Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please call 800-835-4709 or 240-402-8010, extension 1. CBER Consumer Affairs Branch or send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.

Application Type	Biologics License Application Efficacy Supplement
STN	125592/218
CBER Received Date	April 29, 2024
PDUFA Goal Date	February 27, 2025
Division / Office	DCTR/OVRR
Committee Chair	Margaret Dayhoff-Brannigan, Ph.D.
Clinical Reviewer	Anne Miranowski, M.D.
Project Manager	Christina Houck and Leda Lotspeich-Cole, Ph.D.
Priority Review	No
Reviewer Name(s)	Zhong Gao, Ph.D. Mathematical Statistician, TEB2/DB/OBPV
Review Completion Date / Stamped Date	
Supervisory Concurrence	Lihan Yan, Ph.D. Chief, TEB2/DB/OBPV
Applicant	ALK-Abelló A/S
Established Name	House Dust Mite (Dermatophagoides farinae and Dermatophagoides pteronyssinus) Allergen Extract
(Proposed) Trade Name	ODACTRA
Pharmacologic Class	Allergenic Extract
Formulation(s), including Adjuvants, etc	House Dust Mite (Dermatophagoides farinae and Dermatophagoides pteronyssinus) Allergen Extract
Dosage Form(s) and Route(s) of Administration	Tablet for Sublingual Use
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 persons 5 through 65 years of age (This Efficacy Supplement is to support a new age indication in children 5-11 years)

Table of Contents

GLOSSARY

AE	Adverse event
AIT	Allergy immunotherapy
ALK	ALK-Abelló
AR	Allergic rhinitis
AR/C	Allergic rhinitis/rhinoconjunctivitis
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CSR	Clinical study report
DMC	Data monitoring committee
DMS	Daily medication score
DSS	Daily symptom score
eDiary	Electronic diary
eCRF	Electronic case report form
FAS	Full analysis set
FDA	Food and Drug Administration
GLMM	General linear mixed model
HDM	House dust mite
IMP	Investigational medicinal product
IRT	Interactive Response Technology
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
N/A	Not applicable
PD	Protocol deviation
PRQLQ	Pediatric rhinoconjunctivitis quality of life questionnaire
QoL	Quality of life
SABA	Short-acting β2-agonist
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SLIT	Sublingual immunotherapy
SQ-HDM	SQ-HDM is the dose unit for the HDM SLIT-tablet
TCCS	Total combined conjunctivitis score
TCRS	Total combined rhinitis score
TCS	Total combined score (of rhinoconjunctivitis symptoms and medication)
TEAE	Treatment-emergent adverse event

LIST OF TABLES

LIST OF FIGURES

1. Executive Summary

ALK-Abelló A/S submitted a Clinical Efficacy Supplement to BLA 125592 to support a new age indication in children 5-11 years for ODACTRA™ (House Dust Mite Allergen Extract, also referred to as 12 SQ-HDM). The proposed updated indication for ODACTRA is an immunotherapy for house dust mite induced allergic rhinitis, with or without conjunctivitis, in persons 5 through 65 years of age. The primary source to support the application was based on results from Phase 3 Study MT-12. Study MT-12 was also conducted to fulfill the last outstanding Required Pediatric Assessment Post-Marketing Requirement (PMR) issued in connection with approval of STN: BL 125592/157, January 20, 2023.

Efficacy:
Study MT-12 was a randomized, parallel-group, double-blind, placebo-controlled, multi-center, phase 3 trial conducted in Europe and North America evaluating the efficacy and safety of 12 SQ-HDM in children (5-11 years old) with HDM AR/C with or without asthma. The primary efficacy endpoint analysis showed that treatment with 12 SQ-HDM, compared with placebo, resulted in a relative reduction of 22.0% (95% CI: 12.0%, 31.1%) in the average daily total combined rhinitis score (TCRS) during the primary efficacy assessment period. The results met the FDA acceptance criterion for study success, i.e., the point estimate of the relative reduction should be at least 15% and an associated lower bound of the 95% CI should be at least 10%. For key secondary endpoints, treatment with 12 SQ-HDM, compared with placebo, resulted in a statistically significant reduction in average rhinitis daily symptom score (DSS), average rhinitis daily medication score (DMS), and average daily total combined score (TCS) during the primary efficacy assessment period, respectively.

Safety:
In Study MT-12, as compared with the placebo group, a notably higher proportion of subjects in the 12 SQ-HDM group reported TEAE (12 SQ-HDM 86.9% vs. Placebo 80.0%), IMP-related TEAE (12 SQ-HDM 75.4% vs. Placebo 53.5%), solicited TEAE (12 SQ-HDM 76.3% vs. Placebo 56.2%), IMP-related solicited TEAE (12 SQ-HDM 74.7% vs. Placebo 50.2%). The proportion of subjects reporting treatment-emergent SAEs was 2.2% in the 12 SQ-HDM group and 0.8% in the placebo group; all SAEs were assessed as unlikely related to investigational medical product (IMP) by the investigators.

In conclusion, the Phase 3 study MT-12 met the statistical success criteria for the primary and key secondary efficacy endpoints, providing the principal evidence for efficacy. Regarding safety evaluation, a higher proportion of the subjects receiving 12 SQ-HDM had TEAE, IMP-related TEAE, solicited TEAE, and IMP-related solicited TEAE than those receiving placebo in Study MT-12. I recommend approval of this application, provided the clinical reviewer finds the safety profile acceptable for approval.

2. Clinical and Regulatory Background

2.1 **Disease or Health-Related Condition(s) Studied**

House dust mite (HDM) induced allergic rhinitis, with or without conjunctivitis (AR/C). For more details, please refer to the clinical review.

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

Medical treatment for AR/C includes allergen avoidance, symptom-relieving medication, and allergen immunotherapy (AIT). HDM allergen (D. farinae and D. pteronyssinus allergens) products for subcutaneous use (SCIT) are commercially available in North America.

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

The first national Marketing Authorization was issued to ALK-Abelló A/S (ALK) by Denmark on 23 September 2015, under the tradename of ACARIZAX. In September 2015, the HDM SLIT tablet, licensed by ALK to Torii Pharmaceutical Co., Ltd. under the trade name of MITICURE, was approved for use in Japan. In 2017, the HDM SLIT tablet was approved in the US as allergy immunotherapy for adults (18-65 years) with HDM AR/C. In 2023, the indication was extended to include the adolescent population (12-17 years).

