Clinical Trial Protocol

Trial ID: MT-04

Title of Trial: 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 (HDM) allergy immunotherapy tablet (AIT)

Development phase: III

EudraCT no: 2010-018621-19

Sponsor: Global Clinical Development
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Approval of Final Protocol – ALK

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List of Abbreviations

ACQ  Asthma Control Questionnaire
AE   Adverse Event
AIT  Allergy Immunotherapy Tablet
ARIA Allergic Rhinitis and its Impact on Asthma
AQLQ(s) Asthma Quality of Life Questionnaire with standardised activities
CHMP Committee for Medicinal Products for Human use
CPMP Committee for Proprietary Medicinal Products
CRF Case Report Form
CRO Clinical Research Organisation
Der far Dermatophagoides farinae
Der pte Dermatophagoides pteronyssinus
DU Development Unit
EC European Community
EMEA European Medicines Agency
ESI Event of Special Interest
EU European Union
FAS Full Analysis Set
FEV1 Forced Expiratory Volume in one second
GCP Good Clinical Practice
GINA Global Initiative for Asthma
HDM House Dust Mite
ICH International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS Inhaled Glucocorticosteroid
ICTR Integrated Clinical Trial Report
ID Identification
IEC Independent Ethics Committee
IgE Immunoglobulin of isotype E
IgG4 Immunoglobulin of isotype G4
IMP Investigational Medicinal Product
IRB Institutional Review Board
LABA Long-Acting β2-Agonists
LAMA Long-Acting Muscarinic Antagonists
MAOI Monoamine Oxidase Inhibitors
MedDRA Medical Dictionary for Regulatory Activities
N Number
NCR Non Carbon Required
PEF Peak Expiratory Flow
<table>
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<th>Per Protocol</th>
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<tr>
<td>SABA</td>
<td>Short-Acting β₂-Agonists</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SAP</td>
<td>Statistical Analysis Plan</td>
</tr>
<tr>
<td>SAS</td>
<td>Statistical software package from SAS® Institute</td>
</tr>
<tr>
<td>SF-36</td>
<td>Short Form (36) Health Survey</td>
</tr>
<tr>
<td>SI</td>
<td>International System of Units</td>
</tr>
<tr>
<td>SIT</td>
<td>Specific Immunotherapy</td>
</tr>
<tr>
<td>SMC</td>
<td>Safety Monitoring Committee</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
<tr>
<td>SPT</td>
<td>Skin Prick Test</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
</tr>
<tr>
<td>TC</td>
<td>Telephone Contact</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>Wk</td>
<td>Week</td>
</tr>
<tr>
<td>WPAI:ASTHMA</td>
<td>Work Productivity and Activity Impairment - Asthma</td>
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1 Protocol Synopsis

<table>
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<th>Title of trial:</th>
<th>Efficacy of ALK house dust mite allergy immunotherapy tablet in subjects with house dust mite induced asthma.</th>
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<tr>
<td>Trial ID:</td>
<td>MT-04</td>
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<td>Development phase:</td>
<td>III</td>
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<tr>
<td>EudraCT no:</td>
<td>2010-018621-19</td>
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<td>Objectives:</td>
<td>Primary Objective:</td>
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<td>To evaluate the efficacy of the ALK house dust mite (HDM) allergy immunotherapy tablet (AIT) (6 Development Unit (DU) and 12 DÜ) given once daily compared to placebo in subjects with HDM induced asthma, as measured by reducing the risk for an asthma exacerbation.</td>
</tr>
<tr>
<td></td>
<td>Secondary Objectives:</td>
</tr>
<tr>
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<td>• To determine the effects of ALK HDM AIT on asthma symptoms and immunology.</td>
</tr>
<tr>
<td></td>
<td>• To evaluate the effects of ALK HDM AIT on lung function, asthma control, safety, symptomatic medication, asthma quality of life, and pharmacoconomics.</td>
</tr>
<tr>
<td>Definition of Asthma Exacerbation:</td>
<td>To fulfil the criteria for a moderate asthma exacerbation the subject must experience one or more of the following criteria leading to a change in treatment:</td>
</tr>
<tr>
<td></td>
<td>a) Nocturnal awakening(s) due to asthma requiring short-acting β₂-agonist (SABA) use for at least 2 consecutive nights or an increase of minimum 0.75 in daily symptom score from baseline value on at least 2 consecutive days.</td>
</tr>
<tr>
<td></td>
<td>b) An increase from baseline value in occasions of SABA use on at least 2 consecutive days (a minimum increase of 4 puffs per day).</td>
</tr>
<tr>
<td></td>
<td>c) ≥ 20% decrease in morning or evening peak expiratory flow (PEF) from baseline value on at least 2 consecutive days or ≥ 20% decrease in forced expiratory volume in one second (FEV₁) from baseline value.</td>
</tr>
<tr>
<td></td>
<td>d) Visit to the emergency room or unscheduled visit to the trial centre for asthma treatment not requiring systemic corticosteroids.</td>
</tr>
<tr>
<td></td>
<td>If the subject experience one of the following events, this will be</td>
</tr>
</tbody>
</table>
characterised as a severe asthma exacerbation:

e) Need of systemic corticosteroids for 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.

Trial design:

This is a randomised, parallel-group, double-blind, placebo-controlled, multi-national, multi-centre trial in Europe.

Figure 1. Trial design

During period 1 (screening period) eligible subjects will be switched from their regular asthma controller medication (e.g. combination products) to equivalent doses of inhaled corticosteroid (ICS) and SABA as needed.

At randomisation and throughout period 2 (treatment maintenance period), the subject will receive investigational medicinal product (IMP) in addition to ICS and SABA.

Period 3 (ICS reduction period) will begin approximately October 2011. During this period, the subject will have the ICS reduced by 50% and after 3 months 100%, while continuing treatment with IMP for these 6 months. SABA will be provided for symptomatic use for the whole period.

During period 3 (ICS reduction period) the primary efficacy objective of reducing the risk for an asthma exacerbation will be assessed by measuring time to first moderate or severe asthma exacerbation fulfilling the criteria of the protocol.
**Trial population:** Approximately 800 subjects will be randomised in the trial. The target is that 532 subjects will receive active treatment (ALK HDM 6 DU or 12 DU) and 266 subjects will receive placebo.

Key inclusion criteria:

- Written informed consent obtained before entering the trial.
- Male or female ≥ 18 years.
- A clinical relevant history consistent with HDM induced asthma of at least 1 year prior to trial entry.
- Use of asthma medication (e.g. combination products) for the control of 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 400-800 mcg.
- Documented\(^1\) reversible airway obstruction as judged by one of the following criteria:
  a) Improvement in absolute FEV\(_1\) ≥ 12% and 200 ml after administration of SABA.
  b) Improvement in PEF > 20% after administration of SABA.
  c) Diurnal variability in PEF > 20% after administration of SABA.
  d) Bronchial provocation test:
     1. A decrease in FEV\(_1\) > 15% after 6 min of sustained exercise.
     2. A decrease in FEV\(_1\) ≥ 10% from baseline is recorded after a 6 minutes period of hyperpnea in dry air.
     3. A decrease in FEV\(_1\) ≥ 15% from baseline or ≥ 10% from value obtained after the previous dose after mannitol inhalation challenge.
     4. A decrease in FEV\(_1\) ≥ 20% from baseline after methacholine inhalation challenge.
- Asthma control level above or equal to 1.0 (asthma control questionnaire (ACQ) ≥ 1.0) at visit 1 (screening).
- Asthma control level between 1.0 and 1.5\(^2\) (1.0 ≤ ACQ ≤ 1.5) at visit 3 (randomisation).
- Electronic diary compliance rate between visit 2 and visit 3 ≥ 80% at visit 3 (randomisation).

\(^1\) Historical test performed within the last 2 years is accepted.
\(^2\) If ACQ > 1.5 (uncontrolled) the dose of ICS can be adjusted at the discretion of the investigator and the visit should be rescheduled to 2 weeks later.
• FEV₁ > 60% of predicted value³.
• A clinical history consistent with HDM induced allergic rhinitis for at least 1 year.
• Positive skin prick test (SPT) response (wheal diameter ≥ 3 mm larger than the negative control) to *Dermatophagoides pteronyssinus* (*Der pte*) or *Dermatophagoides farinae* (*Der far*).
• Positive specific IgE against *Der pte* or *Der far* (≥ IgE class 2; ≥ 0.70 KU/L).

Key exclusion criteria:
• A clinical history of persistent allergic asthma or rhinitis caused by an allergen to which the subject is regularly exposed and sensitised (except HDM).
• A clinical history of intermittent allergic asthma or rhinitis if the seasonal allergen is causing symptoms in the period of the year corresponding the ICS reduction period (period 3)
• Previous treatment with immunotherapy with HDM allergen for more than 1 month within the last 5 years.
• Hospitalisation for more than 12 hours due to asthma exacerbation within the last 3 months prior to screening visit.

<table>
<thead>
<tr>
<th>Assessments:</th>
<th>Asthma exacerbation.</th>
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<tbody>
<tr>
<td></td>
<td>Asthma symptoms.</td>
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<tr>
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<td>Lung function (FEV₁ and PEF).</td>
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<tr>
<td></td>
<td>Asthma symptomatic medication.</td>
</tr>
<tr>
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<td>Asthma control (ACQ).</td>
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<tr>
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<td>Asthma quality of life (Asthma Quality of Life Questionnaire with standardised activities (AQLQ(s))).</td>
</tr>
<tr>
<td></td>
<td>Adverse events.</td>
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<td>Immunology.</td>
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<td>Safety.</td>
</tr>
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<td>Pharmacoeconomics (Short Form (36) Health Survey (SF-36), Work Productivity and Activity Impairment – Asthma (WPAI:ASTHMA)).</td>
</tr>
</tbody>
</table>

| Trial medication:          | Subjects will randomly (1:1:1) be allocated to treatment with either: |

³ For predicted values, the European Community for Coal and Steel: Standardization of Lung Function Tests is to be used (4).
• ALK HDM AIT 12 DU, oral lyophilisate for sublingual administration once daily.
• ALK HDM AIT 6 DU, oral lyophilisate for sublingual administration once daily.
• Placebo, oral lyophilisate for sublingual administration once daily.

Subjects will also receive treatment with ICS, SABA and if needed oral steroid.

| Trial schedule: | First subject first visit: Q3 2010. |
| | Last subject last visit: Q1 2012. |
| | End of trial and database closure: Q2 2012. |
# 2 Flow Chart

<table>
<thead>
<tr>
<th>Visit Title</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
<th>End of trial</th>
<th>TC Follow-up</th>
<th>Unscheduled</th>
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<tbody>
<tr>
<td>Visit ID</td>
<td>V1</td>
<td>V2</td>
<td>V3</td>
<td>V4</td>
<td>V5</td>
<td>V6</td>
</tr>
<tr>
<td>Time frame</td>
<td>V1</td>
<td>±5days</td>
<td>V3</td>
<td>±20wks</td>
<td>V3</td>
<td>±32wks</td>
</tr>
<tr>
<td>Time window</td>
<td>±7 to 5wks</td>
<td>±5days</td>
<td>±5days</td>
<td>±5days</td>
<td>±5days</td>
<td>±5days</td>
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<td>Visits to GP/specialist/hospital</td>
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<td>Demography and body measurements</td>
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<td>Reversibility test</td>
<td>X</td>
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</tbody>
</table>

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4 In the case of a withdrawal, the assessments listed at visit 13 (end of trial) must be performed at the last visit the subject attend.

5 Unscheduled visits or telephone contacts should be conducted as necessary. The evaluations/examinations stated should only be performed if deemed necessary by the investigator.

6 To be obtained before any trial related procedures are performed.
### Clinical Trial Protocol

<table>
<thead>
<tr>
<th>Visit Title</th>
<th>Screening</th>
<th>Randomisation</th>
<th>Treatment maintenance</th>
<th>ICS reduction</th>
<th>ICS withdrawal</th>
<th>End of trial</th>
<th>TC Follow-up</th>
<th>Unscheduled</th>
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<tbody>
<tr>
<td><strong>Visit id</strong></td>
<td>V1</td>
<td>V2</td>
<td>V3</td>
<td>V4</td>
<td>V5</td>
<td>V6</td>
<td>V7</td>
<td>V8</td>
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<tr>
<td><strong>Timeframe</strong></td>
<td>-7 to -5wks</td>
<td>+5days</td>
<td>0</td>
<td>+5days</td>
<td>+5days</td>
<td>+5days</td>
<td>+5days</td>
<td>+5days</td>
</tr>
<tr>
<td><strong>In- and exclusion criteria</strong></td>
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<td>X</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Randomisation</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Blood sampling (haematological and clinical chemical) | X | | | | | | X | X
| Blood sampling (specific IgE against Der pte and Der far) | X | | | | | | | |
| Blood sampling (immunology) | X | X | X | X | | | X | X
| Urinalysis        | X                  |               |                       |               |               |              |              | X           |
| Urine pregnancy test, if appropriate | X | X | | | | | | X
| Dust sampling for HDM load | X | | | | | | | X
| Dust sample collected | X | | | | | | | X
| Diary and peak flow meter issued | X | | | | | | | X
| Daily diary recording | X | | | | | | | X
| Review diary entries | X | | X | X | X | X | X | X |

**Notes:**
- Historical test performed within the last 2 years is accepted.
- Urine pregnancy tests should be performed during the trial according to local requirements (e.g., every 4th week). An urine pregnancy test must always be performed, if a menstrual period is missed.
- Asthma symptoms, lung function (measured by electronic peak flow meter) and medication use should be recorded by the subject in an electronic diary on a daily basis.
- Repeat instructions about use of the electronic diary and peak flow meter. Special emphasis should be put on action required by the subject in case of an alert.
## Trial Period

### Visit Title

<table>
<thead>
<tr>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
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<tbody>
<tr>
<td>Screening</td>
<td>Rando</td>
<td>Treatment maintenance</td>
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<tr>
<td>V1</td>
<td>V2</td>
<td>V3</td>
</tr>
<tr>
<td>V1</td>
<td>V2</td>
<td>V3</td>
</tr>
</tbody>
</table>

### Timeframe

- **V1**: -7 to 5wks
- **V2**: +5days
- **V3**: 0
- **V4**: +4wks
- **V5**: +12wks
- **V6**: +20wks
- **V7**: +32wks
- **V8**: 01 Sep 2011
- **TC1**: 03 Oct 2011
- **V9**: +1wk
- **V10**: +6wks
- **V11**: +12wks
- **V12**: +18wks
- **V13**: +24wks
- **V14**: +1wk

### Time window

- ±2days
- ±5days
- ±5days
- ±5days
- ±5days
- ±5days
- ±2days
- ±5days
- ±5days
- ±2days
- ±5days
- ±2days
- ±2days
- ±2days

### Diary and peak flow meter collected

- X
- X

### ICS dose reduced by 50%

- X

### ICS withdrawn 100%

- X

### Asthma action plan

- X
- X
- X
- X
- X
- X
- X
- X
- X

### Asthma exacerbation assessed

- X
- X
- X
- X
- X

### AEs assessed

- X
- X
- X
- X
- X
- X
- X
- X
- X
- X
- X
- X
- X
- X

### Concomitant medication recorded

- X
- X
- X
- X
- X
- X
- X
- X
- X
- X
- X
- X
- X
- X

### IMP dispensed

- X
- X
- X
- X

### Symptomatic medication dispensed

- X
- X
- X
- X
- X
- X
- X
- X
- X
- X
- X
- X

### Trial medication packages collected

- X
- X
- X
- X
- X
- X
- X
- X
- X
- X
- X
- X
- X
- X

### Drug accountability

- X
- X
- X
- X
- X
- X
- X
- X
- X
- X
- X
- X
- X
- X

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11 Once the subject has signed the informed consent concomitant medication/changes to concomitant medication as well as adverse events must be recorded.

12 First intake must be under medical supervision for 30 min.

13 The subject’s regular asthma controller medication is switched to ICS and SABA.

14 Except ICS.

15 Both IMP and symptomatic medication packages.

16 If compliance of IMP is outside range of 80-120% the subject should be re-trained in IMP procedures.
3 Introduction

3.1 Disease Background and Current Treatment Modalities

Asthma is a disease of diffuse airway inflammation caused by a variety of triggering stimuli resulting in reversible broncho constriction. It is estimated that over 30 million people in Europe have asthma (5) and deaths from asthma have reached 180,000 patients annually (6). The economic cost of asthma across Europe is thought to be in the region of €17 billion per year with an annually productivity loss estimated at €9.8 billion (7). The economic and social costs of asthma are largely due to uncontrolled disease, and are likely to rise as its prevalence, complexity and severity increases (8).

Asthma is a heterogeneous disease characterised by episodic airway obstruction resulting in shortness of breath, cough, wheezing, chest tightness etc. These symptoms are often associated with limitations in daily activities, impairment of lung function and use of symptomatic medication. An inherent characteristic of asthma is acute deteriorations (exacerbations) triggered by allergens and other factors.

There is evidence supporting that house dust mite (HDM) exposure is the most common indoor allergen associated with asthma worldwide (9;10), and 75%-85% of people with asthma display a positive result in a skin prick test (SPT) (i.e. produce specific IgE) to HDM allergens (11). The symptoms of asthma due to HDM are caused by airborne fragments of mite bodies and faeces, which are inhaled and thereby reach and activate the human immune system.

The aim of asthma treatment has for many years been to minimise asthma symptoms, optimise lung function and prevent exacerbations. Often, the primary endpoint in trials on asthma therapy has been improvement of lung function. With recognition of the importance of patient perspective and the poor correlation between lung function, inflammation and symptoms, more focus is now placed on asthma control (2). When asthma is controlled there should be no more than occasional recurrence of symptoms and exacerbations should be rare.

Inhaled corticosteroids (ICS) either dispensed alone or in combination with long-acting β2-agonists (LABA) (combination products) are considered the first-line treatment for patients with asthma as ICS are currently the most effective anti-inflammatory medications for treatment of asthma. However, these products control the disease, but when discontinued, increase of inflammation and symptoms are seen.

In a Cochrane review, 75 randomised, placebo-controlled trials of specific immunotherapy (SIT) were examined and efficacy of SIT in asthma was confirmed in terms of reducing asthma symptom scores and medication requirements. One trial indicated that the size of the clinical benefit of SIT is comparable to ICS (12).

Recently, ALK conducted the MT-02 trial, which evaluated the clinical efficacy of ALK HDM allergen immunotherapy tablet (AIT) in subjects with well-controlled mild to moderate HDM
induced asthma. The trial met its primary endpoint, which was reduction in ICS, with a statistically significant and clinically relevant steroid-sparing effect with ALK HDM AIT 6 Development Unit (DU) compared to placebo after 12 months of treatment.

3.2 Stage of Development

The ALK HDM AIT is currently being developed to treat patients with rhinoconjunctivitis and asthma due to HDM allergy. The drug substance is somewhat similar to the one used in Alutard SQ HDM (suspension for subcutaneous immunotherapy).

The ALK HDM AIT drug product is a 1:1 mixture of allergen extracts derived from 2 species of cultivated HDM (*Dermatophagoides pteronyssinus* (*Der pte*) and *Dermatophagoides farinae* (*Der far*). The drug substances are allergen extracts of the source materials where the extract solutions are filtrated, concentrated and stabilised.

The product is an oral lyophilisate for oromucosal administration. Each unit is a freeze-dried, white to off-white, debossed, solid preparation, referred to as a tablet, rapidly disintegrating in the mouth. The matrix used in the ALK HDM AIT is identical to the one used in the ALK grass AIT, Grazax®*, that has obtained a marketing authorisation throughout the European Union (EU) and in Switzerland.

Presently, 3 clinical trials have been conducted, 1 phase I trial in adults (MT-01), 1 phase I trial in children (MT-03), and 1 phase II/III trial in adults and adolescents (age ≥ 14 years) (MT-02).

The results from the MT-01 trial showed that the ALK HDM AIT in doses up to 16 DU given once daily for 28 days was tolerated in adult subjects with HDM induced asthma (with/without rhinoconjunctivitis). From this trial it was concluded that the ALK HDM AIT in doses up to 16 DU had a safety profile allowing investigations in further clinical trials.

In the MT-02 trial, it was concluded that the ALK HDM AIT was very well tolerated in strengths of 1 DU, 3 DU and 6 DU. Concurrently, a reduction relative to placebo in the use of ICS was observed for the 6 DU group. This reduction in ICS use did not compromise the asthma control level of the subjects in the 6 DU group, as assessed by subjective (asthma control questionnaire (ACQ), asthma quality of life with standardised activities (AQLQ(s))) and objective (exacerbations, forced expiratory volume in one second (FEV₁), peak expiratory flow (PEF) parameters.

The phase I trial in children (MT-03) showed that the ALK HDM AIT in doses up to 12 DU given once daily for 28 days was tolerated in paediatric subjects (5-14 yrs) with HDM induced asthma (with/without rhinoconjunctivitis). From this trial, it was concluded that the ALK HDM AIT in doses up to 12 DU (maximum exposed dose) had a safety profile allowing investigations in further paediatric clinical trials.

Overall, it is concluded that the ALK HDM AIT is tolerated in doses up to 16 DU in adults and 12 DU in children, with the most prevalent side effects being local reactions (e.g. ear pruritus, oral pruritus, mouth oedema, and throat irritation) of mild to moderate severity. The 6 DU dose
provided a statistically significant reduction in the use of ICS in patients aged 14-74 years with HDM induced mild to moderate asthma and concomitant rhinoconjunctivitis. Immunological responses similar in nature to those known from subcutaneous immunotherapy (13) were observed.

3.3 Trial Rationale

Immunotherapy has been shown to provide therapeutic benefits to subjects with HDM induced asthma (12). ALK is planning this trial in order to investigate if clinically relevant improvements in lung function and symptoms and with less dependency of asthma controller medication for the patient can be obtained.

In this trial, subjects will be randomised to 1 of 3 treatment groups (2 doses of ALK HDM AIT (6 DU or 12 DU) or placebo) and receive treatment for at least 8 months and up to 18 months. The dose selection is based on the results of the completed phase I (MT-01 and MT-03) and phase II/III (MT-02) trials. When compared to the therapeutically effective dose of the ALK grass AIT, the occurrence of the commonly expected local adverse events (AE) was less frequent for ALK HDM AIT (6 DU) than for the ALK grass AIT. For instance, oral pruritus has been reported occurring in approximately 40% of subjects receiving ALK grass AIT, but only occurred in 19% of the subjects treated with 6 DU of ALK HDM AIT. The reduced AE profile may suggest that a higher dose of ALK HDM AIT may be tolerated; therefore, 12 DU is included in this trial.

The primary objective in this trial is to evaluate the efficacy of once-daily administration of ALK HDM AIT (6 DU and 12 DU) compared to placebo as measured by reducing the risk for an asthma exacerbation in subjects with HDM induced asthma. This objective takes into account both lung function, asthma symptoms and use of asthma medication.

