Integrated Clinical Trial Report

Trial ID: MT-04

Trial title

Efficacy of ALK house dust mite allergy immunotherapy tablet in subjects with house dust mite induced asthma. The MITRA trial.

Investigational medicinal product:	ALK house dust mite allergy immunotherapy tablet
EudraCT no.:	2010-018621-19
Development phase:	III
Indication:	House dust mite respiratory allergy
First subject first visit:	11 August 2011
Last subject last visit:	24 April 2013
Investigator:	Signatory investigator: Prof. Dr. med. [redacted]
Trial sites:	109 sites in 13 countries (AT, DE, DK, ES, FR, GB, HRV, LT, LV, NL, PL, RS, SK)
Sponsor:	Global Clinical Development ALK-Abelló A/S DK-2970 Hørsholm Phone: +45 4574 7576
Medical writer:	[redacted] PhD, ALK-Abelló A/S
Version:	Final
Date:	28 February 2014

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

Synopsis – trial MT-04 (The MITRA trial)

Title of trial
Efficacy of ALK house dust mite allergy immunotherapy tablet in subjects with house dust mite induced asthma. The MITRA trial.

Investigator
Signatory investigator: Prof. Dr. [redacted] Germany
National coordinating investigators: Prim. Univ-Prof. Dr. [redacted] Austria; Prof. Dr. [redacted] Germany; Dr. [redacted] Denmark; Dr. [redacted] Spain; Prof. [redacted] France; Prof. [redacted] United Kingdom; Dr. [redacted] Croatia; Dr. [redacted] Lithuania; Prof. [redacted] Latvia; Dr. [redacted] Netherlands; Dr. [redacted] Poland; Dr. [redacted] Serbia; Dr. [redacted] Slovakia

Trial sites
109 sites in 13 countries (Austria, Germany, Denmark, Spain, France, United Kingdom, Croatia, Lithuania, Latvia, Netherlands, Poland, Serbia, Slovakia)

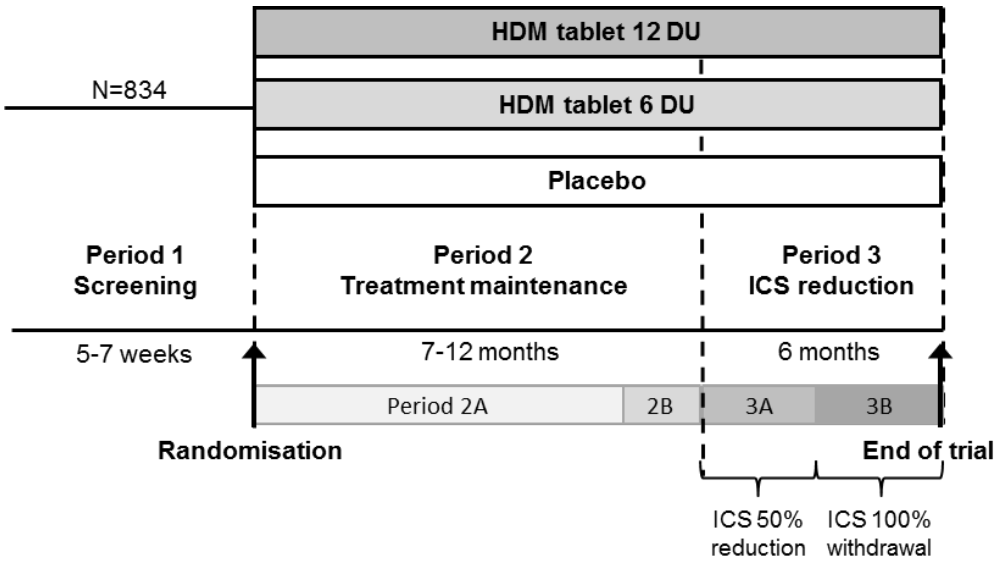
Publication
Virchow JC, Backer V, de Blay F, Prieto L, Villesen H, Ljørring C, Kuna P. ERS/ATS joint statement definition of moderate asthma exacerbation operationalized for use in a randomised, double-blind, placebo-controlled trial (MITRA trial) of the house dust mite allergy immunotherapy tablet (EAACI 2013 abstract #8), Allergy 2013: 68(s97)

Trial period
First subject first visit – 11 August 2011
Last subject last visit – 24 April 2013

Objectives
Primary objective:
To evaluate the efficacy of the ALK house dust mite (HDM) allergy immunotherapy tablet (hereafter HDM tablet) (6DU and 12DU) given once daily compared to placebo in subjects with HDM induced asthma, as measured by reducing the risk for an asthma exacerbation.
Secondary objectives:
To evaluate the effects of the HDM tablet on asthma symptoms, symptomatic medication, lung function, asthma control, asthma quality of life, immunology, pharmacoeconomics and safety

Methodology
This was a randomised, parallel-group, double-blind, placebo-controlled, multi-national, multi-centre trial in Europe including subjects with HDM allergic asthma not well-controlled by inhaled corticosteroids (ICS).

The overall trial design is shown below:



During period 1 (screening period) eligible subjects were switched from their regular asthma controller medication (including combination products) to equivalent doses of ICS (budesonide) and short-acting β2-agonist (SABA) as

needed.

