Application Type	BLA Supplement
STN	125478/293
CBER Received Date	06/17/2020
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Division / Office	DVRPA /OVRR
Committee Chair	Colleen Sweeney
Clinical Reviewer(s)	Anubha Tripathi
Project Manager	Taruna Khurana
Priority Review	No
Reviewer Name(s)	Mridul K. Chowdhury, Mathematical Statistician, VEB/DB/OBE
Supervisory Concurrence	Lihan Yan, Team Leader, VEB/DB/OBE
	Tsai-Lien Lin, Branch Chief, VEB/DB/OBE
Applicant	ALK/Abello A/S
Established Name	Short Ragweed Pollen Allergen Extract
Trade Name	RAGWITEK
Pharmacologic Class	Allergenic
Formulation(s), including Adjuvants, etc	MK-3641, Short Ragweed Pollen Allergen Extract Tablet for Sublingual Use
Dosage Form(s) and Route(s) of Administration	Tablets 12Amb a 1-U Oral
Indication(s) and Intended Population(s)	Treatment of diagnosed ragweed pollen induced allergic rhinitis, with or without conjunctivitis, in children and adolescents 5 through 65 years of age

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GLOSSARY

Abbreviation/Term	Definition
AE	Adverse event
Amb a 1-U	*Ambrosia artemisiifolia* major allergen 1 unit
ANOVA	Analysis of variance
AR	Allergic rhinitis
ARC	Allergic rhinoconjunctivitis
ASaT	All subjects as treated
CI	Confidence interval
CRF	case report form
CSR	Clinical Study Report
DMC	Data Monitoring Committee
DMS	Daily medication score
DSS	Daily symptom score
FAS	Full analysis set
GCP	Good Clinical Practice
ICH	International Council for Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IM	Intramuscular
IRB	Institutional Review Board
LDA	Longitudinal data analysis
LS	Least square
MedDRA	Medical dictionary for regulatory activities
PP	Per-protocol
PREA	Pediatric Research Equity Act
QA	Quality Assurance
QC	Quality Control
QCI	Quality and Continuous Improvement
RS	Ragweed season
SABA	Short-acting beta2-agonist
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SLIT	Sublingual immunotherapy
SOC	System organ class
TCS	Total combined score

1. EXECUTIVE SUMMARY

This application is a clinical efficacy supplement to support extension of the licensed product RAGWITEK® (MK-3641) to include children and adolescents 5 through 17 years of age. The basis of the application is the Phase III clinical study (P008), which was a part of requirements set under the Pediatric Research Equity Act (PREA), and which, as the Agency agreed, may be adequate to support filing of the supplement for review. The clinical study evaluated safety and efficacy of RAGWITEK® (MK-3641) as immunotherapy for the treatment of short ragweed pollen-induced allergic rhinitis (AR), with or without conjunctivitis, confirmed by positive skin test or in vitro testing pollen specific IgE antibodies for short ragweed pollen in pediatric subjects. RAGWITEK® was approved on April 17, 2014 for use in adults 18 through 65 years of age. The current study enrolled 1000 children, double-blind-randomized in a 1:1 ratio to receive either MK-3641 (sublingual immunotherapy) at a dose of 12 Amb a 1-U, or placebo once daily for approximately 20 to 28 weeks. For ragweed season, the duration covered the pre-seasonal (approximately 12 to 20 weeks) treatment period and co-seasonal (approximately 8 weeks) treatment period (ref. schema Figure 1).

The study evaluated the efficacy of MK-3641 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). A significant reduction in the primary endpoint of average TCS during the peak RS was observed in participants treated with MK-3641 compared with placebo (ref. section 6.1.11.1 and Table 2), demonstrating efficacy. Similar reductions were observed in key secondary endpoints as well, where MK-3641 compared with placebo yielded significantly lower average TCS during the entire RS, lower average rhinoconjunctivitis DSS in the peak RS and lower average rhinoconjunctivitis DMS in the peak RS, thus supporting the primary efficacy result (ref. Table 3).

With regards to safety data, a majority of subjects in MK-3641 reported AEs (81.9%), in which 3.9% discontinued due to an AE. The incidences of SAEs were overall low (<2%) and similar in the two arms. The pre-specified local reactions that were more frequent in MK-3641 were mostly mild, transient, and short-lived. Events of clinical interest were infrequent (<2%), with similar proportions of participants in the two arms. The proportions of participants with AEs were comparable across arms, with and without asthma at baseline. Overall, MK-3641 appears to be well tolerated and a general concern for safety was not discerned based on the AE profile and type; which, however, is subject to clinical reviewer's viewpoint.

Overall, the participants treated with MK-3641 demonstrated significantly lower average TCR during the peak RS compared with placebo, showing that the treatment is effective. A general concern for safety signal was not discerned either, but it is a clinical call. From the statistical perspective, I recommend approval of the application.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Background

MK-3641 is a sublingual immunotherapy (SLIT) tablet approved for use in the US and Canada under the trade name of RAGWITEK®, and in 9 European countries and Russia under the trade name of RAGWIZAX®, for the treatment of short ragweed pollen-induced AR, with or without conjunctivitis, in adults. MK-3641 contains *Ambrosia artemisiifolia* (short ragweed) extract. The first dose is administered under supervision by a health-care professional and subsequent doses are self-administered at home.

Prior to the submitted study, 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 the US and Canada under the trade name of GRASTEK®, and in most of Europe, Australia, Russia, and Turkey under the trade name of GRAZAX®, for the treatment of AR and conjunctivitis in adults and children (5 years of age and older).

