Application Type	BLA
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CBER Received Date	December 22, 2021
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Division / Office	DVRPA/OVRR
Committee Chair	Colleen Sweeney, RN, MS.
Clinical Reviewer(s)	Anubha Tripathi, MD
Project Manager	Taruna Khurana, PhD
Priority Review	No
Reviewer Name(s)	Zhong Gao, Ph.D. Mathematical Statistician Therapeutics Evaluation Branch 2, DB/OBPV
Supervisory Concurrence	Lihan Yan, Ph.D. Acting Chief, Therapeutics Evaluation Branch 2, DB/OBPV
Applicant	ALK Abello A/S Denmark
Established Name	House Dust Mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) Allergen Extract
(Proposed) Trade Name	ODACTRA
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	Tablet
Dosage Form(s) and Route(s) of Administration	For sublingual use only
Dosing Regimen	12 SQ-HDM; One tablet daily
Indication(s) and Intended Population(s)	Immunotherapy for house dust mite induced allergic rhinitis, with or without conjunctivitis, in adults 12 through 65 years of age

Table of Contents

1. Executive Summary 3

2. Clinical and Regulatory Background 3

2.1 Disease or Health-Related Condition(s) Studied 3
2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s) 3
2.4 Previous Human Experience with the Product (Including Foreign Experience) 3
2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission 4
2.6 Other Relevant Background Information 4

3. Submission Quality and Good Clinical Practices 4

3.1 Submission Quality and Completeness 4
3.2 Compliance with Good Clinical Practices and Data Integrity 4

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines 4

5. Sources of Clinical Data and Other Information Considered in the Review 4

5.1 Review Strategy 4
5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review 4

6. Discussion of Individual Studies/Clinical Trials 5

6.1 Study MT-18 5
6.1.1 Objective 5
6.1.2 Design Overview 5
6.1.3 Population 5
6.1.4 Study Treatments or Agents Mandated by the Protocol 5
6.1.6 Sites and Centers 5
6.1.7 Surveillance/Monitoring 5
6.1.8 Endpoints 5
6.1.9 Statistical Considerations & Statistical Analysis Plan 5
6.1.10 Study Population and Disposition 6
6.1.11 Efficacy Analyses 6
6.1.12 Safety Analyses 6

7. Integrated Overview of Efficacy 7

8. Integrated Overview of Safety 7

9. Additional Statistical Issues 7

10. Conclusions 7

10.1 Statistical Issues and Collective Evidence 7
10.2 Conclusions and Recommendations 7

1. Executive Summary

ALK Abello A/S Denmark submitted a supplement to Biological License Application (sBLA) to support extension of the current age indication (18-65 years) to adolescents (12-17 years) for ODACTRA, an immunotherapy for house dust mite induced allergic rhinitis, with or without conjunctivitis. CBER determined that additional efficacy data in adolescents 12-17 years of age will not be required for this sBLA because supportive adolescent efficacy data was already submitted to the original BLA (STN 125592). Hence, the review is focused on a Phase-3 single-arm safety study MT-18. The primary endpoint analysis showed that 88.1% of subjects reported at least 1 treatment-emergent adverse event (TEAE). The secondary endpoint analysis showed that 85.4% of subjects reported at least 1 solicited TEAE and 86.2% of subjects reported at least 1 investigational medical product (IMP)-related adverse event (AE). No death or treatment emergent serious adverse event (SAE) were reported in the study.

Since there was no control arm in the study, comparative analysis is not possible to inform safety signal detection. All analyses were descriptive in nature. My review focuses on the accuracy of the pre-defined primary and secondary endpoint analyses and appropriateness of the data presentation. Since the additional safety data were collected in non-US countries, I defer to the clinical reviewer on clinical interpretation of the safety evidence and generalizability to US population.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

House dust mite allergy

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Currently, there are no sublingual immunotherapy (SLIT) treatment options for HDM-induced allergic rhinitis for adolescents in the US

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

ODACTRA was approved for the treatment of house dust mite (HDM)-induced allergic rhinitis, with or without conjunctivitis, in adults 18 through 65 years of age in US in 2017.

In other regions, the indication for the HDM SLIT-tablet includes adolescents as well as adults, and the HDM SLIT-tablet is now approved for adolescents (12 to 17 years of age) in 35 countries in Europe and Asia, as well as in Australia. In addition, a supplemental application for the adolescent indication submitted in Canada is under review and will be supplemented with the MT-18 trial data. In Japan, the HDM SLIT-tablet (6 SQ-HDM dose) is approved for HDM-induced AR for all age groups (no lower age limit).

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

During pre-submission discussion with the applicant, it was concluded that CBER will not require additional efficacy data for a supplemental BLA submission in adolescents 12-17 years of age because supportive adolescent efficacy data was already submitted to the original BLA (STN 125592) and it is not expected that adolescents would biologically differ from adults in treatment response to ODACTRA.

2.6 Other Relevant Background Information

N/A

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The submission is adequately organized for conducting a complete statistical review.

3.2 Compliance with Good Clinical Practices and Data Integrity

The submission presented no data integrity issues.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

N/A

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

This review focuses on Study MT-18 which is a single-arm, open-label trial to evaluate safety of the house dust mite (HDM) sublingual allergy immunotherapy (SLIT) tablet in adolescent subjects (12-17 years of age) with HDM allergic rhinitis/rhinoconjunctivitis (AR/C) with or without asthma.

