Integrated Clinical Trial Report

Trial ID: MT-06

Trial title:

A one-year trial evaluating the efficacy and safety of the ALK house dust mite allergy immunotherapy tablet in adult subjects with house dust mite allergic rhinitis

Investigational medicinal product:	ALK HDM allergy immunotherapy tablet
EudraCT No.:	2011-002277-38
Development phase:	III
Indication:	Allergic rhinitis
First subject first visit:	27 Oct 2011
Last subject last visit:	04 April 2013
Investigators:	Signatory and international coordinating investigator: Prof. [redacted] (FR)
Trial Sites:	100 trial sites in 12 countries (AT, BA, HR, CZ, DK, FR, DE, LV, PL, RO, RS, and UA)
Sponsor:	Global Clinical Development ALK-Abelló A/S DK-2970 Hørsholm Phone: +45 4574 7445 Fax +45 4574 8690
Medical Writer:	[redacted] PhD, MSc, ALK
Version:	Final
Date:	13 February 2014

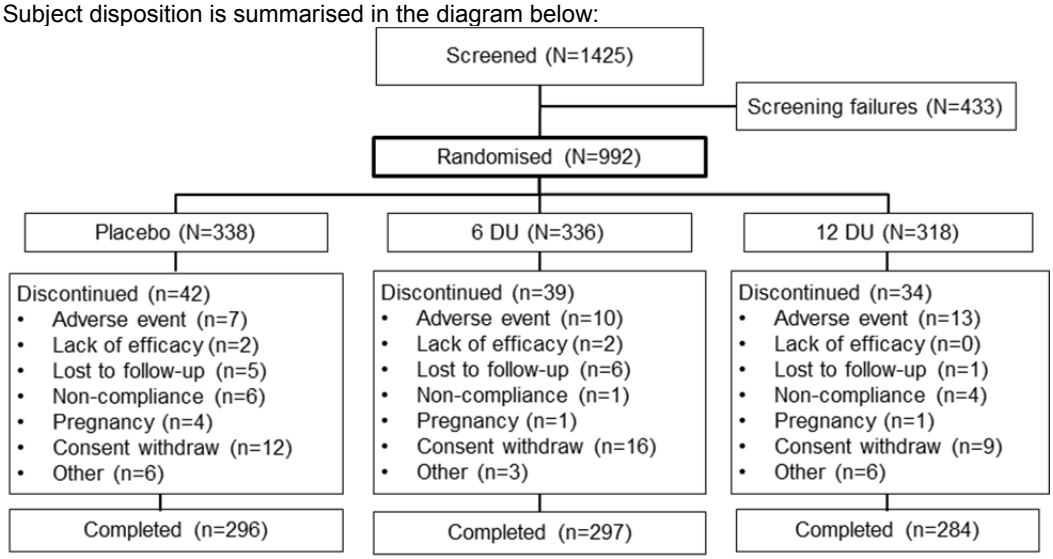
This trial was conducted in compliance with the principles of ICH Good Clinical Practice.

Synopsis – trial MT-06

Title of trial A one-year trial evaluating the efficacy and safety of the ALK house dust mite allergy (HDM) immunotherapy tablet in adult subjects with house dust mite allergic rhinitis.
Investigators [redacted] (France) was appointed the signatory investigator as well as the international coordinating investigator of the trial. The following investigators were appointed national coordinating investigators: Prof. [redacted] (Croatia), Prof. [redacted] (Germany), Dr. [redacted] (Austria), Prof. [redacted] (France), Dr. [redacted] (Denmark) and Dr. [redacted] (Poland).
Trial sites A total of 100 trial sites in 12 countries (Austria, Bosnia and Herzegovina, Croatia, Czech, Denmark, France, Germany, Latvia, Poland, Romania, Serbia, and Ukraine) randomised subjects for the trial.
Publications None
Trial period First subject first visit – 27 October 2011 Last subject last visit – 04 April 2013
Objectives **Primary objective** The primary objective of the trial was: • To evaluate the efficacy of the HDM allergy immunotherapy tablet given once daily compared to placebo in the treatment of HDM allergic rhinitis. The primary endpoint was the average total combined rhinitis score (TCRS) during the last 8 weeks of treatment. The TCRS is the sum of the allergic rhinitis daily symptom score (DSS) and the allergic rhinitis daily medication score (DMS) averaged over the last 8 weeks of treatment. **Secondary objectives** The key secondary objectives of the trial were: • To determine the effect of the HDM allergy immunotherapy tablet on average allergic rhinitis DSS, average allergic rhinitis DMS, average overall Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score and average total combined rhinoconjunctivitis score in the efficacy evaluation period[1]. Additional secondary objectives of the trial were: • To evaluate the safety and tolerability of the HDM allergy immunotherapy tablet. • To determine the effect of the HDM allergy immunotherapy tablet on individual rhinitis and conjunctivitis symptoms, medication use, onset of action, treatment satisfaction, and generic and disease-specific quality of life. Immunological parameters were investigated for a limited subset of the subjects.
Methodology This was a randomised, parallel-group, double-blind, placebo-controlled, multi-national, multi-site trial in Europe.