2.2 Regulatory Activity Related to the Submission

The current submission is a clinical efficacy supplement to support the extension in RAGWITEK® indication to cover children down to 5 years of age. The BLA for RAGWITEK was approved for use in adults 18 through 65 years of age on April 17, 2014. A clinical study P008 was conducted to fulfill the pediatric requirements under PREA. CBER agreed that the efficacy results of this study may be adequate to support filing of the supplemental BLA to extend the indication for review. Study P008 evaluated safety and efficacy of RAGWITEK® as immunotherapy for the treatment of short ragweed pollen-induced allergic rhinitis, with or without conjunctivitis, confirmed by positive skin test or in vitro testing pollen specific IgE antibodies for short ragweed pollen, in pediatric subjects aged 5 to 17 years.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

The clinical development of the product MK-3641, a sublingual immunotherapy tablet, was conducted under two Phase 2/3 studies (Study P05233 and Study P05234, BLA 125478), where a total of approximately 1344 adults aged 18-50 years were administered the investigational product. The product was approved for use in the US and Canada under the trade name of RAGWITEK®, and in 9 European countries and Russia under the trade name of RAGWIZAX®, for the treatment of short ragweed pollen-induced AR, with or without conjunctivitis, in adults.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Please refer to section 2.4

2.6 Other Relevant Background Information

None.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission includes the final study report which is adequately organized and provides detailed statistical analyses and tables for review. The submitted materials were procured in compliance with the quality assurance (QA) and quality control (QC) oversight activities including data verification implemented at the investigation site or centrally by the sponsor under Good Clinical Practices.

3.2 Compliance With Good Clinical Practices

As per Applicant, the study was conducted in conformance with the ethical principles originating from the Declaration of Helsinki, GCP requirements, and applicable country and/or local statutes and regulations regarding Independent Ethics Committee review, informed consent and the protection of human participants in biomedical research.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

Deferred to clinical reviewer's review.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

The primary statistical review of the submission was performed by Dr. Mridul K. Chowdhury.

5.2 BLA Documents That Serve as the Basis for the Statistical Review

The current review is based on the final study report for study P008, entitled "*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*." The submitted report (P008MK3641) and the associated clinical final protocol are submitted to Module 5.3.5.1 for STN 125478/ 293.0, 293.1, 293.2, 293.3. This supplemental BLA also contained comprehensive statistical Tables, SAP, illustrative Figures, and datasets.

5.3 Table of Studies/Clinical Trials

A single study, protocol P008, is included in this submission.

5.4 Consultations

None.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study P008

Title of the Study: 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.

6.1.1 Objectives

The objective of study P008 was to assess the safety and efficacy of RAGWITEK® as immunotherapy for the treatment of short ragweed-induced rhinoconjunctivitis , with or without asthma, in pediatric subjects aged 5 to 17 years.

Primary Efficacy Objective:

To evaluate the efficacy of MK-3641sublingual 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).

Key Secondary Objectives:

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

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

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.

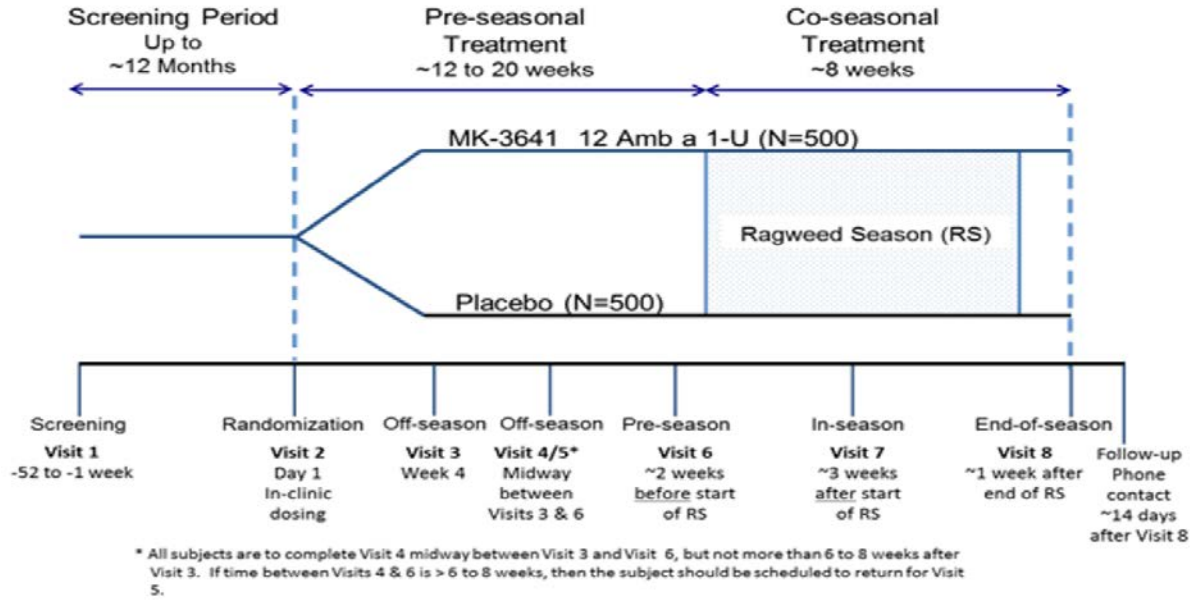
6.1.2 Design Overview

This was a randomized, placebo-controlled, parallel-group, multi-site, double-blind study to evaluate the efficacy and safety of MK-3641 in children aged 5 to 17 years with a history of ragweed pollen-induced allergic rhinitis/rhinoconjunctivitis, with or without asthma. About 1000 children ages 5 to 17 years were randomized in a 1:1 ratio to MK3641 (12 *Ambrosia artemisiifolia* major allergen 1 unit [Amb a 1-U]) or placebo once

daily for approximately 20 to 28 weeks. Randomization was stratified by age group (5 to 11 years or 12 to 17 years) and by baseline asthma status (yes or no). Three separate cohorts were recruited over consecutive ragweed seasons to complete the enrollment goal. This study comprised 3 periods per cohort: screening period (up to 12 months prior to randomization), pre-seasonal treatment period (approximately 12 to 20 weeks), and co-seasonal treatment period (approximately 8 weeks). This is graphically illustrated as well in Figure 1. There were 8 site visits, including the screening, randomization, off-season, pre-season, in-season, and end-of season visits. The first dose of MK-3641 was administered under supervision in the clinic and subsequent doses were self-administered at home.