At randomisation and throughout period 2 (treatment maintenance period), subjects received investigational medicinal product (IMP) in addition to ICS and SABA. During the last approximately 4 weeks of period 2 (designated period 2B), the subject started filling in the electronic dairy and recorded asthma symptoms, medication use and lung function twice daily.

Period 3 (ICS reduction/withdrawal period) began in October 2012. During the first half of this period (period 3A), the subjects had their daily ICS dose reduced by 50% and for the second half (period 3B) ICS was completely withdrawn. Subjects continued treatment with IMP for the entire period and additionally had SABA provided for use as needed. If subjects experienced an asthma exacerbation during period 3A (ICS reduction period), the dose of ICS could be adjusted at the discretion of the investigator and the subject be offered to continue in the trial at the adjusted ICS dose level for the rest of the trial (e.g. the subject should not have the ICS completely withdrawn at a later time point). If subjects experienced an asthma exacerbation during period 3B (ICS withdrawal period), when they did not use any ICS, the subjects should be discontinued from the trial.

The primary endpoint, time to first moderate or severe asthma exacerbation, was measured from start of period 3 (ICS reduction/withdrawal) until the time of first asthma exacerbation or discontinuation of trial (after which the subject would be censored from the primary analysis).

IMP treatment was discontinued for all subjects no later than at the end of period 3 (end of trial).

Number of subjects planned and analysed

The trial was planned to include 800 subjects. 1262 subjects were screened with 428 being screening failures (the most common reasons were negative HDM specific IgE test, lack of documented reversible airway obstruction, withdrawal of consent/lost to follow up prior to randomisation, negative HDM skin prick test, and forced expiratory volume in 1 second [FEV_1]<70% of predicted value). Thus, 834 subjects could be randomised (1:1:1) to placebo, 6DU or 12DU. Below is shown the subject disposition:

	Placebo (N=277)		6DU (N=275)		12DU (N=282)		Active all (N=557)		Overall (N=834)	
Treatment group	**n**	**(%n)**	**n**	**(%n)**	**n**	**(%n)**	**n**	**(%n)**	**n**	**(%n)**
Screened									1262	
Screening failures									428	
FAS	277	(100%)	275	(100%)	282	(100%)	557	(100%)	834	(100%)
- PP set	228	(82%)	218	(79%)	218	(77%)	436	(78%)	664	(80%)
- Entering period 3[a]	257	(93%)	237	(86%)	248	(88%)	485	(87%)	742	(89%)
Trial completers[b]	237	(86%)	229	(83%)	227	(80%)	456	(82%)	693	(83%)
Discontinuations										
- during entire trial	68	(25%)	72	(26%)	77	(27%)	149	(27%)	217	(26%)
Reasons for discontinuations										
- AE	8	(3%)	12	(4%)	25	(9%)	37	(7%)	45	(5%)
- Lack of efficacy	2	(<1%)	1	(<1%)	1	(<1%)	2	(<1%)	4	(<1%)
- Lost to follow-up	5	(2%)	6	(2%)	3	(1%)	9	(2%)	14	(2%)
- NC with protocol	8	(3%)	6	(2%)	7	(2%)	13	(2%)	21	(3%)
- Pregnancy	6	(2%)	1	(<1%)	1	(<1%)	2	(<1%)	8	(<1%)
- Withdrawal of consent	13	(5%)	16	(6%)	15	(5%)	31	(6%)	44	(5%)
- Other[c]	26	(9%)	30	(11%)	25	(9%)	55	(10%)	81	(10%)
• hereof discontinuations following an asthma exacerbation[d]	24	(9%)	22	(8%)	19	(7%)	41	(7%)	65	(8%)

FAS: full analysis set; PP set: pre protocol set; AE: adverse events; NC: non-compliance; N: number of subjects in FAS; n: number of subjects with events; %n: percentage of subjects in treatment group

[a]: subjects who attended visit 9 (ICS reduction) and thereby provided data for the primary efficacy analysis

[b]: 693 attended visit 13 or had an asthma exacerbation fulfilling the primary endpoint (considered trial completers)

[c]: 65 of the 81 'other reasons' were due to asthma exacerbations (see below) during period 3; the remaining reasons included to travel, use of prohibited medication, or planning of pregnancy

[d]: an asthma exacerbation during period 3A (ICS reduction) was not per se requiring trial discontinuation and subjects had the possibility of continuing in the trial up to a maximum of 3 exacerbations. During period 3B (ICS withdrawal) the protocol specified that subjects should be discontinued following an exacerbation