The definition of asthma exacerbation used in this trial is based on the recommendations given in the joint statement made by the American Thoracic Society and the European Respiratory Society 2009 (14). The task force defines asthma exacerbations as events characterised by a change from the subject’s previous status. Severe asthma exacerbations are defined as events that require urgent action in order to prevent a serious outcome, such as hospitalisation. Moderate asthma exacerbations are defined as events that are troublesome to the subject, and prompt a need for a change in treatment, but are not severe. These events are clinically identified by being outside the subject’s usual range of day-to-day asthma variation.

3.4 Risk-Benefit Assessment

Approximately 80% of people with asthma is sensitised to HDM allergens (11). Many of these also show asthma symptoms when exposed to HDM allergens. If treated with immunotherapy the underlying cause of the symptoms is modified and the subject will experience less asthma symptoms due to exposure to HDM allergens and less dependency of ICS.
The objective of the trial is to measure the reduced risk for an asthma exacerbation in subjects with HDM induced asthma. When modifying the immune system by giving the ALK HDM AIT daily, the hypothesis is that the future risk of asthma exacerbations is reduced or avoided, resulting in less stress for the patient.

The most prevalent side effects observed in previous trials with the ALK HDM AIT are local reactions (e.g. ear pruritus, oral pruritus, mouth oedema, and throat irritation) of mild to moderate severity. The risk of severe, systemic allergic adverse reactions, which may occur whenever foreign allergens are introduced, is considered minimised for the ALK HDM AIT, as the sublingual administration will not lead to any significant absorption into the systemic circulation.

Overall, the risk-benefit assessment is considered positive.

### 3.5 Ethical Considerations

This clinical trial will follow the principles of the Helsinki Declaration 1964 and subsequent amendments and clarifications (15). The trial will be approved by the local independent ethics committee (IEC)/institutional review board (IRB) or health authorities before initiation.

Placebo is chosen as control treatment due to the lack of a registered SIT comparator. To ensure that subject safety will not be compromised during the trial, subjects will be closely monitored throughout the entire trial. In order to minimise any risk related to the trial activities, the following tools have been incorporated in the protocol:

- All subjects in the trial will be provided with self-monitoring tools in the form of a pre-programmed electronic diary and a peak flow measurement device to increase awareness of asthma control. Based on individual baseline values the subject will receive an alert when changes in symptoms, lung function, or medication use, that might require medical intervention, appear.

- Each subject will receive a supply of symptomatic medication to be used on regular and as-needed basis (e.g. oral steroid).

- Each subject will receive an individualised written asthma action plan containing specific instructions on the actions required, when symptoms increase or lung function decrease.

- Each subject will be provided with a pocket-size patient card containing contact information for investigator.

Thus, the risks and benefits of participation in the trial for subjects are considered to be well balanced.
4 Trial Objectives

4.1 Primary Objective

The primary objective of the trial is to evaluate the efficacy of the ALK HDM AIT (6 DU and 12 DU) given once daily compared to placebo in subjects with HDM induced asthma, as measured by reducing the risk for an asthma exacerbation.

4.2 Key Secondary Objectives

The key secondary objectives of the trial are to determine the effects of ALK HDM AIT on asthma symptoms and immunology.

4.3 Other Secondary Objectives

Other secondary objectives include evaluating the effects of ALK HDM AIT on lung function, asthma control, safety, symptomatic medication, asthma quality of life, and pharmacoeconomics.
5 Investigational Plan

5.1 Overall Trial Design

This trial is a randomised, parallel-group, double-blind, placebo-controlled, multi-national, multi-centre trial in Europe.

The trial will be initiated when the major pollen seasons in Europe (e.g. grass) are over, and subjects will receive treatment for up to 18 months.

Approximately 800 subjects will be randomised to receive treatment with either ALK HDM AIT 6 DU, 12 DU or placebo.

Figure 1 Trial Design

During period 1 (screening period) eligible subjects will be switched from their regular asthma controller medication (e.g. combination products) to equivalent doses of ICS and short-acting β₂-agonist (SABA) as needed. The subject will measure lung function, report asthma symptoms and SABA use on a daily basis in an electronic diary. The recordings of the last 2 weeks of the screening period will serve as baseline for evaluation of asthma exacerbation.

At randomisation and throughout period 2 (treatment maintenance period), the subject will receive investigational medicinal product (IMP) in addition to ICS and SABA. The subject will be asked about asthma control, health and quality of life.
Period 3 (ICS reduction period) will begin approximately October 2011. During this period, the subject will have the ICS reduced by 50% and after 3 months 100%, while continuing treatment with IMP for these 6 months. SABA will be provided for symptomatic use for the whole period.

The subject will measure lung function, report asthma symptoms and SABA use on a daily basis in an electronic diary. During this period the investigator will have regular contact with the subject either through telephone contacts or visits to the trial centre. Beside this the investigator will also be able to monitor the subject by reviewing diary data on a designated password protected website.

If the subject experiences an asthma exacerbation the subject must contact the investigator and the episode will be treated according to standard care. If the asthma exacerbation occurs during the first 3 months of period 3 (ICS reduction period), the dose of ICS may be adjusted at the discretion of the investigator and the subject may be offered to continue in the trial at the adjusted ICS dose level for the rest of the trial (e.g. the subject will not have the dose of ICS withdrawn at a later time point) in order to give data to the secondary endpoints. Throughout the whole trial unscheduled visits may occur as deemed necessary by the subject or investigator.

The primary endpoint, time to first moderate or severe asthma exacerbation, will be time measured from start of period 3 until the episode occurs. If the subject does not experience an asthma exacerbation during period 3, the subject will end treatment with IMP when period 3 ends.

5.2 Trial Schedule

Planned first subject first visit: Q3 2010
Planned last subject last visit: Q1 2012
End of trial is defined as database closure: Q2 2012

5.3 Discussion of Design

The trial population comprises adults with asthma sensitised to HDM and no other significant allergic or respiratory disease causing symptoms or prompting medication use during the evaluation periods.

The selected design for the present trial has been chosen based on EMEA CPMP guideline “Note for guidance on the clinical investigation of medicinal products in the treatment of asthma” (16) and incorporates the recommendations of the EMEA CHMP guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases (17), and the needs stated in the WHO position paper on allergen immunotherapy for development of sublingual immunotherapy (18).

The clinical efficacy endpoint has been chosen based on the guidelines referenced above as well as the joint statement on endpoints for clinical asthma trials and clinical practice from the American Thoracic Society and the European Respiratory Society 2009 (14). Also publications
covering treatment with ICS (19-21) as well as anti-IgE drug (omalizumab) (22;23) has served as inspiration for the choice of the primary endpoint as well as the overall trial design.

Asthma exacerbations are induced by controlled tapering of ICS. In order to mimic clinical practise and follow the recommendation in GINA regarding down titration of ICS, a 50% reduction in ICS dose is planned for 3 months (2). If the subject has not experienced an asthma exacerbation within these 3 months, a full withdrawal of ICS treatment will follow.

Safety endpoints include AEs, vital signs and laboratory values, which are normally used in characterising the safety profile of an IMP.

Treatment and efficacy measurements will be initiated outside major pollen seasons to minimise bias from other allergies. The duration of treatment is based on the results from MT-02, where a clear significant clinical effect was shown after 12 months. A clear increase in the immunological response was seen after 6 months of treatment and this was increasing over the next 6 months. As efficacy measurement are to be performed during the fall and winter where the concentration of HDM is considered higher than the rest of the year, treatment duration will be minimum 8 months.

The subjects are randomised to 1 of 3 treatment arms, where they will receive treatment on a daily basis in a double-blinded fashion. Besides treatment with IMP, the subjects will receive treatment with ICS and SABA. Products containing both ICS and bronchodilator in the same inhaler device (combination products) are not allowed because the dose of ICS needs to be controlled, while the subjects must be able to use SABA without restrictions. LABA alone is not allowed as it is no longer recommended as an option for add-on treatment at any step of therapy unless used in combination products (2).

5.3.1 Asthma Exacerbation Definition

The definition of asthma exacerbation used in this trial is based on the recommendations given in the joint statement from the American Thoracic Society and the European Respiratory Society 2009. The clinical interpretation presented below is based on recommendations from GINA (2), the joint statement from the American Thoracic Society and the European Respiratory Society 2009 (14) as well as publications covering asthma exacerbations (20;21). The cut-off for daytime symptoms is based on recommendations from a multinational board of clinical experts within asthma treatment.

In order to fulfil the criteria for a moderate asthma exacerbation in practice, the subject must experience one or more of the following criteria leading to a change in treatment:

a) Nocturnal awakening(s) due to asthma requiring SABA use for at least 2 consecutive nights or an increase of minimum 0.75 in daily symptom score from baseline value on at least 2 consecutive days.

b) An increase from baseline value in occasions of SABA use on at least 2 consecutive days (a minimum increase of 4 puffs per day).
c) $\geq 20\%$ decrease in morning or evening PEF from baseline value on at least 2 consecutive days or $\geq 20\%$ 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.

The baseline value is the mean values during the last 14 days of the screening period.

If the subject experience one of the following events, this will be characterised as a severe asthma exacerbation:

e) Need of systemic corticosteroids for 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.

5.4 Trial Population

Approximately 800 subjects will be randomised in the trial. The target is that 532 subjects will receive active treatment (ALK HDM AIT 6 DU or 12 DU) and 266 subjects will receive placebo.

5.4.1 Selection Criteria

Subjects meeting all of the following inclusion criteria and none of the exclusion criteria will be considered for eligible to the trial:

5.4.1.1 Inclusion Criteria

Subjects who meet each of the following criteria are eligible for the trial:

1. Written informed consent obtained before entering the trial.

2. Male or female $\geq 18$ years.

3. A clinical relevant history consistent with HDM induced asthma of at least 1 year prior to trial entry.

4. Use of asthma medication (e.g. combination products) for the control of asthma symptoms for a period of at least 6 months within the past year.

5. Dose of ICS after switching should at randomisation be in a range of budesonide 400-800 mcg.

6. Documented$^{17}$ reversible airway obstruction as judged by one of the following criteria:

   a) Improvement in absolute FEV$_1$ $\geq 12\%$ and 200 ml after administration of SABA.

   b) Improvement in PEF $> 20\%$ after administration of SABA.

   c) Diurnal variability in PEF $> 20\%$ after administration of SABA.

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$^{17}$ Historical test performed within the last 2 years is accepted.
d) Bronchial provocation test:
1. A decrease in $FEV_1 > 15\%$ after 6 min of sustained exercise.
2. A decrease in $FEV_1 \geq 10\%$ from baseline is recorded after a 6 minutes period of hyperpnea in dry air.
3. A decrease in $FEV_1 \geq 15\%$ from baseline or $\geq 10\%$ from value obtained after the previous dose after mannitol inhalation challenge.
4. A decrease in $FEV_1 \geq 20\%$ from baseline after methacholine inhalation challenge.

7. Asthma control level above or equal to 1.0 ($ACQ \geq 1.0$) at visit 1 (screening).
8. Asthma control level between 1.0 and 1.5$^{18}$ ($1.0 \leq ACQ \leq 1.5$) at visit 3 (randomisation).
9. Electronic diary compliance rate between visit 2 and visit 3 $\geq 80\%$ at visit 3 (randomisation).
10. $FEV_1 > 60\%$ of predicted value$^{19}$.
11. A clinical history consistent with mild to severe$^{20}$ HDM induced allergic rhinitis for at least 1 year.
12. Positive SPT response (wheal diameter $\geq 3$ mm larger than the negative control) to Der pte or Der far.
13. Positive specific IgE against Der pte or Der far ($\geq$ IgE Class 2; $\geq$ 0.70 KU/L).
14. Female subjects, who are fertile$^{21}$ must have a negative pregnancy test and be willing to practise appropriate$^{22}$ contraceptive methods throughout the trial.
15. Subject willing and able to comply with trial protocol regimens.

5.4.1.2 Exclusion Criteria

Subjects who meet one or more of the following criteria are excluded from the trial:

1. A clinical history of persistent allergic asthma or rhinitis caused by an allergen to which the subject is regularly exposed and sensitised (except HDM).
2. A clinical history of intermittent allergic asthma or rhinitis if the seasonal allergen is causing symptoms in the period of the year corresponding the ICS reduction period (period 3).

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$^{18}$ If ACQ $> 1.5$ (uncontrolled) the dose of ICS can be adjusted at the discretion of the investigator and the visit should be rescheduled to 2 weeks later.

$^{19}$ For predicted values, the European Community for Coal and Steel: Standardization of Lung Function Tests is to be used (4).

$^{20}$ According to the classification of the mild to severe rhinitis symptoms described in the ARIA Guidelines (24).

$^{21}$ Females are considered infertile/post-menopausal, when there has been no menstruation for minimum 12 months prior to randomisation.

$^{22}$ Adequate contraception methods include oral contraceptives, trans dermal patches or depot injection of a progestogen drug (starting at least 4 weeks prior to IMP administration); double barrier method: condom or occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent; intrauterine device (IUD), intrauterine system (IUS), implant, or vaginal ring (placed at least 4 weeks prior to IMP administration); or male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into trial and is the sole sexual partner for that female subject.
3. Previous treatment with immunotherapy with HDM allergen for more than 1 month within the last 5 years.

4. A clinical history of chronic sinusitis (> 3 months).

5. Hospitalisation for more than 12 hours due to asthma exacerbation within the last 3 months prior to screening visit.

6. Current or previous use of any medication according to Table 2 Prohibited Concomitant Medication (section 5.5.6.3).

7. Symptoms of or treatment for upper respiratory tract infection, or other relevant infectious process at randomisation.

8. Inflammatory conditions in the oral cavity with severe symptoms such as oral lichen planus with ulcerations or severe oral mycosis at randomisation.

9. Physical examination with clinically relevant findings.

10. History of systemic allergic reaction with cardiorespiratory symptoms (e.g. food allergy, drugs or an idiopathic reaction).

11. History of recurrent urticaria during the last 2 years.

12. A history of drug induced (incl. immunotherapy) facial angioedema or a family (parents or siblings) history of hereditary angioedema.

13. Any clinically relevant chronic disease (≥ 3 months duration) (e.g. cystic fibrosis, malignancy, type I diabetes mellitus, malabsorption or malnutrition, renal or hepatic insufficiency).

14. Systemic disease affecting the immune system (e.g. autoimmune disease, immune complex disease, or immune deficiency disease).

15. Immunosuppressive treatment (ATC code L04 or L01) within 3 months prior to the screening visit (except steroids for allergy and asthma symptoms).

16. History of allergy, hypersensitivity or intolerance to IMPs (except Der pte or Der far) or symptomatic medications.

17. Being immediate family of the investigator or trial staff, defined as the investigator's/staff’s spouse, parent, child, grandparent or grandchild.

**5.4.2 Subject Withdrawal**

The subject will be advised in the informed consent form that he/she has the right to withdraw from the trial at any time without prejudice. The subject may also at any time be withdrawn from the trial at the discretion of the investigator or ALK. In case a subject drops out of the trial or is withdrawn from the trial, the withdrawal page in the case report form (CRF) should be completed. On the withdrawal page the investigator should record the date of the withdrawal, who initiated the withdrawal (i.e. subject, investigator or sponsor) and the primary reason for withdrawal.
The subject **must** be withdrawn from the trial under the following circumstances:

- If the subject experiences 1 severe asthma exacerbation causing hospitalisation during the whole period 3 (ICS reduction).
- If the subject experiences 3 asthma exacerbations during the first 3 months of period 3.
- If the subject experiences 1 asthma exacerbation during the last 3 months of period 3.
- If the subject becomes pregnant.
- If, in the investigator’s opinion, continuation in the trial would be detrimental to the subject’s well-being.
- If intolerable AE(s) occurs as determined by the investigator or subject.
- If the subject is lost to follow up.
- If randomisation code is broken, please refer to Section 5.5.3.
- If informed consent is withdrawn.

The subject **may** be withdrawn from the trial under the following circumstances:

- Treatment with prohibited drugs as defined in this protocol, please refer to Section 5.5.6.3, if these drugs are not provided as IMPs or symptomatic medication and if withdrawal is found required by ALK after discussion with the investigator.
- Protocol deviation, violation of selection criteria or deviation from the treatment plan specified in the protocol (e.g. incorrect administration of the IMP or non-attendance at trial assessments) if found required by ALK after discussion with the investigator.
- The permitted period for temporary discontinuation of treatment is exceeded, please refer to Section 5.5.5.

If an AE is involved in a withdrawal, this must be recorded as the primary reason.

In all cases, the primary reason for withdrawal must be recorded in the CRF and in the subject’s medical records. Follow up on the subject is necessary to establish whether the reason was an AE. If so, this must be reported in accordance with the appropriate procedures.

As far as possible, all examinations scheduled for visit 13 (end of trial) must be performed on all subjects who receive IMP but do not complete the trial according to the protocol. The corresponding CRF pages should be completed. If the patient withdraws or is withdrawn due to asthma exacerbation and it is not possible to perform all the examinations at the day of withdrawal, a new visit should be planned preferably within 1 week in order to complete assessments.

Reasonable effort should be made to contact any subject lost to follow up during the course of the trial in order to complete assessments and retrieve any outstanding data and medication/supplies.

Subjects withdrawn after randomisation will not be replaced.
5.5  Treatments

5.5.1  Investigational Medicinal Products

Each subject will be randomly assigned to receive active treatment or placebo.

All subjects enrolled must be identifiable throughout the trial. This will be done by using a 5-digit subject number starting at 50001 allocated to the subject at visit 1 (screening visit).

When the subject is randomised, a randomisation number will be assigned. This must always be the lowest available randomisation number. The randomisation number is a 4-digit number starting at 1001.

The IMP will be provided by ALK and the treatment will start at visit 3 (randomisation visit). Hereafter, IMP will be dispensed at visit 6, 8 and 10. The first dose will be administered under medical supervision lasting at least 30 minutes after the tablet intake.

Active Treatment
Active ingredients: Der pte and Der far extracts
Dosage form: Oral Lyophilisate
Dose/strength: 6 DU and 12 DU

Placebo Treatment
Active ingredients: None
Dosage form: Oral Lyophilisate

The daily dose of IMP is 1 tablet, which should preferably be taken in the morning. The tablet is placed under the tongue and swallowing should be avoided for 1 minute. In addition, eating and drinking is not allowed within 5 minutes after intake of IMP.

5.5.1.1  Packaging, Labelling and Storage

The tablets are supplied in blister cards containing 10 tablets. The blister cards are packed in visit specific boxes with sufficient IMP for the period between 2 dispensing visits.

Labelling will comply with national requirements and Annex 13 (25). The IMP will be identified by batch number/lot number/job number, IMP number and randomisation number.

The IMP must be stored separately from normal clinic stocks in accordance with ALK’s instructions and GMP. Until it is dispensed to the subjects, the IMP must be stored in a securely locked area, only accessible to authorised trial personnel.

Temperature monitoring of the IMP storage is not required.
5.5.2 Randomisation

This trial is a double-blind trial. The placebo tablets are similar to the active IMP in appearance, smell and taste.

Randomisation will be performed by ALK. The randomisation list will be generated by a trial independent statistician. The randomised treatment assignment will be stratified for trial centre.

Randomisation codes are kept strictly confidential, accessible only to authorised persons until the time of unblinding. At the end of the trial all code break envelopes (See Section 5.5.3) will be collected. Reconciliation will be performed between the opened envelopes and the code breaks ALK has been notified about. When the trial has been completed, the data file verified, and the protocol violations identified, the drug codes will be broken and made available for data analysis.

5.5.3 Procedures for Unblinding

2 complete sets of randomisation code envelopes are provided. 1 set is to be retained by International Pharmacovigilance at ALK and 1 set will be distributed to the trial centres.

The code for a particular subject can be broken in a medical emergency if knowing the identity of the treatment allocation would influence treatment of the subject. If possible, the investigator must contact the clinical project manager at ALK or monitor before code break. Whenever a code is broken, the person breaking the code must record the time, date and reason as well as his/her initials in the source documents and on the code envelope. The monitor must be notified immediately after code break and the subject must be withdrawn from the trial.

In case of a suspected unexpected serious adverse reaction (SUSAR), International Pharmacovigilance at ALK must unblind for regulatory purposes (see Section 6.1.3).

All codes (whether broken or not) must be kept throughout the trial period. They will be collected by the monitor at trial centre closure.

5.5.4 Compliance

Subjects will be instructed to bring all residual IMP, all empty blister units/cards and packages to every visit. Compliance will be assessed by tablet counts. Details will be recorded on the IMP accountability form.

Subjects should be re-trained in IMP procedures if IMP compliance at any visit deviates from 80%-120%.

5.5.5 Interruption/Discontinuation of Treatment

Treatment should be discontinued for the following reasons:
• In case of oral surgery, including dental extraction, treatment with IMP should be stopped for 7 days to allow healing of the oral cavity.

• Inflammatory conditions in the oral cavity with severe symptoms such as oral lichen planus with ulcerations or severe oral mycosis. Treatment with IMP should be stopped for 7 days to allow healing.

Treatment may be discontinued for the following reasons:

• Acute upper respiratory tract infection. Treatment with IMP may be stopped for up to 7 days to allow recovering.

• Other reasons if deemed necessary by the investigator.

Interruptions should be kept to a minimum and must not exceed a total of 49 days.²³

If IMP treatment is permanently discontinued, the subjects should be withdrawn from the trial.

ALK should be notified in case of IMP discontinuation due to an AE.

5.5.6 Other Medication

5.5.6.1 Symptomatic Medication

Subjects may during the trial experience asthma symptoms which require additional treatment. Symptomatic medication for this treatment will be provided by ALK to subjects as pre-defined, open-labelled medication. Symptomatic medication must be used in addition to the IMP to which the subjects have been randomised.

Storage of symptomatic medication should be temperature monitored according to storage specifications.

In order to check for compliance as well as to ensure that the patient has enough medication until the next visit, a symptomatic medication accountability form must be maintained and the subject will be asked to bring empty and partly used symptomatic medication containers for each visit.

No symptomatic medication for rhinoconjunctivitis will be provided in the trial. All medication used for treatment of rhinoconjunctivitis symptoms must be recorded as concomitant medication.

Symptomatic Medication for Asthma Symptoms

Symptomatic medication for asthma symptoms is provided as:

ICS: Budesonide inhalation powder, 100-200 mcg/dose

²³ Based on a treatment compliance of 80%.
ICS will be provided for use as maintenance treatment of asthma throughout the trial until visit 11 (ICS withdrawal).

Switching of asthma controller medication incl. combination products to ICS should be according to GINA 2008 figure 3-1 (2), see Table 1. Dose of ICS after switching should at randomisation be in a range of budesonide 400-800 mcg in order for the subject to be eligible.