To supplement the routine trial monitoring outlined in this protocol, an external Data Monitoring Committee (DMC) monitored the interim data from this trial. The voting members of the committee were external to the Sponsor. The members of the DMC were not involved with the trial in any other way (e.g., they were not trial investigators) and had no competing interests that could affect their roles with respect to the trial (Protocol 008-00, page 58).

Figure 1: Study Design



Source: CSR P008MK3641, page 29

6.1.3 Population

At the time of enrollment, the study population consisted of 4-17 (inclusive) year-old males and females with a ≥1-year clinical history of significant ragweed pollen-induced allergic rhinitis/rhinoconjunctivitis (with or without asthma), a positive skin prick test wheal response (≥5 mm larger than saline control), and specific immunoglobulin E reactivity to *Ambrosia artemisiifolia* of at least Class 2 (0.7 kU/L). Participants were to be ≥4 years old on the day of obtaining the informed consent and ≥5 years old at the randomization visit. Participants who were 17 years of age at screening and turned 18

years of age prior to randomization participated in this study. Participants were to have a forced expiratory volume in 1 second ≥80% of predicted at both the screening and randomization visits prior to randomization. Please also refer to clinical reviewer's report for further clinical details on inclusion/exclusion criteria for study participants.

6.1.4 Study Treatments or Agents Mandated by the Protocol

1. Experimental drug **MK-3641**, dose 12 Amb a 1-U, sublingual tablet, administered once daily for up to 28 weeks.
2. **Placebo**, dose not applicable, sublingual tablet, administered once daily for up to 28 weeks.

Restrictions for concomitant medications/therapy and as well the clinical judgment regarding rescue medications and doses are deferred to clinical reviewer. All concomitant/rescue medications use was planned for capture on electronic case report form.

The subject/parent/guardian, the investigator and Sponsor personnel or delegate(s) who were involved in the treatment administration or clinical evaluation of the subjects were unaware of the treatment group assignments.

6.1.6 Sites and Centers

This study was conducted at 103 study centers in 80 sites in 6 countries (Canada, Croatia, Hungary, Serbia, Ukraine, and the US)

6.1.7 Surveillance/Monitoring

The study was conducted by the investigators following ethical principles originating from the Declaration of Helsinki, ICH and GCP requirements, and applicable country and/or local statutes and regulations regarding IEC review, informed consent and the protection of human participants in biomedical research. According to the applicant, the quality assurance and quality control oversight activities were centrally implemented that were intrinsic to all clinical study-related activities, which included on-site monitoring inclusive of source data verification, medical monitoring of clinical study data (including monitoring protocol deviations), and relevant reviews of regulatory submission documents.

6.1.8 Endpoints and Criteria for Study Success

Primary endpoint:
Average TCS during the peak RS.

Study success criterion: 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.

Secondary endpoints:

Efficacy

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

Safety

- Percentage of participants reporting prespecified local application site reactions
- Percentage of participants reporting anaphylaxis and/or systemic allergic reactions
- Percentage of participants treated with epinephrine Describe in detail the prospective primary and secondary endpoint(s) of the study.

The TCS is the sum of the rhinoconjunctivitis daily symptom score (DSS) and the rhinoconjunctivitis daily medication score (DMS). These are based on allergy and asthma symptoms and rescue medications use the subject/parent/guardian recorded in electronic diary (e-diary) each day during the trial. By construct of the scores, the maximum DSS was 18 points if a subject experienced all six symptoms with an intensity of 3 (severe) for each symptom, and for DMS the maximum was 20 indicating high use of rescue medications.

6.1.9 Statistical Considerations & Statistical Analysis Plan

The following include a brief summary of the statistical considerations in the study:

- Treatment assignment
  - Type of assignment: Fixed randomization
  - Randomization ratio: Randomized in a ratio 1:1 to either MK-3641 or placebo.
  - Stratification variables: Age group (5 to 11 years, 12 to 17 years) and baseline asthma status (yes/no).
- Statistical hypotheses tested:
  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.
- Study success criteria prespecified: Significant reduction in average TCS in participants treated with MK-3641 compared to placebo, during the peak RS. The applicant specified that such reduction relative to placebo mean must be below -10% with 95% confidence.
- Significance level: two-sided α=0.05
- Statistical methods
  - Methods:
    For TCS during the peak RS:
    ANOVA for observed data (primary efficacy analysis, FAS),
    ANOVA for observed data (supportive analysis, PP)
    ANOVA for multiple imputation data (sensitivity analysis, FAS).
    For Key secondary endpoints:
    TCS during the entire RS, ANOVA for observed data, FAS

DSS during the peak RS, ANOVA, for observed data, FAS
DMS during the peak RS, log normal (zero-inflated), observed, data, FAS.