Main selection criteria

- Subjects ≥18 years
- A clinical relevant history consistent with HDM induced asthma of at least 1 year prior to trial entry
- Use of an appropriate amount of inhaled corticosteroid (ICS) (incl. combination products) in accordance with the GINA Guideline step 2-4 for the control of the asthma symptoms for a period of at least 6 months within the past year
- Dose of ICS after switching should at randomisation be in a range of budesonide 400-1200 µg
- Documented reversible airway obstruction
- Asthma control questionnaire (ACQ) score above or equal to 1.0 at screening
- ACQ score between or equal to 1.0 and 1.5 at visit 3 (randomisation)
- Electronic diary compliance rate ≥ 80% at visit 3 (randomisation)
- FEV_1≥70% of the predicted value
- A clinical history consistent with mild-severe HDM induced allergic rhinitis for at least 1 year
- A positive skin prick test response to *Dermatophagoides pteronyssinus* and/or *Dermatophagoides farinae*
- Positive specific IgE levels (>0.70kU/L) against *Dermatophagoides pteronyssinus* and/or *Dermatophagoides farinae*
- No clinical history of persistent allergic asthma or rhinitis caused by an allergen to which the subject is regularly exposed and sensitised (except HDM)
- No clinical history of intermittent allergic asthma or allergic rhinitis if the seasonal allergen is causing symptoms in the period of the year corresponding to the ICS reduction period (period 3; October to April)
- No previous treatment with immunotherapy with HDM allergen for more than 1 month within the last 5 years
- No clinical history of chronic sinusitis (>3 months)
- No hospitalisations for more than 12 hours due to an asthma exacerbation within the last 3 months prior to screening visit
- No current or previous use of any medication according to the list of prohibited concomitant medication
- No symptoms of or treatment for upper respiratory tract infections, or other relevant infectious processes at randomisation
- No inflammatory conditions in the oral cavity with severe symptoms such as oral lichen planus with ulcerations or severe oral mycosis at randomisation
- No clinically relevant chronic diseases

Investigational medicinal product, dose and mode of administration, batch numbers

2 active doses of IMP were included in the trial, administered as 1 tablet/day to be applied sublingually:

- HDM tablet 6DU, batch numbers: 1215869, 1276446, 1213919
- HDM tablet 12DU, batch numbers: 1213922, 1276447, 1213925

Reference therapy, dose and mode of administration, batch numbers

The reference therapy was placebo; administered as 1 tablet/day to be applied sublingually:

- Placebo, batch numbers: 1212718, 1298465

Additional therapy

- ICS was provided as budesonide powder for inhalation in strengths of 100 or 200 µg/dose for maintenance treatment of asthma
- SABA was provided as salbutamol for inhalation in strength 200 µg/dose for use as needed for control of asthma symptoms throughout the trial

Duration of treatment

Mean duration: 412 days
Median duration: 441 days
Q5%-Q95%: 91-526 days

Criteria for evaluation – efficacy

Primary endpoint:

- Time to first moderate or severe asthma exacerbation during period 3 (ICS reduction/withdrawal).

The definition of an asthma exacerbation was fulfilled if the subject experienced one or more of the criteria below, and it led to change in treatment. The baseline values (referred to in the criteria below) were the mean values during the last 14 days of the individual subject's screening period. Time to first asthma exacerbation was

measured in days from the start of period 3 (ICS reduction/withdrawal period).

Criteria a)-d) defined a moderate exacerbation:

a) Nocturnal awakening(s) due to asthma requiring SABA use for at least 2 consecutive nights or an increase of a minimum 0.75 in daily symptom score from the baseline value on at least 2 consecutive days
b) An increase from the baseline value in occasions of SABA use on at least 2 consecutive days (a minimum increase of 4 puffs per day)
c) ≥20% decrease in peak expiratory flow (PEF) from baseline value on at least 2 consecutive mornings or evenings or a ≥20% decrease in FEV_1 from baseline value
d) Visit to the emergency room or unscheduled visit to the trial centre for asthma treatment not requiring systemic corticosteroids

Criteria e)-f) defined a severe exacerbation:

e) Need of systemic corticosteroids for the treatment of asthma symptoms for at least 3 days
f) Emergency room visit because of asthma, requiring systemic corticosteroids or hospitalisation for more than 12 hours because of asthma

Key secondary endpoints:

- Time to first asthma exacerbation with deterioration in asthma symptoms (time in days from start of period 3 to the first asthma exacerbation fulfilling criterion a)
- Immunological response measured at the end of the trial in terms of specific IgG_4 against HDM allergens
- Proportion of subjects with a minimal important difference (MID) change in ACQ controlled for change in ICS (end of trial evaluation)
- Proportion of subjects with a MID change in AQLQ(S) controlled for change in ICS (end of trial evaluation)

Other secondary endpoints:

- Time to first asthma exacerbation with increased use of SABA (time in days from start of period 3 to the first asthma exacerbation fulfilling criterion b)
- Time to first asthma exacerbation with deterioration in lung function (time in days from start of period 3 to the first asthma exacerbation fulfilling criterion c)
- Time to first severe asthma exacerbation (time in days from start of period 3 to the first asthma exacerbation fulfilling criterion e or f)
- The number of first asthma exacerbations during period 3
- The total number of asthma exacerbations during period 3
- Asthma symptoms and symptomatic medication:
  - The average total asthma daytime symptom score and the average nocturnal asthma symptom score during period 2B and the first asthma exacerbation free period of period 3
  - Average nocturnal awakenings during period 2B and the first asthma exacerbation free period of period 3
  - SABA use during period 2B and the first asthma exacerbation free period of period 3
  - Proportion of symptom free days, -nights and 24-hour periods during period 2B and the first asthma exacerbation free period of period 3 (symptom free is defined as asthma symptom score =0 and SABA intake=0)
- Lung function:
  - The average morning PEF, evening PEF and diurnal variability during period 2B and the first asthma exacerbation free period of period 3
  - Change from baseline in FEV_1 and FEV_1 in % of predicted value
- Asthma control:
  - ACQ score
- Asthma quality of life:
  - Asthma quality of life questionnaire (AQLQ(S)) score
- Proportion of subjects with MID change in ACQ/AQLQ(S) controlled for change in ICS at visit 9 (ICS reduction) and visit 11 (ICS withdrawal)
- Immunological response:
  - Specific IgE
- Pharmacoeconomics assessments:
  - Short-form health survey (36 questions) (SF-36), treatment satisfaction questionnaire for medication (version II) (TSQM II), work productivity and activity impairment - asthma (WPAI:ASTHMA), health

care resource use and rate of hospitalisation

Criteria for evaluation – safety

- Adverse events (AEs), clinical safety laboratory tests, vital signs, and physical examinations