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

To extend the indication to children 5-11 years of age, the applicant completed a Phase 3 study MT-12 in 2023. This study was the last commitment trial in the US PSP and investigated efficacy and safety in children (5-11 years) with HDM AR/C with or without asthma.

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 generally complied with good data integrity.

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 Phase 3 Study MT-12 which provides the principal efficacy and safety evaluation of the HDM SLIT-tablet in children aged 5 through 11 years with HDM-AR/C.

The applicant also submitted Study MT-11 to provide supporting safety data in children with HDM allergic respiratory disease and inadequately controlled asthma. However, the safety data from Study MT-11 was not included in the label. I defer to the clinical reviewer on role of the MT-11 safety data and will not include Study MT-11 in this review memo.

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

- STN 125592/218.0 Module 2.5. Clinical Overview
- STN 125592/218.0 Module 2.7.3. Summary of Clinical Efficacy
- STN 125592/218.0 Module 2.7.4. Summary of Clinical Safety
- STN 125592/218.0 Module 5.3.5.1. Study MT-12
- STN 125592/218.0 Module 5.3.5.3. Integrated Summary of Safety
- STN 125592/218.5 Response to FDA Information Request dated 15 Oct. 2024

5.3 Table of Studies/Clinical Trials

Table 1. Summary of individual clinical studies

Study ID	Study design	Region	Target population	Main objective	Dose(s) (SQ-HDM) Treatment duration	Number of randomized subjects
MT-12	Phase 3 randomized, double blind, placebo controlled	Europe, North America	AR/C ± asthma 5-11	Pivotal trial for efficacy and safety evaluation	12 SQ-HDM (Approximately 12 months)	Active: 729 Placebo: 731

Note: AR/C ± asthma: HDM allergic rhinitis/rhinoconjunctivitis with or without asthma; AA + AR: HDM allergic asthma and allergic rhinitis.
Source: adapted from Table 1 in Clinical Overview

5.4 Consultations

N/A

5.5 Literature Reviewed (if applicable)

N/A

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study MT-12

Title: A one-year placebo-controlled phase III trial evaluating the efficacy and safety of the house dust mite (HDM) SLIT-tablet in children (5-11 years of age) with HDM allergic rhinitis/rhinoconjunctivitis with or without asthma

6.1.1 Objectives and Endpoints

Table 2. Study MT-12 trial objectives and endpoints

Objective	Endpoint
Primary	
To demonstrate the efficacy of the HDM SLIT tablet compared to placebo in the treatment of HDM AR in children (5-11 years of age) based on total combined rhinitis symptoms and medication use (TCRS) during the primary efficacy assessment period.	• The average daily Total Combined Rhinitis Score (TCRS) during the primary efficacy assessment period
Key secondary	
To demonstrate the efficacy of the HDM SLIT tablet compared to placebo during the primary efficacy assessment period based on: • Rhinitis symptoms (based on DSS) • Rhinitis medication use (based on DMS) • Combined rhinoconjunctivitis symptoms and medication use (based on TCS)	• The average rhinitis Daily Symptom Score (DSS) during the primary efficacy assessment period • The average rhinitis Daily Medication Score (DMS) during the primary efficacy assessment period • The average daily Total Combined Score (TCS) during the primary efficacy assessment period
Secondary	
To evaluate the HDM SLIT tablet compared to placebo during the primary efficacy assessment period based on: • Safety and tolerability • Rhinoconjunctivitis symptoms • Rhinoconjunctivitis medication use • Rhinoconjunctivitis QoL • Asthma symptoms and medication use • Changes in immunological parameters	• Safety and tolerability assessments • Average rhinoconjunctivitis DSS • Average rhinoconjunctivitis DMS • Pediatric rhinoconjunctivitis quality of life questionnaire (PRQLQ) score • Average asthma DSS • Short-acting β2-agonist (SABA) free days • Weekly number of puffs of as-needed SABA use • Changes in immunological parameters • Rhinitis mild days • Rhinitis exacerbation days • Average daily rhinitis CSMS (recommended by the EAACI) • Average daily rhinoconjunctivitis CSMS (recommended by the EACCI)

Source: Table 3 in Study MT-12 CSR

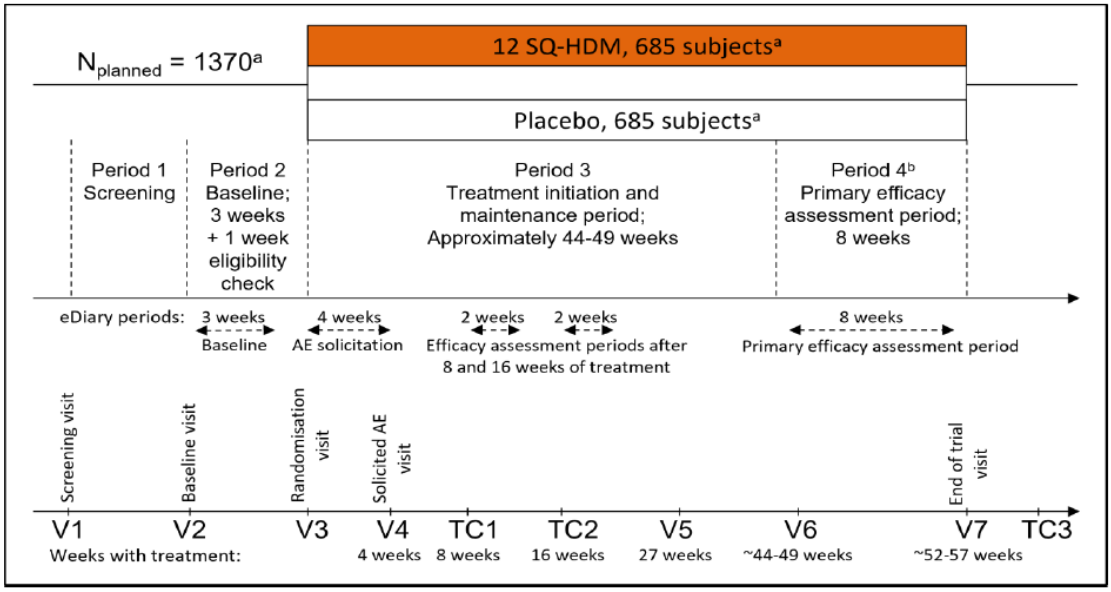
6.1.2 Design Overview

This was a randomized, parallel-group, double-blind, placebo-controlled, multi-center, phase 3 trial conducted in Europe and North America evaluating the efficacy and safety of 12-SQ-HDM in children (5-11 years old) with HDM AR/C with or without asthma.