- The applicant used zero-inflated log normal for the presence of zero values in DMS during the peak RS. The reviewer expanded this analysis to DMS data of the entire RS period, FAS, to facilitate comparison of DMS results between the peak RS period and the entire RS period. Inclusion of covariates: treatment, baseline asthma status, age group, pollen season, and pollen region.
- Sample size. A total of approximately 1000 subjects were planned for randomization in a 1:1 ratio to either MK-3641 or placebo. Assuming a 15% dropout rate, this will give approximately 425 evaluable subjects per arm. Planned power = 90% (2-sided $\alpha = 0.05$) to have the upper bound of the 95% CI for relative difference below -10%. The calculations were 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 were based on previous adult studies for MK-3641 (AIT ragweed) and pediatric trial for MK-7243 (AIT grass).

- Interim analyses planned: none were planned for efficacy
- Definitions of analysis populations. Please refer to section 6.1.10
- Multiplicity
  - Due to multiple secondary endpoints.
    To control family-wise Type I error, a fixed sequence procedure was planned to control multiplicity. The primary and key secondary 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.
- Subgroup analyses planned
  - By gender, age, race/ethnicity, site, baseline asthma status.
- Missing data: Multiple imputation technique was used for missing TCS data. The imputed data when analyzed by the same ANOVA model as used for the observed data in primary analysis showed similar results on treatment difference and treatment difference relative to placebo mean, providing sensitivity analysis.
- Analysis plan for safety: Safety is assessed by descriptive statistics, i.e., proportions of subjects experiencing different adverse events in treatment participants.
- Stopping rules: None for efficacy. Safety was monitored by DMC.

- Study/data monitoring planned by independent personnel: To supplement the routine trial monitoring, an external Data Monitoring Committee (DMC) was planned to monitor the interim data.
- Dropouts and/or Discontinuations: The applicant considered 15% attrition rate based on earlier studies it had conducted for its licensed product. The planned, powered sample size was already adjusted for this attrition. Also, the primary efficacy analysis was based on all observed data and no missing values.
- Blinding techniques: A double-blind/masking technique was planned, where MK-3641 and placebo were packaged identically to maintain that blind/masking. The subject/parent/guardian, the investigator and sponsor personnel or delegate(s) who were involved in the treatment administration or clinical evaluation of the subjects were unaware of the group assignments. In the case of emergency needs (by the investigator) to identify the drug or for serious adverse experiences, contact was made to the emergency unblinding call center.

Statistical analyses

The primary population for efficacy analyses was the Full Analysis Data Set (FAS), which consisted of all randomized and treated participants. The primary efficacy endpoint was the average TCS during the peak ragweed season.

The applicant performed the following analyses. The analysis of variance (ANOVA) model for TCS, with fixed effects of treatment group, baseline asthma status (yes or no), and age group (5 to 11 years or 12 to 17 years). The ANOVA provided 2-sided 95% CI of the treatment difference in adjusted means. Also computed was the treatment difference in adjusted means relative to the adjusted mean of the placebo group, along with the corresponding 2-sided 95% CI obtained by using the bootstrap method. For primary efficacy analysis, the missing data were not imputed. The secondary efficacy analyses followed a similar approach. The per-protocol (PP) analysis was the planned supportive analysis for the primary efficacy endpoint TCS. In addition, the multiple imputation was used for handing missing data in TCS, with sensitivity analysis carried out by using the same ANOVA model used in the primary analysis.

Safety analyses were performed in the All Subjects as Treated population, which consisted of all randomized and treated participants. Participants were included in the treatment group corresponding to the study intervention they actually received during the study. Safety data collected during the clinical study were summarized by using participants' frequencies of experiencing adverse events.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Analysis populations

Full analysis set (FAS) population comprised participants who were treated according to the treatment group to which he/she was randomized: 512 in MK-3641, 510 in Placebo, for primary efficacy analysis.

Per-Protocol (PP) population (PPP) excluded from the FAS, participants who met pre-specified protocol deviations: 367 in MK-3641, 360 in Placebo. The PPP provided supporting analysis.

All-subjects-as-treated (ASaT) population which consisted of all randomized and treated participants: 512 in MK-3641, 510 in Placebo. The ASaT was used for safety analyses.

Compliance with study intervention was high across the intervention groups, with the majority (87.8%) of participants being > 90% compliant. The percent compliance was measured by the quantity, (Number of Days on Therapy) / (Number of Days Should Be on Treatment Period) × 100%, for which the mean±SD was 95.7±7.0 in the MK-3641 arm and 96.1±6.1 in the Placebo arm.

6.1.10.1.1 Demographics

The distributions of the demographic and baseline characteristics were similar between the MK-3641 and the Placebo groups, as expected under randomization. Below is a summary of the overall distributions for the baseline characteristics:

Overall Mean (SD) Age at randomization: 12.1 (3.1) years (range: 5 to 18 years).
Age categories: 410 (40.1%) with age <12 years, 612 (59.9%) with age ≥12 years.
Note: according to applicant, age was based on age at randomization using actual month and year of birth and a data convention of 15 as day of birth; therefore, 9 participants were reported as 18 years of age.
Gender: 643 (62.9%) male, 379 (37.1%) female.
Ethnicity: 973 (95.2%) not Hispanic or Latino, 36 (3.5%) Hispanic or Latino, 9 (0.9%) not reported, 4 (0.4%) unknown.
Race: 950 (93.0%) white, 32 (3.1%) black or African-American, 24 (2.3%) multiple, 10 (1.0%) Asian, 5 (0.5%) Native Hawaiian or other Pacific Islander, 1 (0.1%) American Indian or Alaska Native.
Allergen Sensitization Type: 228 (22.3%) Ragweed only, 794 (77.7%) Ragweed + Others.
Baseline Asthma Status: 436 (42.7%) Yes, 586 (57.3%) No.