### Table 1 Estimated Equipotent Daily Doses of Inhaled Glucocorticosteroids for Adult

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low Daily Dose (mcg)</th>
<th>Medium Daily Dose (mcg)</th>
<th>High Daily Dose (mcg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone dipropionate</td>
<td>200-500</td>
<td>&gt; 500-1000</td>
<td>&gt; 1000-2000</td>
</tr>
<tr>
<td>Budesonide*</td>
<td>200-400</td>
<td>&gt; 400-800</td>
<td>&gt; 800-1600</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>80-160</td>
<td>&gt; 160-320</td>
<td>&gt; 320-1280</td>
</tr>
<tr>
<td>Flunisonide</td>
<td>500-1000</td>
<td>&gt; 1000-2000</td>
<td>&gt; 2000</td>
</tr>
<tr>
<td>Fluticasone**</td>
<td>100-250</td>
<td>&gt; 250-500</td>
<td>&gt; 500-1000</td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>200-400</td>
<td>&gt; 400-800</td>
<td>&gt; 800-1200</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>400-1000</td>
<td>&gt; 1000-2000</td>
<td>&gt; 2000</td>
</tr>
</tbody>
</table>

*Budesonide 160 mcg in combination with formoterol corresponds to budesonide 200 mcg given alone.

**Fluticasone 250 mcg in combination with salmeterol corresponds to fluticasone 250 mcg given alone.

The supply of ICS should be sufficient for treatment during the period between 2 visits.

**Oral steroid:** Prednisone/prednisolone tablet, 5-30 mg

Oral steroid will be provided from visit 2 and throughout the trial. Oral steroid will be provided to be used in accordance with the individual asthma action plan. Oral steroid should only be used to treat acute severe asthma symptoms or acute deterioration of asthma symptoms or lung function in cases where the subject can not get in contact with the investigator.

The supply of oral steroid should only be so the subject can initiate treatment of a severe deterioration according to the individual asthma action plan until further treatment can be initiated.

**SABA:** Salbutamol inhalation powder, 50-200 mcg/dose

SABA will be provided for use as needed for control of bronchospatic symptoms throughout the trial.

The supply of SABA should be sufficient for treatment during the period between 2 visits.
5.5.6.2 Previous and Concomitant Medication

Concomitant medications are all medications being taken by a subject when entering the trial and all medications used in addition to the IMP and ICS during the trial.

Concomitant treatments and medications should be kept to a minimum during the trial. However, if considered necessary for the subject’s well-being and it is considered to be unlikely to interfere with the trial medication, concomitant medication may be prescribed at the discretion of the investigator according to the local standard of care.

At each visit, the investigator must ask the subject about concomitant treatments. All concomitant treatment must be documented in the subject’s medical records and in the CRF (generic name or trade name). Furthermore, each change in concomitant treatment (e.g. new treatment, discontinuation of treatment and change in dosage/routine) during the trial must be documented in the same way.

Relevant previous medication for the last 5 years prior to screening must also be recorded (see Section 5.4.1).

5.5.6.3 Prohibited Concomitant Medication

Prohibited concomitant medications are listed below.

Table 2 Prohibited Concomitant Medication

<table>
<thead>
<tr>
<th>Drug</th>
<th>Time window</th>
<th>Excluded(^{24}) due to possible interference with</th>
</tr>
</thead>
<tbody>
<tr>
<td>An investigational drug</td>
<td>≤ 30 days before visit 1 and until end of trial</td>
<td>Efficacy Safety reasons</td>
</tr>
<tr>
<td>Anti IgE treatment</td>
<td>&lt; 90 days before visit 1 and until end of trial</td>
<td>Efficacy</td>
</tr>
<tr>
<td>Antihistamine</td>
<td>For at least 3 days before SPT testing</td>
<td>SPT results</td>
</tr>
<tr>
<td>- Oral or topical</td>
<td>≤ 90 days before SPT testing</td>
<td>SPT results</td>
</tr>
<tr>
<td>- Long-acting [astemizole]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipsychotic medications with antihistaminic effects (i.e. chlorpromazine, levomepromazine, clozapine, olanzapine, tioridazine)</td>
<td>≤ 7 days before visit 1</td>
<td>SPT results</td>
</tr>
</tbody>
</table>

\(^{24}\) Excluded unless provided by ALK as symptomatic medication in the trial
### Glucocorticosteroids

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Start Date</th>
<th>End Date</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local application (on the skin area used for SPT)</td>
<td>≤ 21 days before SPT testing</td>
<td>SPT results</td>
<td></td>
</tr>
<tr>
<td>Nasal</td>
<td>From visit 9 and until end of trial</td>
<td>Efficacy</td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>≤ 60 days before SPT testing ≤ 60 days before visit 1</td>
<td>SPT results Efficacy</td>
<td></td>
</tr>
<tr>
<td>Short-acting parenteral</td>
<td>≤ 30 days before SPT testing ≤ 30 days before visit 1</td>
<td>SPT results Efficacy</td>
<td></td>
</tr>
<tr>
<td>Long-acting parenteral (intra-articular or intramuscular)</td>
<td>≤ 90 days before visit 1 and until end of trial</td>
<td>Efficacy</td>
<td></td>
</tr>
</tbody>
</table>

### Immunotherapy with Other Allergens

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Start Date</th>
<th>End Date</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaled, topical or oral nedocromil or cromolyn sodium</td>
<td>≤ 14 days before visit 1 and until end of trial</td>
<td>Efficacy</td>
<td></td>
</tr>
<tr>
<td>Leukotriene antagonists / synthase inhibitors</td>
<td>≤ 30 days before visit 1 and until end of trial</td>
<td>Efficacy</td>
<td></td>
</tr>
<tr>
<td>Long-acting β₂-agonists (LABA)</td>
<td>From visit 1 and until end of trial</td>
<td>Efficacy</td>
<td></td>
</tr>
<tr>
<td>Long-acting muscarinic antagonist (LAMA)</td>
<td>From visit 1 and until end of trial</td>
<td>Efficacy</td>
<td></td>
</tr>
<tr>
<td>Mono amine oxidase inhibitors (MAOIs)</td>
<td>≤ 21 days before visit 1 and until end of trial</td>
<td>Adrenaline</td>
<td></td>
</tr>
<tr>
<td>Pizotifen</td>
<td>≤ 7 days before visit 1</td>
<td>SPT results</td>
<td></td>
</tr>
<tr>
<td>Theophyllin</td>
<td>From visit 1 and until end of trial</td>
<td>Efficacy</td>
<td></td>
</tr>
<tr>
<td>Tricyclic antidepressant medications</td>
<td>≤ 14 days before visit 1 and until end of trial</td>
<td>Adrenaline</td>
<td></td>
</tr>
<tr>
<td>Tricyclic antidepressant medications with antihistaminic effects (e.g., doxapine, mianserine)</td>
<td>≤ 14 days before visit 1</td>
<td>SPT results</td>
<td></td>
</tr>
</tbody>
</table>

### 5.5.7 Treatment of Asthma Exacerbation

An asthma exacerbation warrants an unscheduled visit and must be treated according to standard practise:

- A moderate asthma exacerbation may result in an increase in dose of ICS treatment.
- A severe asthma exacerbation requires treatment with systemic steroid.

A telephone contact to the subject should be made 2-4 days after the unscheduled visit in order to ensure that the asthma is improving. If deemed necessary, a follow-up visit 7-10 days after the unscheduled visit may take place in order to review the symptoms and to measure vital signs and FEV₁.
If the asthma exacerbation occurs during the first 3 months of period 3 (ICS reduction period), the dose of ICS may be adjusted at the discretion of the investigator and the subject may be offered to continue in the trial at the adjusted ICS dose level for the rest of the trial (e.g. the subject will not have the dose of ICS withdrawn at a later time point) in order to give data to the secondary endpoints.

The subject must be withdrawn from the trial (see also Section 5.4.2), if the subject experiences:

- 1 severe asthma exacerbation causing hospitalisation during the whole period 3.
- 3 asthma exacerbations during the first 3 months of period 3 (ICS reduction).
- 1 asthma exacerbation during the last 3 months of period 3 (ICS withdrawal).

Asthma exacerbations occurring during period 2 will be treated according to standard care or as described above without leading to withdrawal.

5.5.8 Post-trial Treatment

After the end of the trial, the investigator must ensure trial subjects access to appropriate and available treatment.

5.6 Visit Schedule and Assessments

The trial flowchart is presented in Section 2.

5.6.1 Visit 1 (Screening)

The following procedures will be performed:

- Obtain written informed consent before any trial procedures are performed.
- Issue and collect ACQ. This should preferably be completed before any other trial related activities.
- Demographic data and body measurements, see Section 5.8.5.1.
- Medical history, see Section 5.8.5.2.
- Physical examination, see Section 5.8.4.1.
- Vital signs, see Section 5.8.4.2.
- Measure FEV₁, see Section 5.8.1.6.
- Reversibility test, see Section 5.8.5.5.
- SPT, see Section 5.8.5.4.
- Urine pregnancy test (if appropriate), see Section 5.8.4.3.
- Assess compliance with inclusion and exclusion criteria, see Section 5.4.1.
• Safety laboratory assessments (blood and urine sampling), see Section 5.8.4.3.
• Blood sampling for specific IgE against Der pte or Der far, see Section 5.8.2.
• Blood sampling for immunology, see Section 5.8.2.
• Record AEs, see Section 6.
• Record previous and concomitant medication, see Section 5.5.6.2.
• Schedule date for visit 2.

5.6.2 Visit 2

Prior to the visit, review results from laboratory assessment incl. specific IgE result. Cancel visit if subject is not eligible according to selection criteria, see Section 5.4.1.

The following procedures will be performed:
• Eligible subjects will be switched from their regular asthma controller medication to equivalent doses of ICS and SABA as needed, see Section 5.5.6.1.
• Dispense symptomatic medication, see Section 5.5.6.1.
• Issue individualised asthma action plan, see Section 6.1.5.
• Assess AEs, see Section 6.
• Record changes in concomitant medication, see Section 5.5.6.2.
• Record visits to general practitioner (GP), specialist or hospitals, see Section 5.8.3.
• Issue and instruct the subject in use of electronic diary, see Section 5.10.
• Issue and instruct the subject in use of electronic peak flow meter, see Section 5.8.1.6.
• Issue and instruct the subject in collection of a dust sample, see Section 5.8.5.5.
• Schedule date for visit 3.

5.6.3 Visit 3 (Randomisation)

Investigator must review diary entries prior to the visit, see Section 5.10.

The following procedures will be performed:
• Issue and collect ACQ.
  If ACQ > 1.5 (uncontrolled) the dose of ICS can be adjusted at the discretion of the investigator and the visit should be rescheduled to in 2 weeks time.
• Issue and collect AQLQ(s), SF-36 and WPAI:SHP. These should preferably be completed before any other trial related activities.
• Urine pregnancy test (if appropriate), see Section 5.8.4.3.
• Measure FEV1, see Section 5.8.1.6.
• Re-evaluate inclusion/exclusion criteria (repetition of SPT, blood sampling and urinalysis are not necessary), see Section 5.4.1.

• Randomise subject.

• Assess AEs, see Section 6.

• Record changes in concomitant medication, see Section 5.5.6.2.

• Record visits to GP, specialist or hospitals, see Section 5.8.3.

• Review and adjust if necessary the individualised asthma action plan, see Section 6.1.5.

• Dispense IMP, see Section 5.5.1.
  The first intake of IMP should be taken under medical supervision (at least 30 minutes after tablet intake) in the trial centre.

• Dispense symptomatic medication, see Section 5.5.6.1.
  The subject should if possible maintain the same dose of ICS throughout period 2 (until visit 9).

• Collect empty symptomatic medication packages incl. accountability, see Section 5.5.6.1.

• Collect electronic diary and electronic peak flow meter, see Section 5.10.

• Collect dust sample, see Section 5.8.5.5.

• Schedule date for visit 4.

5.6.4 Visit 4

The following procedures will be performed:

• Issue and collect ACQ. This should preferably be completed before any other trial related activities.

• Measure FEV₁, see Section 5.8.1.6.

• Blood sample for immunology, see Section 5.8.2.

• Assess AEs, see Section 6.

• Record changes in concomitant medication, see Section 5.5.6.2.

• Record visits to GP, specialist or hospitals, see Section 5.8.3.

• Review and adjust if necessary the individualised asthma action plan, see Section 6.1.5.

• Dispense symptomatic medication, see Section 5.5.6.1.
  The subject should if possible maintain the same dose of ICS throughout period 2 (until visit 9).

• Collect empty IMP and symptomatic medication packages incl. accountability, see Section 5.5.4 and 5.5.6.1.

• Schedule date for visit 5.
5.6.5 Visit 5

The following procedures will be performed:

- Issue and collect ACQ. This should preferably be completed before any other trial related activities.
- Measure FEV₁, see Section 5.8.1.6.
- Assess AEs, see Section 6.
- Record changes in concomitant medication, see Section 5.5.6.2.
- Record visits to GP, specialist or hospitals, see Section 5.8.3.
- Review and adjust if necessary the individualised asthma action plan, see Section 6.1.5.
- Dispense symptomatic medication, see Section 5.5.6.1.
  The subject should if possible maintain the same dose of ICS throughout period 2 (until visit 9).
- Collect empty IMP and symptomatic medication packages incl. accountability, see Section 5.5.4 and 5.5.6.1.
- Schedule date for visit 6.

5.6.6 Visit 6

The following procedures will be performed:

- Issue and collect ACQ, AQLQ(s), SF-36 and WPAI:ASTHMA. These should preferably be completed before any other trial related activities.
- Measure FEV₁, see Section 5.8.1.6.
- Blood sampling for immunology, see Section 5.8.2.
- Assess AEs, see Section 6.
- Record changes in concomitant medication, see Section 5.5.6.2.
- Record visits to GP, specialist or hospitals, see Section 5.8.3.
- Review and adjust if necessary the individualised asthma action plan, see Section 6.1.5.
- Dispense IMP, see Section 5.5.1.
- Dispense symptomatic medication, see Section 5.5.6.1.
  The subject should if possible maintain the same dose of ICS throughout period 2 (until visit 9).
- Collect empty and unused IMP and symptomatic medication packages incl. accountability, see Section 5.5.4 and 5.5.6.1.
- Schedule date for visit 7, if subject is randomised before 01 January 2011 otherwise schedule date for visit 8.
5.6.7  Visit 7

Only applicable for subjects randomised before 01 January 2011.

The following procedures will be performed:

- Issue and collect ACQ. This should preferably be completed before any other trial related activities.
- Measure FEV$_1$, see Section 5.8.1.6.
- Assess AEs, see Section 6.
- Record changes in concomitant medication, see Section 5.5.6.2.
- Record visits to GP, specialist or hospitals, see Section 5.8.3.
- Review and adjust if necessary the individualised asthma action plan, see Section 6.1.5.
- Dispense symptomatic medication, see Section 5.5.6.1.
  The subject should if possible maintain the same dose of ICS throughout period 2 (until visit 9).
- Collect empty IMP and symptomatic medication packages incl. accountability, see Section 5.5.4 and 5.5.6.1.
- Schedule date for visit 8.

5.6.8  Visit 8

The following procedures will be performed:

- Issue and collect ACQ, AQLQ(s), SF-36 and WPAI:ASTHMA. These should preferably be completed before any other trial related activities.
- Measure FEV$_1$, see Section 5.8.1.6.
- Assess AEs, see Section 6.
- Record changes in concomitant medication, see Section 5.5.6.2.
- Record visits to GP, specialist or hospitals, see Section 5.8.3.
- Review and adjust if necessary the individualised asthma action plan, see Section 6.1.5.
- Issue and instruct the subject in use of electronic diary, see Section 5.10.
- Issue and instruct the subject in use of electronic peak flow meter, see Section 5.8.1.6.
- Dispense IMP, see Section 5.5.1.
- Dispense symptomatic medication, see Section 5.5.6.1.
  The subject should if possible maintain the same dose of ICS throughout period 2 (until visit 9).
• Collect empty and unused IMP and symptomatic medication packages incl. accountability, see Section 5.5.4 and 5.5.6.1.
• Schedule date for visit 9.

5.6.9 Visit 9 (ICS Reduction)
The following procedures will be performed:
• Issue and collect ACQ, AQLQ(s), SF-36 and WPAI:ASTHMA. These should preferably be completed before any other trial related activities.
• Physical examination, see Section 5.8.4.1.
• Vital signs, see Section 5.8.4.2.
• Measure FEV$_1$, see Section 5.8.1.6.
• Blood sampling for immunology, see Section 5.8.2.
• Review diary entries, see Section 5.10.
• Assess AEs, see Section 6.
• Record changes in concomitant medication, see Section 5.5.6.2.
• Record visits to GP, specialist or hospitals, see Section 5.8.3.
• Review and adjust if necessary the individualised asthma action plan, see Section 6.1.5.
• Repeat instructions about use of electronic diary and electronic peak flow meter, see Section 5.8.1.6 and 5.10.
  Special emphasis should be put on action required by the subject in case of an alert.
• Reduce ICS dose by 50%.
• Dispense symptomatic medication, see Section 5.5.6.1.
• Collect empty IMP and symptomatic medication packages incl. accountability, see Section 5.5.4 and 5.5.6.1.
• Schedule date for telephone contact and visit 10.

5.6.10 Telephone Contact 1
Diary entries should be reviewed prior to the telephone contact, see Section 5.10.
At the telephone contact, the following procedures will be performed:
• Assess AEs, see Section 6.
• Record changes in concomitant medication, see Section 5.5.6.2.
5.6.11 Visit 10

The following procedures will be performed:

- Issue and collect ACQ, AQLQ(s), SF-36 and WPAI:ASTHMA. These should preferably be completed before any other trial related activities.
- Measure FEV₁, see Section 5.8.1.6.
- Review diary entries, see Section 5.10.
- Assess asthma exacerbation if necessary, see Section 5.8.1.1.
- Assess AEs, see Section 6.
- Record changes in concomitant medication, see Section 5.5.6.2.
- Record visits to GP, specialist or hospitals, see Section 5.8.3.
- Review and adjust if necessary the individualised asthma action plan, see Section 6.1.5.
- Dispense IMP, see Section 5.5.1.
- Dispense symptomatic medication, see Section 5.5.6.1.
- Collect empty and unused IMP and symptomatic medication packages incl. accountability, see Section 5.5.4 and 5.5.6.1.
- Schedule date for visit 11.

5.6.12 Visit 11 (ICS Withdrawal)

The following procedures will be performed:

- Issue and collect ACQ, AQLQ(s), SF-36 and WPAI:ASTHMA. These should preferably be completed before any other trial related activities.
- Physical examination, see Section 5.8.4.1.
- Vital signs, see Section 5.8.4.2.
- Measure FEV₁, see Section 5.8.1.6.
- Review diary entries, see Section 5.10.
- Assess asthma exacerbation if necessary, see Section 5.8.1.1.
- Assess AEs, see Section 6.
- Record changes in concomitant medication, see Section 5.5.6.2.
- Record visits to GP, specialist or hospitals, see Section 5.8.3.
- Review and adjust if necessary the individualised asthma action plan, see Section 6.1.5.
- Repeat instructions about use of electronic diary and electronic peak flow meter, see Section 5.8.1.6 and 5.10.
  Special emphasis should be put on action required by the subject in case of an alert.
• Withdraw ICS.
• Dispense symptomatic medication, see Section 5.5.6.1.
• Collect empty IMP and symptomatic medication packages incl. accountability, see Section 5.5.4 and 5.5.6.1.
• Schedule date for telephone contact and visit 12.

5.6.13 Telephone Contact 2

Diary entries should be reviewed prior to the telephone contact see Section 5.10.

At the telephone contact, the following procedures will be performed:
• Assess AEs, see Section 6.
• Record changes in concomitant medication, see Section 5.5.6.2.

5.6.14 Visit 12

The following procedures will be performed:
• Issue and collect ACQ, AQLQ(s), SF-36 and WPAI:ASTHMA. These should preferably be completed before any other trial related activities.
• Measure FEV₁, see Section 5.8.1.6.
• Review diary entries, see Section 5.10.
• Assess asthma exacerbation if necessary, see Section 5.8.1.1.
• Assess AEs, see Section 6.
• Record changes in concomitant medication, see Section 5.5.6.2.
• Record visits to GP, specialist or hospitals, see Section 5.8.3.
• Review and adjust if necessary the individualised asthma action plan, see Section 6.1.5.
• Dispense symptomatic medication (except ICS), see Section 5.5.6.1.
• Collect empty IMP and symptomatic medication packages incl. accountability, see Section 5.5.4 and 5.5.6.1.
• Issue and instruct the subject in collection of a dust sample, see Section 5.8.5.5.
• Schedule date for visit 13.

5.6.15 Visit 13 (End of Trial)

The following procedures will be performed:
• Issue and collect ACQ, AQLQ(s), SF-36 and WPAI:ASTHMA. These should preferably be completed before any other trial related activities.
• Review diary entries, see Section 5.10.
• Assess asthma exacerbation if necessary, see Section 5.8.1.1.
• Physical examination, see Section 5.8.4.1.
• Vital signs, see Section 5.8.4.2.
• Measure FEV₁, see Section 5.8.1.6.
• Safety laboratory assessments (blood and urine sampling), see Section 5.8.4.3.
• Blood sampling for immunology, see Section 5.8.2.
• Urine pregnancy test (if appropriate), see Section 5.8.4.3.
• Assess AEs, see Section 6.
• Record changes in concomitant medication, see Section 5.5.6.2.
• Record visits to GP, specialist or hospitals, see Section 5.8.3.
• Collect electronic diary and electronic peak flow meter, see Section 5.10.
• Collect dust sample, see Section 5.8.5.5.
• Collect empty and unused IMP and symptomatic medication packages incl. accountability, see Section 5.5.4 and 5.5.6.1.
• Schedule date for follow up telephone contact.

5.6.16 Follow up Telephone Contact

At the telephone contact, the following procedures will be performed:
• Record AEs, see Section 6.
  If an AE was ongoing at the previous visit, if a new AE is identified at the telephone contact or if one of the safety laboratory parameters measured at the previous visit showed a clinically significant abnormality, the subject may be asked to return to the trial centre.

5.7 Unscheduled Visits and Telephone Contacts

If the subject experience one or more of the criteria fulfilling the definition of an asthma exacerbation, see Section 5.8.1, the subject must contact the trial centre and make agreements for an unscheduled visit.

The following procedures will be performed if deemed necessary by the investigator:
• Physical examination, see Section 5.8.4.1.
• Vital signs, see Section 5.8.4.2.
• Safety laboratory assessments (blood and urine sampling), see Section 5.8.4.3.
• Measure FEV₁, see Section 5.8.1.6.
• Assess AEs, see Section 6.
• Record changes in concomitant medication, see Section 5.5.6.2.
• Collect empty symptomatic medication packages incl. accountability, see Section 5.5.6.1.
• Review and adjust if necessary the individualised asthma action plan, see Section 6.1.5.