Statistical methods

The following analysis sets were used:

- **Total analysis set** – all subjects who entered the trial, including screening failures. The total analysis set will be 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 will be the primary set for all efficacy analyses and will be used for all baseline/demography tables, efficacy tables, safety tables and subject listings
  - **FAS with multiple imputation (FAS-MI)** – all randomised subjects who discontinued from the trial during period 2 were included in this analysis set as if they were following the same distribution, with regards to the first asthma exacerbation, as the observed placebo group during the efficacy assessment period (period 3), i.e. as if they were having no treatment effect
- **Per-protocol (PP) analysis set** – all subjects in the FAS with no major protocol violations which may influence the primary endpoint. The PP analysis set will be a supplementary set for the primary efficacy analysis
- **Safety analysis set** – identical to the FAS

The primary efficacy analysis was conducted based on the FAS-MI, the FAS and the PP analysis set. All other efficacy analyses were conducted based on FAS.

The primary efficacy analysis of the primary endpoint; time to first moderate or severe asthma exacerbation, was performed with a Cox proportional hazards regression analysis. The model was stratified for country and included treatment group as a factor. Based on this model the first hypothesis to be tested was the hypothesis of no difference between the 3 groups: placebo, 6DU and 12DU.

Log-transformed IgG_4 at end of trial was analysed with a linear mixed effect (LME) model. The model included treatment group, baseline value (visit 1), visit, and treatment group by visit interaction as fixed effects and country and subject as random effects. The response variable was change from baseline in $\log10(IgG_4)$ and this longitudinal analysis of $\log10(IgG_4)$ was based on data from visit 4, visit 6, visit 9 and visit 13/the end of trial visit.

Time to first asthma exacerbation involving deterioration in asthma symptoms (criterion a), was analysed in the same way as described for the primary efficacy endpoint, with the exception of right-censoring in case other criteria than the one evaluated were fulfilled. Thus, the event times were analysed with a Cox proportional hazards model stratifying for country and including treatment group as a factor. The analysis of the hazard rate was accompanied by additional descriptive analyses. Cause-specific cumulative incidence functions over time were calculated by treatment group and presented in plots and tables.

Analyses of the odds for improvement in 'MID change in ACQ (or AQLQ(S)) controlled for ICS' was performed. Change was measured from baseline (visit 3) to visit 13/ the end of trial-visit. The odds for improvement was analysed with a logistic regression analysis with treatment group as categorical fixed effect and baseline ACQ (or AQLQ(S)) and ICS as continuous fixed effects covariates. Country was included as a random effect. Last observation was carried forward if data was missing or if subjects discontinued the trial.

Time to each asthma exacerbation criterion was analysed similar to the key secondary event-time endpoint. All statistical analyses of the cause-specific hazard rates were accompanied by descriptive analyses of the cause-specific cumulative incidence functions, including plot over time and descriptive summary tables.

The frequency of first asthma exacerbations during period 3 was analysed with a generalised linear model having treatment group as a fixed effect and adjusting for covariates such as country. For each subject the binary response of whether asthma exacerbation was experienced or not was used in the analysis of the odds for asthma exacerbation during period 3.

The average total asthma daytime symptom score, average nocturnal asthma symptoms score and average number of nocturnal awakenings (total and those requiring SABA) were summarised by treatment group for period 2B (last 4 weeks of treatment maintenance period) and the first exacerbation free period of period 3 (ICS reduction/withdrawal). The endpoints average total asthma daytime symptom score during period 2B and the first asthma exacerbation free period of period 3A (ICS reduction) and of the entire period 3 were analysed a LME model.

The proportion of subjects having 0, >0-1, >1-2, or >2 nocturnal awakenings per week during period 2B and the first exacerbation free period of period 3 were summarised. The binary response of whether nocturnal awakenings were experienced or not, was used in an analysis of the odds for no nocturnal awakenings during period 2B and the first exacerbation free period of period 3. Estimates were obtained from a logistic regression analysis with treatment group as categorical fixed effect, the baseline average number of nocturnal awakenings as a regression variable and country included as a random effect.

A LME model was used for the analysis of change from baseline (visit 3) in FEV_1 and overall ACQ and AQLQ(S) as well as change from baseline in overall ACQ/AQLQ(S) of to each visit with assessments up to visit 9. The model was similar to the model described for IgG_4 above.

The prescribed total daily dose of ICS (µg/day) was summarised by visit. For visit 9, 11, and 13 (end of trial) the most recent previously prescribed total daily dose of ICS (µg/day) was summarised.

SF-36v2, TSQM II, WPAI:ASTHMA and health care resource use were summarised by treatment group.

Demography of trial population
All baseline characteristics were evenly distributed between treatment groups.

