with nocturnal awakening due to asthma symptoms requiring SABA use during the peak RS and the entire RS.

8.2.3.2 Safety Endpoints

Tier 1 Safety Endpoints

- Proportion of subjects reporting pre-specified local application site reactions (including adverse events related to lip swelling/edema, mouth swelling/edema, palatal swelling/edema, swollen tongue/edema, oropharyngeal swelling/edema, pharyngeal edema/throat tightness, oral pruritus, throat irritation, tongue pruritus, and ear pruritus);
- Proportion of subjects reporting anaphylaxis and/or systemic allergic reactions;
- Proportion of subjects treated with epinephrine.

Tier 2 Safety Endpoints

- Proportion of subjects with any AE;
- Proportion of subjects with any serious AE;
- Proportion of subjects with any drug-related AE;
- Proportion of subjects with any serious and drug-related AE;
- Proportion of subjects who discontinue due to an AE;
- Proportion of subjects with specific AEs or SOCs (incidence ≥ 1% subjects in one or more of the treatment groups).

Tier 3 Safety Endpoints

- Change from baseline in laboratory test parameters at each post-baseline visit;
- Change from baseline in vital sign parameters at each post-baseline visit;
- Summaries by system organ class (SOC) for general AEs, serious AEs, drug-related AEs, and AEs resulting in discontinuation;
- Average duration of pre-specified local application site reactions in minutes on Day 1;
- Average duration of pre-specified local application site reactions in days over Day 2 to Day 14;
- Average duration of pre-specified local application site reactions in days over Day 15 to Day 28.

8.2.3.3 Derivations of Efficacy/Immunologic Endpoints

Ragweed Season

Entire Ragweed Season: the start of the entire ragweed season is the first day of 3 consecutive recorded days with a pollen count of ≥10 grains/m^3; the end of the entire ragweed season is the last day of 3 consecutive recorded days with a pollen count of ≥10 grains/m^3. This is specific for each study site.

Peak ragweed season: the 15 consecutive recorded days within the entire ragweed season with the highest 15-day moving average pollen count. This is specific for each study site.

TCS, Rhinoconjunctivitis DSS, Rhinoconjunctivitis DMS, Asthma DSS

These are defined in Section 4.2.3.1.

8.2.3.4 Derivations of Safety Endpoints

For laboratory tests and vital sign parameters, the baseline value is defined as the last measurement taken prior to randomization. Change from baseline in laboratory and vital signs parameters is calculated by on-treatment value minus the baseline value.

8.2.4 Analysis Populations

8.2.4.1 Efficacy Analysis Populations

The Full Analysis Set (FAS) population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all randomized subjects who receive at least one dose of study treatment. Subjects will be analyzed according to the treatment group to which they are randomized.

A supportive analysis using the Per-Protocol (PP) population will be performed for the primary efficacy endpoint. The PP population excludes subjects due to important deviations from the protocol that may substantially affect the results of the primary efficacy endpoints. The major protocol violations that would lead to exclusion of a subject or a data point are described below:

- Subjects with asthma requiring prescribed high daily doses of inhaled corticosteroids (as defined in the protocol);
- Subjects with chronic sinusitis during the previous 2 years;
- Subjects treated with immunotherapy within 5 years prior to screening;
- Subjects unable to meet medication washout requirements;
- Subjects randomized in the study more than once;
- Subjects who participated in the same study at another site;
- Subjects with pre-seasonal duration of treatment exposure < 56 Days;
- Subjects with a negative skin prick test response to ragweed;
- Subjects with specific IgE to ragweed < 0.7 kU/L;

- Subjects with overall treatment compliance < 75% between Visit 2 and Visit 8;
- Subjects who took prohibited medications as defined in the protocol, with the exception of antihistamines. Subjects who have taken antihistamines (other than sponsor provided rescue medications) will be considered protocol violators if they have taken the medication for 2 or more consecutive days between Visit 6 and Visit 8;
- Subjects who had their blinded treatment randomization code broken.

Analyses related to SABA use and nocturnal awakening will be based on subjects with asthma in the FAS population.

8.2.4.2 Safety Analysis Populations

The All-Subjects-as-Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all randomized subjects who received at least one dose of study treatment. Subjects will be grouped by the study treatment actually received.

8.2.5 Statistical Methods

Statistical testing and inference for efficacy and safety analyses are described in Sections 8.2.5.1 and 8.2.5.2. Controlling of family-wise Type I error rate is described in Section 8.2.6, Multiplicity. Nominal p-values will be computed for tertiary and exploratory efficacy analyses as a measure of strength of association between the endpoint and the treatment effect rather than formal tests of hypotheses. Unless otherwise stated, all statistical tests will be conducted at α=0.05 (2-sided) level.

8.2.5.1 Statistical Methods for Efficacy/Immunologic Analyses

Primary Efficacy Analysis

The primary efficacy endpoint for the current trial is the average TCS during the peak ragweed season. It will be analyzed using the ANOVA model, which includes fixed effects of treatment, baseline asthma status (yes, no), age group (5 to 11 years, 12 to 17 years), pollen season, and pollen region nested within pollen season. Pollen region will be defined based on pollen station, and may include several sites within an acceptable distance between the pollen counters and corresponding sites.

Two-sided 95% CI of the treatment difference in adjusted means will be presented. Also, the treatment difference in adjusted means relative to the adjusted mean of the placebo group will be presented as a percentage with corresponding 2-sided 95% CI derived using the bootstrap method. No missing data will be imputed.

The normality assumption of the ANOVA model will be checked using the Shapiro-Wilk test and inspection of the Q-Q plot. If a severe violation is observed, the primary analysis will be based on Wilcoxon Rank Sum test; the p-value will be reported together with the associated Hodges-Lehmann estimate of the treatment difference and its 2-sided 95% CI. Also, the difference in the treatment group medians relative to the median of the placebo group will be

presented as a percentage with the corresponding 2-sided 95% CI derived using the bootstrap method.

Sensitivity Analysis

The PP analysis will be conducted for the primary efficacy endpoint, where the same ANOVA model and missing data approach will be used. In addition, the following sensitivity analyses will be performed for the primary efficacy endpoint.

- The same ANOVA model based on the FAS population will be used. Missing data will be imputed by the LOCF approach. For each subject, only the observations within the pollen season are eligible to be carried forward.
- The same ANOVA model based on the FAS population will be used. Missing data will be handled by the multiple imputation method. Missing data from both treatment groups will be imputed using the sample distribution of TCS observed from the placebo group, which is considered to be a conservative approach for imputations.
- Longitudinal Data Analysis model based on the FAS population will be used. Daily TCS during the peak season will be the response variable and covariates will include treatment, time, the interaction of treatment by time, baseline asthma status, age group, pollen season, and pollen region nested within pollen season. The Toeplitz structure will be used to model the covariance of the repeated TCS measurements over time within subjects. Additional covariance structures, such as unstructured covariance, may be considered if convergence issues are encountered with the analysis model.

Furthermore, if there are more than 2% of subjects taking prednisone during any one ragweed season in the course of the study, a sensitivity analysis will be conducted for the primary efficacy endpoint, where the usage of prednisone is included in the definition of the rhinoconjunctivitis DMS. The medication scores for prednisone usage are defined in Table 9.

Table 9 Medication Score for Prednisone Usage

Rescue Medication	Subject Dosing Instructions	Score/Dose Unit	Maximum Daily Score
Prednisone tablet 5 mg	Day 1: 1 mg/kg/day, Max 50 mg/day	1.6 (per tablet)	16
	Day 2+: 0.5 mg/kg/day, Max 25 mg/day	1.6 x 2 (per tablet)	16

In addition, in order to minimize missing data, subjects will be allowed to complete the daily e-diary up to 9 am the following morning (in case the subject cannot complete it at their regular time that day). A sensitivity analysis will be conducted for the FAS population, where only the data entered on the same day (instead of next morning) are included. The same ANOVA model and missing data approach will be used.

Key Secondary Efficacy Analyses

The key secondary efficacy endpoints for the current trial include:

- Average TCS during the entire RS;
- Average rhinoconjunctivitis DSS during the peak RS;
- Average rhinoconjunctivitis DMS during the peak RS.

These endpoints will be analyzed based on the FAS population using the same ANOVA model as the primary efficacy endpoint.

Based on the rescue medication usage from previous AIT trials, many subjects used little rescue medication during the trial, which resulted in large amounts of rhinoconjunctivitis DMS records equal to zero. Data with excessive zeroes may not conform to the normality assumption for the ANOVA model and may also prevent the proper application of non-parametric method. In a situation when there are more than 30% of the daily rhinoconjunctivitis DMS equal to zero, the zero-inflated lognormal model [18] will be used as the primary analysis method for rhinoconjunctivitis DMS as appropriate; this model takes the average rhinoconjunctivitis DMS during the peak RS as response and adjusts for the same terms as in the ANOVA model.

Tertiary Efficacy/Immunologic Analyses

The tertiary efficacy/immunologic endpoints for the current trial include:

- Average rhinoconjunctivitis DSS during the entire RS;
- Change from baseline in IgE level against *Ambrosia artemisiifolia* at Visit 6;
- Change from baseline in IgE level against *Ambrosia artemisiifolia* at Visit 8;
- Change from baseline in IgG_4 level against *Ambrosia artemisiifolia* at Visit 6;
- Change from baseline in IgG_4 level against *Ambrosia artemisiifolia* at Visit 8.

Average rhinoconjunctivitis DSS during the entire RS will be analyzed based on the FAS population using the same ANOVA model as the primary efficacy endpoint.

IgE and IgG4 related endpoints will be analyzed separately using the constrained LDA (cLDA) model. The cLDA model assumes a common mean across treatment groups at baseline and different means for different treatments at each post-baseline time point. In this model, the response vector consists of the baseline value and the values observed at each post-baseline time point. The model will adjust for time, the interaction of treatment by time, baseline asthma status, age group, pollen season, and pollen region nested within pollen season. Time is treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. A Toeplitz covariance matrix will be used to model the correlation among repeated measurements. Further details of the model specification, assumptions, and SAS implementation codes will be provided in the sSAP.

Exploratory Efficacy Analyses

The exploratory efficacy endpoints for the current trial include:

- Average Asthma DSS during the peak RS;
- Average Asthma DSS during the entire RS;
- Average daily number of puffs of as-needed SABA used during the peak RS;
- Average daily number of puffs of as-needed SABA used during the entire RS;
- Average weekly number of nights with nocturnal awakening due to asthma symptoms requiring SABA use during the peak RS;
- Average weekly number of nights with nocturnal awakening due to asthma symptoms requiring SABA use during the entire RS.

