Review of Ragwitek PMC Proposal - RAGWITEK

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To:	Elizabeth Valenti, MPH, REHS, Chair
Through:	Michael Nguyen, MD, Acting DE Director
Subject:	BLA 125478
Applicant:	Merck Sharp & Dohme Corp.
Product:	Standardized Allergenic Extract, Short Ragweed (Ambrosia artemisiifolia) MK-3641 RAGWITEK
Proposed Indication:	Immunotherapy for the treatment of short ragweed pollen-induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for short ragweed pollen. RAGWITEK is approved for use in adults 18 through 65 years of age.
Submission Date:	11-MAR-2013
PVP Submission Date:	11-MAR-2013
Action Due Date:	17-APR-2014

1. **Introduction**

a. **Product description**

The product is a sublingual pharmaceutical formulation of the allergen extract from short ragweed pollen, Ambrosia artemisiifolia, (SCH 039641, hereafter referred to as MK-3641 or Ragwitek) to be used as an allergen immunotherapy (AIT) for the treatment of allergic rhinitis (AR)/ allergic rhinoconjunctivits (ARC). MK-3641 is a fast-dissolving, orally disintegrating sublingual tablet for oromucosal delivery of short ragweed allergen. The drug substance is ----------(b)(4)----------.

b. **Pertinent regulatory history**

i. **Prior licensure**

Standardized Allergenic Extract, Short Ragweed (Ambrosia artemisiifolia), MK-3641, has not been previously licensed in any country.

c. **Objectives/Scope of the review**

The purpose of this memorandum is to summarize the sponsor's proposal for a post-market surveillance study to address a request by CBER for additional post-market monitoring for certain serious allergic reactions and eosinophillic esophagitis (EoE), and to document the sponsor's agreed upon commitments to conduct a post-market safety study. A full review of the pharmacovigilance plan and associated safety data was previously documented in the Pharmacovigilance review Memorandum, 9/16/2013.

2. **Materials reviewed**

a. **Routine items:**

i. **Pharmacovigilance Plan:**
STN 125478**-** Section 1.11.4

ii. **Pertinent sections of the licensing application selected by the reviewer**
Post-market Commitment (PMC) Concept Protocol, submitted by the sponsor on March 2, 2014, as an amendment to the BLA (125478/26).
Revised synopses for PMC Studies, submitted by the sponsor on April 9, 2014, as an amendment to the BLA (125478/32).

iii. **Input from CBER Product, Clinical and Statistical reviewers**
Final determination of the safety profile of the product used in the studies submitted to this BLA is pending final clinical, statistical and product reviews.

3. **Summary of Pharmacovigilance Plan Review (from PV Review Memo, 9/16/2013)**

Overview of treatment across studies

The safety database includes 1747 subjects 18 years and older with short ragweed allergy randomized to receive MK-3641. In the clinical program, approximately 20% of subjects suffered from mild concomitant asthma. The population with asthma was limited to those with stable asthma, as judged by the clinical investigator, and excluded subjects with asthma that had resulted in emergency treatment, hospitalization, or treatment with systemic corticosteroids at any time within the 3 months prior to screening. A full review of the safety related results of the clinical studies can be found in the OBE/DE Pharmacovigilance Review Memorandum , 9/16/2013.

Specific anticipated or potential risks included systemic allergic reactions, including anaphylactic reactions and local allergic reactions with potential to compromise airway and acute worsening of asthma symptoms (exacerbation).

EoE was not identified in any patients in the clinical development program. However, based on case reports of EoE associated with use of different sublingual allergen therapy in Europe and biological plausibility of association between oral allergen therapy and EoE, EoE was included in the warnings and contraindications sections of the package insert.

Selected limitations of the Clinical Safety Data for Ragwitek:

- The clinical safety database does not include adequate data on children less than 18 years old. The proposed indication is limited to 18 and above. A pediatric study is planned to begin after licensure.
- Subjects with asthma classified as severe or uncontrolled, and asthmatics using high doses of inhaled corticosteroids (ICS) or controlled with long-acting beta agonists (LABA) were excluded from the studies. (The sponsor reports this is in keeping with current immunotherapy practice guidelines.)

- Subjects with a history of anaphylaxis or angioedema were excluded from the clinical studies.
- Subjects who were pregnant, not using adequate contraception or breast-feeding were excluded from participation in the studies.

The sponsor's proposed pharmacovigilance plan includes routine surveillance as well as specific measures to address the identified risks related to systemic allergic reactions, local reactions with potential for respiratory obstruction, and asthma exacerbation. These pharmacovigilance measures include follow-up questionnaires for reports of these reactions, specific labeling to address these risks, and a planned pediatric study.