The trial design is summarized in Figure 1. A total of 1370 subjects were planned to be randomized (1:1) in 2 cohorts to receive treatment with 12 SQ-HDM or placebo (Cohort

1: First subject first visit Oct. 12, 2019, Last subject randomized March 20, 2020; Cohort 2: First subject first visit July 7, 2020, Last subject randomized April 1, 2021). Due to the COVID-19 pandemic, screening and randomization of cohort 1 was stopped and a cohort 3 was subsequently added to recruit a sufficient number of subjects (Cohort 3: First subject first visit July 7, 2021, Last subject randomized April 1, 2022). Subjects were treated with 12 SQ-HDM or placebo from randomization visit (V3) until the end of trial visit (V7), for approximately 12 months. The trial consisted of four periods: screening (Period 1), a baseline period (Period 2), a treatment initiation and maintenance period (Period 3), and a primary efficacy assessment period during the last 8 weeks (Period 4). The subjects were provided an eDiary (a hand-held electronic device), which was used during the specified eDiary periods to record symptoms and medication use. Additionally, AE solicitation was conducted via the eDiary during the first 28 days of treatment).

Figure 1. Trial Design of Study MT-12



Notes: [a] The actual number of randomized subjects was 1460; 729 in 12 SQ-HDM group and 731 in placebo group
[b] Subjects' primary efficacy assessment period had to be between 01-Sep and 01-Apr and include the dates of the 3-week baseline period from previous year. For pollen allergic subjects, the primary efficacy assessment period had to be outside of the season of their pollen allergy.
HDM = house dust mite, $N_{planned}$ = planned number of subjects, SQ-HDM = dose unit for the HDM SLIT-tablet, TC = telephone call, V = visit
Source: Figure 1 in Study MT-12 CSR.

6.1.3 Population

The trial included subjects aged 5-11 years with HDM AR/C with or without asthma.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The Investigational medicinal product (IMP) was HDM SLIT-tablet (12 SQ-HDM dose) or placebo.

6.1.6 Sites and Centers

The study was conducted in 95 sites in 11 countries: Bulgaria, Canada, France, Germany, Lithuania, Poland, Russia, Slovakia, Spain, Ukraine, and United States.

6.1.7 Surveillance/Monitoring

Please refer to clinical review memo.

6.1.8 Endpoints and Criteria for Study Success

The primary endpoint was the average TCRS during the primary efficacy assessment period. The between treatment comparison was performed. The criterion for the trial success agreed between the Applicant and FDA was a point estimate of the treatment difference relative to placebo of at least 15% and an associated lower bound of the 95% CI of at least 10%.

Please refer to section 6.1.1. for key secondary endpoints and other secondary endpoints.

6.1.9 Statistical Considerations & Statistical Analysis Plan

- Blinding

This was a double-blind trial, where subjects, site personnel, and sponsor trial personnel were blinded to treatment.

- Randomization

All subjects were centrally randomized 1:1 to 12 SQ-HDM or placebo using an Interactive Response Technology (IRT).

- Definitions of analysis populations
  - Total analysis set: All subjects who signed the informed consent form and thus includes screening failures.
  - Full Analysis Set (FAS): All randomized subjects who received at least one dose of investigational medicinal product (IMP). Subjects were analyzed as according to their randomized assignment of treatment.
  - Safety Analysis Set (SAF): All randomized subjects, who received at least one dose of IMP. Subjects were analyzed as treated i.e., according to treatment they actually received.

  FAS and all observed data for the endpoint was used for the observed case analyses (primary analysis for all endpoints).

  In addition, two analysis datasets for efficacy analyses were defined:
  FAS and DPS1: For subjects who complete the study, all data were to be included; for subjects who discontinue IMP, post-discontinuation data were not to be included - included data until discontinuation of treatment. This analysis set was to be used to estimate the trial product estimand for the primary and key secondary objectives.

FAS and DPS2: For subjects who complete the study, all data is included; for subjects who discontinue IMP, all observed data was to be included. This analysis set was to be used to estimate the treatment policy estimand for the primary and key secondary objectives. Please refer to the estimands section below for the descriptions of trial product and treatment policy estimand.

- Sample size planning

The applicant's sample size planning indicated that, with a sample size of 580 subjects per treatment arm, the MT-12 trial had >90% power (2-sided, α=0.05) to detect a statistically significant difference (p-value<0.05) given their assumptions. When further adjusting for a drop-out rate of 15%, the proposed sample size per treatment arm for the MT-12 trial would be 682 subjects (total of 1364 ~ 1370 subjects).

- Statistical Analysis for Primary Efficacy Endpoint

The primary endpoint was the average daily total combined rhinitis score (TCRS) of all observed daily values during the primary efficacy assessment period. The primary endpoint was to be analyzed using all subjects in FAS with at least 1 eDiary record during the primary efficacy assessment period. The analysis was to be performed using a linear mixed effect model (LME). The model includes the square root of the average daily TCRS during the primary efficacy assessment period as response variable, treatment group and cohort as fixed factors, the square root of the baseline average daily TCRS as a covariate, country/region within cohort as a random effect. For the absolute difference the standard error (SE) was approximated, by using the first order Delta method, for 95% CI calculation. The 95% confidence interval for the relative difference was to be calculated using Fieller's theorem. Adjusted means for each treatment group, the absolute treatment difference (Placebo – Active) with 95% confidence interval and p-value, and the relative treatment difference [(Placebo – Active)/Placebo] with 95% confidence interval were to be presented.

Reviewer Comment: *For TCRS, eDiary compliance was high throughout the trial (means above 94%) and similar for the treatment groups (Baseline: Placebo - mean compliance rate 98.4%, 12 SQ-HDM – mean 98.5%; Visit 6: Placebo – mean 94.3%, 12 SQ-HDM – mean 94.4%).*

- Statistical Analysis for Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints were the average of all observed daily values during the primary efficacy assessment period for rhinitis DSS, rhinitis DMS, and TCS. The key secondary endpoints. average rhinitis DSS, average rhinitis DMS, and average daily TCS, were to be analyzed using an observed case analysis similar to the primary analysis of the primary endpoint. All subjects in the FAS with at least 1 eDiary record during the primary efficacy assessment period were to be included. The analysis was to be performed using an LME. The model included the square root of the endpoint as response variable, treatment group and cohort as fixed factors, the square root of the baseline endpoint as a covariate, country/region as a random effect, and with different residual errors specified for each treatment group.