These endpoints will be analyzed using the same ANOVA model as the primary efficacy endpoint. Asthma DSS related endpoints will be analyzed based on the FAS population, while SABA use and nocturnal awakening related endpoints will be analyzed based on subjects with asthma in the FAS population.

In addition, components of the rhinoconjunctivitis DSS (ocular symptoms and nasal symptoms) will be summarized for the peak RS and the entire RS.

Table 10 summarizes the key analysis strategy for the efficacy/immunologic endpoints.

Table 10 Analysis Strategy for the Efficacy/Immunologic Endpoints

Endpoint	Statistical Method[a]	Analysis Population	Missing Data Approach
Primary Efficacy Endpoint			
Average TCS during the peak RS	ANOVA	FAS	Observed data only
			LOCF
			Multiple Imputation[b]
		PP	Observed data only
	Wilcoxon Rank Sum Test; Hodges-Lehmann estimate of treatment difference[c]	FAS	Observed data only
	Longitudinal Data Analysis	FAS	Model based
Key Secondary Efficacy Endpoints			
Average TCS during the entire RS	ANOVA	FAS	Observed data only
Average rhinoconjunctivitis DSS during the peak RS	ANOVA	FAS	
Average rhinoconjunctivitis DMS during the peak RS	ANOVA	FAS	
	Zero-inflated log-normal[c]		
Tertiary Efficacy/Immunologic Analyses			
Average rhinoconjunctivitis DSS during the entire RS	ANOVA	FAS	Observed data only
Change from baseline in IgE level against *Ambrosia artemisiifolia* at Visit 6 and Visit 8	constrained Longitudinal Data Analysis	FAS	Model based

Endpoint	Statistical Method[a]	Analysis Population	Missing Data Approach
Change from baseline in IgG_4 level against *Ambrosia artemisiifolia* at Visit 6 and Visit 8	constrained Longitudinal Data Analysis	FAS	Model based
Exploratory Efficacy Analyses			
Average Asthma DSS during the peak RS and the entire RS	ANOVA	FAS	Observed data only
Average daily number of puffs of as-needed SABA used during the peak RS and the entire RS	ANOVA	FAS (asthma only)	Observed data only
Average weekly number of nights with nocturnal awakening due to asthma symptoms requiring SABA use during the peak RS and the entire RS	ANOVA	FAS (asthma only)	Observed data only

ANOVA = Analysis of Variance; DSS = Daily Symptom Score; DMS = Daily Medication Score; FAS = Full Analysis set; IgE = immunoglobulin E; IgG_4 = immunoglobulin G_4; LOCF = Last non-missing observation carried forward; PP = Per Protocol; RS = Ragweed Season; SABA = short-acting $beta_2$-agonist; TCS = Total Combined Score.

[a] Details of the statistical models are described in Section 8.2.5.

[b] Missing data from both treatment groups will be imputed using the sample distribution of TCS observed from the placebo group.

[c] This method will be applied if excessive zeros are observed in the data.

Handling of Missing Data

The missing data approaches are specified for the primary efficacy endpoint sensitivity analyses (including multiple imputation, LOCF, and model based) and immunologic endpoints (model based). All other analyses will be conducted based on the observed data only. Proportion of subjects with missing data will be summarized for each efficacy/immunologic endpoint.

8.2.5.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests, and vital sign measurements.

The analysis of safety results will follow a tiered approach (Table 11). The tiers differ with respect to the analyses that will be performed. Tier 1 safety endpoints will be subject to inferential testing for statistical significance with p-values and 95% CIs provided for between-group comparisons. Tier 2 safety endpoints will be evaluated via point estimates and 95% CIs for between-group comparisons. Tier 3 safety endpoints will be evaluated via point estimates only.

For this trial, Tier 1 safety endpoints include:

- Proportion of subjects reporting pre-specified local application site reactions (including adverse events related to lip swelling/edema, mouth swelling/edema, palatal swelling/edema, swollen tongue/edema, oropharyngeal swelling/edema, pharyngeal edema/throat tightness, oral pruritus, throat irritation, tongue pruritus, and ear pruritus);
- Proportion of subjects reporting anaphylaxis and/or systemic allergic reactions;

- Proportion of subjects treated with epinephrine.

For the analysis of "Proportion of subjects treated with epinephrine", the denominator will include all subjects in the ASaT population, regardless of whether self-injectable epinephrine was provided or not. Meanwhile, a sensitivity analysis will be conducted where the denominator will include subjects in the ASaT population who were provided with self-injectable epinephrine, and the numerator will be subjects from the denominator subjects who were treated with epinephrine.

Tier 2 safety endpoints for this trial include:

- Proportion of subjects with any AE;
- Proportion of subjects with any serious AE;
- Proportion of subjects with any drug-related AE;
- Proportion of subjects with any serious and drug-related AE;
- Proportion of subjects who discontinue due to an AE;
- Proportion of subjects with specific AEs or SOCs (incidence ≥ 1% subjects in one or more of the treatment groups).

The Tier 1 and Tier 2 safety endpoints will be analyzed using the stratified Miettinen and Nurminen method [1985] with baseline asthma status and age group as stratification factors.

Tier 3 safety endpoints for this trial include:

- Change from baseline in laboratory test parameters at each post-baseline visit;
- Change from baseline in vital sign parameters at each post-baseline visit;
- Change from baseline in pulmonary function test parameters at each post-baseline visit;
- Summaries by SOC for general AEs, serious AEs, drug-related AEs, serious and drug-related AEs, and AEs resulting in discontinuation;
- Average duration of pre-specified local application site reactions in minutes on Day 1;
- Average duration of pre-specified local application site reactions in days over Day 2 to Day 14;
- Average duration of pre-specified local application site reactions in days over Day 15 to Day 28.

Point estimates will be provided for the Tier 3 safety endpoints. In addition, AE summaries (general AEs, serious AEs, drug-related AEs, serious and drug-related AEs, and AEs resulting in discontinuation) by asthma status will also be provided. For pulmonary function test parameters, a cLDA model based analysis will also be conducted (see Section 8.2.5.1 for more details about the cLDA model).

Table 11 summarizes the safety tier and level of analysis for the safety endpoints.

Table 11 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint[a]	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	Proportion of subjects reporting pre-specified local application site reactions (including adverse events related to lip swelling/edema, mouth swelling/edema, palatal swelling/edema, swollen tongue/edema, oropharyngeal swelling/edema, pharyngeal edema/throat tightness, oral pruritus, throat irritation, tongue pruritus, and ear pruritus); Proportion of subjects reporting anaphylaxis and/or systemic allergic reactions; Proportion of subjects treated with epinephrine.	X	X	X
Tier 2	Any AE; Any Serious AE; Any Drug-Related AE; Any Serious and Drug-Related AE; Discontinuation due to AE; Specific AEs or SOCs[b] (incidence ≥1% of subjects in one or more of the treatment groups)		X	X
Tier 3	Change from baseline in laboratory test parameters at each post-baseline visit; Change from baseline in vital sign parameters at each post-baseline visit; Change from baseline in pulmonary function test parameters at each post-baseline visit; Summaries by SOC for general AEs, serious AEs, drug-related AEs, serious and drug-related AEs, and AEs resulting in discontinuation; AE summaries by asthma status; Average duration of pre-specified local application site reactions in minutes on Day 1; Average duration of pre-specified local application site reactions in days over Day 2 to Day 14; Average duration of pre-specified local application site reactions in days over Day 15 to Day 28.			X

AE = adverse event; CI = confidence interval; SOC = System Organ Class; X = results will be provided.
[a] Adverse Experience references refer to both Clinical and Laboratory AEs.
[b] Includes only those endpoints not pre-specified as Tier 1 or Tier 2 endpoints.

In addition, the SLIT Report Card (Section 4.2.3.2) will be completed by the subject/parent/guardian, daily for the first ~28 days of dosing, to collect information on local side effects of SLIT that occur within the first 60 minutes after each daily study drug intake. Identified local AEs will be graded via a programmatic approach and clinical review as mild, moderate, or severe. An exploratory review of the severity grading via the programmatic

approach and that as determined by the investigator's review of the AEs with their subjects/parents/guardians will be conducted.

8.2.5.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

Demographic and Baseline 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 baseline asthma status, inhaled corticosteroid use, duration of allergic rhinitis, sensitization type, ragweed specific IgE, wheal size from skin prick test, and number of puffs of bronchodilator used for FEV_1 reversibility), primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables. The comparability of the treatment groups for each relevant characteristic will be assessed by the summary tables. No statistical hypothesis tests will be performed on these characteristics.

Skin Prick Test (SPT) Analysis

Descriptive statistics (mean, standard deviation, etc.) of the wheal size determined from the SPT will be provided for all randomized subjects.

8.2.6 Multiplicity

A fixed sequence procedure will be applied to control multiplicity. The primary and key secondary efficacy endpoints will be tested in the following order:

- Average TCS during the peak RS;
- Average TCS during the entire RS;
- Average rhinoconjunctivitis DSS during the peak RS;
- Average rhinoconjunctivitis DMS during the peak RS.

A lower order endpoint will be tested only if all higher order endpoints have been tested and claimed statistically significant.

8.2.7 Sample Size and Power Calculations

A total of approximately 1000 subjects will be randomized in a 1:1 ratio to either MK-3641 or placebo. Assuming a 15% dropout rate, this gives approximately 425 evaluable subjects per treatment group.

With 425 subjects per arm, the study will have:

- approximately 90% power (2-sided, $\alpha = 0.05$) to have the upper bound of the 95% CI for relative difference below -10%, and
- more than 90% power (2-sided, $\alpha = 0.05$) to have an estimated relative difference below -15%.

The calculations are based on the assumptions that the true difference between treatment arms in average TCS during peak RS is -2.12, that the average TCS during peak RS from the placebo group is 8.9, and that the standard deviation is 5.60. These assumptions, as well as the assumption on dropout rate, are based on the two MK-3641 (AIT ragweed) adult studies, P05233 and P05234, and the pediatric trial P05239 for MK-7243 (AIT grass).

8.2.8 Subgroup Analyses and Effect of Baseline Factors

Analysis for the primary efficacy endpoint will be provided for the following subgroups of baseline factors:

- Baseline asthma status (yes, no);
- Age group (5 to 11 years, 12 to 17 years);
- Gender (male, female);
- Race (Caucasians, non-Caucasians);
- ICS use for subjects with asthma (yes, no);
- Allergen sensitization type (ragweed only, ragweed + others);
- Geographic region (e.g., US, Canada, Europe). Region classification for each study site will be determined before database lock.