6.1.10.1.3 Subject Disposition

A total of 1942 participants were screened, 1025 were randomized, and 1022 received at least one dose of study intervention. The majority of randomized participants (93.2%) received at least 1 dose of study intervention and completed the study (Table 1).

- In the MK-3641 group, 513 participants were randomized, 512 were treated, 461 (90.0%) completed, and 51 (10.0%) discontinued from the study.
- In the placebo group, 512 participants were randomized, 510 were treated, 491 (96.3%) completed, and 19 (3.7%) discontinued from the study.

Table 1: Disposition of subjects, FAS Population

	MK-3641	MK-3641	Placebo	Placebo	Total	Total
	n	(%)	n	(%)	n	(%)
Subjects in population:	512	(100)	510	(100)	1,022	(100)
Completed	461	(90.0)	491	(96.3)	952	(93.2)
Discontinued	51	(10.0)	19	(3.7)	70	(6.8)
Adverse Event	20	(3.9)	5	(1.0)	25	(2.4)
Lost to follow-up	5	(1.0)	4	(0.8)	9	(0.9)
Non-compliance with Study Drug	5	(1.0)	1	(0.2)	6	(0.6)
Protocol Violation	2	(0.4)	1	(0.2)	3	(0.3)
Withdrawal by Parent/Guardian	9	(1.8)	4	(0.8)	13	(1.3)
Withdrawn by subject	10	(2.0)	4	(0.8)	14	(1.4)
Each subject is counted once for Status for Trial based on the latest corresponding disposition record						

Source. CSR P008MK3641, page 84.

• Major/minor protocol deviations: The most common were the following. Prohibited medications, problems with signing of informed consent form (risk language inadequate, lack of ability of understanding the study purpose, and subject's legal representative not consenting), safety monitoring and study intervention (safety events not reported in time, overdose, incorrect study treatment, medication compliance inadequate, rescue medication not dispensed), trial procedures (no safety laboratory tests and vital signs check conducted at screening).

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint:

Rhinoconjunctivitis Daily Symptom Score During the Peak Ragweed Season

Primary efficacy analyses were based on the study periods of peak ragweed season (RS). During peak RS, the overall mean ± SD (N) pollen counts (grains/mm^3) were 209.1±173.48(319) in 2016, 133.5± 100.27(356) in 2017 and 213.6±163.08(346) in 2018, combined for all regions. From Table 2, the average TCS (SD) scores during peak RS were 4.67 (6.07) and 7.34 (7.37) in the MK-3641 and placebo groups, respectively. The adjusted overall treatment difference in TCS scores, MK-3641 – Placebo, which was -2.73 (95% CI: -3.45, -2.00), was statistically significant based on the ANOVA model. This scores difference when expressed relative to Placebo mean estimate, was -38.3% (95%CI: -46.0, -29.7) and showed statistically significant reduction.

Table 2: Primary Endpoint: Analysis of Average TCS (ANOVA), Peak Ragweed Season, FAS.

Endpoint	MK-3641 (N) Mean Score ± SD	Placebo (N) Mean Score ± SD	Treatment difference† (MK-3641 – Placebo) (95% CI)	Treatment Difference relative to Placebo mean (95% CI)‡
TCS in Peak Season	(460) 4.67± 6.07	(487) 7.34±7.37	-2.73 (-3.45, -2.00)	-38.3% (-46.0, -29.7)

Notes:
TCS = total combined score; N = number of subjects included in the analyses; SD = standard deviation; CI=confidence interval; LS Mean = least square mean;
† TCS were analyzed using ANOVA model, which included fixed effects of treatment, baseline asthma status (yes, no), age group (<12 years, ≥ 12 years), pollen season, and pollen region nested within pollen season. The estimated model provided LS means and their difference between arms.
‡ Treatment difference relative to Placebo was estimated as (LS Mean of MK-3641 - LS Mean of Placebo) / (LS Mean of Placebo) * 100%, where LS Mean was based on the ANOVA model. Confidence interval was calculated by the bootstrap method using 10,000 iterations.

No missing data was imputed

Source. Adapted from CSR P008MK3641, page 49.

The results from the supportive analysis based on the PP population were consistent with the above results from the FAS population. With the overall mean ± SD(N) of TCS during peak RS being 4.77±6.25 (415) in MK-3641 and 7.62±7.56(439) in Placebo, the adjusted, overall treatment difference MK-3641 – Placebo was -2.82 (95% CI: -3.45, -2.00), and this difference when considered relative to Placebo mean was -39.11% (95% CI: -46.02, -29.66); using all along the ANOVA method as used in FAS.

Multiple imputation technique was used for missing TCS data. The technique combines multiple estimates following Rubin's method. Missing data from both treatment groups were imputed using the sample distribution of TCS observed from the placebo group. Based on the same ANOVA approach as above and FAS population, the treatment difference in TCS between MK-3641 and Placebo was -2.31 (95% CI: -3.04, -1.58), and the treatment difference relative to placebo mean was -32.2% (95% CI: -39.1, -23.7). The multiple imputation-based results on treatment difference and treatment difference relative to placebo were comparable with that obtained from all observed data in the primary analysis above.

Overall, the MK-3641 treatment demonstrated statistically significant reduction in TCS scores compared to Placebo, during the peak ragweed season.