Key baseline demographics are summarised below:

Treatment group	**Placebo N=277**		**6DU N=275**		**12DU N=282**		**Overall N=834**	
	n	**(%n)**	**n**	**(%n)**	**n**	**(%n)**	**n**	**(%n)**
Medical history								
HDM allergic asthma, N (%)	277	(100%)	275	(100%)	282	(100%)	834	(100%)
HDM allergic rhinitis, N (%)	277	(100%)	275	(100%)	282	(100%)	834	(100%)
Sensitisation status								
Monosensitised to HDM, N (%)	102	(37%)	90	(33%)	91	(32%)	283	(34%)
Polysensitised, N (%)	175	(63%)	185	(67%)	191	(68%)	551	(66%)
GINA asthma control level								
Partly controlled	200	(72%)	202	(73%)	200	(71%)	602	(72%)
Uncontrolled	77	(28%)	73	(27%)	82	(29%)	232	(28%)
Gender								
Male, N (%)	151	(55%)	133	(48%)	147	(52%)	431	(52%)
Female, N (%)	126	(45%)	142	(52%)	135	(48%)	403	(48%)
Ethnic origin								
Caucasian, N (%)	273	(99%)	272	(99%)	277	(98%)	822	(99%)
Asian, N (%)	1	(<1%)	1	(<1%)	2	(<1%)	4	(<1%)
African, N (%)	1	(<1%)	1	(<1%)	2	(<1%)	4	(<1%)
Hispanic, N (%)	2	(<1%)			1	(<1%)	3	(<1%)
Other, N (%)			1	(<1%)			1	(<1%)
Smoking history								
Non-smoker, N (%)	214	(77%)	198	(72%)	214	(76%)	626	(75%)
Previous smoker, N (%)	36	(13%)	50	(18%)	38	(13%)	124	(15%)
Smoker, N (%)	27	(10%)	27	(10%)	30	(11%)	84	(10%)
Age								
Mean (SD)	33.0 (12.2)		33.6 (11.3)		33.7 (11.6)		33.4 (11.7)	
Median	30		32		32		31	
Min - Max	18.0 - 83.0		18.0 - 75.0		17.0 - 74.0		17.0 - 83.0	
Years with HDM allergic asthma								
Mean (SD)	13.3 (10.6)		12.5 (11.6)		12.9 (11.5)		12.9 (11.2)	
Median	11		10.1		10.2		11	
Min - Max	1.0 - 70.0		0.7* - 61.0		1.0 - 61.7		0.7 - 70.0	
FEV_1 at randomisation (L)								
Mean (SD)	3.52 (0.89)		3.33 (0.79)		3.33 (0.82)		3.39 (0.84)	
Median	3.41		3.23		3.24		3.29	
Min - Max	1.62 - 6.35		1.81 - 5.92		1.67 - 5.57		1.62 - 6.35	
FEV_1 in % of predicted at randomisation								
Mean (SD)	94.34 (13.79)		92.32 (12.66)		91.39 (12.91)		92.67 (13.17)	

Median	92.8	90.6	90.9	91.05
Min - Max	68.00 - 134.40	63.40 - 127.00	69.50 - 131.60	63.40 - 134.40
Prescribed total daily dose of ICS at randomisation				
Mean (SD)	580 (246)	582 (246)	602 (264)	588 (252)
Median	400	400	400	400
Min - Max	400 - 1200	200 - 1200	200 - 1200	200 - 1200
ACQ score at randomisation				
Mean (SD)	1.22 (0.18)	1.24 (0.17)	1.23 (0.17)	1.23 (0.17)
Median	1.17	1.29	1.29	1.29
Min - Max	0.86 - 2.00	0.86 - 1.71	0.71 - 1.57	0.71 - 2.00

*: one subject reported asthma "since childhood" but provided only date for start of asthma treatment (which was 0.7 years before randomisation) thus the criteria of having had asthma for at least 1 year was not violated

An estimate of 'GINA asthma control level' at randomisation suggested that overall 72% of subjects were partly controlled and 28% of subjects were uncontrolled, equally distributed between treatment groups

Efficacy results

In general, the trial confirmed the efficacy of the HDM tablet.

The panels below give an overview of the efficacy results from the trial.

	6DU vs. placebo			12DU vs. placebo		
Primary efficacy endpoint	**HR [$CI_{95\%}$]**	**% risk reduction[a]**	**p-value**	**HR [$CI_{95\%}$]**	**% risk reduction[a]**	**p-value**
Global null hypothesis (placebo=6DU=12DU)						**0.0471**
Time to first asthma exacerbation (FAS-MI)	0.72 [0.52;0.99]	28%	**0.0447**	0.69 [0.50;0.96]	31%	**0.0271**
Time to first asthma exacerbation (FAS)	0.69 [0.49;0.96]	31%	**0.0283**	0.66 [0.47;0.93]	34%	**0.0170**

1st key secondary efficacy endpoint	**HR [$CI_{95\%}$]**	**% risk reduction[a]**	**p-value**	**HR [$CI_{95\%}$]**	**% risk reduction[a]**	**p-value**
Time to first asthma exacerbation with deterioration in asthma symptoms[b]	0.72 [0.49;1.07]	28%	0.1069	0.64 [0.42;0.96]	36%	**0.0312**

2nd key secondary endpoints	**Difference in change from baseline to V13**	**p-value**	**Difference in change from baseline to V13**	**p-value**
Specific IgG_4 (*D. pteronyssinus*)	0.461	**<0.0001**	0.595	**<0.0001**
Specific IgG_4 (*D. farinae*)	0.458	**<0.0001**	0.595	**<0.0001**