In addition, subgroup analysis on the primary efficacy endpoint will be provided for:

- Pollen counts (low, high): The subgroups will be defined based on the median of the subject level accumulated pollen counts during the first 21 days of the pollen season;
- Local application site reaction (had local application site reactions, did not have local application site reactions).

The same ANOVA model as in the primary efficacy analysis will be applied for the subgroup analyses.

8.2.9 Interim Analyses

No efficacy interim analysis is planned for this trial. Safety data will be reviewed by an eDMC.

8.2.10 Compliance (Medication Adherence)

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

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

A day within the study will be considered an "On-Therapy" day if the subject takes all required medication as instructed in Section 5.2. When a subject takes less than or more than the required medication on a day, that day is not considered an On-Therapy day.

For subjects who are followed for the entire study period, the "Number of Days Should be on Therapy" is the number of days from the first scheduled treatment day to the last scheduled treatment day. For subjects who discontinue from the study, the "Number of Days Should Be on Therapy" is the number of days from the first scheduled treatment day to the last dose day.

Summary statistics will be provided on percent compliance for the ASaT population.

8.2.11 Extent of Exposure

The duration of treatment for each subject will be evaluated by calculating the number of days on therapy. The range and mean for days on therapy will be calculated for the ASaT population.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

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

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 12 Product Descriptions

Product Name & Potency	Dosage Form
MK-3641 12 Amb a 1-U	Sublingual Rapid Dissolving Tablet
MK-3641 placebo	Sublingual Rapid Dissolving Tablet

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

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

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

9.2 Packaging and Labeling Information

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

Subjects will receive blinded monthly kits. Each kit will contain 4 blister cards (Table 13).

Table 13 Kits Dispensed Per Visit

Visit Number	Number of Kits to be dispensed
2 (Randomization)	1
3, 4, 6, and 7	2

9.3 Clinical Supplies Disclosure

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

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

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Discard/Destruction/Returns and Reconciliation

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

discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

9.6 Standard Policies

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

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

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

10.1.3 Confidentiality of Investigator Information

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

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

4. other professional documentation.

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

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor or through a secure password-protected electronic portal provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.3 Compliance with Law, Audit and Debarment

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

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

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

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

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

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

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

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

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

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

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

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

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. 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 FDAMA/FDAAA 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 FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this trial or its results to the Clinical Trials Data Bank.

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 7.1.3.5 – Future Biomedical Research 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 Merck focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

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

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

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

b. Informed Consent

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

to any specimens, test results, or medical information once the specimens have been rendered de-identified

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen Collections

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

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

4. Confidential Subject Information for Future Biomedical Research

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

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

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

This first code will be replaced with a second code at a Merck designated storage/lab facility. The second code is linked to the first code via a second key. The specimen is now double coded. Specimens with the second code are sometimes referred to as de-identified specimens. The use of the second code provides additional confidentiality and

privacy protection for subjects over the use of a single code. Access to both keys would be needed to link any data or specimens back to the subject's identification.

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

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

5. Biorepository Specimen Usage

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

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

6. Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact Merck using the designated mailbox (clinical.specimen.management@merck.com) and a form will be provided by Merck to obtain appropriate information to complete specimen withdrawal. Subsequently, the

subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from Merck to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

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

7. Retention of Specimens

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

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

8. Data Security

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

9. Reporting of Future Biomedical Research Data to Subjects

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

concerns of misinterpretation and absence of good clinical practice standards in exploratory research typically used for diagnostic testing.

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

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

10. Gender, Ethnicity and Minorities

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

11. Risks Versus Benefits of Future Biomedical Research

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

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

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

12. Self-Reported Ethnicity

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

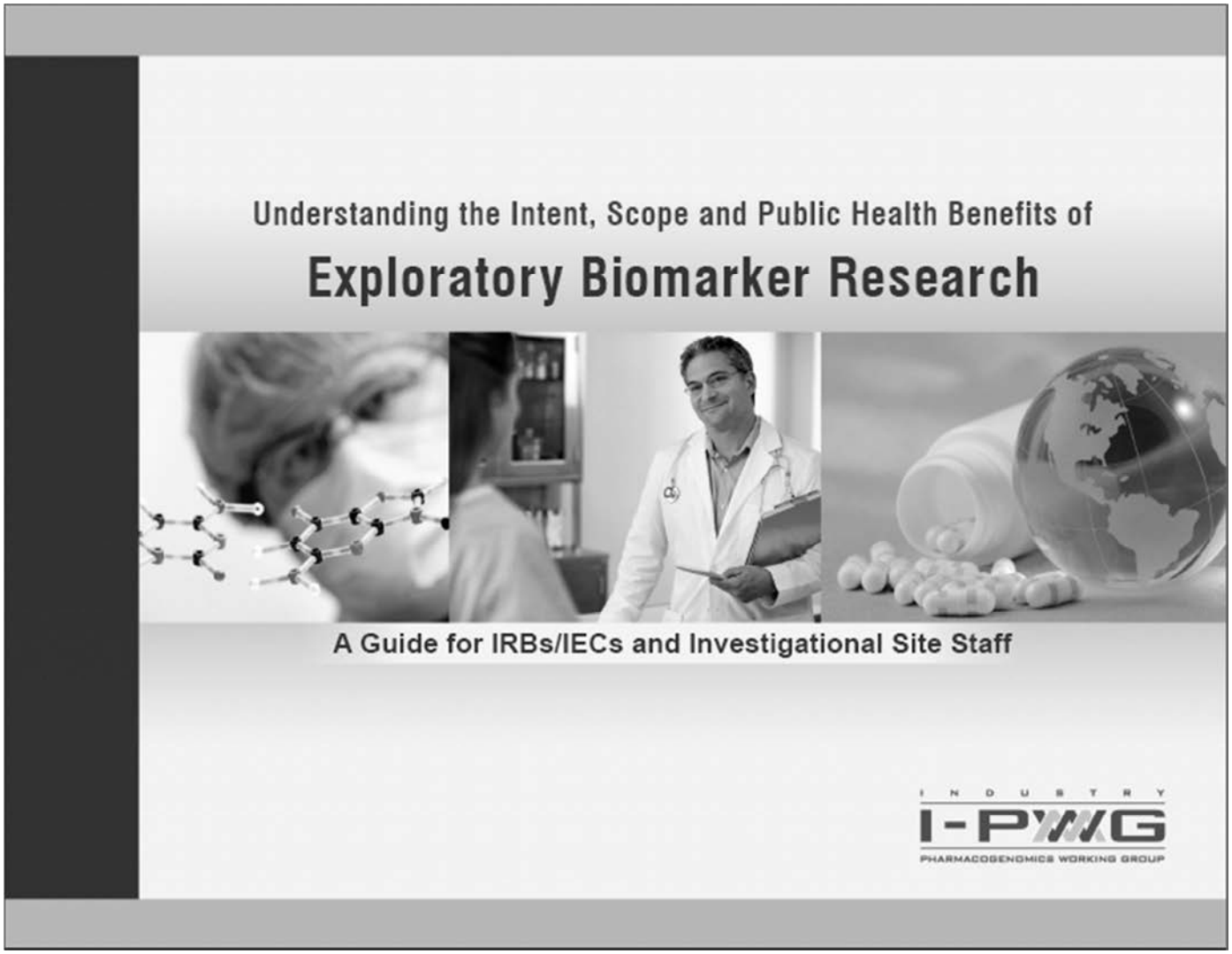
13. Questions

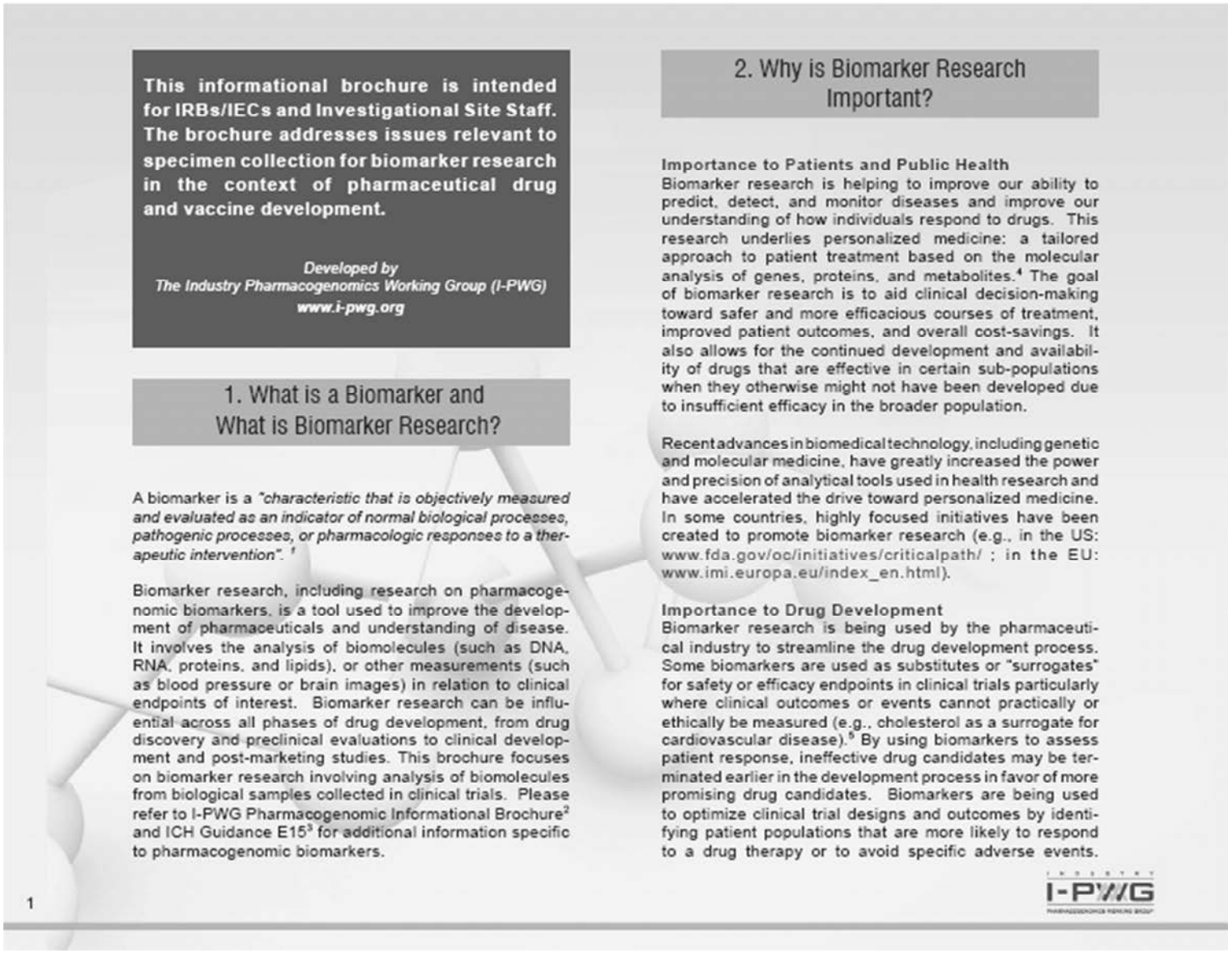
Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

14. References

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

12.3 **Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff**





This informational brochure is intended for IRBs/IECs and Investigational Site Staff. The brochure addresses issues relevant to specimen collection for biomarker research in the context of pharmaceutical drug and vaccine development.