6.1.11.2.1 Analyses of Secondary Endpoints

Similar reductions in the MK-3641 treatment group were demonstrated by the study's secondary endpoints as well (Table 3). Average TCS during the entire RS, average rhinoconjunctivitis DSS during the peak RS, and average rhinoconjunctivitis DMS during the peak RS showed significantly lower scores in the MK-3641 group compared to the

placebo group (columns 4 and5 of Table 3). Additionally, not shown in the table, significant reduction in scores in the MK-3641 group compared to placebo was observed for rhinoconjunctivitis DSS during the entire RS and for DMS during the same period. These reductions relative to placebo were -30.38% (95% CI: -38.62, -20.72) for DSS (Table 14.2-16, P008) and -43.56% (95% CI: -58.20, -28.91) for DMS (reviewer's analysis).

Table 3: Key Secondary Endpoints: Total Combined Scores (TCS), Rhinoconjunctivitis Daily Symptom Scores (DSS) and Rhinoconjunctivitis Daily Medication Scores (DMS), During the Ragweed Season, FAS Population

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Endpoint	MK-3641 (N) Mean Score ± SD	Placebo (N) Mean Score ± SD	Treatment difference (MK-3641 – Placebo) (95% CI)	Treatment Difference relative to Placebo mean (95% CI) †††
Column 1	Column 2	Column 3	Column 4	Column 5
TCS* Entire Season	(466) 4.01 ± 4.89	(491) 5.80 ± 5.65	-1.86 (-2.46, -1.27) †	-32.4% (-40.7, -23.3)
DSS** Peak Season	(468) 2.72 ±3.20	(494) 4.12 ±3.79	-1.40 (-1.81, -0.99) †	-35.4 % (-43.2, -26.1)
DMS‡ Peak Season	(460) 1.91 ± 3.6	(487) 3.20 ± 4.42	-1.84 (-2.60, -1.08) ††	-47.74% (-59.84, -32.46)

Notes.
CI = confidence interval; N = number of subjects included in the analyses; SD = standard deviation;
† LS Mean: TCS and Rhinoconjunctivitis DSS were analyzed using ANOVA model. †† Rhinoconjunctivitis DMS was analyzed using a zero-inflated log-normal model with maximum likelihood (ML) criteria. In reviewer's analyses, zero values of RDMS were present in 41.5% and 57.3% of subjects, respectively, in MK-3641 and Placebo arms.
††† Calculated by the bootstrap method using 10,000 iterations.
Source. Adapted from CSR P008MK3641, *page 52, **page 53, ‡page 54.

6.1.11.2.2 Analysis for other endpoints

The applicant provided analysis for the percentage of subjects free of allergic rhinoconjunctivitis symptoms during the peak ragweed pollen season, which was defined as the proportion of subjects with a total combined score (daily symptom score + daily medication score) of 0 throughout the peak ragweed pollen season. The information on the symptoms and medication use was available from daily e-diary of each subject. Based on the FAS population, the proportion stated above was reported to be 13.89% in the Ragweed SLIT-tablet arm (N=460) and 6.76% in the placebo arm (N=487), resulting in an odds ratio (OR) of 2.23 (95% CI: 1.47, 3.37; p=0.0002). This reported OR was an adjusted one derived from logistic regression analysis with covariates: treatment, baseline asthma status (yes, no), age group (5-11 years, 12-17 years), pollen season and pollen region. In this reviewer's calculations, the proportion of subjects free of symptoms were 16.30% (75/460) and 8.62% (42/487) in the two respective arms as above, with an unadjusted OR=2.06 (95% CI: 1.38, 3.08). Overall, the odds of being symptoms free (without using symptom-relieving medication) during the peak ragweed season for subjects treated with ragweed SLIT-tablet was 2.23 times that of subjects who received placebo. This result seemed consistent with earlier result in Table 2 that showed significant reduction in TCS during peak RS, in MK-3641 subjects compared to placebo.

6.1.11.3 Subpopulation Analyses

The baseline asthma status (yes/no) comprised a dominant subgroup for the ragweed induced allergy study. Among participants with asthma at baseline, the treatment difference between MK-3641 and placebo in terms of TCS during peak RS was -2.87 (95% CI: -3.87, -1.86), and relative to placebo the difference was -43.61% (95% CI: -54.86, -31.4). These respective figures among participants with no asthma at baseline were -2.61 (95% CI: -3.65, -1.58) and -33.81% (95% CI: -43.83, -21.67). Thus, the participants treated with MK-3641 had significant improvement in TCS regardless of baseline asthma status. Significant improvements in TCS regardless of the age (<12 yrs, ≥12 yrs), gender and race categories were also reported (Table 4). For instance, in the age subgroup of <12 yrs, the respective improvements were -2.38 (95% CI: -3.63, -1.12) and -34.05% (95% CI: -47.62, -16.11). In the age ≥12 yrs subgroup, these were -2.92 (95% CI: -3.8, -2.03) and -42.23% (95% CI: -51.75, -31.41), respectively.

Table 4: Average TCS during Peak Ragweed Season and Treatment Differences By Demographic Subgroups, Observed Data Only, Full Analysis Set.