3rd and 4th key secondary endpoints	**Odds ratio**	**p-value**	**Odds ratio**	**p-value**
ACQ controlled for ICS	1.12	0.6106	1.31	0.2147
AQLQ(S) controlled for ICS	1.01	0.9533	0.97	0.8927

HR: hazard ratio; [$CI_{95\%}$]: 95% confidence interval

[a]: estimated by HR; [b]: criterion a includes daily asthma symptom score and nocturnal awakenings requiring SABA

The primary efficacy result of the trial was statistically conclusive and positive. The trial revealed a statistically significantly reduced risk (estimated by HR) for having an asthma exacerbation for both 6DU and 12DU compared to placebo. The efficacy of treatment was evident for the FAS as well as for the FAS-MI, where data for subjects discontinuing the trial prior to the efficacy assessment period (Period 3) was imputed by a multiple imputation methodology including all prematurely discontinued subjects as if they belonged to the placebo group. This supports the robustness of the data. For 12DU both the FAS-MI and FAS results for the primary analysis met the pre-specified clinically relevant reduction in HR for time to first asthma exacerbation of 30% (HR ≤0.70). The pre-specified subgroup analyses of age, gender, mono/poly-sensitisations, and with/without other indoor sensitisations did not show any significant interactions between treatment and subgroup variables.

The first key secondary endpoint of time to first asthma exacerbation with deterioration in asthma symptoms (daytime symptoms or nocturnal awakenings requiring SABA) showed a statistically significant risk reduction of

36% (HR=0.64) for 12DU.

The second key secondary endpoint of change from baseline to visit 13 (end of trial) for specific IgG_4 against *D. pteronyssinus* and *D. farinae*, showed highly statistically significant changes in both active groups. Further analyses showed changes to be significant already from 4 weeks of treatment.

The 3rd and 4th key secondary endpoints were developed for this trial as attempts at making composite endpoints evaluating simultaneously the change from baseline in both ACQ/AQLQ(S) and ICS to end of trial. In practise, the change from baseline to the end of trial visit in the overall ACQ/AQLQ(S) was calculated for each subject and categorised according to the published MID and merged with the change from baseline in ICS. However, none of the endpoints showed significant changes to placebo, as the majority of subjects in all groups reported MID improvements in both ACQ and AQLQ(S) from baseline to visit 13 (end of trial). Thus, for endpoints placed below the 3rd key secondary endpoint (ACQ controlled for ICS) for 12DU in the test hierarchy, no statistical conclusions can be claimed.

The panel below gives an overview of the other secondary efficacy results related to asthma exacerbations.

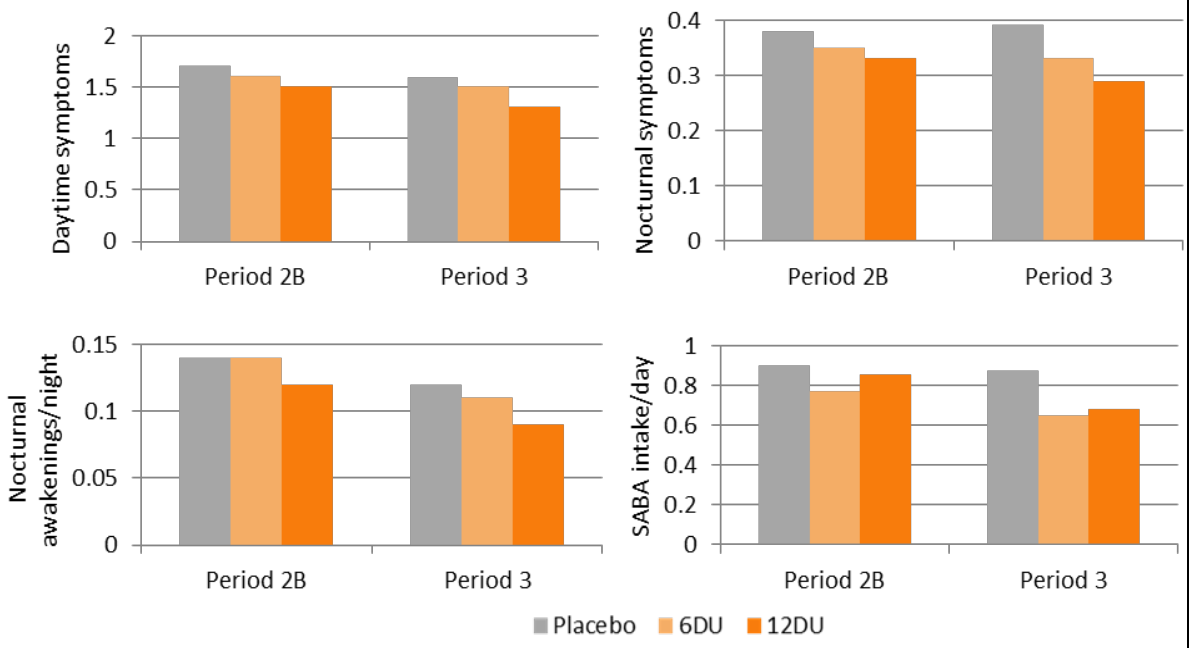
	6DU vs. placebo			**12DU vs. placebo**		
	HR [$CI_{95\%}$]	**% risk reduction[a]**	**p-value**	**HR [$CI_{95\%}$]**	**% risk reduction[a]**	**p-value**
Time to first asthma exacerbation with increased use of SABA	0.62 [0.36;1.07]	38%	0.0857	0.52 [0.29;0.94]	48%	**0.0293**
Time to first asthma exacerbation with deterioration in lung function	0.60 [0.38;0.95]	40%	**0.0297**	0.58 [0.36;0.93]	42%	**0.0221**
Time to first severe asthma exacerbation	0.79 [0.40;1.55]	21%	0.4887	0.49 [0.23;1.08]	51%	0.0761