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

1. What is a Biomarker and What is Biomarker Research?

A biomarker is a *"characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention".* [1]

Biomarker research, including research on pharmacogenomic biomarkers, is a tool used to improve the development of pharmaceuticals and understanding of disease. It involves the analysis of biomolecules (such as DNA, RNA, proteins, and lipids), or other measurements (such as blood pressure or brain images) in relation to clinical endpoints of interest. Biomarker research can be influential across all phases of drug development, from drug discovery and preclinical evaluations to clinical development and post-marketing studies. This brochure focuses on biomarker research involving analysis of biomolecules from biological samples collected in clinical trials. Please refer to I-PWG Pharmacogenomic Informational Brochure[2] and ICH Guidance E15[3] for additional information specific to pharmacogenomic biomarkers.

2. Why is Biomarker Research Important?

Importance to Patients and Public Health
Biomarker research is helping to improve our ability to predict, detect, and monitor diseases and improve our understanding of how individuals respond to drugs. This research underlies personalized medicine: a tailored approach to patient treatment based on the molecular analysis of genes, proteins, and metabolites.[4] The goal of biomarker research is to aid clinical decision-making toward safer and more efficacious courses of treatment, improved patient outcomes, and overall cost-savings. It also allows for the continued development and availability of drugs that are effective in certain sub-populations when they otherwise might not have been developed due to insufficient efficacy in the broader population.

Recent advances in biomedical technology, including genetic and molecular medicine, have greatly increased the power and precision of analytical tools used in health research and have accelerated the drive toward personalized medicine. In some countries, highly focused initiatives have been created to promote biomarker research (e.g., in the US: www.fda.gov/oc/initiatives/criticalpath/ ; in the EU: www.imi.europa.eu/index_en.html).

Importance to Drug Development
Biomarker research is being used by the pharmaceutical industry to streamline the drug development process. Some biomarkers are used as substitutes or "surrogates" for safety or efficacy endpoints in clinical trials particularly where clinical outcomes or events cannot practically or ethically be measured (e.g., cholesterol as a surrogate for cardiovascular disease).[5] By using biomarkers to assess patient response, ineffective drug candidates may be terminated earlier in the development process in favor of more promising drug candidates. Biomarkers are being used to optimize clinical trial designs and outcomes by identifying patient populations that are more likely to respond to a drug therapy or to avoid specific adverse events.

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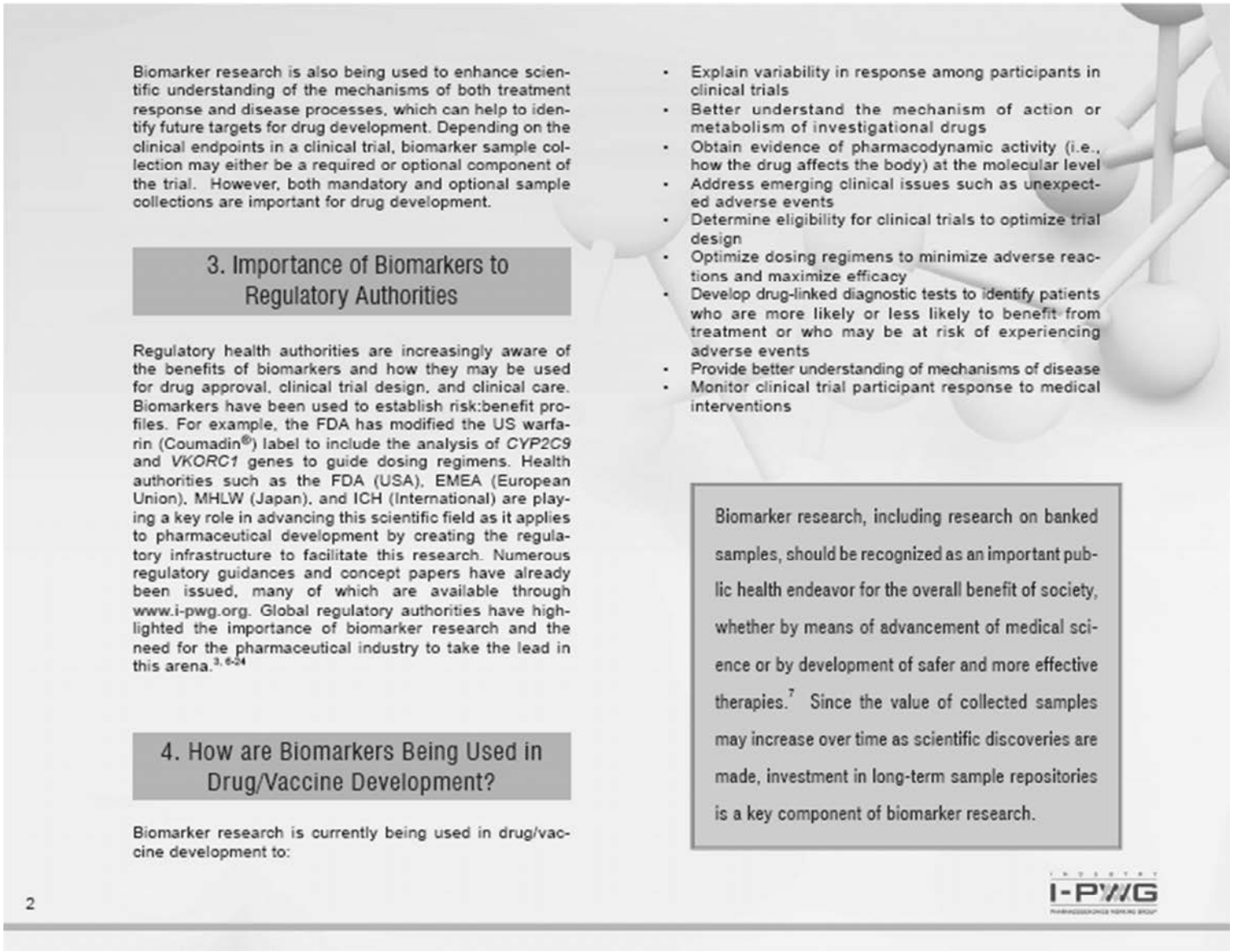
Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either be a required or optional component of the trial. However, both mandatory and optional sample collections are important for drug development.
3. Importance of Biomarkers to Regulatory Authorities
Regulatory health authorities are increasingly aware of the benefits of biomarkers and how they may be used for drug approval, clinical trial design, and clinical care. Biomarkers have been used to establish risk:benefit profiles. For example, the FDA has modified the US warfarin (Coumadin®) label to include the analysis of CYP2C9 and VKORC1 genes to guide dosing regimens. Health 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 by creating the regulatory infrastructure to facilitate this research. Numerous regulatory guidances and concept papers have already been issued, many of which are available through www.i-pwg.org. Global regulatory authorities have highlighted the importance of biomarker research and the need for the pharmaceutical industry to take the lead in this arena.[3, 6-24]
4. How are Biomarkers Being Used in Drug/Vaccine Development?
Biomarker research is currently being used in drug/vaccine development to:
Explain variability in response among participants in clinical trials
Better understand the mechanism of action or metabolism of investigational drugs
Obtain evidence of pharmacodynamic activity (i.e., how the drug affects the body) at the molecular level
Address emerging clinical issues such as unexpected adverse events
Determine eligibility for clinical trials to optimize trial design
Optimize dosing regimens to minimize adverse reactions and maximize efficacy
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 experiencing adverse events
Provide better understanding of mechanisms of disease
Monitor clinical trial participant response to medical interventions
Biomarker research, including research on banked samples, should be recognized as an important public health endeavor for the overall benefit of society, whether by means of advancement of medical science or by development of safer and more effective therapies.[7] Since the value of collected samples may increase over time as scientific discoveries are made, investment in long-term sample repositories is a key component of biomarker research.
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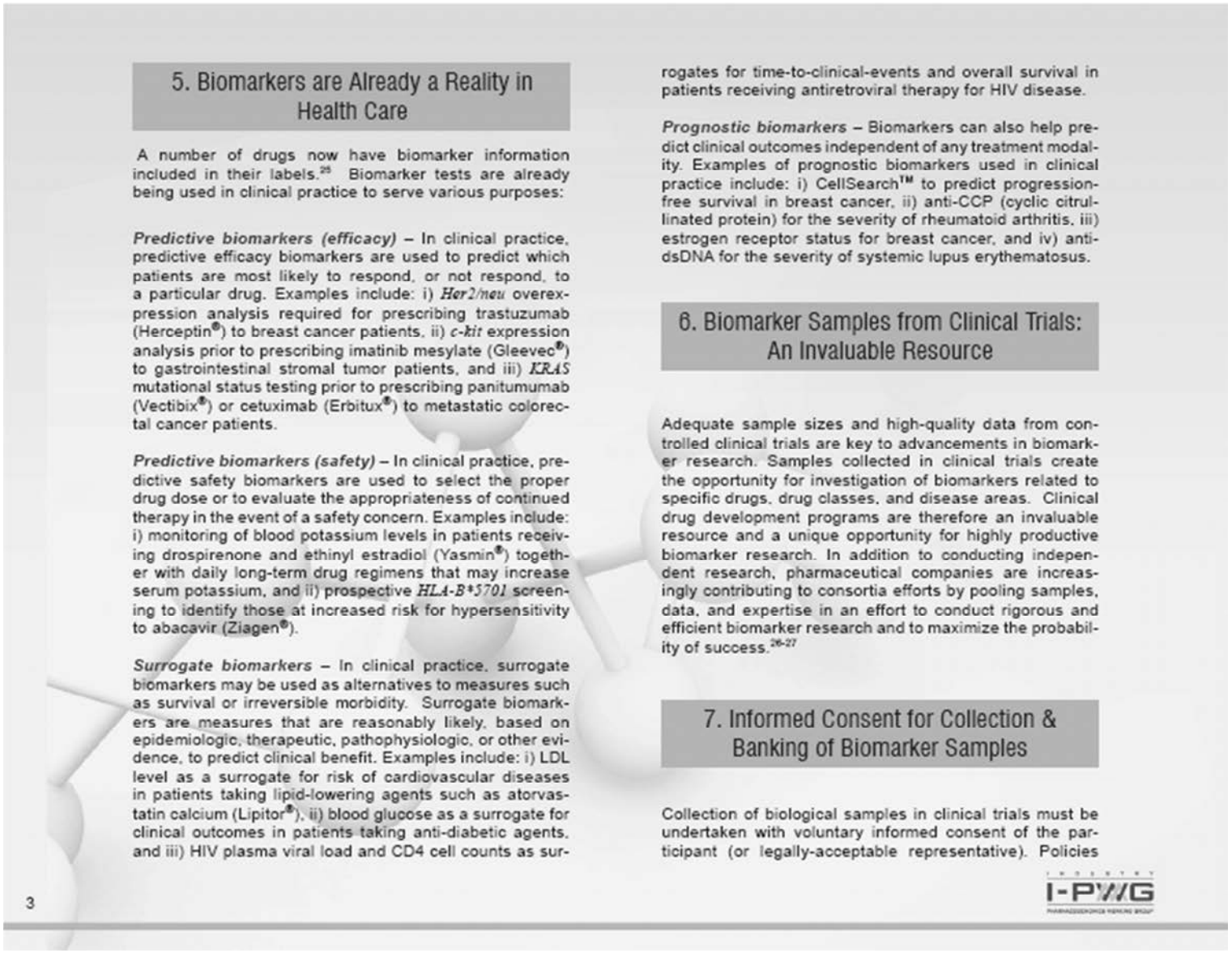