- Multiplicity adjustment

The primary endpoint, key secondary endpoints, and the overall PRQLQ score at end of trial (using observed case analysis) were to be controlled for multiplicity to ensure a maximum overall type I error rate of 5% in the hypothesis testing of these endpoints. The control for multiplicity was done by hierarchical testing, pre-specifying the order of the hypotheses to be tested. For all endpoints the null hypothesis to be tested was the hypothesis of no absolute difference in means between treatment groups. Let μ_1 denote the mean in the HDM SLIT-tablet group, and μ_2 denote the mean in the Placebo group. Then the null hypothesis (H_0) and the alternative hypothesis (H_A) were given as follows: H0: $\mu_1 = \mu_2$ and HA: $\mu_1 \neq \mu_2$.

The order of hypotheses to be tested is:

1. Superiority testing of the HDM SLIT tablet over placebo with respect to the average daily TCRS during the primary efficacy assessment period.
2. Superiority testing of the HDM SLIT tablet over placebo with respect to the average rhinitis DSS during the primary efficacy assessment period.
3. Superiority testing of the HDM SLIT tablet over placebo with respect to the average rhinitis DMS during the primary efficacy assessment period.
4. Superiority testing of the HDM SLIT tablet over placebo with respect to the average daily TCS during the primary efficacy assessment period.
5. Superiority testing of the HDM SLIT tablet over placebo with respect to the overall PRQLQ score at end of trial.

Reviewer Comment: *It should be noted that the success criterion agreed upon by CBER and the applicant for the primary efficacy endpoint TCRS was that, in addition to statistical significance based on the null hypothesis of no difference between the placebo and treatment groups, a point estimate of the treatment difference relative to placebo of should be at least 15% and an associated lower bound of the 95% CI should be at least 10%. Although the proposed sequential hierarchical testing didn't reflect the agreed success criterion for TCRS, the primary efficacy analysis on TCRS met the CBER success criterion.*

- Estimands

The study was designed before the ICH E9 addendum became in effect, and consequently, data after IMP discontinuation was not collected. Therefore, the primary analysis was conducted using an observed case analysis. To evaluate robustness of the primary analyses, the applicant proposed supplementary analyses based on the trial product estimand and the treatment policy estimand.

  - Trial product estimand

    The primary endpoint was to be compared between treatment groups using the trial product estimand for the FAS population and DPS1, following a hypothetical strategy. Subjects for whom the primary endpoint was missing or unobserved (because of either missing diary data or the exclusion of diary data due to IMP discontinuation) were to be included in the analysis through

multiple imputation under the hypothetical situation where subjects continued to take study treatment as planned (Table 3).

Table 3. Trial product estimand analysis approaches

Analysis Approach	Description
Primary approach	▪ For subjects who discontinue IMP due to lack of efficacy, multiple imputation of the missing endpoint was to be from the placebo group. This assumes that had the subject continued to take study treatment, they would have experienced similar efficacy to subjects in the placebo group. ▪ For subjects who do not discontinue IMP, and for subjects who discontinue IMP due to other reasons, multiple imputation of the missing endpoint was to be from their own treatment group.
Sensitivity analysis 1	Relax the assumption about data missing at random for subjects discontinuing treatment due to IMP-related adverse events. ▪ For subjects who discontinue IMP due to lack of efficacy or due to IMP-related adverse events, multiple imputation of the missing endpoint was to be from the placebo group. ▪ For subjects who do not discontinue IMP, and for subjects who discontinue IMP due to other reasons, multiple imputation of the missing endpoint was to be from their own treatment group.
Sensitivity analysis 2	Further relax the assumption about data missing at random: ▪ For subjects who do not discontinue IMP, and for subjects who discontinue IMP due to lost to follow-up or withdrawal of consent, multiple imputation of the missing endpoint was to be from their own treatment group. ▪ For subjects who discontinue IMP due to other reasons, multiple imputation of the missing endpoint was to be from the placebo group.
Sensitivity analysis 3	Tipping point analysis

Source: Adapted from Section 6.2.3.1 in Study MT-12 SAP.

- Treatment policy estimand
  In addition to the trial product estimand, the primary endpoint was to be compared between treatment groups using the treatment policy estimand for the FAS population and DPS2, following a treatment policy strategy. Subjects for whom the primary endpoint was missing (because of missing diary data) will be included in the analysis through multiple imputation as follows (Table 4).

Table 4. Treatment policy estimand analysis approaches

Analysis Approach	Description
Primary approach	▪ For subjects discontinuing IMP due to lack of efficacy or IMP-related adverse events, multiple imputation of the missing endpoint was to be from the placebo group. ▪ For subjects who do not discontinue IMP, and for subjects discontinuing IMP due to other reasons, multiple imputation of the missing endpoint will be from their own treatment group.
Sensitivity analysis 1	Impute all missing values of the endpoint from the placebo group.

Source: Adapted from Section 6.2.3.2 in Study MT-12 SAP.

- Statistical Methods for Safety Analyses: 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 treatment groups were generally similar with regards to demography (Table 3). Among the randomized subjects, 34% of the subjects were female and 66% were male. The vast majority of subjects were White, and not Hispanic or Latino. 95% of subjects were recruited in Europe and 5% in North America.