[1] Note that the key secondary objectives have been changed in the statistical analysis plan from the protocol to include average overall RQLQ score during the efficacy evaluation period.

Number of subjects planned and analysed
Subject disposition is summarised in the diagram below:



Main selection criteria

- Subject 18-65 years of age, with a clinical history consistent with moderate to severe persistent HDM allergic rhinitis (with or without asthma) for at least one year prior to trial entry, with allergic rhinitis symptoms despite having received symptomatic treatment.
- Moderate to severe HDM allergic rhinitis symptoms during the baseline period defined as a daily total rhinitis symptom score of at least 6 or a score of at least 5 with one symptom being severe, during at least 8 days of the 15-days baseline period.
- Use of symptomatic medication for treatment of HDM allergic rhinitis during at least 8 days of the 15-days baseline period.
- Presence of one or more of the following ARIA quality of life items due to HDM allergic rhinitis during the baseline period:
  1) Sleep disturbance
  2) Impairment of daily activities, leisure and/or sport
  3) Impairment of school or work
- If asthma, daily use of ICS should be ≤400mcg budesonide or equivalent (i.e. corresponding to GINA treatment steps 1 or 2).
- Positive skin prick test response (wheal diameter ≥3 mm) to *Dermatophagoides pteronyssinus* (*D. pteronyssinus*) and/or *Dermatophagoides farinae* (*D. farinae*).
- Positive specific IgE against *D. pteronyssinus* and/or *D. farinae* (defined as ≥IgE Class 2; i.e. ≥0.70 kU/L).
- No clinically relevant history of symptomatic seasonal allergic rhinoconjunctivitis and/or asthma caused by an allergen to which the subject is regularly exposed and overlapping with the 8-week efficacy evaluation period.
- No reduced lung function (defined as FEV_1<70% of predicted value after adequate pharmacologic treatment).
- No clinical history of uncontrolled asthma within 3 months prior to screening.

Investigational medicinal product, dose and mode of administration, batch numbers
HDM allergy immunotherapy tablet, 6 DU, oral lyophilisate for oromucosal administration, batch numbers: 1215869, 1213919, 1276446
HDM allergy immunotherapy tablet 12 DU, oral lyophilisate for oromucosal administration, batch numbers: 1213925, 1213922, 1276447

Reference therapy, dose and mode of administration, batch number
Placebo, oral lyophilisate for oromucosal administration, batch number: 1212718

Duration of treatment
Approximately 12 months.

Criteria for evaluation – efficacy

The primary efficacy endpoint was:

- The average TCRS during the efficacy evaluation period.

The key secondary efficacy endpoints were:

- The average total allergic rhinitis DSS during the efficacy evaluation period.
- The average total allergic rhinitis DMS during the efficacy evaluation period.
- The average overall RQLQ score during the efficacy evaluation period.
- The average total combined allergic rhinoconjunctivitis score during the efficacy evaluation period.

Other secondary efficacy endpoints were:

- The average total allergic rhinoconjunctivitis DSS during the efficacy evaluation period.
- The average total allergic rhinoconjunctivitis DMS during the efficacy evaluation period.
- The average total combined conjunctivitis score during the efficacy evaluation period.
- The average total allergic conjunctivitis DSS during the efficacy evaluation period.
- The average total allergic conjunctivitis DMS during the efficacy evaluation period.
- The average total allergic rhinitis DSS, average total allergic rhinitis DMS and average TCRS during one week diary periods at visit 3, 4, 5 and 6.
- The average individual allergic rhinoconjunctivitis DSS during the efficacy evaluation period.
- Frequency (number/percentage) of symptom-free days.
- Global evaluation for efficacy.
- The average overall RQLQ score at visit 3, 4, 5 and 6.
- The change from baseline of overall RQLQ during the efficacy evaluation period and at visit 3, 4, 5 and 6.
- Average individual domains in the RQLQ score (activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, emotional) during the efficacy evaluation period.
- The change from baseline of individual domains in the RQLQ score (activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, emotional) during the efficacy evaluation period.
- The following endpoint was defined post-hoc: days with rhinitis exacerbations.