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

- STN 125592/157.0 Module 2.5. Clinical Overview
- STN 125592/157.6 Module 2.5. Clinical Overview – Addendum
- STN 125592/157.6 Module 2.7.4. Summary of Clinical Safety - Addendum
- STN 125592/157.6 Module 5.3.5.2. Study MT-18 Clinical Study Report

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study MT-18

6.1.1 Objective

The objective of the trial was to evaluate safety and tolerability of the HDM SLIT - tablet in adolescents (12-17 years of age) with 28 days of treatment.

6.1.2 Design Overview

This was a phase III, single-armed, open-label, multi-national, multi-site clinical trial conducted in Europe. The trial investigated safety and tolerability of the HDM SLIT - tablet over 28 days in adolescents (12-17 years of age) with HDM allergic rhinitis/rhinoconjunctivitis with or without asthma.

6.1.3 Population

Approximately 250 male and female adolescent subjects (12-17 years of age) with HDM allergic rhinitis/rhinoconjunctivitis with or without asthma

6.1.4 Study Treatments or Agents Mandated by the Protocol

HDM SLIT – tablet (ODACTRA)

6.1.6 Sites and Centers

A total of 28 centers in Czech Republic, Slovakia, and Germany

6.1.7 Surveillance/Monitoring

Please refer to the clinical review.

6.1.8 Endpoints

- Primary Endpoint: at least 1 treatment-emergent adverse event (TEAE)
- Secondary Endpoints:
  - At least 1 solicited TEAE
  - At least 1 Investigational Medicinal Product (IMP) related AE
  - At least 1 treatment-emergent SAE

6.1.9 Statistical Considerations & Statistical Analysis Plan

- Definitions of analysis populations
  - Total analysis set: all subjects who entered the trial including screening failures. The total population was used for listing reasons for screening failures and AEs before enrolment.
  - Safety analysis set: all subjects who received at least one dose of IMP. This analysis set was used for all other tables and listings.

- Statistical Methods for Safety Analyses

The evaluation of safety results was based on TEAEs of the safety set. TEAEs were defined as AEs with start date on or after the time of first IMP administration and no later than 7 days after last IMP administration. No statistical hypothesis testing was performed. Statistical methods for safety analysis are mainly descriptive.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed
6.1.10.1.1 Demographics
The study population had median age of 14.0 years (min – max: 12-17), 60.1% male subjects, 99.6% White, and 90.5% Non-Hispanic.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
N/A

6.1.10.1.3 Subject Disposition
257 subjects were screened (1 of these was later re-screened), of which 5 were screen failures. 253 subjects were allocated to treatment, and 251 (99.2%) completed the study.

6.1.11 Efficacy Analyses

N/A

6.1.12 Safety Analyses

On average, subjects were exposed for a duration of 28.2 days. 98% of subjects were exposed for at least 28 days. The primary endpoint analysis showed that 88.1% of subjects reported at least 1 TEAE. The secondary endpoint analysis showed that 85.4% of subjects reported at least 1 solicited TEAE and 86.2% of subjects reported at least 1 IMP-related AE (Table 1). There were no reports of treatment emergent SAEs in MT-18.

Table 1. Summary of categorical endpoints (safety set)

		12 SQ-HDM (N = 253)		
Type of Endpoint	Endpoint Description	n	%	90% CL (%)
Primary	At least 1 TEAE	223	88.1%	[84.3; 91.3]
Secondary	At least 1 solicited TEAE	216	85.4%	[81.2; 88.9]
Secondary	At least 1 IMP-related AE	218	86.2%	[82.1; 89.6]
Secondary	At least 1 treatment-emergent SAE	0	0.0%	[0.00; 1.18]

Source: adapted from Table 18 in Study MT-18 Clinical Study Report

Reviewer Comment: *My analysis showed similar results.*

6.1.12.1 Methods
Please refer to section 6.1.9.

6.1.12.3 Deaths
No deaths occurred during the study.

6.1.12.4 Nonfatal Serious Adverse Events
No SAEs were reported in the trial.

6.1.12.5 Adverse Events of Special Interest (AESI)
NA

6.1.12.6 Clinical Test Results
N/A

6.1.12.7 Dropouts and/or Discontinuations
Two subjects discontinued treatment due to TEAE.

7. INTEGRATED OVERVIEW OF EFFICACY

8. INTEGRATED OVERVIEW OF SAFETY

9. ADDITIONAL STATISTICAL ISSUES

N/A

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

The MT-18 study was conducted to evaluate safety of ODACTRA in adolescents (12−17 years). The primary endpoint analysis showed that 88.1% of subjects reported at least 1 TEAE. The secondary endpoint analysis showed that 85.4% of subjects reported at least 1 solicited TEAE and 86.2% of subjects reported at least 1 IMP-related AE. There were no reports of treatment emergent SAEs in MT-18.

10.2 Conclusions and Recommendations

The review of ODACTRA in adolescents (12−17 years) was based on safety assessment in the single-arm study MT-18. Although majority of subjects reported at least one IMP-related AE, no death or treatment emergent SAE were reported in the study. Since there was no control arm in the study, comparative analysis is not possible to inform safety signal detection. All analyses were descriptive in nature. I confirmed the accuracy of the pre-defined primary and secondary endpoint analyses and appropriateness of the data presentation. Since the additional safety data were collected in non-US countries, I defer to the clinical reviewer on clinical interpretation of the safety evidence and generalizability to US population.