Furthermore, the investigator should review diary data on a designated password protected website.

An unscheduled visit may also take place if the subject needs additional symptomatic medication, see Section 5.5.6.1.

Changes to doses of symptomatic medication may be agreed via telephone contacts.

5.8 Assessments

5.8.1 Efficacy Assessments

Primary and secondary efficacy endpoints include assessments of asthma exacerbations, i.e. asthma symptoms, lung function (PEF or FEV\(_1\)), use of asthma rescue medication as well as unscheduled visits to the trial centre, visits to emergency rooms or hospitalisations.

5.8.1.1 Asthma Exacerbation

If the subject experience one or more of the following criteria leading to change in treatment, the subject fulfil the criteria for an asthma exacerbation. Criteria a)-c)\(^{25}\) will be captured by entries in the electronic diary, and if any of the criteria are fulfilled the subject will be prompted by the electronic diary to contact the trial centre and make agreements for an unscheduled visit.

a) Nocturnal awakening(s) due to asthma requiring SABA use for at least 2 consecutive nights or an increase of minimum 0.75 in daily symptom score from baseline value on at least 2 consecutive days.

b) An increase from baseline value in occasions of SABA use on at least 2 consecutive days (a minimum increase of 4 puffs per day).

c) \(\geq 20\%\) decrease in morning or evening PEF from baseline value on at least 2 consecutive days or \(\geq 20\%\) 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.

The baseline value is the mean value during the last 14 days of the screening period.

If the subject experience one of the following events, this will be characterised as a severe asthma exacerbation:

\(^{25}\) Except FEV\(_1\) as this will be measured in the clinic.
e) Need of systemic corticosteroids for 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.

During the unscheduled visit the subject’s symptoms will be evaluated including asthma history,  
vital signs and FEV\textsubscript{1}.

For asthma exacerbation during period 3 the investigator must tick the appropriate asthma  
exacerbation criterion/criteria as per protocol definition on the asthma exacerbation CRF page.

5.8.1.2 Asthma Symptoms

Asthma symptoms must be assessed and graded by the subject in the electronic diary. The  
subject will assess night symptoms in the morning just after getting up, and daytime symptoms  
in the evening just before going to bed (see Appendix 2).

5.8.1.3 Use of Short-Acting β\textsubscript{2}-Agonist

Use of SABA will be recorded daily in the electronic diary by the subject.

5.8.1.4 Asthma Control

Asthma control covering the last week will be assessed by asking the subject to complete the  
ACQ (7 item weekly) (see Appendix 3).

5.8.1.5 Asthma Quality of Life

Asthma quality of life will be assessed by asking the subject to complete the AQLQ(s) (see  
Appendix 4).

5.8.1.6 Lung Function

Lung function will be measured by PEF and FEV\textsubscript{1}.

PEF measurement must be performed every morning and evening by the subject. The highest  
value of 3 consecutive measurements will transmitted to the electronic diary.

The FEV\textsubscript{1} measurements will be performed with a spirometer available at the trial centre. The  
FEV\textsubscript{1} is measured as 3 valid measurements and the highest value will be transcribed to the CRF.  
The predicted FEV\textsubscript{1} will be calculated based on the statistics from the European Community for  
Coal and Steel: Standardization of Lung Function Tests (4).
5.8.2 Immunological Assessments

To confirm the diagnosis of specific allergy against *Der pte* or *Der far* blood samples will be drawn for determination of specific IgE. These samples will be analysed centrally at a certified laboratory selected by ALK and the results will be reported to the trial centre for assessment of subject eligibility.

To assess the immunological response of the treatment, blood samples will be drawn for determination of allergen-specific antibodies and other immunological parameters. At each time point, approximately 10 ml blood will be drawn in silicone-free serum gel tubes. The samples will be analysed by the research department at ALK.

Residuals of the blood samples will be stored by ALK in a research biobank. The purpose of the storage is to be able to continue the research of the immunological processes, which are responsible for the observed clinical effect in patients treated with specific immunotherapy, and which today is not fully understood. One of the goals of this research is to identify one or more surrogate markers, which can predict clinical efficacy in the individual patient, i.e. which can help ensuring optimal treatment for future patients with specific allergies. The surrogate markers may be antibody levels, cytokine profiles, cell surface markers, specific set of proteins or metabolites, combinations hereof, etc.

When the subjects are asked to consent to the participation in the trial, they will be asked specifically if they can accept the storage of their samples within the research biobank at ALK. The answer to this question will be recorded on the consent form for retention of blood samples form, as well as on the CRF. If storage is not accepted by the subject, the blood samples will be destroyed after trial completion.

5.8.3 Pharmacoeconomic Assessments

In order to measure the subject’s perception of the quality of life and work impact during the course of the trial, the subject will be asked to complete AQLQ(s) (Appendix 4), SF-36 (Appendix 5) and WPAI:ASTHMA (Appendix 6).

Visits to GP, specialists or hospitals will also be recorded.

5.8.4 Safety Assessments

Safety assessments will include recording of all AEs, serious adverse events (SAEs), findings from physical examinations, vital signs and lung function measurements as well as the safety laboratory assessments (incl. pregnancy test).

5.8.4.1 Physical Examination

All subjects will undergo a standard physical examination.
Significant findings that are present at screening must be recorded as medical history in the CRF. Significant findings found after signing consent, which meet the definition of an AE, must be recorded on an AE page in the CRF.

The examination should be based on the following body systems: head (ear, nose, throat and eyes), oral inspection, respiratory (auscultation/stethoscopy examination of the lungs), heart (auscultation/stethoscopy examination of the heart), abdomen, urogenital, musculoskeletal, neurological, lymph nodes, skin, and other abnormalities (see Appendix 7).

5.8.4.2 Vital Signs

Vital signs will include measurement of blood pressure and heart rate in a seated position (after ≥ 3 minutes of seated inactivity).

5.8.4.3 Safety Laboratory Assessments

All laboratory assessments will be performed centrally at a certified laboratory selected by ALK. The clinical laboratory values will be reported to the investigator by the laboratory and he/she must immediately review them for significance. Results will be expressed in international System of units (SI units).

Laboratory procedures are described in a separate laboratory manual that also details blood sampling and shipment procedures.

Blood samples (approximately 10 ml per sample) should be taken using standard venepuncture techniques.

The following laboratory variables will be measured:

Haematology:

Erythrocytes, haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), platelets, leukocytes, neutrophils, eosinophils, basophils, lymphocytes and monocytes.

Blood chemistry:

Creatinine, urea, total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST) / serum glutamic-oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT) / serum glutamic pyruvic transaminase (SGPT), lactate dehydrogenase (LDH), sodium, potassium and calcium.

Urinalysis:

pH, protein, glucose, ketone, urobilinogen, bilirubin, blood and nitrate.
Furthermore, fertile female subjects will be tested for pregnancy by urine pregnancy test according to local requirements (e.g. every 4th week). If a menstrual period is missed, urine pregnancy test must be taken.

5.8.5 Other Assessments

5.8.5.1 Demography and Body Measurements

Subjects’ demographic data (date of birth, ethnic origin and sex) as well as the subjects’ height and weight will be recorded.

5.8.5.2 Medical History

The relevant allergy and asthma medical history, incl. smoking history will be recorded.

5.8.5.3 Previous and Concomitant Medication

The subjects’ uses of relevant previous medication incl. asthma and allergy medication prior to screening must be recorded, see Section 5.5.6.2.

The subjects’ use of any concomitant medication incl. asthma and allergy medication must be recorded throughout the trial.

5.8.5.4 Skin Prick Test

SPT will be performed according to ALK procedure (see Appendix 8).

The panel of extracts for SPT include the following species:
- House Dust Mites – *Dermatophagoides pteronyssinus*.
- House Dust Mites – *Dermatophagoides farinae*.
- Moulds – *Alternaria alternate*.
- Moulds – *Cladosporium herbarium*.
- Animal hair/dander – Cat.
- Animal hair/dander – Dog.
- Animal hair/dander – Horse.
- Grass – *Phleum pratense*.
- Weed – *Artemisia vulgaris*.
- Tree - *Betula verrucosa*.
- Tree – *Cupressus* (depending upon region).
• Tree – *Corylus* (depending upon region).
• Tree – *Alnus* (depending upon region)
• Tree – *Fraxinus* (depending upon region)
• Tree – *Salix alba* (depending upon region)
• Tree – *Populus alba* (depending upon region)
• Weed – *Ambrosia artemisiifolia* (depending upon region).
• Weed – *Parietaria judaica* (depending upon region)
• Histamine (positive control).
• Saline (negative control).

### 5.8.5.5 Reversibility Test

Reversible airway obstruction will be judged by improvement in lung function after administration of SABA or conduct of bronchial provocation test. Historical test performed within the last 2 years is accepted.

### 5.9 House Dust Mite Exposure

Subjects will be asked to collect a dust sample by vacuum cleaning their bed. The specific procedure to be followed is described in Appendix 9.

### 5.10 Electronic Diary

The subject will assess asthma symptoms and use of SABA by filling in questions daily in the electronic diary. PEF is measured daily by an electronic peak flow meter that transmit the data to the electronic diary.

The subject will receive instructions from the investigator on how to fill in the electronic diary twice daily i.e. in the morning just after getting up and at night before going to bed, and on how to use the electronic peak flow meter.

The most important messages subjects should receive during the instruction are:

- It is important to evaluate symptoms correctly and consistently.
- Give careful thought to evaluations of symptoms.
- Be consistent in the method used to assess symptoms.
- Contact the investigator, trial nurse or equivalent in case of doubt.

If diary compliance falls to below 80% the subject should be motivated and re-instructed in the importance of filling in the diary daily.
The investigator will at all times be able to review the diary data on a designated password protected website.

Based on individual baseline values the subject will during period 3 (from visit 8 and onwards) receive an alert on the electronic diary when changes in symptoms, lung function or medication use, that might require medical intervention, appear (e.g. increased symptoms, decrease in lung function or increase in SABA use corresponding to the criteria for a moderate asthma exacerbation). The subject will in the alert be asked to contact the investigator as soon as possible for arrangement of a possible unscheduled visit.

The investigator will receive a copy of the alert by email or fax (as agreed), so he/she may contact the subject if the subject does not react.

5.10.1 Methods of Data Collection for Electronic Diary

Diary data is transmitted to the database on a daily basis.

The investigator and the safety advisor from International Pharmacovigilance at ALK will receive data compliance reports at regular intervals. If data is missing for a subject (e.g. subject has not transmitted data, the electronic diary is malfunctioning, the subject has not filled in the diary etc.) for a period of 2 days, the investigator will receive an alert about the non-compliance by email or fax (as agreed) telling him/her to contact the subject.
6 Adverse Events

Information about AEs, whether reported by the subject, discovered by the investigator by questioning, review of diary records or detected through physical examination, laboratory test or other means, will be collected and recorded on the AE form and followed up as appropriate.

All AEs experienced by the subject and occurring from the subject has signed the informed consent and until follow up telephone contact whether or not observed in connection to the trial procedures and conduct of the trial or even before the subject receives the IMP must be recorded and reported on an AE form in the CRF.

6.1 Definitions

6.1.1 Adverse Event Definitions

AEs are defined according to ICH Harmonised Tripartite Guideline E2A, Step 5 (26).

- AE is any untoward medical occurrence in a patient or clinical trial subject administered a trial product and which does not necessarily have a causal relationship with this treatment.
- An AE can therefore be any unfavourable and unintended sign (including e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- A clinical laboratory AE is defined as any clinical laboratory abnormality regarded as clinically significant, i.e. an abnormality that suggests a disease or organ toxicity and is of a severity which requires active management (i.e. change of dose, discontinuation of trial product, more frequent follow up or diagnostic investigation).

The following are not considered AEs:

- Pre-planned procedures (documented as concomitant illness/medical history on the CRF at screening) unless the condition for which the procedures were planned has worsened from the first trial related activity after the subject has signed the informed consent form.
- Pre-existing conditions (incl. asthma symptoms) found as a result of screening procedures.
- Asthma exacerbation during period 3 unless the event fulfils the definition of a SAE.
- Fluctuations in asthma symptoms as part of the subject’s normal variation. However, during period 2 (treatment maintenance period) worsening of asthma requiring treatment with systemic corticosteroids for at least 3 days, emergency room visit because of asthma, requiring systemic corticosteroids, or unscheduled visits to the trial centre due to asthma worsening must be reported as AEs.
6.1.2 Serious Adverse Event Definitions

A SAE is any untoward medical occurrence or effect that at any dose:

- Results in death.
- Is life-threatening (this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe).
- Requires in-patient hospitalisation or prolongation of existing hospitalisation (overnight stay).
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is judged medically important (this refers to an event that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed).

6.1.3 Adverse Event Assessment Definitions

Severity

The severity of an AE is assessed by the investigator using the following definitions:

- Mild: Transient symptoms, no interference with the subject’s daily activities.
- Moderate: Marked symptoms, moderate interference with the subject’s daily activities.
- Severe: Considerable interference with the subject’s daily activities, unacceptable.

Causal Relationship to Investigational Medicinal Product

The causal relationship between an (S)AE and the IMP is assessed by the investigator using the following definitions:

- Possible: A causal relationship is conceivable and cannot be dismissed.
- Unlikely: The event is most likely related to a different aetiology than the IMP.

For SAEs, ALK also makes an assessment of causality.

An AE is considered causally related to the use of the IMP when the relationship assessment is possible. Events assessed as unlikely related to the use of IMP will be considered as having no relationship to treatment.

Any SUSAR reported to ALK is subject to regulatory reporting.
Outcome

The outcome of a (S)AE is assessed by the investigator using the following definitions:

- **Recovered**: Fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the subject signed the informed consent.
- **Recovered with sequelae**: As a result of the AE the subject suffered persistent and significant disability/incapacity (e.g. became blind, deaf, paralysed). Any AE recovered with sequelae should be classified as an SAE.
- **Not recovered**: The subject’s condition has not improved and the symptoms are unchanged at the time of trial completion; the condition is improving but a stop date has not been reached at follow up visit/telephone contact (non-serious events only) or in cases of chronic conditions, e.g. cancer, where the subject died from another event.
- **Fatal**: Event that results in death.
- **Unknown**: The subject’s condition is unknown. This term should only be used when no other definition is possible e.g. the subject is lost to follow up.

6.1.4 Event of Special Interest Definitions

Events of special interest (ESI) are AEs where detailed information is requested for safety reasons in addition to the AE form(s). Systemic allergic reactions and withdrawal due to AEs are considered ESI in this trial.

The ESI form for a systemic allergic reaction must be filled in under the following circumstances for non-serious cases:

- If any reaction is treated with epinephrine.
- If a facial oedema involving periorbital swelling occurs.
- If a subject faints or has other signs of hypotension that has no obvious aetiology.
- If a cutaneous reaction (urticaria, pruritus) progresses rapidly (within minutes) from the initial localisation.
- Objective swelling in the oro-pharynx accompanied by either hoarseness or stridor.

The ESI form for withdrawals must be filled in under the following circumstances for non-serious cases:

- AEs leading to withdrawals or discontinuation of the trial subject.

The investigator must fill in the appropriate ESI CRF page in case of an event of special interest is detected during the trial.

The investigator must provide the ESI form by fax to ALK within 5 working days:
FAX NO: + 45 45 74 86 15

The ESI form together with the corresponding AE form(s) will form basis for continuous safety surveillance of the IMP.

6.1.5 Asthma Action Plan

The investigator must provide the subject with an individualised asthma action plan (see Appendix 10). The asthma action plan must contain information about what actions the subject must take in case the investigator can not be reached or in case the electronic diary malfunctions.

6.1.6 Internal Safety Monitoring Committee.

An internal safety monitoring committee (SMC) will be established by ALK for this trial.

The SMC will convene at pre-specified intervals in accordance with a written procedure (Safety Monitoring Committee Procedure) to evaluate all received safety data (i.e. diary alerts, AE, SAE, ESI and laboratory data). Based on the review of safety data, the SMC will make recommendations according to the procedure.

6.2 Collection, Recording and Reporting of Adverse Events

All events meeting the definition of an AE must be collected and reported from the first trial-related activity after the subject signs the informed consent and until the follow up telephone contact.

At each contact with the trial centre, the subject must be asked about AEs in an objective manner like: “Have you experienced any problems since the last contact?”

AEs according to the definition, either observed by the investigator or reported by the subject, must be recorded by the investigator and evaluated. AEs must be recorded on the AE form. One single AE form must be used per AE from start to resolution. For SAEs, the SAE form must also be filled in.

If the same AE is recurring more than 1 day in row (e.g. itching in the mouth 5 min after intake of the daily dose of IMP for 5-10 minutes), the AE form will only be filled in on the first day with the description and start date. Once the recurrent AE is no longer present, the AE form should be completed with a stop date. If the AE re-appears on a subsequent day, a new AE form should be filled in.

The investigator should record the diagnosis, if available. If no diagnosis is available the investigator should record each sign and symptom as individual AEs.

For asthma exacerbation during period 3 the investigator must tick the appropriate asthma exacerbation criterion/criteria as per protocol definition on the asthma exacerbation CRF page.
Severity of asthma exacerbation throughout the trial must be graded as per protocol definition. If the asthma exacerbation fulfils the criterion for a SAE, an AE and subsequent SAE form must be filled in.

6.2.1 Serious Adverse Events

The investigator must report initial information on all SAEs to ALK within 24 hours of obtaining knowledge of the event.

The information must be provided by fax to ALK:

FAX NO: +45 45 74 86 15

EMERGENCY PHONE NO: +45 20 81 77 24

Furthermore, the investigator must complete and fax/post copies of the AE and SAE CRF pages to ALK within 5 days of obtaining knowledge of the SAE. The monitor must be informed accordingly.

ALK must inform the health authorities and IECs/IRBs in accordance with local requirements in force and the ICH guidelines for Good Clinical Practice (GCP) (27) and the EU Directive 2001/20/EC (28).

6.2.2 Adverse Events after Trial Completion

AEs occurring after the follow up telephone contact, which the investigator considers to be related to the IMP, must be reported by fax to ALK using the fax number listed in Section 6.2.1.

6.3 Follow-up on Adverse Events

6.3.1 Follow-up on Non-Serious Adverse Events

All AEs classified as non-serious must be followed until the subject has recovered or until the follow up telephone contact, whichever comes first and until all queries have been resolved.

Cases of chronic conditions can after the subject has completed the trial be closed with the outcome “recovering” or “not recovered”.

6.3.2 Follow-up on Serious Adverse Events

All AEs classified as serious should be followed until the outcome of the event is “recovered”, “recovered with sequelae”, or “death”, and until all queries have been resolved.

Cases of chronic conditions e.g. cancer can after the subject has completed the trial be closed with the outcome “not recovered”.

Clinical Trial Protocol
Trial ID: MT-04
Version: Final
Date: 12 Apr 2010
The investigator must forward follow up information on SAEs to ALK within 5 calendar days of obtaining the follow up information.

6.4 Pregnancy

Female subjects must be advised to notify the investigator immediately if becoming pregnant.

The investigator must report any pregnancy reported during the trial to ALK. The subject will consent on enrolment that the investigator will report any pregnancy during the trial to ALK and will consent to provide information about the pregnancy, delivery and health of infant until the age of 1 month. The investigator must report information on pregnancy and follow up within 14 calendar days of obtaining the information, using the pregnancy form.

Any subject becoming pregnant during the trial will be withdrawn from the trial (see Section 5.4.2).

For cases of parental exposure, information about the father (e.g. date of exposure of IMP, occupation, environmental factors, medical history and concomitant medication) and the mother (e.g. concomitant diseases, possible date of conception, course of pregnancy, treatments), must be collected. The investigator must report information on pregnancy and follow up within 14 calendar days of obtaining the information, using the pregnancy form.

Complications in relation to pregnancy must be reported as AEs. In case of late spontaneous abortion, any malformation of the foetus, stillbirth or a congenital anomaly/birth defect, the event must be reported and followed up as a SAE.

Any abnormalities observed in an infant (up to 2 years of age) and suspected to be related to intra-uterine exposure to the IMP should be reported to ALK.

6.5 Overdose, Abuse and Misuse of Investigational Medicinal Product

If doses higher than the recommended dose are taken, whether intentionally or unintentionally, the risk of AEs increases. This includes the risk of systemic allergic reactions or severe local reactions. For the purpose of this protocol an overdose is defined as any (cumulative) dose taken in 1 day that exceeds the dose intended by the protocol, regardless of whether the dose has caused any AEs.

Cases of overdose should be reported as an AE using the AE form in the subjects CRF using the terminology: “accidental overdose” or “intentional overdose” as descriptive term, and stating whether or not the incident was related to other observed or experienced symptoms or events. If an event is classified as an SAE, it must be reported as such. Abuse and misuse of the IMP should be reported in the same way on an AE form using the descriptive term “abuse of IMP” or “misuse of IMP” respectively.

In case of overdose, abuse or misuse of IMP, the subject may be withdrawn from the trial (see Section 5.4.2).
7 Data Management

7.1 Data Collection

7.1.1 Case Report Form

The investigator must enter the information required by the protocol in the CRFs. The CRFs will be supplied as non carbon required (NCR) paper.

The monitor will review the CRFs for completeness and accuracy and instruct the personnel at the trial centre to make any required corrections or additions.

As soon as the CRFs are monitored and considered correctly completed the original CRFs are sent to ALK by the monitor. 1 copy of the CRF is retained at the trial centre.

Once the CRFs are received by ALK, their receipt is recorded and the original is forwarded to the responsible data management staff for processing.

7.1.2 Electronic Diary

The electronic diary is dispatched as described in Section 5.10. Diary data will be entered by the subject and transferred to the vendor database on a daily basis. Once all electronic diary data has been collected the diary database will be closed and transferred from the vendor to ALK. The diary data will not be subject to data validation (query processing). Documentation of the data load from the vendor to ALK will be described in the data handling report.

7.1.3 Laboratory and Immunological Data

Results of laboratory assessments will be provided by the central laboratory selected by ALK and sent electronically to data management at ALK.

Immunology results will be provided from research department at ALK and forwarded electronically to data management at ALK.

Documentation of data loads for laboratory and immunological data will be provided in the data handling report.

7.2 Data Processing

Data items from the CRFs are entered into the trial database using double data entry with verification upon second entry. Text items (e.g. comments) are entered once.

Subsequently, the information entered into the database is systematically checked by data management staff, using error messages printed from validation programs and database listings.
Errors or omissions will be entered on data clarification forms, which will be returned to the trial centre for resolution. A copy of the signed data clarification form is to be kept with the CRFs at the trial centre, and once the original is received by ALK the resolutions will be entered into the database.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List (version 2\textsuperscript{nd} quarter 2003 or later).