The pharmacodynamics endpoints were:

- Change from baseline to end of treatment of $\log_{10}$(IgE) for both HDM species.
- Change from baseline to end of treatment of $\log_{10}$(IgG_4) for both HDM species.

In addition, a number of patient satisfaction endpoints were assessed.

Criteria for evaluation – safety

Safety assessments included adverse events (AEs), AE discontinuations, serious adverse events (SAEs), vital signs, safety laboratory assessments, FEV_1 and physical examinations.

Statistical methods

The following analysis sets were defined:

- Total-analysis set – All subjects who entered the trial. This analysis set includes screening failures and was used for listing reasons for screening failures and AEs before randomisation.
- Full analysis set (FAS) – All randomised subjects in accordance with the ICH intent-to-treat principle. The FAS was the primary set for all efficacy analyses.
- Per protocol set (PP) – All subjects who did not have major protocol deviations that would affect the primary endpoint. Consequently, subjects in the FAS who meet one or more of the following criteria were excluded from the PP:
    A. Violated the inclusion/exclusion criteria significantly.
    B. Took prohibited medication too close to or during the efficacy evaluation period that may influence the primary endpoint.
    C. Had IMP compliance in the entire trial below 75%.
    D. Had IMP compliance in the efficacy evaluation period complying with the treatment stop date being more than a month (i.e. 30 days) prior to the last diary record in the efficacy evaluation period.
    E. Provided insufficient diary data defined as below 21 daily diary records in the efficacy evaluation period.
    F. Had any other significant protocol deviations influencing the primary efficacy endpoint.

  The final determination of protocol deviations, and thereby the composition of the PP analysis set, was

made prior to the final unblinding of the database and is documented in Appendix D of the Statistical Analysis Plan (SAP).

- Safety set (SS) – All randomised subjects, i.e. the SS is identical to the FAS. The SS was used for safety tables and listings.

Where nothing else is mentioned all statistical tests were performed with a 5% significance level, and all tests and confidence intervals (95%) were two-sided.

The primary efficacy analysis was based on a linear mixed effect (LME) model and performed on the FAS using a multiple imputation strategy for missing data (dataset denoted the FAS-MI). The response variable in the LME was the square root of the TCRS and covariates included the average rhinitis DSS at baseline and country. The primary outcome was the pairwise comparison between all 3 treatment groups using a t-test in the LME model. The resulting p-values were reported together with the associated difference in (back-transformed) adjusted means with 95% confidence intervals.

Fisher's least significant difference (LSD) procedure was used to control for multiplicity in the primary efficacy analysis. Using an F-test in the LME model, the first hypothesis to be tested was the global hypothesis of no difference in means between the 3 groups: placebo, 6 DU and 12 DU. If, and only if, this global hypothesis was rejected ($p<0.05$), all pairwise comparison between treatment groups were performed (12 DU versus placebo, 6 DU versus placebo and 12 DU versus 6 DU).

Additional analyses of the primary endpoint included analyses using the same LME model on all non-missing observations of FAS, on the PP, and on the FAS with imputation of missing data using the method of last observation carried forward (LOCF).

Multiplicity for the key secondary endpoints was controlled for by hierarchical testing in the following order:

1. The average total allergic rhinitis DSS during the efficacy evaluation period.
2. The average total allergic rhinitis DMS during the efficacy evaluation period.
3. The average overall RQLQ(S) score during the efficacy evaluation period.
4. The average total combined allergic rhinoconjunctivitis score during the efficacy evaluation period.

The 4 key secondary hypotheses were first to be tested for the 12 DU group and then, if all were statistically significant, for the 6 DU group.

The key secondary efficacy analyses were based on LME models and performed on the FAS using a multiple imputation strategy for missing data for the key secondary endpoints 1 and 2 and on non-missing observations of FAS for all of the key secondary endpoints.