5. Biomarkers are Already a Reality in Health Care

A number of drugs now have biomarker information included in their labels.[25] Biomarker tests are already being used in clinical practice to serve various purposes:

Predictive biomarkers (efficacy) – In clinical practice, predictive efficacy biomarkers are used to predict which patients are most likely to respond, or not respond, to a particular drug. Examples include: i) *Her2/neu* overexpression analysis required for prescribing trastuzumab (Herceptin®) to breast cancer patients, ii) *c-kit* expression analysis prior to prescribing imatinib mesylate (Gleevec®) to gastrointestinal stromal tumor patients, and iii) *KRAS* mutational status testing prior to prescribing panitumumab (Vectibix®) or cetuximab (Erbitux®) to metastatic colorectal cancer patients.

Predictive biomarkers (safety) – In clinical practice, predictive safety biomarkers are used to select the proper drug dose or to evaluate the appropriateness of continued therapy in the event of a safety concern. Examples include: i) monitoring of blood potassium levels in patients receiving drospirenone and ethinyl estradiol (Yasmin®) together with daily long-term drug regimens that may increase serum potassium, and ii) prospective *HLA-B*5701* screening to identify those at increased risk for hypersensitivity to abacavir (Ziagen®).

Surrogate biomarkers – In clinical practice, surrogate biomarkers may be used as alternatives to measures such as survival or irreversible morbidity. Surrogate biomarkers are measures that are reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit. Examples include: i) LDL level as a surrogate for risk of cardiovascular diseases in patients taking lipid-lowering agents such as atorvastatin calcium (Lipitor®), ii) blood glucose as a surrogate for clinical outcomes in patients taking anti-diabetic agents, and iii) HIV plasma viral load and CD4 cell counts as surrogates for time-to-clinical-events and overall survival in patients receiving antiretroviral therapy for HIV disease.

Prognostic biomarkers – Biomarkers can also help predict clinical outcomes independent of any treatment modality. Examples of prognostic biomarkers used in clinical practice include: i) CellSearch™ to predict progression-free survival in breast cancer, ii) anti-CCP (cyclic citrullinated protein) for the severity of rheumatoid arthritis, iii) estrogen receptor status for breast cancer, and iv) anti-dsDNA for the severity of systemic lupus erythematosus.

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

Adequate sample sizes and high-quality data from controlled clinical trials are key to advancements in biomarker research. Samples collected in clinical trials create the opportunity for investigation of biomarkers related to specific drugs, drug classes, and disease areas. Clinical drug development programs are therefore an invaluable resource and a unique opportunity for highly productive biomarker research. In addition to conducting independent research, pharmaceutical companies are increasingly contributing to consortia efforts by pooling samples, data, and expertise in an effort to conduct rigorous and efficient biomarker research and to maximize the probability of success.[26-27]

7. Informed Consent for Collection & Banking of Biomarker Samples

Collection of biological samples in clinical trials must be undertaken with voluntary informed consent of the participant (or legally-acceptable representative). Policies

3

I-PWG

and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.[28-31]

Optional vs. Required Subject Participation

Depending on the relevance of biomarker research to a clinical development program at the time of protocol development, the biomarker research may be a core required component of a trial (e.g., key to elucidating the drug mechanism of action or confirming that the drug is interacting with the target) or may be optional (e.g., to gain valuable knowledge that enhances the understanding of diseases and drugs). Informed consent for the collection of biomarker samples may be presented either in the main clinical informed consent form or as a separate informed consent form, with approaches varying somewhat across pharmaceutical companies. The relevance of biomarker research to a clinical development program may change over time as the science evolves. The samples may therefore increase in value after a protocol is developed.

Consent for Future Research Use

While it can be a challenge to specify the details of the research that will be conducted in the future, the I-PWG holds the view that future use of samples collected for exploratory biomarker research in clinical trials should be permissible when i) the research is scientifically sound, ii) participants are informed of the scope of the intended future research, even if this is broadly defined (see potential uses in Section 4 above), iii) autonomy is respected by providing the option to consent separately to future use of samples or by providing the option to terminate further use of samples upon request (consent withdrawal / sample destruction), and iv) industry standards for confidentiality protection per Good Clinical Practice guidelines are met.[3, 31] Importantly, any research using banked samples should be consistent with the original informed consent, except where otherwise permitted by local law or regulation.

Important elements of informed consent for **future use** of samples include, but are not limited to:[39]

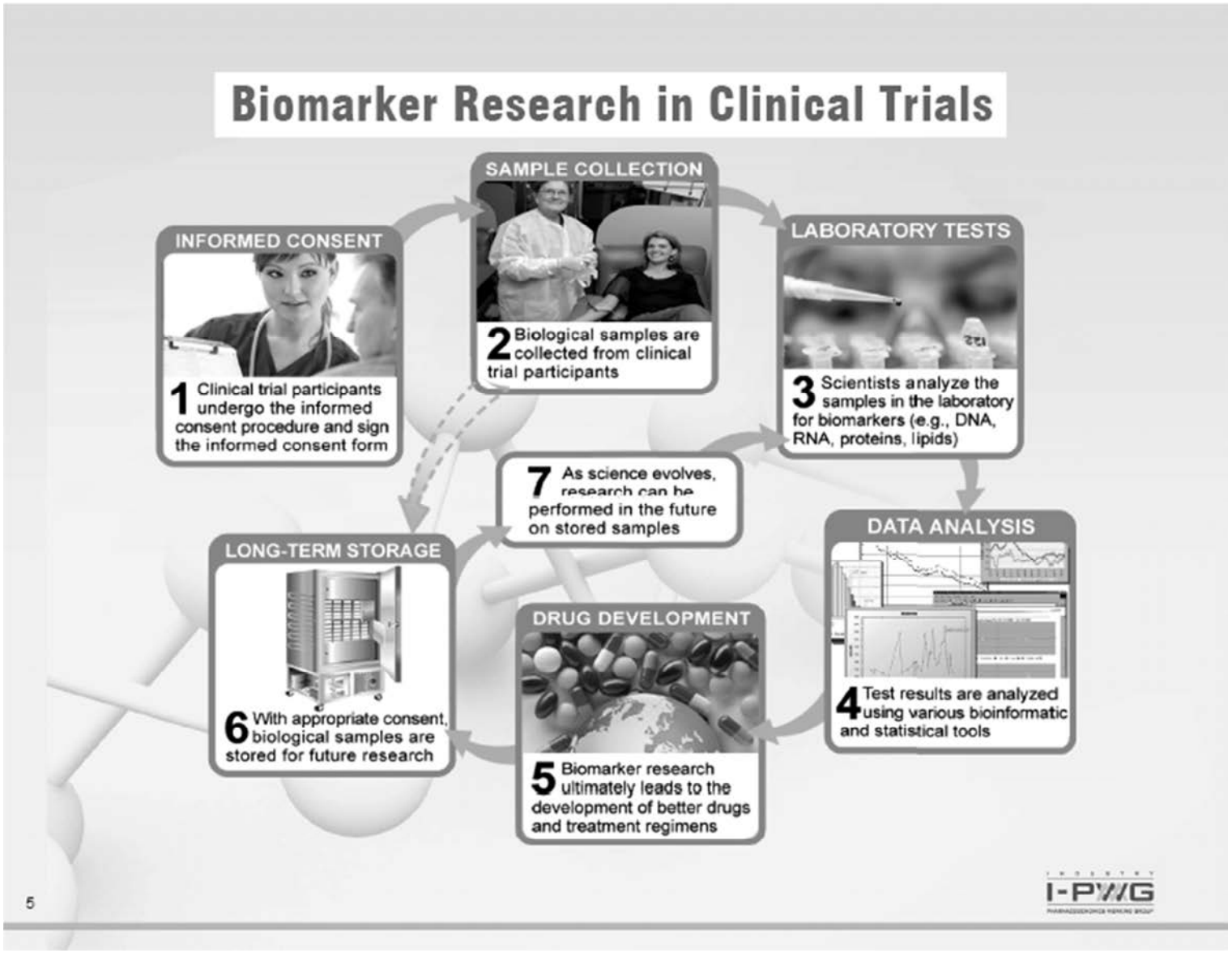
The scope of research – Where the scope of the potential future research is broad, participants should be informed of the boundaries of the research. While it may not be possible to describe the exact analytical techniques that will be used, or specific molecules that will be analyzed, it is possible to clearly articulate in reasonable detail the type of research to be conducted and its purpose. Information regarding whether stored samples may be shared with other parties or utilized for commercialization purposes should also be addressed.

Withdrawal of consent / sample destruction – The informed consent form should inform participants of their right to withdraw their consent / request destruction of their samples. This should include the mechanisms for exercising that right and any limitations to exercising that right. For example, participants should be informed that it is not possible to destroy samples that have been anonymized.[3] In addition, according to industry standards and regulatory guidance, participants should be informed that data already generated prior to a consent withdrawal request are to be maintained as part of the study data.[38]

The duration of storage – The permissible duration of storage may vary according to the nature and uses of the samples and may also vary on national, state, and local levels. The intended duration of storage, including indefinite storage, should be specified.