Medical history and AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) (version 10.1 or later).

When the database has been declared to be complete and accurate, the database will be locked and data will be unblinded. Any changes to the database after that time can only be made by joint written agreement between the clinical project manager, the responsible statistician and the data manager.
8 Statistical Methods

Statistical analyses will be carried out by ALK.

All computation will be performed using SAS® version 9.2 or above.

All analyses requiring significance testing will be two-sided at a 5% significance level, unless otherwise specified. All confidence intervals will be two-sided 95% confidence intervals.

Before unblinding, a separate statistical analysis plan (SAP) detailing the specifications given below will be prepared and agreed upon. This includes a detailed description of the full analysis set (FAS) and the per protocol (PP) analysis.

Any changes in the statistical methods compared to the final SAP will be documented in the integrated clinical trial report (ICTR). Post-hoc analyses, if any, will be clearly marked.

8.1 Sample Size and Power Considerations

The primary endpoint is time to first moderate or severe asthma exacerbation after ICS reduction. Maneechotesuwan et al. (21) found that 4 out of 12 (33%) placebo treated subjects did not have an asthma exacerbation during 12 weeks of complete withdrawal of ICS. The definition of an asthma exacerbation was very similar to the suggested definition in this protocol. The estimate may, however, be slightly overestimated because subjects who had an exacerbation during the 2-weeks ICS withdrawal run-in period were withdrawn.

In the present trial, the ICS reduction period consist of 3 months 50% ICS reduction followed by 3 months 100% ICS withdrawal. Therefore, based on the data from Maneechotesuwan et al (21) an estimate of 35% in the placebo group not having an asthma exacerbation is considered to be a conservative overestimate, as subjects may experience asthma exacerbations already on 50% ICS reduction. Hence, it is assumed that about 65% of subjects in the placebo group will experience asthma exacerbations as defined in section 5.3.1.

Based on the MT-02 trial (doses of 1 DU, 3 DU and 6 DU) it is estimated that about 20% of the subjects in the placebo group may experience an asthma exacerbation during the first 3 months of period 3 (i.e. ICS 50% reduction). In a MT-02 subgroup (ACQ ≥ 1.0; 400 mcg ≤ ICS ≤ 800 mcg), about 20% (30/147) experienced 2 consecutive days with a 20% decrease in morning PEF compared to baseline during the ICS down-tapering and stable period (approximately 3 months). There was no difference between treatment groups. As more asthma exacerbations are expected to be observed during the first 3 months of period 3 than during the MT-02 ICS down-tapering period adjusting for control, 20% is considered a conservative underestimate. This is supported by the fact that the asthma exacerbation definition in the present trial also includes criteria on asthma symptoms, SABA use etc. It is also known, that the ICS dose could be reduced by more than 50% during the up to 3 months long ICS down-tapering period without loss of asthma control for about 40%-55% of subjects in the placebo group (22;23;29).
The power calculations at a 5% significance level, calculated for different differences to placebo based on both a Fisher's exact conditional test for two proportions as well as proportional hazards, and given that 65% of the subjects in the placebo group will experience an asthma exacerbation and that 240 subjects are included in each treatment group, is shown below (see Table 3).

### Table 3 Power Calculation

<table>
<thead>
<tr>
<th>Assumptions</th>
<th>Difference between ALK HDM AIT and placebo</th>
<th>Power based on</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absolute</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>N=240 per treatment group. α=5%.</td>
<td>20%</td>
<td>0.57</td>
</tr>
<tr>
<td>In placebo group 65% of subjects experience asthma exacerbations.</td>
<td>16%</td>
<td>0.64</td>
</tr>
<tr>
<td></td>
<td>15%</td>
<td>0.66</td>
</tr>
<tr>
<td></td>
<td>13%</td>
<td>0.70</td>
</tr>
<tr>
<td></td>
<td>10%</td>
<td>0.76</td>
</tr>
<tr>
<td>For power based on survival proportional hazards are assumed.</td>
<td>5%</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Below is illustrated fictive data for a placebo group that fulfils the assumption of 35% having no asthma exacerbations during the complete 6 months ICS reduction period and 80% during the first 3 months on 50% reduced ICS dose (Figure 2). Moreover, assumptions for the ALK HDM AIT 6 DU and 12 DU are absolute differences to placebo of 13% and 16%. The data follows proportional hazards. Based on 240 subjects per treatment group the overall power in this example to detect first a 16% difference between 12 DU and placebo and then to detect a 13% difference between 6 DU and placebo is 80% (=0.95x0.84x100%).
Figure 2  Proportion Free of Asthma Exacerbations after ICS Reduction

An absolute difference of approximately 13% is considered clinically relevant. Hence, it is estimated that 240 subjects per treatment group will provide at least 80% power to detect a 13% absolute difference between ALK HDM AIT 12 DU and placebo in the proportions of subjects with asthma exacerbations at the 5% significance level. With an expected drop out of about 10%, 266 subjects should be randomised per treatment arm (i.e. a total of 798 subjects).

8.2 Analysis Data Sets

The total analysis set is all subjects who entered the trial. This analysis set includes screening failures. The total population will be used for listing reasons for screening failures and AEs before randomisation.

The FAS is all randomised subjects in accordance with the ICH intent-to-treat principle. This analysis set will be the primary set for all efficacy analyses. The FAS will be used for all baseline/demography tables, efficacy tables, safety tables and subject listings.

The PP analysis set is all subjects in the FAS with no major protocol violations which may influence the primary endpoint (please refer to the SAP for further details). The PP analysis set will be a supplementary set for selected efficacy analyses.

The safety analysis set is identical to the FAS.

8.3 Baseline Characteristics

Demographic and other baseline characteristics will be summarised by treatment group displaying number of subjects, mean, standard deviation, median, 25 and 75-percentiles, minimum and maximum for continuous variables and frequency tables for categorical variables.
8.4 Extent of Exposure

Extent of IMP exposure and IMP accountability will be summarised by treatment group.

8.5 Concomitant Therapy

Concomitant medication and illness will be summarised by means of descriptive statistics.

8.6 Endpoints

8.6.1 Primary Endpoint

The primary endpoint is the time to first moderate or severe asthma exacerbation during period 3 (ICS reduction).

Time to first asthma exacerbation is measured in days from start of period 3 (ICS reduction). The definition of asthma exacerbation used is that the subject must experience one or more of the criteria listed below.

At least one of the following criteria must be fulfilled and lead to a change in treatment to meet the definition of a moderate exacerbation:

a) Nocturnal awakening(s) due to asthma requiring SABA use for at least 2 consecutive nights or an increase of minimum 0.75 in daily symptom score from baseline value on at least 2 consecutive days.

b) An increase from baseline value in occasions of SABA use on at least 2 consecutive days (a minimum increase of 4 puffs per day).

c) \( \geq 20\% \) decrease in morning or evening PEF from baseline value on at least 2 consecutive days or \( \geq 20\% \) decrease in FEV1 from baseline value.

d) Visit to the emergency room or unscheduled visit to the trial centre for asthma treatment not requiring systemic corticosteroids.

The baseline value is the mean values during the last 14 days of the screening period.

If the subject experience one of the following events, this will be characterised as a severe asthma exacerbation:

\( e) \) Need of systemic corticosteroids for 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.

8.6.2 Key Secondary Endpoints

Key secondary endpoints are:
- Time to first deterioration in asthma symptoms.
  Time in days from start of period 3 (ICS reduction) to the first asthma exacerbation fulfilling criterion a), see section 8.6.1.

- Immunology measured at end of trial in terms of specific IgE-blocking factor against HDM allergens.

### 8.6.3 Other Secondary Endpoints

- Severe asthma exacerbation.
  - Time to first severe asthma exacerbation.
    Time in days from start of period 3 to the first severe asthma exacerbation fulfilling criterion e) or f), see section 8.6.1.

- Asthma exacerbations during period 3.
  - The frequency of asthma exacerbations (number/percentage of subjects) during period 3.

- Asthma symptoms.
  - The average overall symptom score over the first asthma exacerbation free period during the first 3 months of period 3.
  - The average overall symptom score over the first asthma exacerbation free period during entire period 3.
  - Symptom free days during period 3.
    A symptom free day is defined as a day with:
    - No asthma symptoms (symptom score =0).
    - No need for SABA.
    - No increase in ICS or use of oral steroid.

- Symptomatic medication.
  - Time to first increased use of SABA.
    Time in days from start of period 3 to the first asthma exacerbation fulfilling criterion b), see section 8.6.1.

- Lung function.
  - The average morning PEF and diurnal variability over the first asthma exacerbation free period during first 3 months of period 3.
  - The average morning PEF and diurnal variability over the first asthma exacerbation free period during entire period 3.
  - Time to first deterioration in lung function.
    Time in days from start of period 3 to the first asthma exacerbation fulfilling criterion c), see section 8.6.1.
- Change in FEV₁ from baseline to visit 9 (ICS reduction).
- Asthma control.
  - The overall ACQ for the last week of period 2 (treatment maintenance) before period 3 (assessed at visit 9).
- Asthma quality of life.
  - The overall AQLQ(s) for the last week of period 2 (treatment maintenance) before period 3 (assessed at visit 9).
- Immunology.
  - Specific IgE, IgG4, and other immunological assessments.
- Quality of Life and Pharmacoeconomics Assessments.
  - Development and changes in ACQ, AQLQ(s), SF-36, and WPAI:ASTHMA.
  - Health care resource use and rate of hospitalisation.
- Safety.
  - AEs, SAEs, AE withdrawals, clinical lab tests, vital signs, physical examination.

8.7 Multiplicity

Multiplicity will be controlled by the pre-specified order of the hypothesis to be tested. The null hypotheses to be tested are the equality of active ALK HDM AIT to placebo. The order of hypothesis to be tested is:

1. The primary efficacy analysis of ALK HDM AIT 12 DU compared to placebo.
2. The primary efficacy analysis of ALK HDM AIT 6 DU compared to placebo.

The second hypothesis test will only be carried out if the first is statistically significant at the 5% level. If the first comparison is statistically significant (p < 0.05) then the second comparison is also tested at the 5% level.

Additional endpoints and analyses are supportive in nature and will not be controlled for multiplicity.

8.8 Efficacy Analyses

8.8.1 Primary Efficacy Analysis

The primary efficacy analysis of the primary endpoint, time to first moderate or severe asthma exacerbation, will be performed with a Cox proportional hazards regression analysis. The model includes treatment group, trial centre, and baseline ICS dose as fixed effects and baseline ACQ score as a covariate. Depending on the number and size of trial centres, pooling of trial centres
may be considered or trial centres may be replaced by regions. Based on this model the comparison of each active dose against placebo will be conducted in a step-down method, starting with ALK HDM AIT 12 DU followed by ALK HDM AIT 6 DU. The hierarchical ordering of the comparisons implies that no statistical conclusions can be based on the second comparison (ALK HDM AIT 6 DU vs. placebo) unless the first comparison (ALK HDM AIT 12 DU vs. placebo) is statistically significant (p < 0.05). For each active treatment group the estimated adjusted relative risk compared to placebo will be presented together with the two-sided 95% Wald confidence interval.

Sensitivity analysis and model control will be conducted to assess the model assumption of non-informative drop-out during period 3, and proportional hazards. Also the assumption of non-informative drop-out during period 2 will be assessed and the drop-out rate evaluated.

### 8.8.2 Key Secondary Efficacy Analyses

The key secondary event-time endpoints will be 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(s) evaluated are fulfilled.

IgE-blocking factor at end of trial will be analysed with a linear mixed effects model with treatment group, baseline IgE-blocking factor value as fixed effects and trial centre as a random effect.

### 8.8.3 Other Secondary Efficacy Analyses

Time to first severe asthma exacerbation will be analysed similar to the key secondary event-time endpoints.

Frequency of asthma exacerbations during period 3 will be analysed with a generalised linear model including treatment group as fixed effect and adjusting for covariates such as trial centre.

Other secondary efficacy endpoints including immunology will be analysed with a linear mixed effects model with treatment group and baseline value as fixed effects and trial centre as a random effect. For immunology data, also visit and treatment group by visit interaction will be included as fixed effects and a random subject effect.

### 8.9 Safety Analyses

#### 8.9.1 Analyses of Adverse Events

AEs will be summarised by treatment group, system organ class and preferred term displaying number of subjects in treatment group, number and percentage of subjects having the event as well as number and percentage of events. Furthermore, the AEs will be summarised according to severity, relationship, outcome, action and seriousness. The analyses will be described further in the SAP.
8.9.2 Analyses of Other Safety Parameters

Laboratory assessments and vital signs will be summarised by treatment group displaying number of subjects, mean, standard deviation, median, 25 and 75-percentiles, minimum and maximum for continuous variables and frequency tables for categorical variables.

8.10 Interim Analysis

No interim analysis is planned.

8.11 Other Topics

Subjects who withdraw before period 3 are not included in the primary efficacy analysis. For subjects who withdraw between visit 9 (ICS reduction) and visit 13 (end of trial), the time to asthma exacerbation is right-censored at the date of withdrawal. Handling of other missing data as well as additional sensitivity analysis will be described in the SAP.

8.12 Pharmacoeconomic Analyses

Information about the subject’s perception of quality of life and work impact during the course of the trial and health care resource use are collected.

Details for the evaluation of health care resource use, rate of hospitalisation, questionnaire data and derivation of subscales (scoring algorithms) including handling of missing observations will be described in the SAP.
9 Procedures and Instructions

9.1 Contact Persons and Numbers

The telephone numbers and fax numbers of the sponsor are listed in the investigator’s centre file. The title, name, address and contact details of investigators and clinical research organisations are listed in a separate document.

9.2 Monitoring

Before trial initiation, an ALK representative will present and discuss the protocol and the CRFs with the investigators and trial centre staff. During the trial the monitor will visit the trial centre regularly to check the completeness of subject records, the accuracy of entries into the CRFs, the adherence to the protocol and to GCP, the progress of enrolment and also to ensure that the IMPs are stored, dispensed and accounted for according to specifications. Key trial personnel must be available to assist the monitor during these visits.

The investigator must give the monitor direct access to source data/documents (e.g. relevant hospital or medical records) to confirm their consistency with the CRF entries. No information in these records about the identity of the subjects should leave the trial centre.

9.2.1 Recording of Data and Retention of Documents

The investigator must complete the CRFs as instructed by ALK at trial initiation. All entries in the CRFs must be made as described in the general instructions on the CRF or as described by ALK at trial initiation.

Subject data collected in CRFs during the trial will be documented anonymously and the subjects will only be identified by the subject number/randomisation number. If, as an exception, it is necessary for safety or regulatory reasons to identify the subject, both ALK and the investigator are bound to keep this information confidential.

The investigator must maintain source documents for each subject in the trial (all demographic and medical information, including laboratory data etc.) and give a copy of the signed informed consent to the subject. Investigator should keep the original. Data without a written or electronic source record will be defined in the protocol and will be recorded directly in the CRFs, which then will be documented as being the source data, please refer to Section 9.2.2.

Essential documents must be retained by the investigator for as long as needed to comply with national and international regulations. ALK will notify the investigator(s)/trial centre(s) when the trial-related records are no longer required. The investigator agrees to adhere to the document retention procedures by signing the protocol.
9.2.2 Source Data

The following data should be documented in the subject’s medical record as source data:

- Details of the trial (trial ID, subject number/randomisation number, diagnosis).
- Date of informed consent.
- Subject’s date of birth.
- Concomitant diseases and medication.
- Relevant medical history (incl. specific allergy and asthma history and date of diagnosis).
- All AEs and SAEs should be described in details if an event occurs.
- Date and number of each trial visit including signature or initials of persons conducting the trial visit.
- Date and information of any relevant telephone contact with the subject and signature or initials of persons conducting or receiving the call.
- IMP dispensed/returned.
- Subject withdrawal from the trial including reason.

Documentation of FEV$_1$, SPT, and laboratory results must be kept in the subject’s medical record; signed and dated by the investigator or the trial centre staff conducting the assessment. Documentation of FEV$_1$ results must be copied and signed by the investigator. 1 copy should be kept together with the original in the subject’s medical record.

The following data may be recorded directly in the CRF and is considered as source data (if acceptable by national legislation and hospital routine):

- In/exclusion criteria.
- Subject’s ethnic origin and gender.
- Vital signs.
- Physical examination.
- Smoking history.
- Pregnancy test taken and outcome of test.

For electronic diary data there will be no other source documentation than the database.

9.3 Handling of Investigational Medicinal Product and Symptomatic Medication

All IMP and symptomatic medications for use in this trial will be supplied to the trial centre by ALK. IMP and symptomatic medications must be kept in an appropriate secure area (e.g. locked cabinet) and stored according to the conditions specified on the drug labels. The investigator must maintain an accurate record of the shipment and dispensing of IMP and symptomatic
medications in an accountability form, a copy of which must be given to ALK at the end of the trial. An accurate record of date and amount of IMP and symptomatic medications dispensed to and returned by each subject must be available for inspection at any time.

The IMP and symptomatic medications will be dispensed to the subject with the instruction to return all unused, partly used and empty drug containers to each visit. Unused and partly used tablet blister units and cards and other drug containers are to be taken home again if dispensing of IMP or symptomatic medication is not part of the visit procedure.

Accountability will be checked by the monitor during centre visits and at the completion of the trial by review of the IMP and symptomatic medication accountability form and by checking the randomisation number and number of tablets handed out, entered in the CRF.

All IMP and symptomatic medications are to be used only for this trial and not for any other purpose. The investigator must not destroy any drug labels or any partly-used or unused drug supply. At the end of the trial, the investigator will return all used and unused drug containers, drug labels and a copy of the completed drug accountability form to the ALK appointed monitor or to the ALK address provided.

9.4 Disclosure and Confidentiality

By signing the protocol, the investigator agrees to keep all information provided by ALK in strict confidence and to request similar confidentiality from his/her staff. Trial documents provided by ALK (protocol, Investigator’s Brochures, CRFs and other material) will be stored appropriately to ensure their confidentiality. The information provided by ALK to the investigator may not be disclosed to others without direct written authorisation from ALK, except to the extent necessary to obtain informed consent from subjects who wish to participate in the trial.

Financial disclosure from the investigators will be obtained before the trial.

9.5 Discontinuation of Trial

ALK reserves the right to discontinue any trial under the conditions specified in the clinical trial agreement.

9.6 Ethics and Good Clinical Practice

This trial must be carried out in compliance with the protocol, which is designed to ensure adherence to the Declaration of Helsinki and the principles of GCP, as described in:

- The Declaration of Helsinki (1964, and its amendments and subsequent clarifications) (15).

9.6.1 Institutional Review Board/Independent Ethics Committee/Health Authorities

Before implementing this trial, the protocol, the proposed informed consent form and other information to subjects as well as other documents required, must be reviewed by a properly constituted IEC/IRB and provided to the national (and local, if applicable) health authority.

A signed and dated statement that the protocol and informed consent have been approved by the IEC/IRB and the health authority must be obtained by ALK before trial initiation.

For the IEC/IRB the name and occupation of the chairman and the members of the IEC/IRB must be supplied to ALK as well as a statement that the IEC/IRB works in accordance with ICH GCP.

IECs/IRBs will receive updates on trial progress according to local regulations.

9.6.2 Protocol Amendments and Other Changes in Trial Conduct

Substantial changes (as defined in EU guidance documents (31;32)) to this protocol require a protocol amendment that must be signed off by ALK and the investigator(s) and be approved by IEC/IRB or health authorities as applicable before implementation.

The requirements for approval of the substantial changes should in no way prevent any immediate action from being taken by the investigator or by ALK in the interest of preserving the safety of all subjects included in the trial.

Amendments affecting only administrative aspects of the trial do not require formal protocol amendments or IEC/IRB or health authorities’ approval but the IEC/IRB or health authorities of each trial centres must be kept informed of such administrative changes.

9.6.3 Informed Consent

All subjects are to provide informed consent in accordance with the origins of the Declaration of Helsinki and the applicable laws of the country.

It is the responsibility of the investigator or his/her designee to obtain the written informed consent from the subject. The subject will sign and date the informed consent form before he/she enters the trial (i.e. before any trial related activity). The investigator will explain the nature of the trial, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail and provide the subject with a copy of the information sheet. The subject will be given sufficient time to consider the trial before deciding whether to participate. Each subject must be informed that participation in the trial is voluntary and that he/she may withdraw from the trial at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.
In the case of amendments to the final protocol, such that it would directly affect the subject’s participation in the trial (e.g. a change in any procedure), the subject information sheet and informed consent form must be amended to incorporate this modification and the subject must agree to sign the amended form indicating that he/she re-consent to participate in the trial.

The informed consent form must be submitted by the investigator for IEC/IRB approval. ALK supplies a proposed informed consent form, which complies with regulatory requirements and is considered appropriate for the trial. Any changes to the proposed consent form suggested by the investigator must be agreed upon by ALK before submission to the IEC/IRB, and a copy of the approved version must be provided to the monitor after IEC/IRB approval.

9.6.4 Audit and Inspections

Within ALK, a clinical quality management unit exists. The unit conducts audits of clinical research activities in accordance with internal standard operating procedures (SOPs) to evaluate compliance with the principles of GCP.

A regulatory authority or IEC/IRB may also wish to conduct an inspection (during the trial or even after its completion). If an inspection is requested by a regulatory authority, the investigator must inform ALK of the request immediately.

The investigator must be available during the audit and give the auditors/inspectors direct access to source data/documents.
10 Reporting of Results

10.1 Integrated Clinical Trial Report

Data will be reported in the ICTR in compliance with the requirements of the current version of ICH E3: Structure and Content of Clinical Study Report, ICH-GCP Guidelines and ALK SOPs.

The signatory investigator will review and sign the ICTR.

10.2 Publication of Results

ALK retains exclusive ownership of all data, results, reports, findings, discoveries and any other information collected during this trial. Therefore, ALK reserves the right to use the data from the present trial either in the form of CRF (or copies of these), or in the form of a report, with or without comments and with or without analysis, in order to submit them to the health authorities of any country.

By signing the investigator agreement, the investigator agrees that the results of this trial may be used for submission to national or international registration and supervising authorities. The authorities will be notified of the investigator's name, address, qualifications and extent of involvement.

It is envisaged that the findings of this trial including sub-studies, and if relevant the epidemiology of the screened population and the selection process, will, in due time and by mutual agreement, be published in international journals or presented at scientific meetings. All presentations/publications must be review by ALK prior to public presentation/submission. For multicentre trials, it is mandatory that the first publication is based on data from all trial centres, analysed as stipulated in the protocol and in the SAP. Authorship is based on the International Committee of the Medical Journal Editors “Uniform Requirements” (Vancouver Declaration). If number of authors is restricted, selection will be based on fulfilment of 1) involvement in the development of the protocol, 2) coordinating investigators, and 3) top recruiters.