Demographic subgroups	MK-3641	Placebo	Treatment Difference† from Placebo	Treatment Difference relative to Placebo
	N, mean ± SD	N, mean ± SD	(95% CI)	(95% CI)
Age <12 yrs	195, 5.24±6.91	193, 7.73±8.00	-2.38 (-3.63, -1.12)	-34.05% (-47.62, -16.11)
Age ≥12 yrs	265, 4.25±5.34	294, 7.08±6.92	-2.92 (-3.80, -2.03)	-42.23% (-51.75, -31.41)
Male	293, 4.55±6.22	309, 7.48±7.65	-2.89 (-3.78, -1.99)	-40.94% (-50.29, -30.19)
Female	167, 4.88±5.80	178, 7.11±6.87	-2.50 (-3.73, -1.27)	-35.57% (-49.00, -21.13)
Caucasian	426, 4.86±6.21	456, 7.57±7.48	-2.80 (-3.57, -2.04)	-38.65% (-46.94, -30.03)
Non-Caucasian	34, 2.22±3.06	31, 3.90±4.19	-1.02 (-3.19, 1.16)	-31.15% (-82.67, 58.10)

†TCS were analyzed using ANOVA model, which included fixed effects of treatment, baseline-asthma status (yes, no), age group (<12 years, ≥ 12 years), pollen season, and pollen region nested within pollen season. The estimated model provided LS means and their difference between arms.

Source: Adapted from CSR P008MK3641, page 204-205.

6.1.11.4 Dropouts and/or Discontinuations

While the overall majority of randomized subjects (93.2%) completed the study (Table 1), 6.8% subjects reported dropouts/discontinuations, with primary reasons attributed to AEs and withdrawal by subjects. The withdrawal happened with or without parental or guardian's influence. The overall discontinuations were more frequent in the MK-3641 group (51/512, 10.0%) compared to the placebo group (19/510, 3.7%). Since the dropout/discontinuation rate was low, the impact of missingness on the study results/conclusion is expected to be minimal.

6.1.11.5 Exploratory and Post Hoc Analyses

None.

6.1.12 Safety Analyses

Overview of Adverse Events (AE)

Listing of AEs by participants followed MedDRA version 21.1. The analysis population was All-Subjects-as-Treated population (ref. 6.1.10).

A summary of all AEs is provided in Table 5. Overall 74.6% of participants reported at least one AE. This proportion was 81.9% in the MK-3641 group and 67.2% in the placebo group. In these two respective groups, the proportions reporting drug-related AEs were 65.9% and 31.4%. SAEs occurred to 1.4% in MK-3641 participants compared to 1.8% in the placebo group. Discontinuation due to an AE or drug-related AE appeared more frequent with the MK-3641 group. Such discontinuation was reported from a minimum of 3.3% participants in MK-3641 compared to 1.4% in placebo. No deaths were reported in the study. Most participants had non-serious AEs, reported by 81.9% in the MK-3641 group and 66.8% in the placebo group.

Table 5: Adverse Event Summary, All Subjects as Treated Population

	MK-3641	MK-3641	Placebo	Placebo	Total	Total
	n	(%)	n	(%)	n	(%)
Subjects in population	513	-	509	-	1,022	-
with one or more adverse events	420	(81.9)	342	(67.2)	762	(74.6)
with no adverse event	93	(18.1)	167	(32.8)	260	(25.4)
with drug-related† adverse events	338	(65.9)	160	(31.4)	498	(48.7)
with non-serious adverse events	420	(81.9)	340	(66.8)	760	(74.4)
with serious adverse events	7	(1.4)	9	(1.8)	16	(1.6)
with serious drug-related adverse events§	3	(0.6)	1	(0.2)	4	(0.4)
with dose modification‡ due to an adverse event	55	(10.7)	34	(6.7)	89	(8.7)
who died	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	20	(3.9)	5	(1.0)	25	(2.4)

Note.
† Determined by the investigator to be related to the drug.
‡ Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
§ One serious drug-related adverse event (oral pruritus in the MK3641 Active group) was associated with an overdose; this AE did not meet ICH criteria for seriousness.

Source: Adapted from CSR P008MK3641, page 58

Most Frequently Reported Adverse Events

Overall, AEs were reported in higher proportion of participants in the MK-3641 group compared to the placebo group (81.9 % vs 67.2%, Table 5. The most frequently reported adverse events from the MK-3641 group were Throat irritation (49.5%), Oral pruritus (48.1%), and Ear pruritus (34.5%) (Table 6). These were followed by Pharyngeal oedema (11.3%), Glossodynia (12.5%), Lip swelling (12.9%), Nausea (13.6%), and Oral pain

(12.5%), among others. The proportions reporting these individual AEs in the placebo group were lower compared to participants treated with MK-3641.

Table 6: Subjects with Adverse Events (Incidence ≥ 2% in One or More Treatment Groups), All Subjects as Treated.

	MK-3641	MK-3641	Placebo	Placebo
	n	(%)	n	(%)
Subjects in population	513	-	509	-
Ear and labyrinth disorders	184	(35.9)	40	(7.9)
Ear pruritus	177	(34.5)	35	(6.9)
Respiratory, thoracic and mediastinal disorders	315	(61.4)	191	(37.5)
Throat irritation	254	(49.5)	98	(19.3)
Oropharyngeal pain	25	(4.9)	29	(5.7)
Asthma	15	(2.9)	25	(4.9)
Cough	30	(5.8)	30	(5.9)
Pharyngeal oedema	58	(11.3)	8	(1.6)
Sneezing	16	(3.10	16	(3.1)
Gastrointestinal disorders	317	(61.8)	155	(30.5)
Abdominal pain	16	(3.1)	12	(2.4)
Abdominal pain upper	54	(10.5)	30	(5.9)
Aphthous ulcer	15	(2.9)	7	(1.4)
Diarrhoea	26	(5.1)	21	(4.1)
Enlarged uvula	33	(6.4)	2	(0.4)
Glossitis	24	(4.7)	7	(1.4)
Glossodynia	64	(12.5)	13	(2.6)
Lip oedema	13	(2.5)	0	(0.0)
Lip pruritus	17	(3.3)	1	(0.2)
Lip swelling	66	(12.9)	7	(1.4)
Mouth swelling	18	(3.5)	0	(0.0)
Nausea	70	(13.6)	43	(8.4)
Oral pain	64	(12.5)	16	(3.1)
Oral pruritus	247	(48.1)	62	(12.2)
Stomatitis	34	(6.6)	6	(1.2)
Swollen tongue	56	(10.9)	4	(0.8)
Tongue pruritus	23	(4.5)	3	(0.6)
Tongue ulceration	12	(2.3)	5	(1.0)
Vomiting	22	(4.3)	15	(2.9)
General disorders and administration site conditions	47	(9.2)	31	(6.1)
Pyrexia	29	(5.7)	20	(3.9)
Infections and infestations	131	(25.5)	129	(25.3)
Upper respiratory tract infection	10	(1.9)	15	(2.9)
Viral infection	7	(1.4)	10	(2.0)
Nasopharyngitis	38	(7.4)	36	(7.1)
Nervous system disorders	63	(12.3)	65	(12.8)
Dysgeusia	21	(4.1)	12	(2.4)
Headache	45	(8.8)	49	(9.6)
Skin and subcutaneous tissue disorders	38	(7.4)	26	(5.1)