In the protocol, the minimal clinically relevant difference between active and placebo in the TCRS was pre-defined to be 20% as based on the World Allergy Organization task force recommendations but with no further scientific justification. In the SAP it was therefore further specified that the rationale for choosing 20% was that this corresponds to an absolute difference of 1 in the TCRS. An absolute reduction of 1 in the TCRS is considered to be clinically relevant and can be translated into an actual clinically meaningful effect for the individual patients. Thus, an absolute reduction of 1 in the TCRS was considered the minimal clinically relevant difference for this trial.

Demography of trial population

Key demographic data (for the FAS) are summarised in the table below:

Treatment group	Placebo N = 338	Active 6 DU N = 336	Active 12 DU N = 318	Active All N = 654	Overall N = 992
HDM-allergic rhinitis, N (%)	338 (100%)	336 (100%)	318 (100%)	654 (100%)	992 (100%)
HDM-allergic asthma, N (%)	152 (45%)	152 (45%)	152 (48%)	304 (46%)	456 (46%)
Sensitisation status					
Monosensitised, N (%)	106 (31%)	98 (29%)	109 (34%)	207 (32%)	313 (32%)
Polysensitised, N (%)	232 (69%)	238 (71%)	209 (66%)	447 (68%)	679 (68%)
Gender, N (%)					
Male	166 (49%)	165 (49%)	163 (51%)	328 (50%)	494 (50%)
Female	172 (51%)	171 (51%)	155 (49%)	326 (50%)	498 (50%)
Age (years)					
Mean (SD)	32.2 (10.9)	32.5 (11.2)	32.1 (10.6)	32.3 (10.9)	32.3 (10.9)
Median	29.0	30.0	30.0	30.0	30.0
P25%- P75%	23.0 – 39.0	23.0 – 40.0	23.0 – 39.0	23.0 – 40.0	23.0 – 39.0
P5% - P95%	19.0 – 53.0	19.0 – 54.0	19.0 – 52.0	19.0 – 53.0	19.0 – 53.0
Min – max	18.0 – 66.0	18.0 – 66.0	18.0 – 63.0	18.0 – 66.0	18.0 – 66.0
Ethnic origin, N (%)					
Caucasian	331 (98%)	330 (98%)	314 (99%)	644 (98%)	975 (98%)
Asian	1 (<1%)	1 (<1%)	1 (<1%)	2 (<1%)	3 (<1%)
African	1 (<1%)	1 (<1%)	-	1 (<1%)	2 (<1%)
Hispanic	1 (<1%)	-	1 (<1%)	1 (<1%)	2 (<1%)
Other	4 (1%)	4 (1%)	2 (<1%)	6 (<1%)	10 (<1%)
Smoking history, N (%)					
Non-smoker	272 (80%)	275 (82%)	261 (82%)	536 (82%)	808 (81%)
Previous smoker	30 (9%)	29 (9%)	26 (8%)	55 (8%)	85 (9%)
Smoker	36 (11%)	32 (10%)	31 (10%)	63 (10%)	99 (10%)

The 3 treatment groups were similar with regard to all baseline demographic data.

In addition, subject baseline body measurements and vital signs were within normal ranges and similar between treatment groups.

Efficacy, quality of life and pharmacodynamics

In general, the trial confirmed the efficacy of both administered doses.

Efficacy and quality of life

The table below gives an overview of the primary efficacy results from the trial:

Endpoint	Analysis set	Treatment group	Adjusted mean TCRS [95% CI]	Absolute difference to placebo [95% CI]	p-value
Primary efficacy endpoint					
TCRS	FAS-MI (N=992)	Global*	-	-	0.003
		Placebo	6.81 [6.48;7.13]	-	-
		6 DU	5.74 [5.42;6.05]	1.07 [0.34;1.80]	0.004
		12 DU	5.71 [5.40;6.02]	1.09 [0.35;1.84]	0.004
	FAS with observations (N=879)	Placebo	6.76 [5.94;7.63]	-	-
		6 DU	5.58 [4.81;6.40]	1.18 [0.45;1.91]	0.002
		12 DU	5.53 [4.77;6.35]	1.22 [0.49;1.96]	0.001

TCRS = total combined rhinitis score; FAS-MI = full analysis set with imputation of missing data; CI = confidence interval.
*Global refers to the primary efficacy analysis of the global null hypothesis of no difference in the TCRS between the 3 treatment groups.