Investigators agree not to present data gathered from 1 trial centre or a small group of trial centres before the full publication unless formally agreed by all other investigators and ALK.

ALK has the right to review and comment any manuscript within 30 days of receipt, but cannot prevent publications of findings.

ALK will review the communications for accuracy (thus avoiding potential discrepancies with submissions to health authorities), verify that the confidential information is not being inadvertently divulged and provide any relevant supplementary information.
11 Finance and Insurance

ALK has subscribed to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating subjects and arising out of these trial procedures performed strictly in accordance with this protocol as well as with applicable law and professional standards.
12 Reference List


(3) IOC Medical and Scientific Department. Beta2 adrenoceptor agonists and the Olympic Games in Beijing. 1-5. 2008. Ref Type: Generic


(5) European Federation of Allergies and Airway diseases Patients' Associations. Asthma Fact Sheet. 2009. Ref Type: Generic

(6) WHO. Bronchial Asthma. WHO Fact Sheet 206. 2000. Ref Type: Generic


(10) Platts Mills TA, Vervloet D, Thomas W, Aalberse RC, Chapman M. Indoor allergens and asthma: Report of the third international workshop. The Journal of Allergy and Clinical Immunology 1997;100, no. 6, part 1(December, Suppl.).


(31) European Commission. Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use (CT2). 2006.

(32) European Commission. Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial (CT1). 2005.
Appendix 1

Investigator Agreement on Protocol

TRIAL ID: 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.

Version: 12 April 2010

I have read the clinical trial protocol and agree that it contains all the information required to conduct the trial. I agree to conduct the trial as set out in the protocol. In particular, I agree to adhere to the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, the guidelines on Good Clinical Practice, and applicable regulatory requirements.

I understand that all documentation that has not previously been published will be kept in the strictest confidence. This documentation includes the clinical trial protocol, Investigator’s Brochure, case report forms, and other scientific data.

Responsible investigator at the local trial centre

<table>
<thead>
<tr>
<th>Printed Name</th>
<th>Location</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
</table>
### Appendix 2

The following is the questions asked in the electronic diary.

<table>
<thead>
<tr>
<th>Morning Diary</th>
<th>#</th>
<th>Title</th>
<th>Text</th>
<th>Answer</th>
<th>Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Good Morning</td>
<td>Please do the breathing test and fill in the questionnaire before taking your morning medicine.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0 Morning Diary</td>
<td></td>
<td>AIM1+ instruction text (see below)</td>
<td></td>
<td></td>
<td>AIM1+ subject’s instruction is inserted between “Good Morning screen” and M0</td>
</tr>
<tr>
<td>M0 Morning Diary</td>
<td></td>
<td>On the next screens you will be asked about how your asthma was during the night.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1 Morning Diary</td>
<td></td>
<td>Please describe the severity of your worst asthma symptom (wheezing, coughing, shortness of breath, or chest tightness) during the night.</td>
<td>0 no symptoms</td>
<td>M1 to M2a if previous Evening Diary completed  M1 to M2b if previous Evening Diary missed</td>
<td></td>
</tr>
<tr>
<td>M1 Morning Diary</td>
<td></td>
<td></td>
<td>1 mild symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1 Morning Diary</td>
<td></td>
<td></td>
<td>2 moderate symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1 Morning Diary</td>
<td></td>
<td></td>
<td>3 severe symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M2a Morning Diary</td>
<td></td>
<td>How many puffs of bronchodilator did you use since you completed your Evening Diary?</td>
<td></td>
<td>Always M2a to M3</td>
<td></td>
</tr>
<tr>
<td>M2b Morning Diary</td>
<td></td>
<td>How many puffs of bronchodilator did you use in the past 12 hours?</td>
<td></td>
<td>Always M2b to M3</td>
<td></td>
</tr>
<tr>
<td>M3 Morning Diary</td>
<td></td>
<td>How many times did you wake up due to asthma symptoms (wheezing, coughing, shortness of breath, or chest tightness)?</td>
<td>0-99</td>
<td>If &gt;0 then continue to M4  If = 0 then continue to “Thank you” screen</td>
<td></td>
</tr>
<tr>
<td>M4 Morning Diary</td>
<td></td>
<td>When you woke up due to your asthma symptoms, did you use any bronchodilator?</td>
<td>1Yes 2No</td>
<td>If “Yes” in M4 and 0 in M2a or M2b then the following prompt should appear: “You have entered 0 puffs but also reported using your bronchodilator when you woke up. Please review your responses.”</td>
<td></td>
</tr>
<tr>
<td>M5 Morning Diary</td>
<td></td>
<td>Your entries indicate that your asthma symptoms are worsening, please contact your study doctor now.</td>
<td></td>
<td>Appear only if Alert</td>
<td></td>
</tr>
</tbody>
</table>

Thank you. Remember to take the trial medicine together with your other asthma medicine. Please connect the LogPad to the charger for charging and transmission of data.
<table>
<thead>
<tr>
<th>#</th>
<th>Title</th>
<th>Text</th>
<th>Answer</th>
<th>Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Evening Diary</td>
<td>Good Evening. Please do the breathing test and fill in the questionnaire before taking your evening medicine.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E0 Evening</td>
<td>AIM1+ instruction text (see below)</td>
<td></td>
<td>AIM1+ subject’s instruction is inserted between “Good Evening screen” and E0</td>
</tr>
<tr>
<td>E1</td>
<td>Evening Diary</td>
<td>On the next screens you will be asked about how your asthma was during the day.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E2</td>
<td>Evening Diary</td>
<td>Please describe the severity of your cough today.</td>
<td>0 no cough 1 mild cough 2 moderate cough 3 severe cough</td>
<td></td>
</tr>
<tr>
<td>E3</td>
<td>Evening Diary</td>
<td>Please describe the severity of your wheeze today.</td>
<td>0 no wheeze 1 mild wheeze 2 moderate wheeze 3 severe wheeze</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Evening Diary</td>
<td>Please describe the severity of your chest tightness/shortness of breath today.</td>
<td>0 no chest tightness/shortness of breath 1 mild chest tightness/shortness of breath 2 moderate chest tightness/shortness of breath 3 severe chest tightness/shortness of breath</td>
<td></td>
</tr>
<tr>
<td>E4</td>
<td>Evening Diary</td>
<td>Please describe your exercise induced symptoms today.</td>
<td>0 no symptoms 1 mild symptoms 2 moderate symptoms 3 severe symptoms</td>
<td></td>
</tr>
<tr>
<td>E5a</td>
<td>Evening Diary</td>
<td>How many puffs of bronchodilator did you use since you completed your Morning Diary?</td>
<td>0-99</td>
<td>Always go to “Thank you “screen</td>
</tr>
<tr>
<td>E5b</td>
<td>Evening Diary</td>
<td>How many puffs of bronchodilator did you use in the past 12 hours?</td>
<td>0-99</td>
<td>E4 to E5b if previous Morning diary missed</td>
</tr>
<tr>
<td>E6</td>
<td>Evening Diary</td>
<td>Your entries indicate that your asthma symptoms are worsening, please contact your study doctor now.</td>
<td></td>
<td>E4 to E5a if previous Morning diary completed</td>
</tr>
<tr>
<td></td>
<td>Evening Diary</td>
<td>Thank you. Please connect the LogPad to the charger for charging and transmission of data.</td>
<td></td>
<td>Appear only if Alert</td>
</tr>
</tbody>
</table>

Evening Diary
## AIM1+ instructions text

<table>
<thead>
<tr>
<th>#</th>
<th>Title</th>
<th>AIM1+ Text</th>
<th>Answer</th>
<th>Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PEF measurement</td>
<td>You must perform 3 blows into the AM1+. Before each blow please press</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Once done, please tap the forward arrow.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>PEF measurement</td>
<td>On your AM1+ repeatedly press</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>until it displays</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Once done, please tap the forward arrow.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>AM1+</td>
<td>Communicating with AM1+ ...</td>
<td></td>
<td>“Bluetooth Serial Port Preparing… Connecting… Cancel “</td>
</tr>
<tr>
<td>4</td>
<td>AM1+</td>
<td>Unable to communicate with the AM1+. Please make sure the AM1+ is within 3 meters and displays</td>
<td></td>
<td>Try again = 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>displays</td>
<td></td>
<td>Skip communication = 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Would you like to:</td>
<td></td>
<td>&quot;Warning, use this option only if you lost or damaged your AM1+</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Any other reason will result in loss of valuable information from your Diary.&quot;</td>
</tr>
<tr>
<td>5</td>
<td>PEF measurement</td>
<td>The LogPad only received %i measurement(s) from the AM1+. Please perform %j additional blow(s).</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Before each blow please press</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Once done, please tap the forward arrow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Measurement</td>
<td>Thank you for your measurements.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Your highest value was:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PEF: %s L/min</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix 3

ASTHMA CONTROL QUESTIONNAIRE

UK ENGLISH VERSION

© 2001
QOL TECHNOLOGIES Ltd.
For further information:

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This translation has been made possible through a grant from YAMANO/IUCHI
Translated by MAPI RESEARCH INSTITUTE
Senior Translator: Pr Elizabeth Juniper

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APRIL 2001
### ASTHMA CONTROL QUESTIONNAIRE®
**ENGLISH FOR THE UK**

**PATIENT ID:** _____________________________

**DATE:** _____________________________

Page 1 of 2

Please answer questions 1 - 6.

Circle the number of the response that best describes how you have been during the past week.

1. On average, during the past week, how often were you **woken by your asthma** during the night?
   - 0 Never
   - 1 Hardly ever
   - 2 A few times
   - 3 Several times
   - 4 Many times
   - 5 A great many times
   - 6 Unable to sleep because of asthma

2. On average, during the past week, how **bad were your asthma symptoms when you woke up** in the morning?
   - 0 No symptoms
   - 1 Very mild symptoms
   - 2 Mild symptoms
   - 3 Moderate symptoms
   - 4 Quite severe symptoms
   - 5 Severe symptoms
   - 6 Very severe symptoms

3. In general, during the past week, how **limited were you in your activities because of your asthma**?
   - 0 Not limited at all
   - 1 Very slightly limited
   - 2 Slightly limited
   - 3 Moderately limited
   - 4 Very limited
   - 5 Extremely limited
   - 6 Totally limited

4. In general, during the past week, how **much shortness of breath** did you experience because of your asthma?
   - 0 None
   - 1 A very little
   - 2 A little
   - 3 A moderate amount
   - 4 Quite a lot
   - 5 A great deal
   - 6 A very great deal
ASTHMA CONTROL QUESTIONNAIRE©
(ENGLISH FOR THE UK)

PATIENT ID:__________________________

DATE:________________________________

5. In general, during the past week, how much time did you **wheeze**?
   0 Never
   1 Hardly any of the time
   2 A little of the time
   3 A moderate amount of the time
   4 A lot of the time
   5 Most of the time
   6 All the time

6. On average, during the past week, how many puffs/inhalations of short-acting bronchodilator (eg. Ventolin/Bricanyl) have you used each day?
   (If you are not sure how to answer this question, please ask for help)
   0 None
   1 1 - 2 puffs/inhalations most days
   2 3 - 4 puffs/inhalations most days
   3 5 - 8 puffs/inhalations most days
   4 9 - 12 puffs/inhalations most days
   5 13 - 16 puffs/inhalations most days
   6 More than 16 puffs/inhalations most days

To be completed by a member of the clinic staff

7. FEV₁ pre-bronchodilator: ................. 0 > 95% predicted
   1 95 - 90%
   2 89 - 80%
   3 79 - 70%
   4 69 - 60%
   5 59 - 50%
   6 < 50% predicted

FEV₁ predicted:.............................

FEV₁ % predicted:..........................
(Record actual values on the dotted lines and score the FEV₁ % predicted in the next column)
Appendix 4

ASTHMA QUALITY OF LIFE QUESTIONNAIRE WITH STANDARDISED ACTIVITIES (AQLQ(S))

SELF-ADMINISTERED
UNITED KINGDOM VERSION

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QOL TECHNOLOGIES LTD.
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WWW.goltech.co.uk

Translated by MAPI RESEARCH INSTITUTE
Translator: Prof. Elizabeth Juniper

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AUGUST 1999

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) (UNITED KINGDOM)
SELF-ADMINISTERED

PATIENT ID _________________________
DATE _____________________________

Please complete all questions by circling the number that best describes how you have been during the last 2 weeks as a result of your asthma.

HOW LIMITED HAVE YOU BEEN DURING THE LAST 2 WEEKS IN THESE ACTIVITIES AS A RESULT OF YOUR ASTHMA?

<table>
<thead>
<tr>
<th>Activity</th>
<th>Totally Limited</th>
<th>Extremely Limited</th>
<th>Very Limited</th>
<th>Moderate Limitation</th>
<th>Some Limitation</th>
<th>A Little Limitation</th>
<th>Not at all Limited</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. STRENUOUS ACTIVITIES (such as hurrying, exercising, running up stairs, sports)</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>2. MODERATE ACTIVITIES (such as walking, housework, gardening, shopping, climbing stairs)</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>3. SOCIAL ACTIVITIES (such as talking, playing with pets/children, visiting friends/relatives)</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>
4. **WORK-RELATED ACTIVITIES** *(tasks you have to do at work)*
   
   | 1 | 2 | 3 | 4 | 5 | 6 | 7 |

*If you are not employed or self-employed, these should be tasks you have to do most days.*

5. **SLEEPING**
   
   | 1 | 2 | 3 | 4 | 5 | 6 | 7 |

**HOW MUCH DISCOMFORT OR DISTRESS HAVE YOU FELT DURING THE LAST 2 WEEKS?**

<table>
<thead>
<tr>
<th>A Very Great Deal</th>
<th>A Great Deal</th>
<th>A Good Deal</th>
<th>Moderate Amount</th>
<th>Some</th>
<th>Very Little</th>
<th>None</th>
</tr>
</thead>
</table>

6. How much discomfort or distress have you felt over the last 2 weeks as a result of CHEST TIGHTNESS?

   | 1 | 2 | 3 | 4 | 5 | 6 | 7 |

1
## ASHMA QUALITY OF LIFE QUESTIONNAIRE (S)
(UNITED KINGDOM)
SELF-ADMINISTERED

### PATIENT ID ____________________

### DATE ________________________

---

**IN GENERAL, HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS DID YOU:**

<table>
<thead>
<tr>
<th>Question</th>
<th>All of the Time</th>
<th>Most of the Time</th>
<th>A Good Bit of the Time</th>
<th>Some of the Time</th>
<th>A Little of the Time</th>
<th>Hardly Any of the Time</th>
<th>None of the Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.  Feel CONCERNED ABOUT HAVING ASTHMA?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>8.  Feel SHORT OF BREATH as a result of your asthma?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>9.  Experience asthma symptoms as a RESULT OF BEING EXPOSED TO CIGARETTE SMOKE?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>10. Experience a WHEEZE in your chest?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>11. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF CIGARETTE SMOKE?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

### HOW MUCH DISCOMFORT OR DISTRESS HAVE YOU FELT DURING THE LAST 2 WEEKS?

<table>
<thead>
<tr>
<th>A Very Great Deal</th>
<th>A Great Deal</th>
<th>A Good Deal</th>
<th>Moderate Amount</th>
<th>Some</th>
<th>Very Little</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>12. How much discomfort or distress have you felt over the last 2 weeks as a result of COUGHING?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

---

**IN GENERAL, HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS DID YOU:**

<table>
<thead>
<tr>
<th>Question</th>
<th>All of the Time</th>
<th>Most of the Time</th>
<th>A Good Bit of the Time</th>
<th>Some of the Time</th>
<th>A Little of the Time</th>
<th>Hardly Any of the Time</th>
<th>None of the Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>13. Feel FRUSTRATED as a result of your asthma?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>14. Experience a feeling of CHEST HEAVINESS?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>
### ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S)

(UNITED KINGDOM)

SELF-ADMINISTERED

<table>
<thead>
<tr>
<th>IN GENERAL, HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS DID YOU:</th>
<th>All of the Time</th>
<th>Most of the Time</th>
<th>A Good Bit of the Time</th>
<th>Some of the Time</th>
<th>A Little of the Time</th>
<th>Hardly Any of the Time</th>
<th>None of the Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>15. Feel CONCERNED ABOUT THE NEED TO USE MEDICATION for your asthma?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>16. Feel the need to CLEAR YOUR THROAT?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>17. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO DUST?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>18. Experience DIFFICULTY BREATHING OUT as a result of your asthma?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>19. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF DUST?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>20. WAKE UP IN THE MORNING WITH ASTHMA SYMPTOMS?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>21. Feel AFRAID OF NOT HAVING YOUR ASTHMA MEDICATION AVAILABLE?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>22. Feel bothered by HEAVY BREATHING?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>23. Experience asthma symptoms as a RESULT OF THE WEATHER OR AIR POLLUTION OUTSIDE?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>24. Were you WOKEN AT NIGHT by your asthma?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>25. AVOID OR LIMIT GOING OUTSIDE BECAUSE OF THE WEATHER OR AIR POLLUTION?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>26. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO STRONG SMELLS OR PERFUME?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>
**ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S)**  
(UNITED KINGDOM)  
SELF-ADMINISTERED

**PATIENT ID _______________________**

**DATE _______________________**

---

Page 4 of 5

---

**IN GENERAL, HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS DID YOU:**

<table>
<thead>
<tr>
<th>Question</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>27. Feel AFRAID OF GETTING OUT OF BREATH?</td>
<td>1 All of the Time, 2 Most of the Time, 3 A Good Bit of the Time, 4 Some of the Time, 5 A Little of the Time, 6 Hardly Any of the Time, 7 None of the Time</td>
</tr>
<tr>
<td>28. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF STRONG SMELLS OR PERFUME?</td>
<td>1 All of the Time, 2 Most of the Time, 3 A Good Bit of the Time, 4 Some of the Time, 5 A Little of the Time, 6 Hardly Any of the Time, 7 None of the Time</td>
</tr>
<tr>
<td>29. Has your asthma INTERFERED WITH GETTING A GOOD NIGHT’S SLEEP?</td>
<td>1 All of the Time, 2 Most of the Time, 3 A Good Bit of the Time, 4 Some of the Time, 5 A Little of the Time, 6 Hardly Any of the Time, 7 None of the Time</td>
</tr>
<tr>
<td>30. Have a feeling of FIGHTING FOR AIR?</td>
<td>1 All of the Time, 2 Most of the Time, 3 A Good Bit of the Time, 4 Some of the Time, 5 A Little of the Time, 6 Hardly Any of the Time, 7 None of the Time</td>
</tr>
</tbody>
</table>

**HOW LIMITED HAVE YOU BEEN DURING THE LAST 2 WEEKS?**

<table>
<thead>
<tr>
<th>Question</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>31. Think of the OVERALL RANGE OF ACTIVITIES that you would have liked to have done during the last 2 weeks. How much has your range of activities been limited by your asthma?</td>
<td>1 Most Not Done, 2 Several Not Done, 3 Very Few Not Done, 4 No Limitation</td>
</tr>
</tbody>
</table>

---

4
32. Overall, among ALL THE ACTIVITIES that you have done during the last 2 weeks, how limited have you been by your asthma?

<table>
<thead>
<tr>
<th></th>
<th>Totally Limited</th>
<th>Extremely Limited</th>
<th>Very Limited</th>
<th>Moderate Limitation</th>
<th>Some Limitation</th>
<th>A Little Limitation</th>
<th>Not at all Limited</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

**DOMAIN CODE:**
- Symptoms: 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30
- Activity Limitation: 1, 2, 3, 4, 5, 11, 19, 25, 28, 31, 32
- Emotional Function: 7, 13, 15, 21, 27
- Environmental Stimuli: 9, 17, 23, 26
Appendix 5
SF-36v2™ Health Survey

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey!

For each of the following questions, please tick the one box that best describes your answer.

1. In general, would you say your health is:

<table>
<thead>
<tr>
<th>Excellent</th>
<th>Very good</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

2. Compared to one year ago, how would you rate your health in general now?

<table>
<thead>
<tr>
<th>Much better now than one year ago</th>
<th>Somewhat better now than one year ago</th>
<th>About the same as one year ago</th>
<th>Somewhat worse now than one year ago</th>
<th>Much worse now than one year ago</th>
</tr>
</thead>
<tbody>
<tr>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

SF-36v2™ Health Survey © 1992-2002 by Health Assessment Lab, Medical Outcomes Trust and QualityMetric Incorporated. All rights reserved.
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IQOLA SF-36v2 Standard, English (United Kingdom) 8/02
3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

<table>
<thead>
<tr>
<th></th>
<th>Yes, limited a lot</th>
<th>Yes, limited a little</th>
<th>No, not limited at all</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>a</strong> Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports</td>
<td>□ 1 □ 2 □ 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>b</strong> Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf</td>
<td>□ □ □</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>c</strong> Lifting or carrying groceries</td>
<td>□ 1 □ 2 □ 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>d</strong> Climbing several flights of stairs</td>
<td>□ 1 □ 2 □ 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>e</strong> Climbing one flight of stairs</td>
<td>□ 1 □ 2 □ 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>f</strong> Bending, kneeling, or stooping</td>
<td>□ 1 □ 2 □ 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>g</strong> Walking more than a mile</td>
<td>□ 1 □ 2 □ 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>h</strong> Walking several hundred yards</td>
<td>□ 1 □ 2 □ 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>i</strong> Walking one hundred yards</td>
<td>□ 1 □ 2 □ 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>j</strong> Bathing or dressing yourself</td>
<td>□ 1 □ 2 □ 3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4. During the **past 4 weeks**, how much of the time have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

<table>
<thead>
<tr>
<th></th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>a Cut down on the amount of time you spent on work or other activities</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>b Accomplished less than you would like</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>c Were limited in the kind of work or other activities</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>d Had difficulty performing the work or other activities (for example, it took extra effort)</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

5. During the **past 4 weeks**, how much of the time have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

<table>
<thead>
<tr>
<th></th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>a Cut down on the amount of time you spent on work or other activities</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>b Accomplished less than you would like</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>c Did work or other activities less carefully than usual</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>
6. **During the past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>□1</td>
<td>□2</td>
<td>□3</td>
<td>□4</td>
<td>□5</td>
</tr>
</tbody>
</table>

7. **How much bodily pain have you had during the past 4 weeks?**

<table>
<thead>
<tr>
<th>None</th>
<th>Very mild</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>□1</td>
<td>□2</td>
<td>□3</td>
<td>□4</td>
<td>□5</td>
<td>□6</td>
</tr>
</tbody>
</table>

8. **During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?**

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little bit</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>□1</td>
<td>□2</td>
<td>□3</td>
<td>□4</td>
<td>□5</td>
</tr>
</tbody>
</table>
9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

<table>
<thead>
<tr>
<th></th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>a Did you feel full of life?</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>b Have you been very nervous?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
</tr>
<tr>
<td>c Have you felt so down in the dumbs that nothing could cheer you up?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
</tr>
<tr>
<td>d Have you felt calm and peaceful?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
</tr>
<tr>
<td>e Did you have a lot of energy?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
</tr>
<tr>
<td>f Have you felt downhearted and low?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
</tr>
<tr>
<td>g Did you feel worn out?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
</tr>
<tr>
<td>h Have you been happy?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
</tr>
<tr>
<td>i Did you feel tired?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
</tr>
</tbody>
</table>

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

<table>
<thead>
<tr>
<th></th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td></td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
</tr>
</tbody>
</table>
11. How TRUE or FALSE is each of the following statements for you?