Source: Adapted from CSR P008MK3641, page 59-60

Pre-specified Local Application Site Reactions

More participants in the MK-3641 group reported pre-specified local application site reactions (64.52%) compared to the placebo group (26.92%). The pre-specified local application site reactions include 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. Most of the local application site reactions were reported as mild in intensity by the investigator and no pre-specified local application site reactions were reported as an SAE.

With regard to asthma, 2.9% of MK-3641 subjects reported this AE compared to 4.9% in Placebo, and most of these AEs were concluded by investigator as mild or moderate in intensity.

Among participants with Asthma at baseline, the MK-3641 group reported AEs more often (80.8%) than the placebo group (72.4%). In participants without Asthma at baseline, these proportions were respectively 82.7% and 63.4%. In general, the AE profile appeared similar in participants with and without asthma at baseline.

Events of Clinical Interest

The events of clinical interest (ECIs) were infrequent and reported in <2% participants, with similar participant proportions between arms. One or more ECIs were reported by 10 (1.9%) participants treated by MK-3641, and in the placebo group 7 (1.4%) participants reported the events. The most frequently reported ECI was overdose (defined as >1 tablet/day), reported by 6 (1.2%) and 5 (1.0%) participants in MK-3641 and placebo, respectively. The ECI, anaphylactic reactions, anaphylaxis and/or systemic allergic reactions were reported from 4 (<1%) participants, with 3 being from MK-3641 arm (N=513) and 1 from placebo group (N=509). Based on the comparison [0.58% (3/513) vs 0.20% (1/509)] the difference (in %) of 0.39 (95% CI: -0.57, 1.53), p=0.320] between arms was not statistically significant. Similar balance in proportions (<1%) was also reported for 2 AEs treated with epinephrine, one being from each arm.

6.1.12.1 Methods

All randomized and treated subjects comprised the analysis population for safety analysis (ref. section 6.1.10), and descriptive statistics including proportions reporting AEs or local application site reactions were used.

6.1.12.3 Deaths

No deaths were reported.

6.1.12.4 Nonfatal Serious Adverse Events

Serious adverse events (SAEs) were reported in 7 (1.4%) of subjects in the MK-3641 group and 9 (1.8%) of the placebo recipients. Of these, 3 (0.6%) MK-3641 recipients and 1 (0.2%) recipient reported the drug-related SAEs. Please defer to the clinical review for additional information.

6.1.12.5 Adverse Events of Special Interest (AESI)

Please refer to medical officer's review. For events of clinical interest (ECI), please see under section 6.1.12.

7. INTEGRATED OVERVIEW OF EFFICACY

The trial comprised one single study P008 (section 6.1). Integration of several studies is not applicable. Please see sections 6.1.11 for efficacy results.

8. INTEGRATED OVERVIEW OF SAFETY

The trial comprised one single study P008 (section 6.1). Integration of several studies is not applicable. Please see sections 6.1.12 for safety results.

9. ADDITIONAL STATISTICAL ISSUES

None

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Efficacy Conclusions

The analyses showed that treatment with MK-3641 significantly lowered the average TCS during the peak RS in subjects with ragweed-induced allergic rhinitis/rhinoconjunctivitis, compared with placebo, meeting the primary objective of efficacy.

The analyses also showed that MK-3641, compared with placebo, significantly lowered the average TCS during the entire RS, average rhinoconjunctivitis DSS during the peak RS, and average rhinoconjunctivitis DMS during the peak RS.

Safety Conclusion

Overall, AEs were reported in a higher proportion of participants treated with MK-3641, compared to placebo (81.9% vs 67.2%). Most participants had non-serious AEs, reported by 81.9% in the MK-3641 group and 66.8% in the placebo group. The MK-3641 treatment seemed well tolerated as only 3.9% discontinued due to an AE. Most of the

local application site reactions reported were considered mild in intensity by the investigator and no pre-specified local application site reactions were reported as an SAE. No deaths were reported. It appeared that a general safety signal in the MK-3641 participants was not discerned from the analyses, but ultimately it is a clinical call.

10.2 Conclusions and Recommendations

Overall, the study provided results supporting that the MK-3641 ragweed sublingual immunotherapy tablet is effective in children ages 5 through 17 years with ragweed-induced allergic rhinitis/rhinoconjunctivitis. A general concern for safety was not discerned from the data but I defer to the clinical reviewer's decision. From the statistical perspective, I recommend approval of the application.