The MT-06 trial came out positive with a statistically significant and clinically relevant reduction of the TCRS in the efficacy evaluation period for both the 6 DU and the 12 DU group compared to placebo.

Analysis of the TCRS over the entire time course of the trial showed that a statistically significant and clinically relevant treatment effect meeting the clinical relevance criterion of 1 was present already from 14 weeks of treatment in both active groups. In addition, the clinically relevant treatment effect observed from 14 weeks of treatment continued for the entire duration of the trial, i.e. the absolute difference in the TCRS between both active groups and placebo was ≥1 from 14 weeks and at all subsequent time points during the trial indicating an all-year-round treatment effect.

In general, for both active groups, all key secondary and secondary endpoints were numerically improved as compared to placebo.

The table below gives an overview of the key secondary efficacy results from the trial:

Endpoint	Analysis set	6 DU		12 DU	
		Absolute difference to placebo [95% CI]	p-value	Absolute difference to placebo [95% CI]	p-value
Key secondary efficacy endpoints					
Rhinitis DSS	FAS-MI (N=992)	0.38 [0.01;0.74]	0.042	0.47 [0.11;0.82]	0.01
	FAS with observations (N=879)	0.40 [0.03;0.76]	0.032	0.54 [0.18;0.89]	0.003
Rhinitis DMS	FAS-MI (N=992)	0.63 [0.11;1.15]	0.017	0.54 [0.01;1.07]	0.045
	FAS with observations (N=879)	0.69 [0.18;1.20]	0.008	0.60 [0.08;1.13]	0.024
Overall RQLQ	FAS with observations (excl. RS, HR, and BA)* (N = 711)	0.13 [-0.05;0.31]	0.162	0.19 [0.02;0.37]	0.031
Combined rhinoconjunctivitis score	FAS with observations (excl. RS and HR)# (N = 754)	1.38 [0.32;2.45]	0.011¤	1.21 [0.13;2.28]	0.029

DSS = daily symptom score; DSS = daily medication score; RQLQ = rhinitis quality of life questionnaire; FAS-MI = full analysis set with imputation of missing data; CI = confidence interval; RS = Serbia; HR = Croatia; BA = Bosnia and Herzegovina; The absolute differences given are adjusted means.
*: For the RQLQ analysis, subjects from RS, HR, and BA were excluded from the FAS because no validated RQLQ questionnaire was available in local language in these countries.
#: For the analysis of the combined rhinoconjunctivitis score, subjects from RS and HR were excluded from the FAS. This was due to the fact that no eye drops were available in RS and that the only eye drops being available in HR were lodoxamide tromethamine. Accordingly, eye drops were not scored in these countries.
¤: According to the hierarchical testing strategy as defined in the SAP, the analysis of the combined rhinoconjunctivitis score was non-confirmatory for the 6 DU group since the analysis of the RQLQ score in this group was not statistically significant. This analysis can therefore not be used to make confirmatory conclusions.

For the 12 DU group, a statistically significant effect was confirmed for all key secondary endpoints with statistically significant reductions of the rhinitis DSS, rhinitis DMS, overall RQLQ score and combined rhinoconjunctivitis scores in the efficacy evaluation period compared to placebo.

For the 6 DU group, a statistically significant effect was confirmed for 2 out of the 4 key secondary endpoints with statistically significant reductions of the rhinitis DSS and rhinitis DMS in the efficacy evaluation period compared to placebo. The observed reduction of the overall RQLQ score in the efficacy evaluation period was not statistically significant making analysis of the combined rhinoconjunctivitis score non-confirmatory.

The table below gives an overview of the secondary efficacy results from the trial:

Endpoint	Analysis set	6 DU		12 DU	
		Absolute difference to placebo [95% CI]	p-value	Absolute difference to placebo [95% CI]	p-value
Secondary efficacy endpoints					
Rhinoconjunctivitis DSS	FAS with observations (N = 879)	0.40 [-0.10;0.89]	0.118	0.68 [0.19;1.17]	0.006
Rhinoconjunctivitis DMS	FAS with observations (excl. RS and HR)* (N = 754)	0.92 [0.19;1.65]	0.013	0.65 [-0.12;1.41]	0.097
Combined conjunctivitis score	FAS with observations (excl. RS and HR)* (N = 754)	0.21 [-0.13;0.55]	0.220	0.19 [-0.15;0.53]	0.279
Conjunctivitis DSS	FAS with observations (N = 879)	0.01 [-0.15;0.17]	0.898	0.13 [-0.02;0.29]	0.087
Conjunctivitis DMS	FAS with observations (excl. RS and HR)* (N = 754)	0.19 [-0.01;0.39]	0.065	0.19 [-0.02;0.39]	0.077
Change from baseline overall RQLQ	FAS with observations (excl. RS, HR, and BA)¤ (N = 691)	-0.13 [-0.31;0.05]	0.162	-0.19 [-0.37;-0.02]	0.031
Endpoint	**Analysis set**	**6 DU**		**12 DU**	
		Odds ratio (active vs. placebo) [95% CI]	**p-value**	**Odds ratio (active vs. placebo) [95% CI]**	**p-value**
Symptom-free days#	FAS with observations (N = 879)	2.33 [1.32;4.13]	0.004	2.28 [1.28;4.07]	0.005
Global evaluation	FAS with observations (N = 882)	1.50 [1.04;2.16]	0.029	1.42 [0.98;2.05]	0.062
Days with rhinitis exacerbations (post-hoc analysis)	FAS with observations (N = 879)	0.63 [0.40; 1.00]	0.050	0.45 [0.28; 0.72]	0.001

DSS = daily symptom score; DSS = daily medication score; RQLQ = rhinitis quality of life questionnaire; FAS-MI = full analysis set with imputation of missing data; CI = confidence interval; RS = Serbia; HR = Croatia; BA = Bosnia and Herzegovina; The absolute differences given are adjusted means.
*: Analysis is performed on the FAS excluding subjects from RS and HR since no eye drops were available in RS and the only eye drops being available in HR were lodoxamide tromethamine. Thus, eye drops were not scored in these countries.
¤: This analysis of the RQLQ is performed on the FAS excluding subjects from BA, RS, and HR since no RQLQ questionnaire is available in local language in these countries.
#: A symptom-free day = a day without any symptomatic medication (budesonide allowed) and with a rhinoconjunctivitis DSS of 0.

For the 12 DU group, a statistically significant effect was demonstrated for 3 out of 8 pre-defined secondary endpoints with a statistically significant reduction of the rhinoconjunctivitis DSS, a higher change from baseline of the overall RQLQ score in the efficacy evaluation period and a higher proportion of symptom-free days compared to placebo.

For the 6 DU group, a statistically significant effect was demonstrated for 3 out of 8 pre-defined secondary endpoints with a significant reduction of the rhinoconjunctivitis DMS in the efficacy evaluation period, a higher proportion of symptom-free days and a higher proportion of subjects assessing their symptoms as being improved after treatment as compared to placebo.

Post-hoc analysis of days with rhinitis exacerbations (i.e. defined as days with a rhinitis DSS of 6 or of 5 with 1 symptom being severe based on the criteria originally set for inclusion) showed that the number of days with

exacerbations was statistically significantly reduced in the 2 active groups compared to placebo with indication of a dose response. The number of days with rhinitis exacerbations was halved in the 2 active groups compared to placebo, i.e. 7% and 5% of days with rhinitis exacerbations in 6 DU and 12 DU, respectively, compared to 11% in placebo. Similar results were found in an analysis of days with rhinitis exacerbations despite the use of rhinitis symptomatic medication.

Pharmacodynamics
For pharmacodynamics assessments (i.e. specific IgE and IgG_4 against *D. pteronyssinus* and *D. farinae*), blood samples were drawn from a limited subset of the trial population (i.e. subjects from German sites who gave consent, N = 74 (7.5% of the overall trial population)).

In general, the trial demonstrated an immunological effect of the HDM allergy immunotherapy tablet in both investigated doses. The immunological data indicated a dose response with higher inductions of immunological parameters in the 12 DU group compared to the 6 DU group.

Immediately after initiation of treatment the level of specific IgE increased in both active groups reaching a peak 4 weeks after treatment start after which the level slightly decreased. The increase in the 12 DU group was numerically higher compared to the 6 DU group. No change in IgE levels was observed in the placebo group. For specific IgG_4, the level also increased immediately after treatment initiation in both active groups again with a numerically higher increase in the 12 DU group compared to the 6 DU group. In the 6 DU group, the level of IgG_4 reached a plateau after 14 weeks of treatment followed by an overall stable level during the rest of the trial. In the 12 DU group, the IgG_4 level followed a steady increase during the entire trial. No change in IgG_4 levels over time was observed in the placebo group.