4

I-PWG


Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
7 As science evolves, research can be performed in the future on stored samples
DATA ANALYSIS
4 Test results are analyzed using various bioinformatic and statistical tools
LONG-TERM STORAGE
6 With appropriate consent, biological samples are stored for future research
DRUG DEVELOPMENT
5 Biomarker research ultimately leads to the development of better drugs and treatment regimens
5
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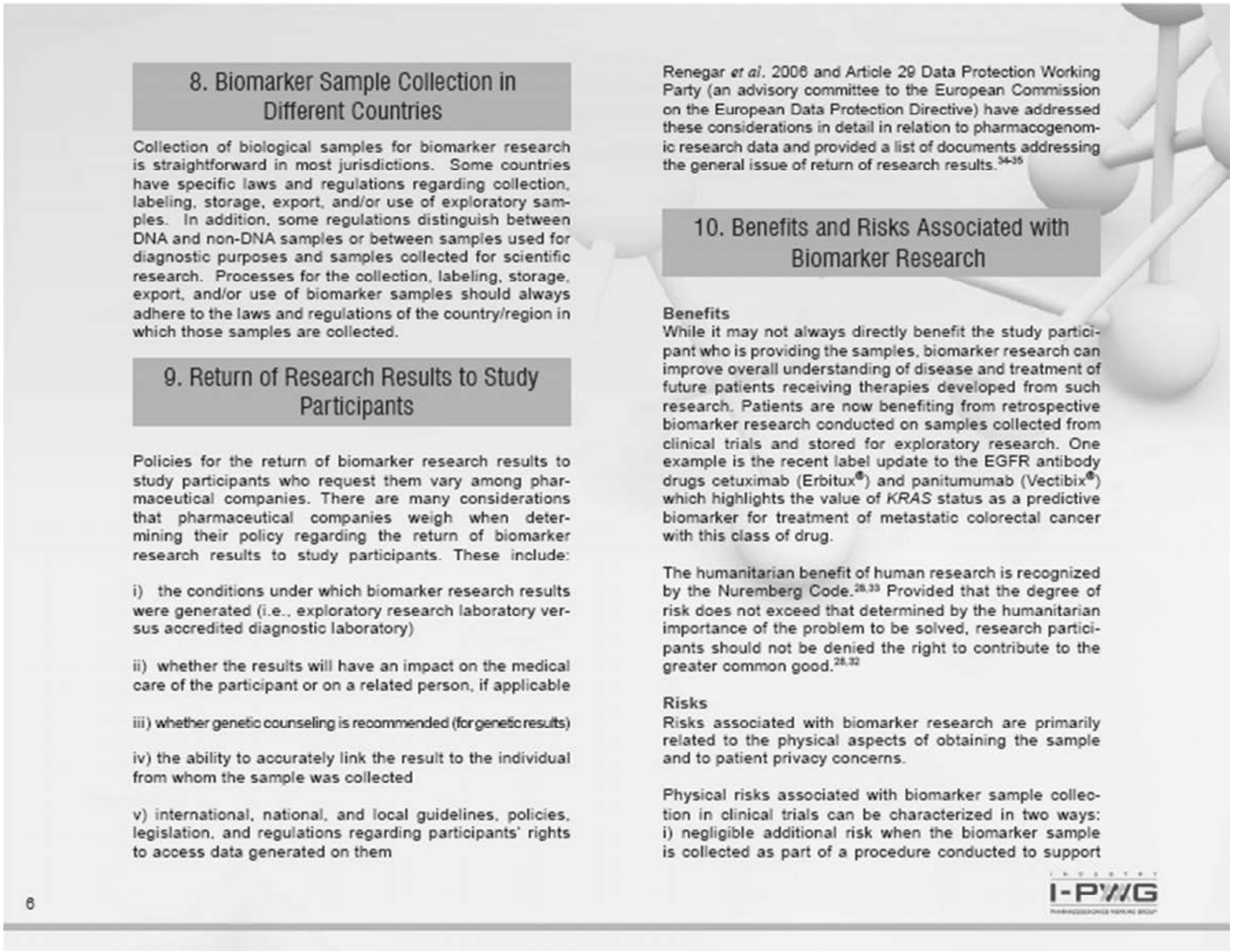

8. Biomarker Sample Collection in Different Countries

Collection of biological samples for biomarker research is straightforward in most jurisdictions. Some countries have specific laws and regulations regarding collection, labeling, storage, export, and/or use of exploratory samples. In addition, some regulations distinguish between DNA and non-DNA samples or between samples used for diagnostic purposes and samples collected for scientific research. Processes for the collection, labeling, storage, export, and/or use of biomarker samples should always adhere to the laws and regulations of the country/region in which those samples are collected.

9. Return of Research Results to Study Participants

Policies for the return of biomarker research results to study participants who request them vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of biomarker research results to study participants. These include:

i) the conditions under which biomarker research results were generated (i.e., exploratory research laboratory versus accredited diagnostic laboratory)

ii) whether the results will have an impact on the medical care of the participant or on a related person, if applicable

iii) whether genetic counseling is recommended (for genetic results)

iv) the ability to accurately link the result to the individual from whom the sample was collected

v) international, national, and local guidelines, policies, legislation, and regulations regarding participants' rights to access data generated on them

Renegar *et al*. 2008 and Article 29 Data Protection Working Party (an advisory committee to the European Commission on the European Data Protection Directive) have addressed these considerations in detail in relation to pharmacogenomic research data and provided a list of documents addressing the general issue of return of research results.[34-35]

10. Benefits and Risks Associated with Biomarker Research

Benefits

While it may not always directly benefit the study participant who is providing the samples, biomarker research can improve overall understanding of disease and treatment of future patients receiving therapies developed from such research. Patients are now benefiting from retrospective biomarker research conducted on samples collected from clinical trials and stored for exploratory research. One example is the recent label update to the EGFR antibody drugs cetuximab (Erbitux®) and panitumumab (Vectibix®) which highlights the value of *KRAS* status as a predictive biomarker for treatment of metastatic colorectal cancer with this class of drug.

The humanitarian benefit of human research is recognized by the Nuremberg Code.[28,33] Provided that the degree of risk does not exceed that determined by the humanitarian importance of the problem to be solved, research participants should not be denied the right to contribute to the greater common good.[28,32]

Risks

Risks associated with biomarker research are primarily related to the physical aspects of obtaining the sample and to patient privacy concerns.

Physical risks associated with biomarker sample collection in clinical trials can be characterized in two ways: i) negligible additional risk when the biomarker sample is collected as part of a procedure conducted to support

6

I-PWG

other core trial objectives, and ii) some added risk where the sampling procedure would otherwise have not been performed as a core component of a trial. Risks are also determined by the invasiveness of the sample collection procedure.

Privacy risks are generally those associated with the inappropriate disclosure and misuse of data. Pharmaceutical companies have policies and procedures for confidentiality protection to minimize this risk for all data collected and generated in clinical trials. These may vary across companies, but are based on industry standards of confidentiality and privacy protection highlighted in the following section. Importantly, privacy risks inherent to biomarker data are no greater than other data collected in a clinical trial.

11. Privacy, Confidentiality, and Patient Rights

Maintaining the privacy of study participants and the confidentiality of information relating to them is of paramount concern to industry researchers, regulators, and patients. Good Clinical Practice (GCP), the standard adhered to in pharmaceutical clinical research, is a standard that

"...provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected",

where confidentiality is defined as, *"The prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity."*

This standard dictates that *"the confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements."* [31]

Exploratory biomarker research in pharmaceutical development is commonly conducted in research laboratories that are not accredited to perform diagnostic tests used for healthcare decision-making. Therefore, results from exploratory biomarker research usually are not appropriate for use in making decisions about a trial participant's health. In addition, exploratory research data should not be included as part of a participant's medical record accessible for use by insurance companies. Legislation and policies to protect individuals against discrimination based on genetic information continually evolve based on social, ethical, and legal considerations. Examples of such legislation include the Human Tissue Act 2004 (UK) and the Genetic Information Nondiscrimination Act (GINA) 2008 (USA).[36-37]

12.Where to Get More Information?

Educational resources related to biomarker and pharmacogenomic research that caters to health care professionals, IRBs/IECs, scientists, and patients are continually being created and are publicly available. Links to many of these resources are available through the I-PWG website: www.i-pwg.org.

13. What is I-PWG?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in pharmacogenomic 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 pharmacogenomic and other biomarker research for key stakeholders. The I-PWG interacts with regulatory author-

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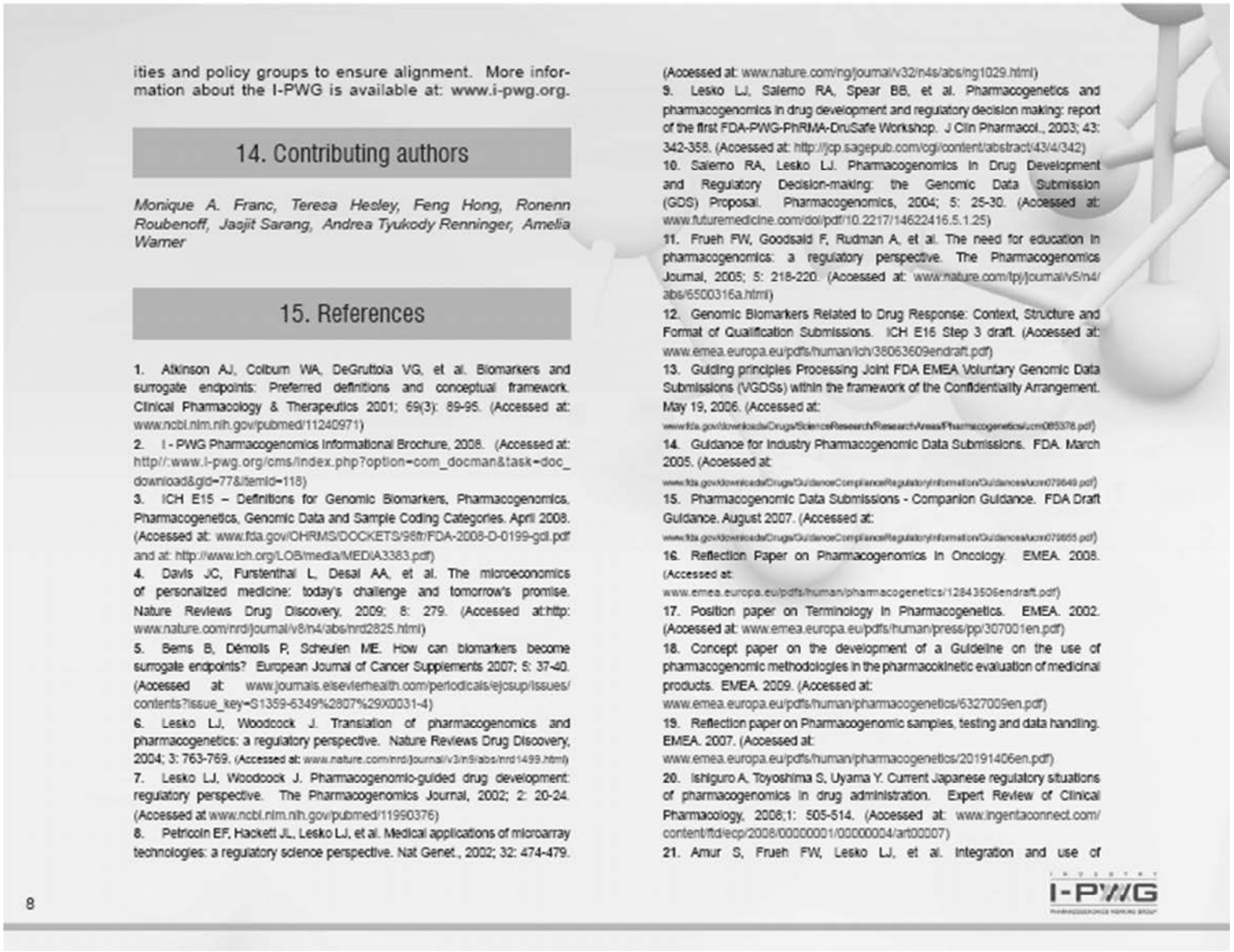