4. **Integrated Risk Assessment**
    a. The proposed pharmacovigilance measures are adequate for addressing the identified and potential risks and do not trigger a post-market requirement for a safety study.
    b. However, CBER requested that the sponsor augment their pharmacovigilance activities by proposing a study, to be conducted as a post-market commitment (PMC), to additionally monitor the risk of allergic reactions and EoE in the US should this product be licensed. While sublingual immunotherapy in severe or uncontrolled asthmatics is a contraindication under current immunotherapy practice guidelines, subjects with persistent and with moderate asthma were excluded from the clinical studies and therefore, the safety of Ragwitek in this population has not been characterized. A postmarket study enrolling all patients prescribed the product without these exclusions could provide additional information on the incidence and risk factors for serious allergic reactions in the population using the product in actual use.
5. Review of Sponsor's Protocol Synopsis
    a. The sponsor proposes to conduct two sub-studies, one using a large claims database representing 25-30 million patients and one using electronic medical records (EMR) from an integrated healthcare organization. The claims-based study will enroll all new users of Ragwitek identified through claims data from a large US health insurance database for a period of at least three years from launch of Ragwitek. The EMR study will identify all new users of Ragwitek in an integrated healthcare provider organization which is anticipated to represent less than 5 million patients. The sponsor will conduct the studies for at least 3 years and until at least 10,000 patients are accrued between both post-market studies. The primary outcomes for these studies will be "local and systemic allergic reactions resulting in hospitalization, emergency department care, or ambulatory visits that are associated with epinephrine injections (hereafter referred to as "serious allergic reactions") and EoE. The integrated healthcare system will pick up the events that are associated with early exposures based on use of starter packs as well as events that might occur during exposure to longer term therapy. The claims database will offer a larger sample size to assess the incidence and risk factors for the longer term outcomes (i.e., those that occur after the starter pack exposure).
    b. The objectives are as follows:

i. Estimate the incidence of serious allergic reactions in patients receiving Ragwitek resulting in hospitalization, emergency department care, or epinephrine injection in the ambulatory setting.
ii. Conduct a case series analysis of exposed patients who experience a serious allergic event to describe potential risk factors.
iii. Describe characteristics of patients initiating Ragwitek with respect to demographics, concomitant medications and co-morbidities.
iv. Note: Revision of the objectives to include EoE is expected in the final protocol, to be submitted after approval should the product be approved.

c. The sponsor noted several limitations associated with the proposal:
i. Claims data will not capture new users during the initial treatment, which will usually be conducted via a starter pack (5-day pack) given to patients by the prescribing physician. As most serious allergic reactions would be expected to happen during these early treatments, this exclusion will limit the studies ability to measure an accurate incidence of serious allergic reactions in all patient exposures, and could bias the results as the remaining cohort will consist of patients who tolerated the early doses without allergic reactions. The EMR study will help to calculate a rate of allergic reactions that includes these early exposures and reactions.
ii. Claims data will capture patterns of treatment refills but will not capture interruption of day-to-day therapy.
iii. Self-administration of epinephrine in the community setting will not be captured with claims data.
iv. Esophageal symptoms representing EoE may cause health care providers (including primary care providers) to advise patients to discontinue Ragwitek without establishing a formal diagnosis of EoE. Since no treatment would be needed if symptoms resolved after discontinuation, the diagnosis of EoE may never be made, and these patients would not be captured in post-market studies using claims or EMR data. (Not noted by the sponsor in the concept protocol but expected to be reflected in the final protocol when submitted).
v. Medical charts may not be available for all patients with outcomes of interest.

6. Summary of Agreed Upon Study Proposal
a. Source population: The claims database study will use a US health insurance claims database expected to represent 25-30 million patients. The EMR study will use an integrated healthcare provider as the source data, and is anticipated to represent less than 5 million patients. The sponsor notes that they will have to identify an integrated health system that: (1) utilizes sufficient amounts of this product in their system which is affected by regional exposure to the antigens, and (2) is able to ascertain in-office exposures and administrations through starter packs.
b. Cohort Identification: The study will enroll all new users of Ragwitek based on dispensing claims (in the claims study) or EMR evidence of in-office administration or dispensing (EMR study). The studies will also capture exposures to other immunotherapies (e.g. beta-agonist or steroid inhalers).
c. Outcome: The primary outcome for the studies will be local and systemic allergic reactions resulting in hospitalization, emergency department care, or

ambulatory visits that are associated with epinephrine injections (i.e., “serious allergic reactions”) and EoE. Allergic reactions will be ascertained through diagnosis codes for anaphylaxis, anaphylactic reaction, anaphylactic shock, systemic allergic reaction, or upper airway obstruction. Outcomes will also be identified through codes for procedures to treat these conditions, such as emergency endotracheal intubation or surgical airway. Each outcome identified through automated data will be adjudicated by a panel of clinicians who are experts in the field using medical chart review.

d. Analysis Plan:
   i. Determine incidence rate of the study outcome
   ii. Describe demographic characteristics, important comorbidities and concomitant medications, including allergy immunotherapy and calendar month. The sponsor will also describe dispensing patterns of Ragwitek preceding the events, based on claims data, as well as any mention of treatment interruption or suspected allergic trigger documented in the medical record.
   iii. Time at risk, which will be detailed in the protocol, will be calculated based on days’ supply of medication plus a 7 day grace period after exposure ends. Sensitivity analyses will apply a 14 day period after exposure ends. A secondary analysis will limit the exposure to the first 30 days of drug use.
   iv. There is no pre-specified sample size, however, based on commercial forecasts, the sponsor expects to enroll at least 10,000 new Ragwitek users.
e. Timelines: The sponsor anticipates submitting a full protocol by 31 JAN 2015 for the claims based study and November 2015 for the EMR study. As this is a retrospective cohort study, patients available for the cohort will begin to accrue with product launch (anticipated Q2 2014), and data collection is anticipated to end three years later (Q2 2017), with a final study report to be submitted Q2 2018, however, these timelines may be extended if the 10,000 patient minimum is not reached

7. **Recommendations**

Based upon the submitted information and current clinical knowledge, at this time OBE/DE agrees that routine pharmacovigilance as proposed by the sponsor is appropriate should this product be licensed.

While limited by a relatively small size and lack of controlled comparison group, the post-market study to be conducted by the sponsor as a post-market commitment will provide further enhanced monitoring for serious allergic reactions and EoE.