Table 5. Demographics Characteristics (FAS)

	Placebo (N=731)	12 SQ-HDM (N=727)
Age at Screening (years)		
Mean (SD)	8.0 (1.9)	8.0 (1.9)
Median	8.0	8.0
Min – Max	4 - 11	4 - 11
Sex, n (%)		
Female	254 (34.7%)	241 (33.1%)
Male	477 (65.3%)	486 (66.9%)
Race, n (%)		
Asian	3 (0.4%)	1 (0.1%)
Black or African American	4 (0.5%)	1 (0.1%)
White	714 (97.7%)	722 (99.3%)
American Indian or Alaska Native	-	1 (0.1%)
Multiple	3 (0.4%)	1 (0.1%)
Other	7 (1.0%)	1 (0.1%)
Ethnicity, n (%)		
Hispanic or Latino	19 (2.6%)	26 (3.6%)
Not Hispanic or Latino	697 (95.3%)	688 (94.6%)
Not Reported	15 (2.1%)	13 (1.8%)
Country, n (%)		
Bulgaria	90 (12.3%)	91 (12.5%)
Canada	20 (2.7%)	18 (2.5%)
Lithuania	47 (6.4%)	47 (6.5%)
Poland	177 (24.2%)	176 (24.2%)
Russia	166 (22.7%)	163 (22.4%)
Slovakia	33 (4.5%)	33 (4.5%)
Ukraine	165 (22.6%)	165 (22.7%)
United States	19 (2.6%)	21 (2.9%)
France	1 (0.1%)	2 (0.3%)
Germany	9 (1.2%)	8 (1.1%)
Spain	4 (0.5%)	3 (0.4%)

Source: Table 13 in Study MT-12 CSR

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
The treatment groups were similar with regards to allergy history and baseline allergy characteristics (Table 6).

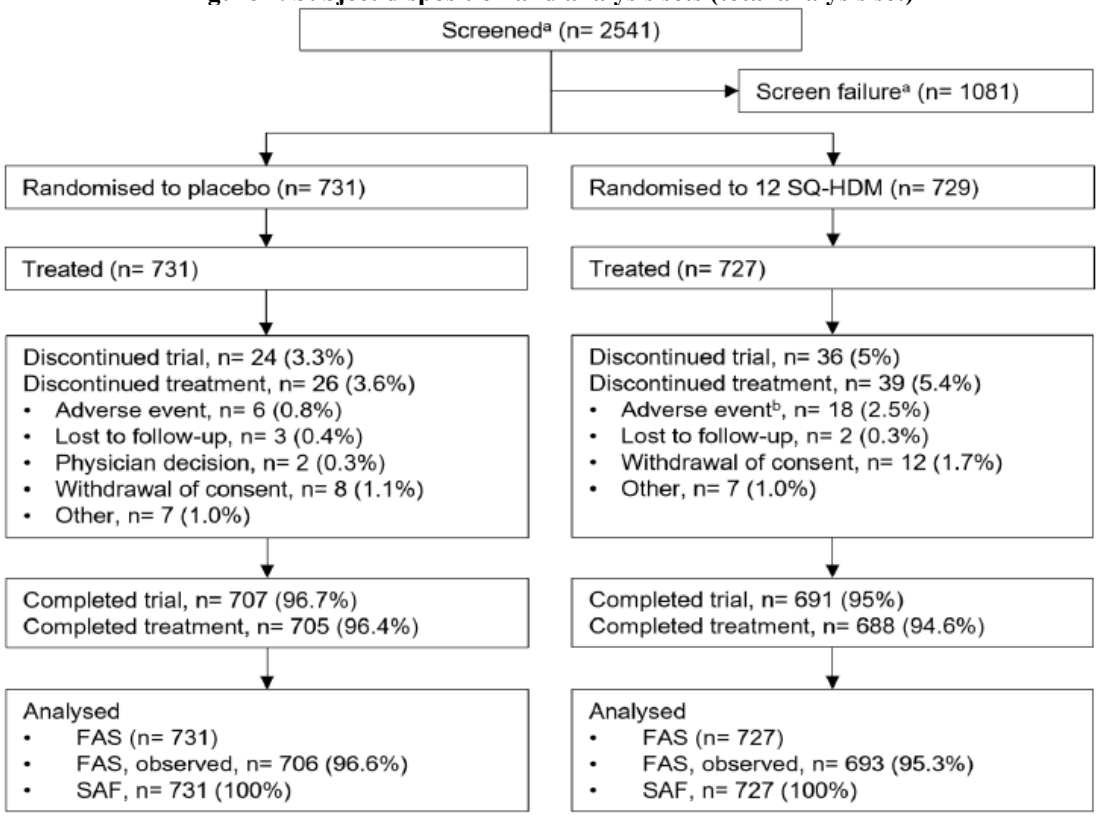
Table 6. Summary of allergy history and baseline characteristics (FAS)

	Placebo (N=731)	12 SQ-HDM (N=727)
Allergy history, n (%)		
HDM allergic rhinitis or rhinoconjunctivitis	731 (100%)	726 (99.9%)
HDM allergic rhinitis	440 (60.2%)	453 (62.3%)
HDM allergic rhinoconjunctivitis	291 (39.8%)	273 (37.6%)
Mean duration of HDM AR/C, years (SD)	2.8 (1.8)	2.7 (1.8)
Baseline sensitizations, n (%)		
Monosensitization (HDM only)	360 (49.2%)	337 (46.4%)
Polysensitization (HDM and others)	371 (50.8%)	390 (53.6%)
Pollen sensitization	247 (33.8%)	267 (36.7%)
Mean SPT wheal size, diameter in mm (SD)		
D. pteronyssinus	7.1 (2.5)	7.1 (2.5)
D. farinae	6.5 (2.3)	6.5 (2.6)
Mean IgE levels at baseline, kU/L (SD)		
IgE against *D. pteronyssinus*	50.7 (36.0)	49.4 (35.1)
IgE against *D.farinae*	53.1 (34.7)	53.2 (34.6)
Highest of *D. farinae* and *D. pteronyssinus*	59.2 (35.3)	58.8 (34.5)
Median pulmonary function at baseline, % predicted (Min - Max)		
FEV_1	96.8 (70 - 179)	97.1 (58 - 193)
FVC	95.3 (61 - 184)	96.2 (52 -163)

Source: Table 14 in Study MT-12 CSR

6.1.10.1.3 Subject Disposition
Overall, 1458 subjects were randomized and treated, and 1393 (95.5%) completed treatment (Figure 2). The number of subjects who discontinued from trial or treatment was slightly higher in the 12-SQ-HDM group than the placebo group.