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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8

I-PWG

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12.4 Approximate Blood Volumes Drawn by Trial Visit and by Sample Types

Trial Visit:	Screening Visit 1	Randomization Visit 2	Treatment Visit 6	Treatment Visit 8
Blood Parameter	**Approximate Blood Volume (mL)**			
Hematology	2.0			
Serum Chemistry	2.5			
Serum-specific IgE	5.0			
Immunologic Sample (IgE, IgG_4)		10[a]	10[a]	10[a]
Expected Total (mL)	9.5	10[a]	10[a]	10[a]

[a] Samples will only be collected at selected sites. Leftover main study serum samples will be stored at the end of the study for future biomedical research if the subject/parent/guardian consents to future biomedical research.

12.5 Algorithm for Assessing Out-of-Range Laboratory Values

For all safety laboratory values obtained at prestudy evaluation (see Table 6 in Section 7.1.3.2):

A. If all values are normal, the subject may enter the study.

B. If ≥1 value is outside the normal range, the following choices are available:

1. The subject may be excluded from the study;
2. The subject may be included in the study if the investigator agrees that the abnormal value(s) is not clinically relevant. The sponsor may be consulted if uncertainty exists.
3. The subject may be included in the study if the abnormality is anticipated because of the disease state; e.g., an elevated eosinophils count in a subject with asthma (this should be noted in the "comments" section of the appropriate case report form); or
4. The abnormal test may be repeated (go to item C).

C. If the repeat test value is within the normal range, the subject may enter the study.

D. If the repeat test value is still abnormal, the investigator will evaluate the potential subject with a complete history and physical examination, looking especially for diseases that could result in an abnormality in the laboratory value in question. If such diseases can be excluded, and if the investigator feels that the abnormal laboratory value is not clinically relevant, then the subject may enter the study. The Sponsor may be consulted in the decision of whether or not to enroll the subject in the study, if uncertainty exists.

E. If there is any clinical uncertainty regarding the significance of an abnormal value, the subject will be excluded from the study.

F. For the purposes of this protocol, if the following tests are within 10% of the upper or lower limits of normal value they will not be considered clinically abnormal and subjects can be enrolled in the study: ***bilirubin, BUN, creatinine, glucose, alkaline phosphatase, total white blood cell count, and platelets***. Subjects outside this range must be evaluated according to protocol.

G. The subject cannot proceed to Visit 2 until all abnormalities have been resolved according to this protocol.

12.6 Allergy Rescue Medications for Rhinoconjunctivitis Symptoms

Use of any rescue medications for rhinitis/conjunctivitis symptoms must be approved by the investigator or designee. The use of rescue medication is subject to the following step-wise requirements:

Step 1

Loratadine syrup, 1 mg/mL or Loratadine oral tablet, 5 mg (for 5 years old) or 10 mg (for 6 to 17 years old), will be dispensed to the subject at Visit 6 but must not be used before the investigator has confirmed that in his/her opinion the RS has started and the subject has an adequate level of symptoms as evaluated in accordance with the following procedure:

The subject must be instructed to contact the investigator in case of rhinitis/conjunctivitis symptoms and the need for rescue medication. The investigator will then ask the subject to score his/her nose and eye symptoms (i.e., runny nose, blocked nose, sneezing, itchy nose, gritty feeling/itchy/red eyes, and watery eyes) using a scale from 0 to 3 (0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms).

Once the investigator has confirmed a total symptom score of ≥4 and the RS has started, the subject may be authorized to start using Step 1 medication. The total symptom score and the date of this authorization must be recorded in the source documents as required by the sponsor.

Once symptoms are improved, the subject should reduce or stop use of rescue medication.

Step 1b

Olopatadine hydrochloride 0.1% ophthalmic solution will be dispensed to the subject at Visit 6 but should only be used in addition to Step 1 Loratadine syrup or oral tablet if eye symptoms persist in spite of Step 1 treatment.

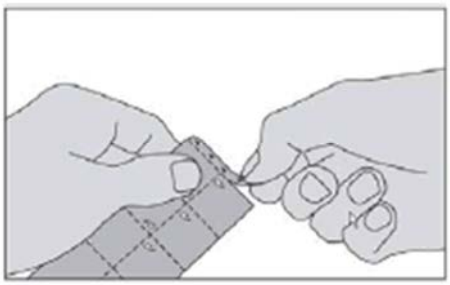
Once symptoms are improved, the subject should reduce or stop use of this rescue medication.

Step 2

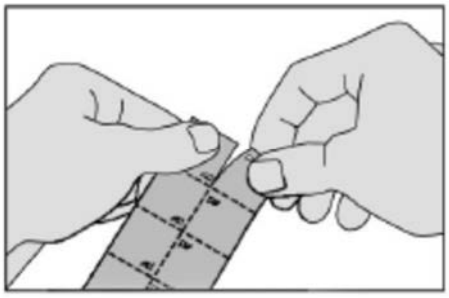
Mometasone furoate monohydrate nasal spray 50 mcg will be dispensed to the subject at Visit 6 but should only be used if symptoms are not satisfactorily controlled by Step 1 medication as evidenced by a persisting minimum total symptom score of ≥4. The subject should again call the investigator for authorization to use mometasone furoate monohydrate nasal spray to be taken in addition to Step 1 medication.

Once symptoms are improved, the subject should reduce or stop use of this rescue medication.

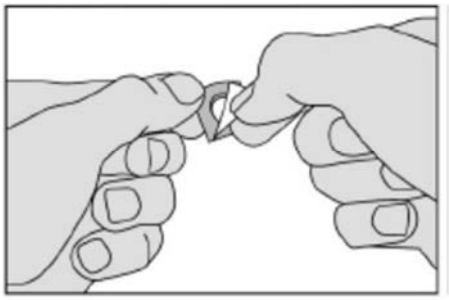
12.7 Instructions for Opening the Ragweed Sublingual Tablet (Oral Lyophilisate) from the Pack



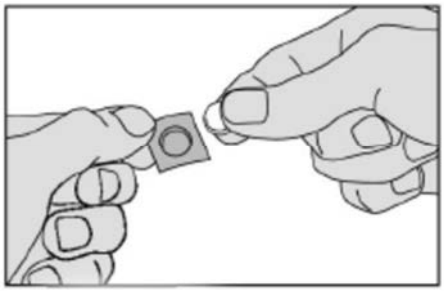
1. Tear off the blank perforated strip at the end of the oral tablet pack, opposite the labeled end.



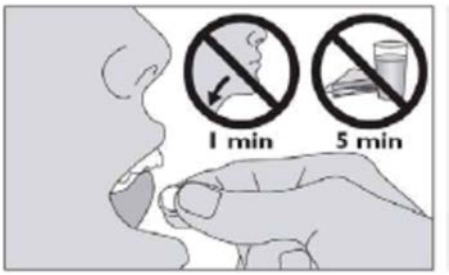
2. Tear a square off the oral tablet pack along the perforated lines.