The statistical analyses showed that the overall higher change from baseline in both IgE and IgG_4 observed for the 2 active groups compared to placebo was statistically significant.

Safety results
The safety evaluations demonstrated a favourable safety profile of the HDM allergy immunotherapy tablet in both administered doses. Indications of a dose response were observed for some of the evaluated safety parameters (proportion of subjects reporting AEs and number of discontinuations due to AEs).

The safety conclusions are summarised briefly below:

- 58% of the subjects in the overall trial population reported AEs during the trial with more subjects reporting AEs in the 2 active groups (i.e. 63% and 67% of the subjects in the 6 DU and 12 DU group, respectively) compared to placebo (46% of the subjects).
- Most of the AEs reported in the active groups were assessed as IMP-related with 59% and 67% of the AEs assessed as possibly related to the treatment in the 6 DU and 12 DU groups, and 29% of the AEs assessed as possibly related in the placebo group.
- The majority of all IMP-related AEs were mild or moderate in severity. This pattern applied to all 3 treatment groups.
- A total of 30 severe AEs were reported by 27 (3%) of the subjects during the trial with no overall difference in reporting rate between the 3 treatment groups. 9 of the severe AEs (reported by 8 subjects) were IMP-related. More IMP-related severe AEs were reported in actively treated subjects with 3 (<1%) subjects reporting 3 severe events and 5 subjects (2%) reporting 6 severe events in the 6 DU and 12 DU groups, respectively. No severe IMP-related AEs were reported in the placebo group.
- The most frequently reported IMP-related AEs (defined as AEs reported in ≥2 % of the subjects in at least one of the active treatment groups) were local reactions in mouth and throat such as oral pruritus, throat irritation, and oedema mouth. These were mostly reported within the first 1-2 days after the first IMP intake with few having an onset on later time points.
- SAEs were reported by 12 subjects during the trial; 8 subjects from the placebo group and 4 subjects from the 6 DU group. No SAEs were reported in the 12 DU group. All SAEs were assessed as unlikely related to the treatment.
- 30 subjects (3%) discontinued the trial due to 50 AEs. More subjects discontinued the trial in the active groups compared to placebo; 10 (3%) subjects from the 6 DU group, 13 (4%) subjects from the 12 DU group, and 7 (2%) subjects from the placebo group discontinued due to AEs.
- 1 subject from the 12 DU group received adrenaline after the first IMP intake due to mild laryngeal oedema (no vital risk). The subject subsequently continued the trial and completed the trial without other AEs except for mild oral pruritus.
- No changes as a result of the treatment were observed with regard to clinical laboratory data, vital signs and FEV_1.

Conclusions

The MT-06 trial came out positive with a statistically significant and clinically relevant reduction of the TCRS in the 6 DU as well as the 12 DU group compared to placebo. The trial thereby confirms the efficacy of both administered doses of the HDM allergy immunotherapy tablet in adult subjects with HDM allergic rhinitis.

A statistically significant and clinically relevant treatment effect was observed for both active dose groups from 14 weeks of treatment and onwards for the entire duration of the trial suggesting an early onset of action as well as an all-year-round treatment effect.

For the 12 DU group, a statistically significant effect was confirmed for all key secondary endpoints with statistically significant reductions of the rhinitis DSS, rhinitis DMS, overall RQLQ score and combined rhinoconjunctivitis scores in the efficacy evaluation period compared to placebo. For the 6 DU group, a statistically significant effect was confirmed for 2 out of the 4 key secondary endpoints (rhinitis DSS and rhinitis DMS).

The trial demonstrated an immunological effect of the HDM allergy immunotherapy tablet in both investigated doses. The immunological data indicated a dose response with numerically higher inductions of specific IgE and IgG_4 in the 12 DU group compared to the 6 DU group.

The safety evaluations demonstrated a safety profile of the HDM allergy immunotherapy tablet in both administered doses compatible with at-home administration. Indications of a dose response were observed for some of the evaluated safety parameters (proportion of subjects reporting AEs and number of discontinuations due to AEs).

In conclusion, a favourable benefit-risk profile was demonstrated for the HDM allergy immunotherapy tablet in both administered doses, i.e. 6 DU and 12 DU, in adult subjects with HDM allergic rhinitis.

Date of the final report:	13 February 2014

This trial was conducted in compliance with the principles of ICH Good Clinical Practice.