Figure 2. Subject disposition and analysis sets (total analysis set)



[a] Rescreened subjects were counted once as subjects screened and once as screen failures, whether or not they failed rescreening
[b] 2 subjects discontinued with primary reason 'severe or persistent symptoms of oesophagitis'. These events were also reported as AEs.
Source: Figure 2 in Study MT-12 CSR

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoints

The primary efficacy endpoint analysis showed that treatment with 12 SQ-HDM, compared with placebo, resulted in a statistically significant absolute reduction of 1.0 (95% CI: 0.5, 1.4; p<0.0001), corresponding to a relative reduction of 22.0% (95% CI: 12.0, 31.1) in the average daily TCRS during the primary efficacy assessment period (Table 5). The results met the FDA acceptance criterion for trial success that a point estimate of the treatment difference relative to placebo of should be at least 15% and an associated lower bound of the 95% CI should be at least 10%.

Table 7. Analysis of average daily TCRS during the primary efficacy period – observed case (FAS)

	N_{FAS}	n_{obs}	Adjusted mean (SE)	Estimate [95% CI]
Placebo	731	706	4.4 (0.3)	
12 SQ-HDM	727	693	3.4 (0.3)	
Placebo-12 SQ-HDM				1.0 [0.5, 1.4]
(Placebo-12 SQ-HDM)/Placebo (%)				22.0 [12.0, 31.1]

Notes: N_{FAS} = number of subjects in FAS, n_{obs} = number of subjects with observations contributing to the analysis, TCRS = total combined rhinitis score.
Source: Table 18 in Study MT-12 CSR.

Reviewer Comment: *I have verified the primary efficacy endpoint analysis.*

The applicant conducted sensitivity analysis on the primary efficacy endpoint:

- Sensitivity analysis – potential data issues

The primary analysis with observed case was repeated excluding subjects with potential data issues (randomized in error, siblings in same cohort, subjects in Ukraine without IMP). The result showed a statistically significant absolute reduction of 1.0 (95% CI: 0.5, 1.5; p<0.0001), corresponding to a relative reduction of 22.6% (95% CI: 12.7, 31.7) (Table 8).

- Trial product estimand

Analysis of the primary endpoint using the main analytical approach showed an absolute reduction of 1.0 (95% CI: 0.5, 1.5; p<0.0001), corresponding to a relative reduction of 22.2% (95% CI: 12.2, 31.2) in average daily TCRS during the primary efficacy assessment period after treatment with 12 SQ-HDM, compared with placebo (Table 8). The sensitivity analyses 1 and 2 showed a similar trend with the main analytical approach (Table 8). An additional tipping point analysis was performed to investigate the missing at random assumption in the sensitivity analysis. A p-value of 0.05 was reached by applying a penalty of 13.5 to all imputed values for the 12 SQ-HDM group. As the tipping point of 13.5 is not considered a clinical plausible difference between the treatment groups, the analysis supports the sensitivity analyses.

- Treatment policy estimand

Analysis of the primary endpoint using the main analytical approach showed an absolute reduction of 1.0 (95% CI: 0.5, 1.4; p<0.0001), corresponding to a relative reduction of 21.8% (95% CI: 11.8, 30.8) in average daily TCRS during the primary efficacy assessment period after treatment with 12 SQ-HDM, compared with placebo (Table 8). The sensitivity analysis showed similar results.

Table 8. Overview of analyses of the primary endpoint, average daily TCRS during the primary efficacy period (FAS)

Analysis frame	Analysis name	Absolute treatment difference [95% CI]	Relative treatment difference (%) [95% CI]
Observed case	Primary analysis	1.0 [0.5, 1.4]	22.0 [12.0, 31.1]
Observed case	Sensitivity analysis (potential data issues)	1.0 [0.5, 1.5]	22.6 [12.7, 31.7]
Trial product estimand	Main analytical approach	1.0 [0.5, 1.5]	22.2 [12.2, 31.2]
Trial product estimand	Sensitivity 1	1.0 [0.5, 1.4]	21.9 [11.9, 30.9]
Trial product estimand	Sensitivity 2	1.0 [0.5, 1.4]	21.4 [11.4, 30.5]

Analysis frame	Analysis name	Absolute treatment difference [95% CI]	Relative treatment difference (%) [95% CI]
Treatment policy estimand	Main analytical approach	1.0 [0.5, 1.4]	21.8 [11.8, 30.8]
Treatment policy estimand	Sensitivity	0.9 [0.5, 1.4]	21.1 [11.0, 30.2]

Source: Table 19 in Study MT-12 CSR.

Reviewer Comment: *The applicant conducted sensitivity and additional analyses of the primary endpoint to evaluate robustness of the primary analysis results for potential data issues as well as treatment discontinuation due to lack of efficacy, IMP-related adverse event, and other reasons. These analyses provided similar results to support that 12 SQ-HDM significantly improved average daily TCRS during the primary efficacy assessment period compared to placebo.*

6.1.11.2 Analyses of Secondary Endpoints

- Rhinitis endpoint, average rhinitis Daily Symptom Score (DSS)

Average rhinitis DSS evaluates the treatment effect based on the reduction in daily rhinitis symptoms. Higher scores indicate more severe symptoms. The analysis results showed that treatment with 12 SQ-HDM, compared with placebo, resulted in a statistically significant reduction in average rhinitis DSS during the primary efficacy assessment period (Table 9).

Table 9. Analysis of average rhinitis DSS during the primary efficacy period – observed case (FAS)

	N_{FAS}	n_{obs}	Adjusted mean (SE)	Estimate [95% CI]
Placebo	731	706	1.9 (0.1)	
12 SQ-HDM	727	693	1.5 (0.1)	
Placebo-12 SQ-HDM				0.4 [0.2, 0.6]
(Placebo-12 SQ-HDM)/Placebo (%)				22.2 [12.8, 30.8]

Source: Table 20 in Study MT-12 CSR.

- Rhinitis endpoint, average rhinitis Daily Medication Score (DMS)

Average rhinitis DMS evaluates the treatment effect based on the reduction in daily rhinitis medication use. Higher scores indicate more medication use. The results indicated that treatment with 12 SQ-HDM, compared with placebo, resulted in a statistically significant reduction in average rhinitis DMS during the primary efficacy assessment period (Table 10).

Table 10. Analysis of average rhinitis DMS during the primary efficacy period – observed case (FAS)

	N_{FAS}	n_{obs}	Adjusted mean (SE)	Estimate [95% CI]
Placebo	731	706	1.9 (0.2)	
12 SQ-HDM	727	693	1.4 (0.2)	
Placebo-12 SQ-HDM				0.5 [0.2, 0.8]
(Placebo-12 SQ-HDM)/Placebo (%)				25.3 [10.5, 38.3]

Source: Table 22 in Study MT-12 CSR.