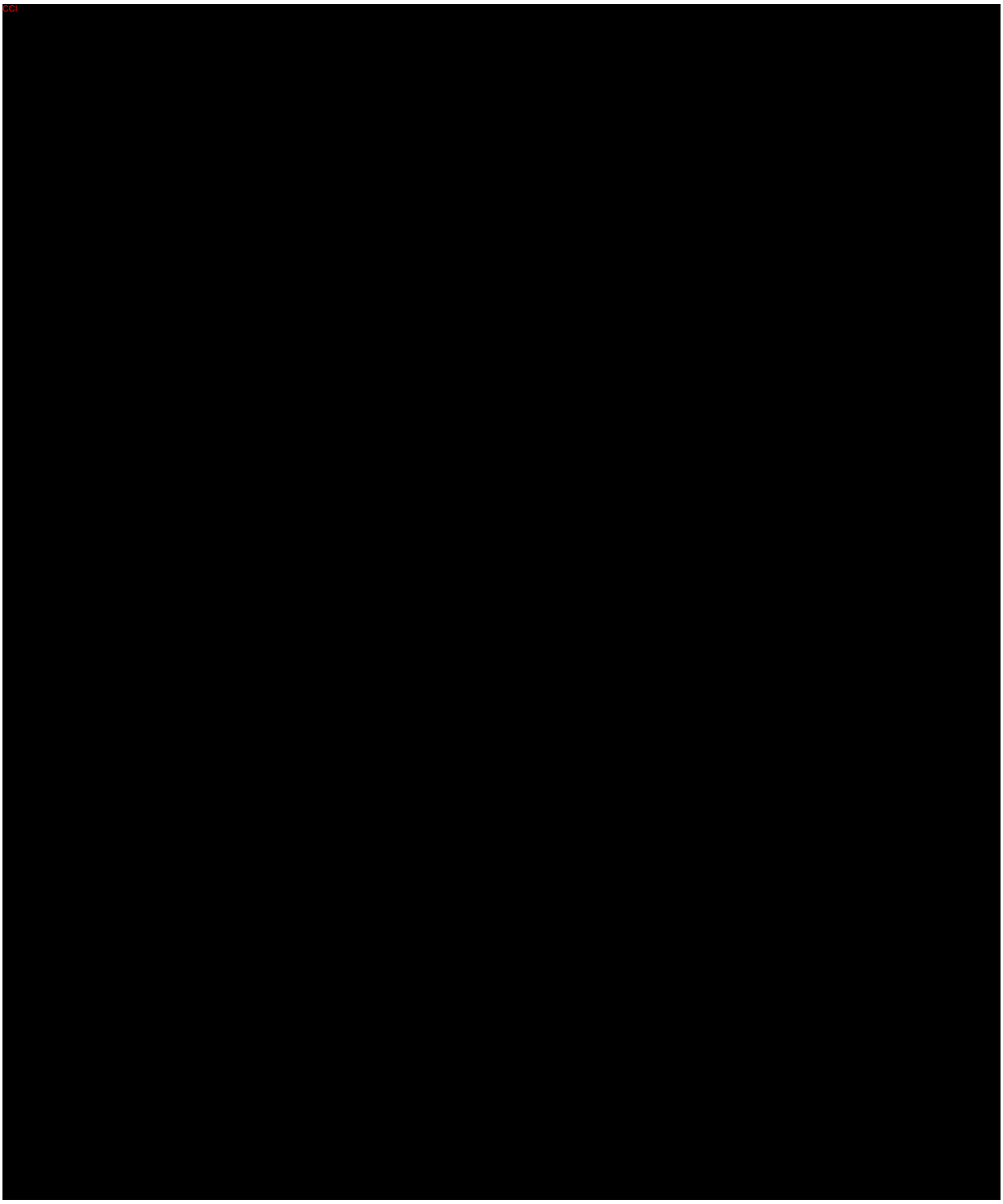
3. Do not force the oral tablet through the foil. It may damage the oral tablet as it easily breaks. Instead, fold back the marked corner of the foil and then pull it off.



4. Make sure that the tablet is free of all lidding foil before removal. Remove the oral tablet carefully from the foil and take the oral tablet immediately.



5. Place the oral tablet under the tongue. Allow it to remain there for a few seconds until it has dissolved. Do not swallow during the first minute. Do not eat or drink for at least 5 minutes.



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PARENT/GUARDIAN AUTHORIZATION SIGNATURE DATE

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FORM MODIFIED WITH PERMISSION FROM FARE 10/2014

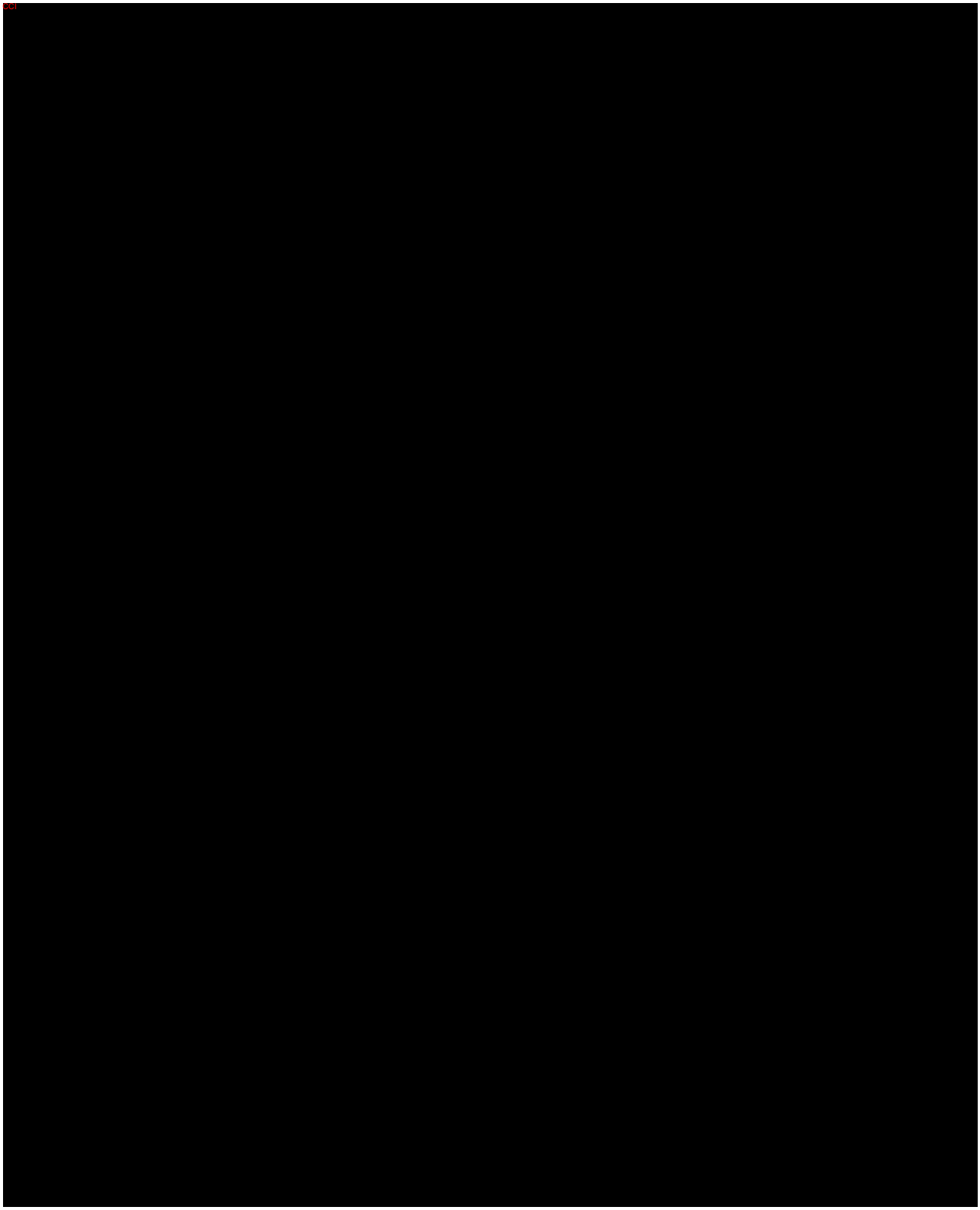
This plan can be modified within and outside the US to meet local standards for the use (or type) of epinephrine dispensed, and for calls to 911 or alternative local emergency services.

12.9 Method for Performing Post-Bronchodilator Reversibility Testing

In assessing short-acting β-agonist (SABA) response in the clinic, 2 to 8 puffs of SABA (albuterol/salbutamol) will be administered via a metered-dose inhaler (MDI). Investigator and/or subject/parent/guardian can choose to end procedure after Step 9 for any reason.

Procedure

1. Perform pre-bronchodilator spirometry (baseline FEV_1).
2. Shake the metered-dose inhaler.
3. Tilt the head back slightly and breathe out.
4. Place device in mouth.
5. Press down on inhaler to release medication.
6. Breathe in slowly (3 to 5 seconds) to total lung capacity.
7. Hold breath for 10 seconds.
8. Wait 30 seconds between each puff and repeat the same sequence 3 additional times.
9. After either 2 or 4 inhalations of SABA (per investigator discretion), wait approximately 10 minutes and then perform spirometry. Compare results with baseline spirometry.
   - If there is a **<** 5% change or ≥ 12% change in absolute FEV_1, then end procedure and record results in appropriate eCRF.
   - If there is a **≥ 5%** to < 12% change in FEV_1, continue to Step 10.
10. Repeat steps 2-7 to administer an additional 2 inhalations of SABA with approximately 30 seconds between inhalations.
11. Wait approximately 10 minutes, perform spirometry, and compare with baseline FEV_1.
    - If there is a **<** 10% change or ≥ 12% change in absolute FEV_1, then end procedure and record results in appropriate eCRF.
    - If there is a **≥ 10**% to < 12% change in FEV_1, continue to Step 12.
12. Repeat steps 2-7 to administer an additional 2 inhalations of SABA with approximately 30 seconds between inhalations.
13. Wait approximately 10 minutes, perform spirometry, compare with baseline FEV_1, and record results in appropriate eCRF.



12.13 List of Abbreviations

Abbreviation	Definition
aDSS	Asthma Daytime Symptom Score
AE(s)	Adverse event(s)
AIT	Allergy immunotherapy
ALT	Alanine aminotransferase
AMA	American Medical Association
ANOVA	Analysis of variance
AR	Allergic rhinitis
ARC	Allergic rhinoconjunctivitis
ASaT	All subjects as treated
AST	Aspartate aminotransferase
BAU	Bioequivalent allergy unit
β-hCG	Beta-human chorionic gonadotropin
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CI	Confidence interval
cLDA	Constrained longitudinal data analysis
CSR	Clinical study report
DMC	Data Monitoring Committee
DMS	Daytime Medication Score
DNA	Deoxyribonucleic acid
DPI	Dry-powder inhaler
DSS	Daytime Symptom Score
ECI	Event of clinical interest
eCRF	Electronic case report form
e-diary	Electronic diary
eDMC	External Data Monitoring Committee
EMA/EMEA	European Medicines Agency
EOC	Executive Oversight Committee
ERC	Ethical Review Committee
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act

Abbreviation	Definition
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
HFA	Hydrofluoroalkane
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICS	Inhaled corticosteroid
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
IgG_4	Immunoglobulin G_4
IMP	Investigational medicinal product
IRB	Institutional Review Board
IUD	Intrauterine device
IVRS	Interactive voice response system
IWRS	Interactive web response system
LABA	Long-acting $beta_2$-agonist
LOCF	last observation carried forward
MDI	Metered-dose inhaler
NAEPP	National Asthma Education and Prevention Program
OTC	Over-the-counter
PFT	Pulmonary function test
PGt	Pharmacogenetic
PIN	Personal identification number
PK/PD	Pharmacokinetic/Pharmacodynamic
PP	Per protocol
Protocol CI	Protocol coordinating investigator
RNA	Ribonucleic acid
RS	Ragweed season
SABA	Short-acting $beta_2$-agonist
SAC	Scientific Advisory Committee
SAE(s)	Serious adverse event(s)
SAP	Statistical Analysis Plan
SCIT	Subcutaneous immunotherapy

Abbreviation	Definition
SLIT	Sublingual immunotherapy
SM	Study medication
SOC	System organ class
SOP	Standard operating procedure
SPT	Skin prick test
SQ-U	Standardized quality unit
TCS	Total Combined Score
US	United States
WAO	World Allergy Organization
WBC	White blood cell

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

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

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	