	Odds ratio	**p-value**	**Odds ratio**	**p-value**
Odds for an asthma exacerbations during period 3	0.72	0.1045	0.65	**0.0336**

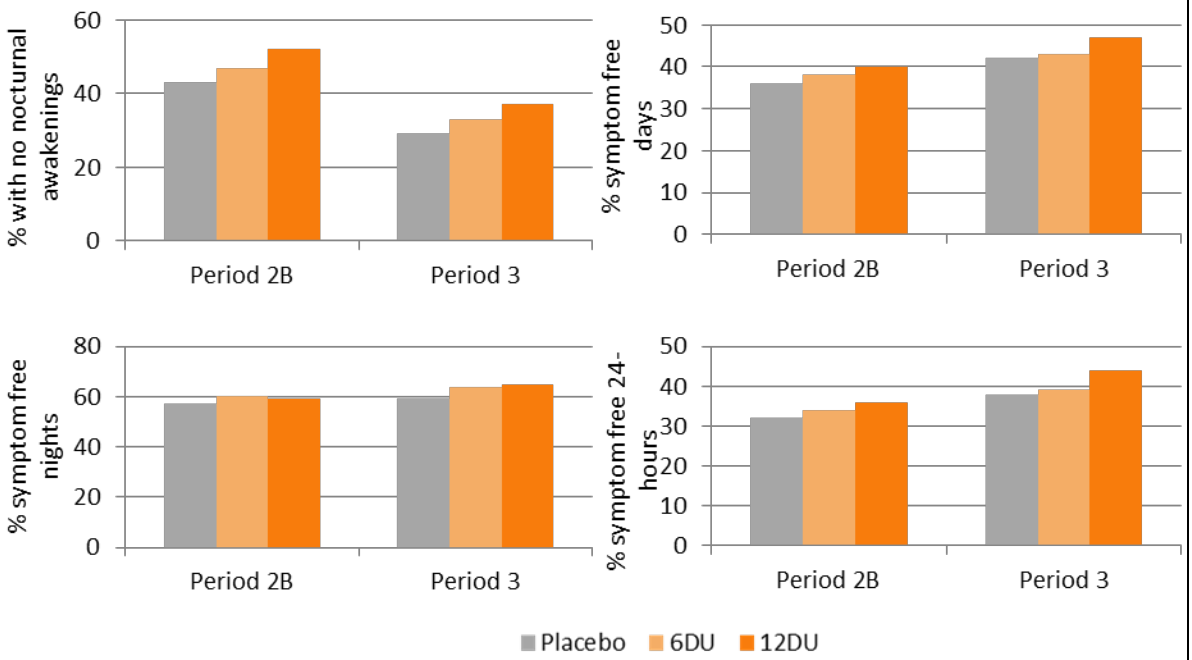
HR: hazard ratio; [$CI_{95\%}$]: 95% confidence interval
[a]: estimated by HR

The other secondary efficacy results related to asthma exacerbations supported the primary analysis in particular for the 12DU dose. Statistically significant risk reductions (estimated by HR) were found for asthma exacerbations with increased use of SABA and asthma exacerbations with deterioration in lung function. For severe asthma exacerbations, the risk reduction of 51% was found to be just above the 5% significance level (p=0.0761).

The panel below give an overview of mean values of asthma daytime and nocturnal symptom scores, nocturnal awakenings, and SABA intake for period 2B and the first asthma exacerbation free period of period 3.



The panel below give an overview of % subjects with no nocturnal awakenings, and mean values of proportion of asthma symptom free days, nights, and 24-hour periods for period 2B and the first asthma exacerbation free period of period 3.



The secondary endpoints related to asthma symptoms and medication use (presented in the 2 panels above) showed that the treatment effect of the HDM tablet was also evident prior to ICS reduction (assessed during period 2B). Thus, all endpoints were numerically improved in the active groups compared to placebo, both during period 2B (the last 4 weeks of the treatment maintenance period) and during the first exacerbation free period of period 3 (ICS reduction/withdrawal). Post hoc analyses showed statistically significant differences in the asthma daytime symptom score between 12DU and placebo during period 2B (p=0.0450). In addition, the odds for no nocturnal

awakenings were statistically significant for 12DU versus placebo during both period 2B (p=0.0409) and the first asthma exacerbation free period of period 3 (p=0.0454).

Safety results
The safety evaluations demonstrated a favourable safety profile for both 6DU and 12DU. A dose response relationship was observed for the AEs, in particular for proportion of subjects reporting IMP-related AEs and number of discontinuations due to IMP-related AEs.