- Rhinoconjunctivitis endpoint, average daily Total Combined Score (TCS)

Average rhinoconjunctivitis TCS evaluates the treatment effect based on the reduction in daily rhinoconjunctivitis symptoms and medication use. Higher scores indicate more severe symptoms and/or more medication use. The results indicated that treatment with 12 SQ-HDM, compared with placebo, resulted in a statistically significant reduction in average daily TCS during the primary efficacy assessment period (Table 11).

Table 11. Analysis of average daily TCS during the primary efficacy period – observed case (FAS)

	N_{FAS}	n_{obs}	Adjusted mean (SE)	Estimate [95% CI]
Placebo	731	706	5.2 (0.4)	
12 SQ-HDM	727	693	4.0 (0.4)	
Placebo-12 SQ-HDM				1.1 [0.6, 1.7]
(Placebo-12 SQ-HDM)/Placebo (%)				22.2 [12.0, 31.5]

Source: Table 24 in Study MT-12 CSR.

- Secondary endpoint, Pediatric rhinoconjunctivitis quality of life questionnaire (PRQLQ) score at the end of trial

The PRQLQ score at the end of the trial (Visit-7) was not one of the key secondary endpoints but was included by the applicant as the fifth test in the testing hierarchy. The PRQLQ measures the effect of rhinoconjunctivitis on subject's quality of life on a scale of 0-6. Higher scores indicate worse rhinoconjunctivitis-related quality of life. The results showed that treatment with 12 SQ-HDM, compared with placebo, resulted in a statistically significant reduction in the PRQLQ score at the end of trial (V7) (Table 12).

Table 12 Analysis of overall PRQLQ score at visit 7 – observed case (FAS)

	N_{FAS}	n_{obs}	Adjusted mean (SE)	Estimate [95% CI]
Placebo	731	690	1.0 (0.1)	
12 SQ-HDM	727	695	0.8 (0.1)	
Placebo-12 SQ-HDM				0.2 [0.1, 0.2]
(Placebo-12 SQ-HDM)/Placebo (%)				16.6 [8.8, 24.0]

Source: Table 26 in Study MT-12 CSR

Reviewer Comment:

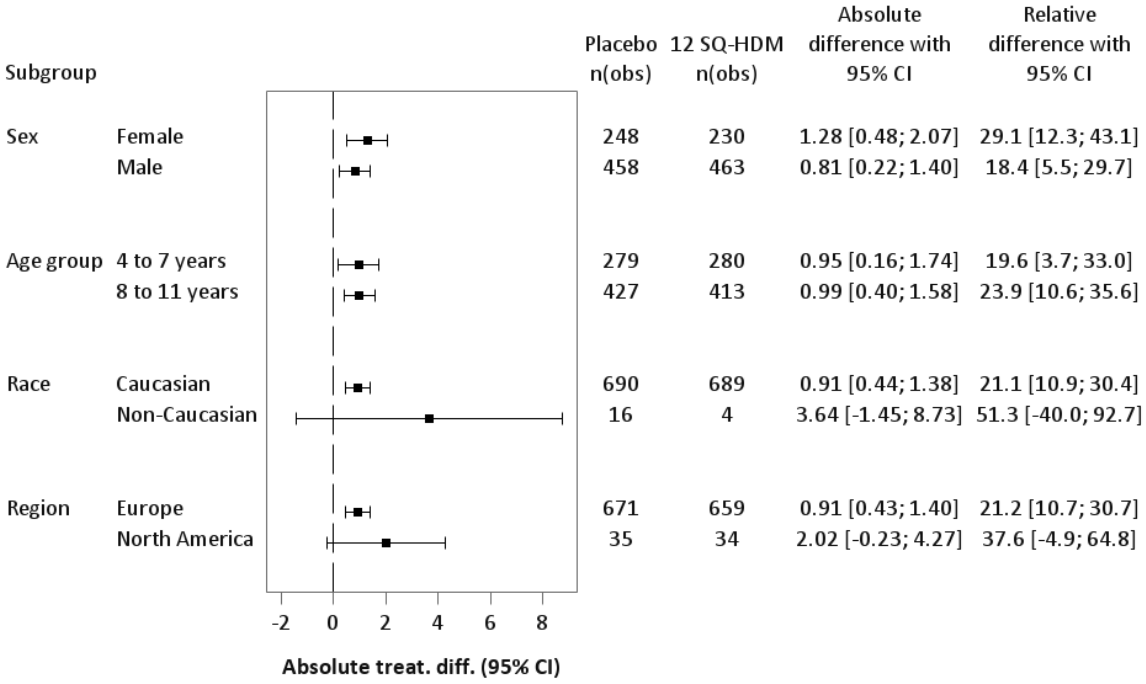
- *My analysis showed similar results that there was statistically significant difference between the active treatment and placebo groups in the key secondary endpoints DSS, DMS and TCS.*
- *The applicant conducted sensitivity analysis on DSS, DMS and TCS based on the trial product estimand and treatment policy estimand. The results were supportive of the primary analyses.*
- *The PRQLQ score was not pre-specified as a key secondary endpoint, however, the applicant included it as part of the hierarchy for hypothesis testing. Subsequently, the applicant included its results in the label. During the labelling meeting, PRQLQ was considered as less well understood by physicians on its*

clinical meanings, and will be deleted from the label. I defer to the clinical reviewer for decision making.

6.1.11.3 Subpopulation Analyses

The demographic subgroup analysis for subjects in the different age, sex, race, and region subgroups showed a similar trend in treatment effect of 12 SQ-HDM (Figure 3). Due to the small number of non-Caucasian children and of children in North America in the study, the results showed wide 95% confidence interval crossing zero. The subgroup analyses by race and by geographical region should be interpreted with caution.

Figure 3. Forest plot of demographic subgroup analyses of average daily TCRS during the primary efficacy period - observed case (FAS)



Source: Response to FDA information request dated 15 October 2024

The subgroup analyses were performed for the primary and key secondary endpoints by baseline asthma status. Most results showed a positive 12 SQ-HDM treatment effect for the primary and key secondary endpoints in both subjects with and without concomitant asthma, with the exception of rhinitis DMS in subjects without asthma at baseline (showing a similar trend of treatment difference). Results are not presented here.