<table>
<thead>
<tr>
<th>Definitely true</th>
<th>Mostly true</th>
<th>Don’t know</th>
<th>Mostly false</th>
<th>Definitely false</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

a. I seem to get ill more easily than other people.................[ ] 1.................[ ] 2.................[ ] 3.................[ ] 4.................[ ] 5

b. I am as healthy as anybody I know ..................................[ ] 1.................[ ] 2.................[ ] 3.................[ ] 4.................[ ] 5


Thank you for completing these questions!
Appendix 6

Work Productivity and Activity Impairment Questionnaire:
ASTHMA V2.0 (WPAI:Asthma)

The following questions ask about the effect of your asthma on your ability to work and perform regular activities. Please fill in the blanks or circle a number, as indicated.

1. Are you currently employed (working for pay)? _____ NO ___ YES

   If NO, check “NO” and skip to question 6.

The next questions are about the past seven days, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your asthma? Include hours you missed on sick days, times you went in late, left early, etc., because of your asthma. Do not include time you missed to participate in this study.

   _____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____ HOURS

4. During the past seven days, how many hours did you actually work?

   _____ HOURS  (If “0”, skip to question 6.)
5. During the past seven days, how much did your asthma affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If asthma affected your work only a little, choose a low number. Choose a high number if asthma affected your work a great deal.

Consider only how much asthma affected productivity while you were working.

<table>
<thead>
<tr>
<th>Asthma had no effect on my work</th>
<th>Asthma completely prevented me from working</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td></td>
</tr>
</tbody>
</table>

CIRCLE A NUMBER

6. During the past seven days, how much did your asthma affect your ability to do your regular daily activities, other than work at a job?

*By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If asthma affected your activities only a little, choose a low number. Choose a high number if asthma affected your activities a great deal.*

Consider only how much asthma affected your ability to do your regular daily activities, other than work at a job.

<table>
<thead>
<tr>
<th>Asthma had no effect on my daily activities</th>
<th>Asthma completely prevented me from doing my daily activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td></td>
</tr>
</tbody>
</table>

CIRCLE A NUMBER

WPAI:Asthma V2.0 (US English)
## Appendix 7

### Standard Physical Examination

<table>
<thead>
<tr>
<th>Body System</th>
<th>Minimum Examinations to be completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Appearance</td>
<td>Nutritional status, consciousness, skin colours, temperature and developmental status (in children)</td>
</tr>
<tr>
<td>Head (Ears, Eyes, Nose and Throat)</td>
<td><strong>Ears</strong> Inspection of auricles and external canal (otoscopy is not required)</td>
</tr>
<tr>
<td></td>
<td><strong>Eyes</strong> Inspection of conjunctivae and eyelids</td>
</tr>
<tr>
<td></td>
<td><strong>Examination of pupils including reaction to light</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Nose</strong> Inspection of nasal mucosa</td>
</tr>
<tr>
<td></td>
<td><strong>Throat</strong> Inspection of tonsils and uvula</td>
</tr>
<tr>
<td>Oral Inspection</td>
<td>Inspection of lips, mucosa and tongue</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Assessment of respiratory effort, including respiratory rate and use of accessory respiratory muscles</td>
</tr>
<tr>
<td></td>
<td>Palpation and percussion of chest</td>
</tr>
<tr>
<td></td>
<td>Auscultation/ stethoscopy of lungs</td>
</tr>
<tr>
<td>Heart</td>
<td>It is up to the investigators discretion to evaluate whether a physical examination of the heart is necessary based on auscultation/ stethoscopy of the heart. A full physical examination will not be performed*.</td>
</tr>
<tr>
<td>Abdomen</td>
<td>A physical examination will not be performed*. It is up to the investigators discretion to evaluate whether a physical examination of the abdomen is necessary based on questions regarding pain, tenderness and swelling</td>
</tr>
<tr>
<td>Urogenital</td>
<td>A physical examination will not be performed*. It is up to the investigators discretion to evaluate whether a physical examination of the genitourinary system is necessary based on questions regarding sores, lesions, pain, frequency or pattern change, incontinence, infections etc. For females, questions regarding birth control, menstrual regularity, menopause etc. must be asked</td>
</tr>
<tr>
<td>Musculoskeletal and Neurological</td>
<td>It is up to the investigators discretion to evaluate whether a physical examination is necessary*. Based on questions regarding pain, tenderness and swelling of joints and/or musculature, sores lesions, disturbance of sensation and examination and observations of gait, station and agility at displacements the musculoskeletal/neurological systems are assessed as normal/abnormal</td>
</tr>
<tr>
<td>Lymph Nodes</td>
<td>A physical examination will not be performed*. It is up to the investigators discretion to evaluate whether a physical examination of the lymph nodes is necessary based on the questions regarding pain, tenderness and swelling.</td>
</tr>
<tr>
<td>Skin</td>
<td>Inspection and palpation of skin and subcutaneous tissue</td>
</tr>
<tr>
<td></td>
<td>Inspection and/or palpation of digits and nails</td>
</tr>
<tr>
<td>Other Abnormality</td>
<td>If applicable</td>
</tr>
</tbody>
</table>

* In case a physical examination is not done, the CRF page “Physical Examination” is ticked “ND” next to the specific body system which is not physically examined.
Appendix 8

Guideline for Skin Prick Testing. Double Determination

1. INTRODUCTION

This guideline is to provide information on the procedure for performing a Skin Prick Test (SPT).

2. MATERIALS

1. Negative control (Saline buffer)
2. Positive control (Histamine dihydrochloride 10 mg/ml)
3. Allergen extracts in solution
4. Sterile disposable lancets
5. ALK-Metre (gauge)
6. Soluprick (ballpoint) pen
7. Soluprick page
8. Tape numbered and unnumbered

3. PROCEDURE

3.1 The SPT performed with the ALK Lancet is a traditional SPT.

3.2 Use of antihistamines is not allowed for at least 3 days before the test (Hismanal® for 30 days).

3.3 The SPT is preferably performed on the volar side of the forearm. Alternatively the test can be performed on the back of the patient.

3.4 The skin must be dry and clean and may be disinfected with 70% alcohol.

3.5 Using the numbered tape on the inside of the forearm the correct distance between the allergens and the safety in evaluating the wheals are given.

3.6 An allergen extract is introduced superficially into the skin and the response after 15 minutes is recorded.

3.7 Place a drop of each of the positive and negative control solutions at two separate marks (+/- marks on the tape). The positive control (histamine) is expected to produce a wheal, to confirm that the patient has a response. The negative control is saline buffer, and no reaction is expected.
3.8 Apply in droplets of the allergen solutions on the skin in an appropriate distance from each other, by using the number tape.

3.9 The superficial layer of the skin is pierced with the sterile ALK-Lancet perpendicular (in an angle of approximately 90°) to the skin through the droplet. Keep a light and constant pressure. Pull the lancet straight up.

**Use a new disposable lancet for each of the allergens.**

For this trial you need to do a double determination. For each allergen, this is done by making the second piercing on the other side of the numbered tape (at the same number) using the same lancet – there will be enough allergen left on the lancet to produce a reaction.

3.10 Excess allergen extract should be removed by laying a tissue on the arm. Avoid wiping to prevent mixing of the allergens.

3.11 The test sites are observed for the presence of erythema (redness) and wheal (lump) formation after 15 minutes.

It is important to ask the patient not to scratch the skin test sites as this may affect the results. Do not remove the numbered tape until after recording of the test results.

If you want to ensure that your handling procedure is correct the following exercise is recommended before performing the SPT:

Follow the above assay procedure. Instead of applying allergen extracts to the skin you should apply 10 droplets of positive control. The correct handling technique will result in equal reaction/wheal size.

4. **RECORDING OF SKIN PRICK TEST RESULTS**

4.1 Using a test reaction gauge, the size of the wheal should be recorded.

The mean wheal diameter is determined as: 

\[ W = \frac{D + d}{2} \]

- \( D \) = the longest diameter
- \( d \) = diameter perpendicular to \( D \)
- \( W \) = Wheal Size

4.2 Wheat sizes \( \geq 3 \text{ mm} \) \( (= W) \) are regarded as positive.

**NB! Please note that in case of dermografism, diameter of the wheal for *Dermatophagoides pteronyssinus* and/or *Dermatophagoides farinae* must be \( \geq 3 \text{ mm} \) greater than the saline control.**

4.3 Draw around the wheal with your Soluprick pen.

4.4 Place the plain tape over your drawings and pull the tape off again. Your drawings should now have been transferred to the tape.

4.5 The tape should hereafter be placed on the Soluprick page, you have been provided with. This page should hereafter be stored with the patient’s notes.
Appendix 9

Procedure for Collecting Dust Samples

Before collecting a dust sample
You will need a vacuum cleaner with a tube attachment that will connect to the collection device. Before you start, please check to see that the provided sampling kit contains all of the following:

Collection device
  • Filter dish with filter, preloaded into the collection device.
  • Rubber O-ring for tight fitting on the vacuum tube.
  • Plastic lid for the filter dish.
  • Zip-lock plastic bag.
  • Envelope and label.

Attaching the collecting device
Slide the flexible O-ring over the end of your vacuum tube. Then, fit the collection device on the end of the vacuum tube, using the O-ring to provide a tight seal.

Collecting a dust sample
Before vacuum your bed, remove any large particles such as food, small pieces of paper, or other extraneous material. Vacuum the entire top sheet, bottom sheet, pillowcase, mattress cover and mattress for about 5 minutes. IMPORTANT: Collect the sample before laundering the bed-clothes. Check to see that an adequate volume of dust has been collected. The dust sample should appear to be about the size of a tablespoon of material. If the sample does not appear to be large enough, then repeat the dust collection procedure.

After collecting the dust sample
  • Fill in the label.
  • Hold the collection device with the nozzle pointing up and remove the vacuum tube.
  • Detach the nozzle from the base of the collection device, by disengaging the side clips.
  • Remove the filter dish with the filter, which now contains the sample. Be careful not to spill the dust sample.
  • Fix the plastic lid securely over the filter dish and place the label on the lid.
  • Seal the dish in the small zip-lock bag.
  • Place the sample in the envelope and bring this for the next visit to your study doctor.
Appendix 10

The following is an example of an asthma action plan.

<table>
<thead>
<tr>
<th>WHEN WELL</th>
<th>WHEN NOT WELL</th>
<th>IF SYMPTOMS GET WORSE</th>
<th>DANGER SIGNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma under control <em>(almost no symptoms)</em></td>
<td>Asthma getting worse <em>(waking from sleep, first sign of a cold, using more reliever)</em></td>
<td>Asthma is severe <em>(difficulty with normal activity, feel that asthma is out of control)</em></td>
<td><em>(symptoms get worse very quickly, need reliever more than 2 hourly)</em></td>
</tr>
<tr>
<td>Preventer</td>
<td>Preventer</td>
<td>Start prednisolone/prednisone and contact doctor</td>
<td>Continue reliever</td>
</tr>
<tr>
<td>Dose</td>
<td>Dose</td>
<td>Dose</td>
<td>Dial 112 for ambulance</td>
</tr>
<tr>
<td>Continue taking the allergy vaccine tablet daily.</td>
<td>Continue on this increased dosage for days before returning to the dose you take when well.</td>
<td>Stay on this dose until your peak flow is above on two consecutive mornings</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduce prednisolone/prednisone to dose daily for days, then cease</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Extra steps to take: <em>(e.g. Continue taking the allergy vaccine tablet daily).</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>When your symptoms get better, return to the dose you take when well.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note: Please fill in the peak flow levels and doses according to your individual treatment plan.*
WHEN WELL
You will
• be free of regular night-time wheeze or cough or chest tightness
• have no regular wheeze or cough or chest tightness on waking or during the day
• be able to take part in normal physical activity without getting asthma symptoms
• need reliever medication less than 3 times a week (except if it is used before exercise)

WHEN NOT WELL
You will
• have increasing night-time wheeze or cough or chest tightness
• have symptoms regularly in the morning when you wake up
• have a need for extra doses of reliever medication
• have symptoms which interfere with exercise
(You may experience one or more of these)

IF SYMPTOMS GET WORSE, THIS IS AN ACUTE ATTACK
You will
• have one or more of the following: wheeze, cough, chest tightness or shortness of breath
• need to use your reliever medication at least once every 3 hours or more often

DANGER SIGNS
• Your symptoms get worse very quickly
• Wheeze or chest tightness or shortness of breath continue after using reliever medication or return within minutes of taking reliever medication
• Severe shortness of breath, inability to speak comfortably, blueness of lips

IMMEDIATE ACTION IS NEEDED: CALL AN AMBULANCE

Doctor’s stamp and/or contact details:
Clinical Trial Protocol Amendment
General Protocol Amendment no. 1

Trial ID: MT-04

Title of Trial: 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 (HDM) allergy immunotherapy tablet (AIT)

Development Phase: III
EudraCT no: 2010-018621-19
Sponsor: Global Clinical Development
ALK-Abelló A/S
DK-2970 Hørsholm
Phone: +45 4574 7576

Document status: Final
Date: 05-April-2011
Approval of General Protocol Amendment no. 1 – ALK

Approved by ALK-Astellas:
General Protocol Amendment no. 1, dated 05-April-2011 to the Clinical Trial Protocol, dated 12-April-2010, is approved by:

Amendment originator:
Bente Tholstrup  
Clinical Project Manager Expert

Responsible statistician:
Christian Ljørring  
Principal Statistician

On behalf of head of originating department:  
Eas Dige, MD  
EU QPPV, Director, Global Clinical Development
Approval of General Protocol Amendment no. 1 – International Coordinating Investigator

Approved by International Coordinating Investigator:

General Protocol Amendment no. 1, dated 05-April-2011 to the Clinical Trial Protocol, dated 12-April-2010, is approved by:

International Coordinating Investigator:

Johann Christian Virchow
Prof. Dr. med.
Abteilung für Pneumologie / Internistische Intensivmedizin
Klinik 1 – Zentrum für Innere Medizin,
Universitätsklinikum Rostock,
Ernst-Haydemann-Str. 6,
18057 Rostock,
Germany

Signature

Date 5.4.2011
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List of Abbreviations

ACQ    Asthma Control Questionnaire
AE     Adverse Event
AIT    Allergy Immunotherapy Tablet
AQLQ(s) Asthma Quality of Life Questionnaire with standardised activities
CRF    Case Report Form
e-CRF  Electronic Case Report Form
EMA    European Medicines Agency
FAS    Full Analysis Set
FEV₁   Forced Expiratory Volume in 1 second
GINA   Global Initiative for Asthma
HDM    House Dust Mite
ICS    Inhaled Corticosteroids
ICTR   Integrated Clinical Trial Report
IgE    Immunoglobulin of isotype E
IgG₄   Immunoglobulin of isotype G₄
IMP    Investigational Medicinal Product
MedDRA Medical Dictionary for Regulatory Activities
NCR    Non Carbon Required
PEF    Peak Expiratory Flow
PEI    Paul-Ehrlich Institut, German regulatory authority
PP     Per Protocol
RABA   Rapid-Acting inhaled β₂-Agonists (according to GINA Guideline)
SABA   According to GINA Guideline: Short-Acting oral β₂-Agonists
       For the purpose of this protocol: Short-Acting inhaled β₂-Agonists
SAP    Statistical Analysis Plan
SAS    Statistical software package from SAS® Institute
SAWP   EMA Scientific Advice Working Party
SF-36   Short Form (36) Health Survey
SPT    Skin Prick Test
TSQM II Treatment Satisfaction Questionnaire for Medication, Version II
WPAI:ASTHMA Work Productivity and Activity Impairment – Asthma
1 Summary of Amendment

The MITRA trial has been postponed for one year in order to obtain scientific advice from the European Medicines Agency (EMA). The scientific advice from EMA, which was obtained in February 2011, supported the trial design, but had some issues regarding selection criteria and the statistical analyses to be performed.

This amendment is prepared in order to reflect that the trial has been postponed by one year, to implement commitments made to regulatory authorities during the protocol approval process, to implement the advices from EMA, and to optimize the protocol on a couple of other issues.

Overall, the main changes are as follows:

- Timelines have been postponed by a year, and the interval from Visit 10 to Visit 11 has been extended by 2 weeks.
- Changes to which ALK has committed to during the protocol approval process, mainly concerning in- and exclusion criteria:
  - Inclusion criterion 10 has been amended to raise the lower limit for FEV$_1$ from FEV$_1 > 60\%$ to FEV$_1 \geq 70\%$ of predicted (advised by EMA)
  - In inclusion criterion 12 it has been clarified that subjects may be sensitized to both Der $pte$ and Der $far$.
  - In inclusion criterion 13 it has been clarified that subjects may have positive specific IgE against both Der $pte$ and Der $far$.
- Changes as advised by EMA during scientific advice:
  - Inclusion criterion on requirement of ICS use prior to entry has been amended to specify that the dose of ICS should be in accordance with GINA Guideline step 2-4
  - Section 8 on statistics has been revised to address the issues raised by EMA regarding the primary analysis of the primary endpoint. The primary analysis is changed to include imputation for missing data.
- Optimization of the use of subject questionnaires, including using AQLQ(s) at unscheduled visits in order to capture periods with asthma exacerbation, and introduction in selected countries of a new questionnaire, TSQM II, to rate patient satisfaction. WPAI:ASTHMA and SF-36 are omitted at Visit 8.
- To allow on an individual subject basis for further extension of Period 1 (Screening).
- Implementation of electronic CRFs in Denmark as a pilot project.
2 Changes to the Protocol

Additions to the original protocol are listed below, with reference to the sections affected. Text deleted is marked with strike-through, while added text is in **bold italics**.

All assessments will be performed as described in the original protocol. In cases where changes/additions have been made, the appropriate section has been included in this amendment. Repetition of otherwise unchanged sections have not been included in this amendment.

2.1 Medical Expert (page 2)

**Text has been changed to read as follows:**

Medical expert:
Kim Simonsen *Ea Dige, MD*
ALK-Abelló A/S
Bøge Allé 6-8
2970 Hørsholm
Denmark
+45 – 45747576

**Reason for change**
Kim Simonsen no longer works at ALK. Ea Dige, MD, has taken over the role of medical expert.
2.2 Signature page from International Coordinating Investigator

Text (page) has been added as follows:

**Approval of Consolidated Clinical Trial Protocol incorporating General Protocol Amendment 1 – International Coordinating Investigator**

Approved by International Coordinating Investigator:  
Consolidated Clinical Trial Protocol incorporating General Protocol Amendment 1, dated 05-Apr-2011, is approved by:

---

**International Coordinating Investigator:**

Johann Christian Virchow  
Prof. Dr. med.  
Abteilung für Pneumologie / Internistische Intensivmedizin  
Klinik I – Zentrum für Innere Medizin,  
Universitätsklinikum Rostock  
Ernst-Heydemann-Str. 6  
18057 Rostock  
Germany

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**Reason for change**

The final protocol dated 12-April-2010 did not include a signature page for the international coordinating investigator.
2.3 List of Appendices

Text has been changed to read as follows:

List of Appendices
Appendix 1: Investigator Agreement on *Consolidated Clinical Trial* Protocol *incorporating General Protocol Amendment 1*
Appendix 2: Electronic Diary Questions
Appendix 3: Asthma Control Questionnaire
Appendix 4: Asthma Quality of Life Questionnaire with standardised activities
Appendix 5: Short Form (36) Health Survey
Appendix 6: Work Productivity and Activity Impairment Questionnaire - Asthma version
Appendix 7: Standard Physical Examination
Appendix 8: Skin Prick Test Procedure
Appendix 9: Procedure for Collecting Dust Sample
Appendix 10: Asthma Action Plan
**Appendix 11: Treatment Satisfaction Questionnaire for Medication, Version II**
**Appendix 12: General Protocol Amendment no. 1**

Reason for change
The appendix section is updated to include an investigator agreement to the consolidated protocol, and to include the amendment as an appendix. Furthermore, a new questionnaire on treatment satisfaction is introduced in selected countries.
2.4 List of Abbreviations

Text has been changed to read as follows:
(Note: abbreviations not listed below remain unchanged in the protocol)

List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>e-CRF</td>
<td>Electronic Case Report Form</td>
</tr>
<tr>
<td>RABA</td>
<td>Rapid-Acting inhaled β₂-Agonists (according to GINA Guideline)</td>
</tr>
<tr>
<td>SABA</td>
<td>According to GINA Guideline: Short-Acting oral β₂-Agonists</td>
</tr>
<tr>
<td>For the purpose of this protocol: Short-Acting inhaled β₂-Agonists</td>
<td></td>
</tr>
<tr>
<td>TSQM II</td>
<td>Treatment Satisfaction Questionnaire for Medication, Version II</td>
</tr>
</tbody>
</table>

Reason for change:
According to GINA guideline 2009 SABA is defined as short-acting oral β₂-agonists, and RABA as rapid-acting inhaled β₂-agonists. The present protocol needs to refer to short-acting inhaled β₂-agonists. Therefore, for the purpose of this protocol SABA is defined as short-acting inhaled β₂-agonists. Furthermore, e-CRFs are introduced in Denmark, and a new questionnaire, TSQM II, is introduced in selected countries.
2.5  Section 1. Protocol Synopsis

The protocol synopsis repeats elements of the protocol text. Changes to the protocol are changed both in the synopsis and relevant text sections of the consolidated protocol. However, in the present amendment the changes will be mentioned only in relation to the relevant protocol sections, and will, thus, not contain an amended protocol synopsis. For an amended protocol synopsis, please refer to Consolidated Clinical Trial Protocol incorporating General Amendment 1.