The safety conclusions are summarised briefly below:

- 72% of the subjects in the overall trial population reported a total of 2084 AEs during the trial with more subjects reporting AEs in the 2 active groups (63% of the subjects in the placebo group, 74% in the 6DU group and 79% in the 12DU group)
- The majority of all AEs (1417 events, 68%) were assessed as unlikely related to the IMP (86% of all AEs in placebo, 67% of all AEs in 6DU, and 58% of all AEs in 12DU)
- The majority of all IMP-related AEs were mild (80% of all AEs) or moderate (19% of all AEs) in severity. This pattern applied to all 3 treatment groups
- 57 severe AEs were reported by 45 (5%) of the subjects during the trial. 14 subjects reported 17 severe AEs in placebo, 11 subjects reported 15 severe AEs in 6DU and 20 subjects reported 25 severe AEs in 12DU
- 12 of the severe AEs (reported by 11 subjects) were assessed as IMP-related (3 subjects (1%) with 3 AEs in placebo, 2 subjects (<1%) with 2 events in 6DU, and 6 subjects (2%) with 7 AEs in 12DU)
- The most frequently reported IMP-related AEs were local reactions in the mouth and throat such as oral pruritus, throat irritation, and oedema mouth. These were primarily reported with onset on the 1st or 2nd day of IMP administration, and with onset within 1-2 minutes after IMP administration
- SAEs were reported by 28 subjects during the trial; 11 subjects from the placebo group, 10 subjects from the 6DU group, and 7 subjects from the 12DU group
- 5 SAEs were assessed as IMP-related: 1 event of erosive oesophagitis in the placebo group (assessed as SUSAR and unblinded); 1 event of hepatocellular injury in the placebo group (assessed as SUSAR and unblinded); 1 event of laryngeal oedema in 6DU; 1 event of arthralgia in 6DU (assessed as SUSAR; reported after unblinding), and 1 event of asthma in 12DU
- 30 subjects (4%) discontinued the trial due to 57 IMP-related AEs: 4 (1%) subjects from the placebo group, 9 (3%) subjects from the 6DU group, and 17 (6%) subjects from the 12DU group
- No deaths occurred in the trial
- There were no reports of local allergic reactions compromising the airways
- There were no reports of anaphylactic reactions (including anaphylactic shocks) or AEs requiring treatment with adrenaline

No changes as a result of the treatment were observed with regard to clinical laboratory assessments, physical examinations or vital signs

Conclusions
The MT-04 trial demonstrated that the HDM tablet was effective in HDM allergic asthma. Both 6DU and 12DU had treatment effect, but 12DU was the more efficacious dose.

The primary efficacy analysis of the time to first asthma exacerbation for FAS-MI showed a statistically significant difference between active treatment and placebo. The HR for experiencing an asthma exacerbation for 12DU versus placebo was 0.69 (p=0.0271) and for 6DU versus placebo 0.72 (p=0.0477). Corresponding numbers for the FAS with observations were a HR of 0.66 for 12DU versus placebo (p=0.0170) and a HR of 0.69 for 6DU versus placebo (p=0.0283). For 12DU both the FAS-MI and FAS results for the primary analysis met the pre-specified clinically relevant reduction in HR for time to first asthma exacerbation of 30% (HR ≤0.70).

The key secondary endpoints were supportive of the primary endpoint. The time to first asthma exacerbation with deterioration in asthma symptoms were significantly reduced by 12DU compared to placebo. In addition, 12DU induced a significant change from baseline in specific IgG_4. For the analyses of ACQ/AQLQ(S) adjusted for ICS use, there were around 80% of subjects in all 3 groups with improvements, but there were no statistically significant differences between groups.

Other secondary endpoints related to asthma exacerbations, supported the primary findings of the trial. This included time to first asthma exacerbation with increased use of SABA, time to first asthma exacerbation with deterioration in lung function, time to first severe asthma exacerbation and numbers of asthma exacerbations. Thus, treatment with the HDM tablet was shown to be effective for the primary endpoint and this was supported by secondary endpoints assessing asthma symptoms, lung function and medication use.

The MT-04 trial was designed and powered as an ICS reduction/withdrawal trial with the primary aim of investigating asthma exacerbations. However, the trial also demonstrated a treatment effect prior to the ICS reduction, with all secondary asthma symptom and medication endpoints being numerically improved in the active groups compared to placebo (assessed in period 2B). Post hoc analyses confirmed statistically significant differences in 12DU versus placebo in daily asthma symptom score during period 2B and in proportion of subjects with no nocturnal awakenings both during period 2B and during the first exacerbation free period of period 3. The safety evaluations demonstrated a favourable safety profile of the HDM tablet in both administered doses. There was a dose response in the IMP-related AEs, but the events were mostly rated as mild in intensity also for the 12DU dose, and rarely leading to discontinuation. The few severe AEs and SAEs reported as related to treatment (any dose) were isolated events managed by standard medical therapy. No events required treatment with adrenaline and no events compromised the airways. There was no apparent signal for specific treatment-related events reported as serious or rated as severe. In conclusion, this trial showed a significant treatment effect of the HDM tablet on the primary efficacy endpoint supported by additional efficacy endpoints and immunological changes, and with an overall favourable safety profile of both administered doses, i.e. 6DU and 12DU, in adult subjects with HDM allergic asthma not well-controlled by ICS.
Date of the report 28-February-2014
This trial was conducted in compliance with the principles of ICH Good Clinical Practice.