- Baseline pollen sensitization status

The subgroup analysis showed a positive 12 SQ-HDM treatment effect compared with placebo, for average daily TCRS in both subjects with and without baseline pollen sensitization.

- Baseline allergen sensitization status

The subgroup analysis showed a statistically significant 12 SQ-HDM treatment effect compared with placebo, for TCRS in both subjects sensitized to HDM only and subjects sensitized to HDM and other allergens.

6.1.11.4 Dropouts and/or Discontinuations

The dropout rates were low in the study. The applicant performed sensitivity analyses to evaluate the impact of the different estimand approaches. The sensitivity analyses showed a similar trend of treatment effect as the primary analysis.

6.1.11.5 Exploratory and Post Hoc Analyses

N/A

6.1.12 Safety Analyses

Most subjects in both treatment groups reported TEAEs and solicited TEAEs; the frequencies were higher in the 12 SQ-HDM group than in the placebo group. The proportions of subjects reporting IMP-related TEAEs, solicited TEAEs, and IMP-related solicited TEAE were notably higher in the 12 SQ-HDM group than those in the placebo group (Table 13).

Table 13. Summary of safety profile (SAF)

Subjects experiencing	**Placebo (N=731) n**	**Placebo %n**	**12 SQ-HDM (N=727) n**	**12 SQ-HDM %n**
TEAE	585	80.0%	632	86.9%
IMP-related TEAE	391	53.5%	548	75.4%
IMP-related severe TEAE	2	0.3%	4	0.6%
IMP-related treatment-emergent SAE	0	0.0%	0	0.0%
IMP-related TEAE leading to discontinuation of IMP[a]	7	1.0%	13	1.8%
Solicited TEAE	411	56.2%	555	76.3%
IMP-related solicited TEAE	367	50.2%	543	74.7%
IMP-related treatment-emergent systemic allergic reaction including anaphylaxis	1	0.1%	2	0.3%
IMP-related TEAE treated with adrenaline/epinephrine	0	0.0%	0	0.0%
IMP-related treatment-emergent severe local swelling or oedema of the mouth and/or throat	0	0.0%	2	0.3%
IMP-related TEAE of eosinophilic oesophagitis	0	0.0%	0	0.0%

Source: Table 37 in Study MT-12 CSR

6.1.12.1 Methods

Descriptive methods were used for safety analysis.

6.1.12.3 Deaths

No deaths occurred during the trial.

6.1.12.4 Nonfatal Serious Adverse Events

The proportion of subjects reporting treatment-emergent SAEs was 2.2% and 0.8%, respectively, in the 12 SQ-HDM group and the placebo group. All SAEs were assessed as unlikely related to IMP by the investigators.

6.1.12.5 Adverse Events of Special Interest (AESI)

- Three subjects in the 12 SQ-HDM group and 2 in the placebo group reported 1 mild or moderate, nonserious systemic allergic reaction/anaphylactic reaction each, as evaluated by the investigator. None of the events were treated with adrenaline/epinephrine and all had an outcome of recovered. 2 of the events in 12 SQ-HDM group were assessed as possibly related to IMP.
- No TEAEs treated with adrenaline/epinephrine were reported in the trial.
- 2 subjects in the 12 SQ-HDM group reported severe, non-serious TEAEs of 'local swelling or oedema of the mouth and/or throat', which were assessed as possibly related to IMP.

6.1.12.6 Clinical Test Results

N/A

6.1.12.7 Dropouts and/or Discontinuations

The proportion of subjects reporting TEAEs leading to IMP discontinuation was 2.3% and 1.0% in the 12 SQ-HDM group and placebo group. The discontinuation rate due to IMP-related TEAEs was 1.8% and 1.0% in the 12 SQ-HDM and placebo groups, respectively. Four subjects in the 12 SQ-HDM group discontinued IMP due to SAEs (PTs of attention deficit hyperactivity disorder, hallucinations, immune system disorder and pseudomonas bronchitis), all assessed as unlikely related to treatment.

9. ADDITIONAL STATISTICAL ISSUES

N/A

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Efficacy:
Study MT-12 was a randomized, parallel-group, double-blind, placebo-controlled, multi-center, phase 3 trial conducted in Europe and North America evaluating the efficacy and safety of 12-SQ-HDM in children (5-11 years old) with HDM AR/C with or without asthma. The primary efficacy endpoint analysis showed that treatment with 12 SQ-HDM, compared with placebo, resulted in a statistically significant absolute reduction of 1.0 (95% CI: 0.5, 1.4; $p<0.0001$), corresponding to a relative reduction of 22.0% (95% CI: 12.0, 31.1) in the average daily TCRS during the primary efficacy assessment period. The results met the FDA acceptance criterion for the trial, i.e., point estimate of the treatment difference relative to placebo being at least 15% and an associated lower bound of the 95% CI being at least 10%. For key secondary endpoints, treatment with 12 SQ-HDM, compared with placebo, resulted in a statistically significant reduction in average rhinitis

DSS, average rhinitis DMS, and average daily TCS during the primary efficacy assessment period, respectively.

Safety:
In Study MT-12, as compared with the placebo group, a notably higher proportion of subjects in the 12 SQ-HDM group reported TEAE (12 SQ-HDM 86.9% vs. Placebo 80.0%), IMP-related TEAE (12 SQ-HDM 75.4% vs. Placebo 53.5%), solicited TEAE (12 SQ-HDM 76.3% vs. Placebo 56.2%), IMP-related solicited TEAE (12 SQ-HDM 74.7% vs. Placebo 50.2%). The proportion of subjects reporting treatment-emergent SAEs was 2.2% in the 12 SQ-HDM group and 0.8% in the placebo group; all SAEs were assessed as unlikely related to investigational medical product (IMP) by the investigators. I defer to the clinical reviewer on whether the safety profile is acceptable for approval.

10.2 Conclusions and Recommendations

The Phase 3 study MT-12 met the statistical success criteria for the primary and key secondary efficacy endpoints. A higher proportion of the subjects receiving 12 SQ-HDM had TEAE, IMP-related TEAE, solicited TEAE, and IMP-related solicited TEAE than those receiving placebo in Study MT-12. I defer to the clinical reviewer on whether the safety profiles of the product would lead to safety concerns. If the safety profile is acceptable, I would recommend approval of this product for the intended indication from the statistical perspectives.