2.6  Section 2, Flow Chart

Text has been changed to read as follows:
### 2 Flow Chart

<table>
<thead>
<tr>
<th>Visit Title</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>V1</td>
<td>V3</td>
<td>V9</td>
</tr>
<tr>
<td>Randomisation</td>
<td>V2</td>
<td>V4</td>
<td>V10</td>
</tr>
<tr>
<td>Treatment maintenance</td>
<td>V5</td>
<td>V5</td>
<td>V11</td>
</tr>
<tr>
<td>ICS reduction</td>
<td>V6</td>
<td>V6</td>
<td>V12</td>
</tr>
<tr>
<td>ICS withdrawal</td>
<td>V7</td>
<td>V7</td>
<td>V13 TC</td>
</tr>
<tr>
<td>End of trial</td>
<td>V8</td>
<td>V8</td>
<td>UN TC</td>
</tr>
<tr>
<td>TC Follow up</td>
<td>V9</td>
<td>V9</td>
<td></td>
</tr>
<tr>
<td>Unscheduled</td>
<td>TC1</td>
<td>V9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>V10</td>
<td>V9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>V11</td>
<td>V9</td>
<td></td>
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<tr>
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<td>V9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>V13</td>
<td>V9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TC</td>
<td>V9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UN</td>
<td>V9</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time frame</th>
<th>V1</th>
<th>V3</th>
<th>V9TC1</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1 +5 days</td>
<td>0</td>
<td>V3 +4wks</td>
<td>01 Sep 2012</td>
</tr>
<tr>
<td>V3 +12wks</td>
<td>V3 +20wks</td>
<td>03 Oct 2012</td>
<td></td>
</tr>
<tr>
<td>V5 +20wks</td>
<td>V9 +1wk</td>
<td>V9 +14wks</td>
<td></td>
</tr>
<tr>
<td>V7 +4wks</td>
<td>V9 +16wks</td>
<td>V9 +24wks</td>
<td></td>
</tr>
<tr>
<td>V9 +32wks</td>
<td>V9 +32wks</td>
<td>V9 +52wks</td>
<td></td>
</tr>
<tr>
<td>V11 TC1 +1wk</td>
<td>V12 TC1 +4wks</td>
<td>V13 TC1 +1wk</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time window</th>
<th>±2days</th>
<th>±5days</th>
<th>±5days</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1</td>
<td>±5days</td>
<td>±5days</td>
<td>±5days</td>
</tr>
<tr>
<td>V2</td>
<td>±5days</td>
<td>±5days</td>
<td>±5days</td>
</tr>
<tr>
<td>V3</td>
<td>±5days</td>
<td>±5days</td>
<td>±5days</td>
</tr>
<tr>
<td>V4</td>
<td>±5days</td>
<td>±5days</td>
<td>±5days</td>
</tr>
<tr>
<td>V5</td>
<td>±5days</td>
<td>±5days</td>
<td>±5days</td>
</tr>
<tr>
<td>V6</td>
<td>±5days</td>
<td>±5days</td>
<td>±5days</td>
</tr>
<tr>
<td>V7</td>
<td>±5days</td>
<td>±5days</td>
<td>±5days</td>
</tr>
<tr>
<td>V8</td>
<td>±5days</td>
<td>±5days</td>
<td>±5days</td>
</tr>
<tr>
<td>V9 TC1</td>
<td>±5days</td>
<td>±5days</td>
<td>±5days</td>
</tr>
<tr>
<td>V10</td>
<td>±5days</td>
<td>±5days</td>
<td>±5days</td>
</tr>
<tr>
<td>V11 TC2</td>
<td>±5days</td>
<td>±5days</td>
<td>±5days</td>
</tr>
<tr>
<td>V12 TC1</td>
<td>±5days</td>
<td>±5days</td>
<td>±5days</td>
</tr>
<tr>
<td>V13 TC1</td>
<td>±5days</td>
<td>±5days</td>
<td>±5days</td>
</tr>
<tr>
<td>TC</td>
<td>±5days</td>
<td>±5days</td>
<td>±5days</td>
</tr>
<tr>
<td>UN TC</td>
<td>±5days</td>
<td>±5days</td>
<td>±5days</td>
</tr>
</tbody>
</table>

| Informed consent                | X        |          |          |
| ACQ                             | X        | X        | X        |
| AQLQ(s)                         | X        | X        | X        |
| SF-36                           | X        | X        | X        |
| WPAI/ASTHMA                     | X        | X        | X        |
| TSQM II                         | X        |          |          |
| Visits to GP/specialist/hospital | X        | X        | X        |
| Demography and body measurements | X        |          |          |

1. In the case of a withdrawal, the assessments listed at visit 13 (end of trial) must be performed at the last visit the subject attend.
2. Unscheduled visits or telephone contacts should be conducted as necessary. If the subject does not meet the target ACQ score between 1.0-1.5, visit 3 may, on an individual basis, and at investigator discretion, be rescheduled again a number of times with 2 weeks intervals, provided that the deadline for randomisation can still be met.
3. To be obtained before any trial related procedures are performed.
4. TSQM II only to be performed in Germany and France.
Reason for change:
Timelines for the trial has changed to reflect that the trial has been postponed for a year. The time between Visit 10 and Visit 11 has been extended by 2 weeks in order to avoid visits and telephone contacts during the Christmas season.

A new questionnaire, TSQM II, on treatment satisfaction has been added, while one measuring point (at Visit 8) has been deleted for the SF-36 and WPAI:ASTHMA questionnaires. Furthermore, AQLQ(s) has been added to be handed out at unscheduled visits, and filled in 2-4 days later, to capture quality of life during asthma exacerbations.

From the MT-02 trial it is anticipated that a number of subjects will have difficulties reaching the target ACQ score of 1.0-1.5 within 4-6 weeks after switching to trial ICS. To allow time for more subjects to reach the target ACQ score of 1.0-1.5, it is allowed to extend the screening period further on an individual basis, if investigator and the subject wish to do so. However, this will only be allowed if it can be done without exceeding the deadline for randomisation.

2.7 Section 5.1, Overall Trial Design

Text has been changed to read as follows:
During period 1 (screening period) eligible subjects will be switched from their regular asthma controller medication (e.g. combination products) to equivalent doses of ICS and short-acting **inhaled** β₂-agonist (SABA) as needed. The subject will measure lung function, report asthma symptoms and SABA use on a daily basis in an electronic diary. The recordings of the last 2 weeks of the screening period will serve as baseline for evaluation of asthma exacerbations.

**The timelines in the above Figure 1 allow for 1 week between Visit 1 and Visit 2, and 4 weeks of change to trial ICS. If the subject does not meet the target ACQ score between 1.0-1.5, Visit 3 may, on an individual basis, and at investigators discretion, be rescheduled again a number of times with 2 weeks intervals, provided that the deadline for randomisation can still be met.**

At randomisation and throughout period 2 (treatment maintenance period), the subject will receive investigational medicinal product (IMP) in addition to ICS and SABA. The subject will be asked about asthma control, health and quality of life.

Period 3 (ICS reduction period) will begin approximately October 2011 – 2012. During this period, the subject will have the ICS reduced by 50% and after 3 months 100%, while continuing treatment with IMP for these 6 months. SABA will be provided for symptomatic use for the whole period.

Reason for change:
According to GINA guideline 2009 SABA is defined as short-acting oral β₂-agonists, and RABA as rapid-acting inhaled β₂-agonists. The present protocol needs to refer to short-acting inhaled β₂-agonists. Most allergy- and lung-physicians define SABA as short-acting inhaled β₂-agonists. Therefore, for the purpose of this protocol SABA is defined as short-acting inhaled β₂-agonists.

From the MT-02 trial it may be anticipated that a significant number of subjects will have difficulties becoming stable within approx. 6 weeks after switching to trial ICS. To allow time for
more subjects to reach the target ACQ score of 1.0-1.5, it is allowed to extend the screening period further on an individual basis, if investigator and the subject wish to do so. However, this will only be allowed if it can be done without exceeding the deadline for randomisation.

Furthermore, the trial has been delayed by one year in order to obtain scientific advice from EMA.

2.8 Section 5.2, Trial Schedule

Text has been changed to read as follows:

Planned first subject first visit: Q3 2010 Q3 2011
Planned last subject randomised: Q1 2012
Planned last subject last visit: Q1 2012 Q1 2013
End of trial is defined as database closure: Q2 2012 Q2 2013

Reason for change:
The trial has been delayed by one year in order to obtain scientific advice from EMA. For clarification of the trial timelines, timing of planned last subject randomised has been added.

2.9 Section 5.3.1, Asthma Exacerbation Definition

Text has been changed to read as follows:

In order to fulfil the criteria for a moderate asthma exacerbation in practice, the subject must experience one or more of the following criteria leading to a change in treatment:

a) Nocturnal awakening(s) due to asthma requiring SABA use for at least 2 consecutive nights or an increase of minimum 0.75 in daily symptom score from baseline value on at least 2 consecutive days.

b) An increase from 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 morning and evening PEF from baseline value on at least 2 consecutive days mornings or evenings or ≥ 20% decrease in FEV₁ from baseline value.

d) Visit to the emergency room or unscheduled visit to the trial centre for asthma treatment not requiring systemic corticosteroids.

Reason for change:
To clarify that the specified changes in PEF only need to be either morning or evening measurements, not both.
2.10 Section 5.4.1.1, Inclusion Criteria

Text has been changed to read as follows:

4. Use of asthma medication an appropriate amount of inhaled corticosteroid (incl. e.g. 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.

Reason for change:
To clarify that only subjects on inhaled corticosteroids (GINA Guideline step 2-4) are eligible for the trial. Subjects on oral corticosteroids (GINA Guideline step 5) are excluded.

2.11 Section 5.4.1.1, Inclusion Criteria

Text has been changed to read as follows:

5. Dose of ICS after switching should at randomisation be in a range of budesonide 400-800 mg. 1200 mcg.

Reason for change:
Inclusion criterion no. 4 has been amended to specify inclusion of subjects on ICS treatment at GINA Guideline step 2-4. Accordingly the upper limit for daily budesonide use at randomisation is increased from 800 to 1200 mcg. The rationale for this change is that the patient group with medium to high dose daily ICS use up to 1200 mcg is considered to benefit the most by the add-on treatment with the HDM AIT. An increase in ICS when already on a high daily dose is not an optimal option both due to the flattening of the dose-response curve for ICS, and due to the potential side-effects of ICS at higher dosages; i.e. the increase in ICS may be effective (Evidence category D according to GINA levels of evidence), however, may be associated with severe side effects (Evidence category A) (GINA 2009). Importantly, the inclusion of subjects using 1200 mcg ICS daily is considered justified from a safety point of view, when the lung function of the subject is not severely impaired (FEV1<70% of predicted value) and the asthma is not uncontrolled (WAO Position Paper 2009).

2.12 Section 5.4.1.1, Inclusion Criteria

Text has been changed to read as follows:

10. FEV₁ ≥ 60% ≥ 70% of predicted value.

Reason for change:
The ALK HDM AIT is being developed in subjects with partly controlled asthma. Before focusing on level of disease control, GINA used to classify asthma severity by clinical features before treatment. Accordingly, severe asthma was defined by FEV₁ ≤ 60% predicted. This was
reflected in the inclusion criterion for this trial, where subjects with an FEV$_1$ > 60% of predicted values were to be included.

However, as EMA has pointed out, current scientific knowledge classifies a FEV$_1$ < 70% of predicted values with concordant pharmacological treatment as contraindication for specific immunotherapy. This is due to the fact that asthma appears to be a significant risk factor for systemic reactions and FEV$_1$ < 70% of predicted values represents a risk factor for developing a bronchial reaction. Current guidelines (WHO position paper on Sub-Lingual Immunotherapy (Bousquet et al., 2009), WHO position paper on Allergen immunotherapy (Canonica, 1998)) list FEV$_1$ < 70% of predicted value as a relative contraindication. EMA finds that exclusion of subjects with FEV$_1$ < 70% of predicted values would be vital for the participant’s safety.

Consequently, the criterion for including subjects has been changed to FEV$_1$ ≥ 70% of predicted value.

2.13 Section 5.4.1.1, Inclusion Criteria

Text has been changed to read as follows:

12. Positive SPT response (wheal diameter ≥ 3 mm larger than the negative control) to Der pte and/or Der far.

Reason for change:

Subjects may be sensitised to both Der pte and Der far.

2.14 Section 5.4.1.1, Inclusion Criteria

Text has been changed to read as follows:

13. Positive specific IgE against Der pte and/or Der far (≥ IgE Class 2; ≥ 0.70 KU/L).

Reason for change:

Subjects may have positive specific IgE against both Der pte and Der far.

2.15 Section 5.5.5, Interruptions/Discontinuation of Treatment

Text has been changed to read as follows:

Interruptions should be kept to a minimum and must not exceed a total of 49 days should not exceed a total of 20% of the days on IMP treatment.
Reason for change:
The original 49 days limit was based on 8 months of treatment. Not all subjects will have exactly 8 months of treatment, and the limit has therefore been amended to apply also to a longer/shorter treatment period. The requirement for IMP compliance should not be limited to Period 2.

2.16 Section 5.5.6.1, Symptomatic Medication

Text has been changed to read as follows:

Symptomatic Medication for Asthma Symptoms
Switching of asthma controller medication incl. combination products to ICS should be according to GINA 2008 figure 3-1 (ref.), see Table 1. Dose of ICS after switching should at randomisation be in a range of budesonide 400 - 800 to 1200 mcg in order for the subject to be eligible.

Reason for change:
Inclusion criterion no. 4 has been amended to specify inclusion of subjects on ICS treatment at GINA Guideline step 2-4. Accordingly the upper limit for daily budesonide use at randomisation is increased from 800 to 1200 mcg. The rationale for this change is that the patient group with medium to high dose daily ICS use up to 1200 mcg is considered to benefit the most by the add-on treatment with the HDM AIT. An increase in ICS when already on a high daily dose is not an optimal option both due to the flattening of the dose-response curve for ICS, and due to the potential side-effects of ICS at higher dosages; i.e. the increase in ICS may be effective (Evidence category D according to GINA levels of evidence), however, may be associated with severe side effects (Evidence category A) (GINA 2009). Importantly, the inclusion of subjects using 1200 mcg ICS daily is considered justified from a safety point of view, when the lung function of the subject is not severely impaired (FEV1<70% of predicted value) and the asthma is not uncontrolled (WAO Position Paper 2009).

2.17 Section 5.5.6.3, Prohibited Concomitant Medication

Text has been changed to read as follows:

Table 2 Prohibited Concomitant Medication

<table>
<thead>
<tr>
<th>Drug</th>
<th>Time window</th>
<th>Excluded due to possible interference with</th>
</tr>
</thead>
<tbody>
<tr>
<td>An investigational drug</td>
<td>≤ 30 days before visit 1 and until end of trial</td>
<td>Efficacy, Safety reasons</td>
</tr>
<tr>
<td>Anti IgE treatment</td>
<td>&lt; 90 days before visit 1 and until end of trial</td>
<td>Efficacy</td>
</tr>
</tbody>
</table>
Antihistamine
- Oral or topical
- Long-acting [astemizole] For at least 3 days before SPT testing SPT results
  ≤ 90 days before SPT testing SPT results
Antipsychotic medications with antihistaminic effects (i.e., chlorpromazine, levomepromazine, clozapine, olanzapine, tioridazine)
Glucocorticosteroid
- Local application (on the skin area used for SPT) ≤ 7 days before visit 1 SPT results
- Nasal From visit 9 and until end of trial Efficacy
- Oral 26 ≤ 60 days before SPT testing ≤ 60 days before visit 1 and until end of trial SPT results Efficacy
- Short-acting parenteral ≤ 30 days before SPT testing ≤ 30 days before visit 1 and until end of trial SPT results Efficacy
- Long-acting parenteral (intrarticular or intramuscular) ≤ 90 days before visit 1 and until end of trial Efficacy
Immunotherapy with other allergens From visit 1 and until end of trial Efficacy
Inhaled, topical or oral nedocromil or cromolyn sodium ≤ 14 days before visit 1 and until end of trial Efficacy
Leukotriene antagonists / synthase inhibitors ≤ 30 days before visit 1 and until end of trial Efficacy
Long-acting β2-agonists (LABA) From visit 1 and until end of trial Efficacy
Long-acting muscarinic antagonist (LAMA) From visit 1 and until end of trial Efficacy
Mono amine oxidase inhibitors (MAOIs) ≤ 21 days before visit 1 and until end of trial Adrenaline
Pizotifene ≤ 7 days before visit 1 SPT results
Theophyllin From visit 1 and until end of trial Efficacy
Tricyclic antidepressant medications ≤ 14 days before visit 1 and until end of trial Adrenaline
Tricyclic antidepressant medications with antihistaminic effects (e.g., doxapine, mianserine) ≤ 14 days before visit 1 SPT results

25 Excluded unless provided by ALK as symptomatic medication in the trial
26 Oral glucocorticosteroids in period 3 should be used exclusively for treatment of asthma symptoms.

Reason for change:

For efficacy reasons, oral and short-acting parenteral glucocorticosteroids should not be used at any time during the trial, unless provided by sponsor for treatment of asthma symptoms.

PEI (the German health authority) is concerned that, as steroids are also used in severe cases of rhinitis/rhinoconjunctivitis, the use of steroids for this purpose could influence the primary endpoint in this trial. A commitment had therefore been made to PEI (the German health authorities) to add a footnote explaining that oral and short-acting parenteral corticosteroids in
period 3 should be used exclusively for treatment of asthma symptoms. As short-acting parenteral corticosteroids are not provided by the sponsor during the trial, the requested footnote is modified to only include oral corticosteroids.

2.18 Section 5.6.3, Visit 3 (Randomisation)

Text has been changed to read as follows:
Investigator must review diary entries prior to the visit, see Section 5.10.
The following procedures will be performed:
- Issue and collect ACQ.
  If ACQ > 1.5 (uncontrolled) the dose of ICS can be adjusted at the discretion of the investigator and the visit should be rescheduled to in 2 weeks time.27
- Issue and collect AQLQ(s), SF-36 and WPAI:SHP.ASTHMA. These should preferably be completed before any other trial related activities.

27 If the subject does not meet the ACQ criteria, Visit 3 may, at investigators discretion, be rescheduled again a number of times, provided that the deadline for randomisation can still be met. In such cases, the date of the ACQ assessment that did not reach target and the ACQ score is recorded on a specific page in the CRF.

Reason for change:
From the MT-02 it may be anticipated that a significant number of subjects will have difficulties reaching the target ACQ score of 1.0-1.5 within 4-6 weeks after switching to trial ICS. To allow time for more subjects to reach the target ACQ score, it is allowed to extend the screening period further on an individual basis, if both the investigator and the subject wish to do so. However, this will only be allowed if it can be done without exceeding the deadline for randomisation.
There was an error in the final protocol with respect to the WPAI questionnaire.

2.19 Section 5.6.4, Visit 4

Text has been changed to read as follows:
- In Germany and France only: Issue and collect TSQM II. This should preferably be completed before any other trial related activities.

Reason for change:
To implement the TSQM II questionnaire in selected countries.
2.20 Section 5.6.6, Visit 6

Text has been changed to read as follows:

- Schedule date for visit 7, if subject is randomised before 01 January 2011 otherwise schedule date for visit 8.

Reason for change:
To reflect that the trial has been postponed for one year.

2.21 Section 5.6.7, Visit 7

Text has been changed to read as follows:
Only applicable for subjects randomised before 01 January 2011.

Reason for change:
To reflect that the trial has been postponed for one year.

2.22 Section 5.6.8, Visit 8

Text has been changed to read as follows:

- Issue and collect ACQ and AQLQ(s), SF-36 and WPAI:ASTHMA. These should preferably be completed before any other trial related activities.
- In Germany and France only: Issue and collect TSQM II. This should preferably be completed before any other trial related activities.

Reason for change:
To implement TSQM II questionnaire in selected countries, and to omit SF-36 and WPAI:ASTHMA questionnaires at Visit 8.

2.23 Section 5.6.15, Visit 13 (End of Trial)

Text has been changed to read as follows:

- In Germany and France only: Issue and collect TSQM II. This should preferably be completed before any other trial related activities.
Reason for change:
To implement TSQM II questionnaire in selected countries.

2.24 Section 5.7, Unscheduled Visits and Telephone Contacts

Text has been changed to read as follows:
If the subject experience one or more of the criteria fulfilling the definition of an asthma exacerbation, see Section 5.8.1, the subject must contact the trial centre and make agreements for an unscheduled visit.

*If an unscheduled visit during Period 3 is due to an asthma exacerbation, an AQLQ(s) should be issued, and the subject should be instructed to fill it in 2-4 days later. 2-4 days later, the subject should be contacted by telephone to ensure that the asthma is improving (see Section 5.5.7), and to remind the subject to fill in the AQLQ(s) and bring it back to the clinic at the next visit. Note: if the unscheduled visit occurs 2 or more days after the asthma exacerbation has peaked, the AQLQ(s) may be issued, filled in, and collected during the unscheduled visit. In this case, the AQLQ(s) should preferably be filled in before any other trial related activities.*

*Furthermore, for all unscheduled visits, the following procedures will be performed if deemed necessary by the investigator.*:

Reason for change:
To capture AQLQ(s) data during asthma exacerbations.

2.25 Section 5.8.1.1, Asthma Exacerbation

Text has been changed to read as follows:
c) ≥ 20% decrease in morning and evening PEF from baseline value on at least 2 consecutive days mornings or evenings or ≥ 20% decrease in FEV₁ from baseline value.

Reason for change:
To clarify that the specified changes in PEF need only to be morning or evening measurements, not both.

2.26 Section 5.8.1.3, Use of Short-Acting β₂-Agonist

Text has been changed to read as follows:

5.8.1.3 Use of Short-Acting Inhaled β₂-Agonist
Reason for change:
According to GINA guideline 2009 SABA is defined as short-acting oral β2-agonists, and RABA as rapid-acting inhaled β2-agonists. The present protocol needs to refer to short-acting inhaled β2-agonists. Most allergy- and lung-physicians define SABA as short-acting inhaled β2-agonists. Therefore, for the purpose of this protocol SABA is defined as short-acting inhaled β2-agonists.

2.27 Section 5.8.3, Pharmacoeconomic Assessments

Text has been added as follows:
In Germany and France, subjects will also be asked to complete a TSQM II (Appendix 11).

Reason for addition:
To measure subject’s satisfaction with the treatment.

2.28 Section 5.8.5.4, Skin Prick Test

Text has been changed to read as follows:
- Tree – Salix alba/viminalis (depending upon region)

Reason for change:
The diagnostic product, Soluprick, is not available as Salix alba. Due to a high degree of cross-reactivity between the Salix species, a Salix viminalis extract will result in the same reaction. Therefore, Salix viminalis will be offered instead of Salix alba.

2.29 Section 6.1.3, Adverse Event Assessment Definition

Text has been added as follows:

Causal Relationship to Trial Procedures
An SAE does not necessarily have a causal relationship to the conduct of the trial. Any SAE reported to ALK must be assessed with a negative or a positive relationship to the trial procedures – the relationship to the trial procedures is assessed by answering the following question on the SAE Form: “Was the event related to trial procedures other than the IMP?”

“Yes”: The event is considered to be related to the trial procedures.

“No”: The event is considered not to be related to the trial procedures.

Events assessed with a positive causal relationship (Yes) to the trial procedures are subject to regulatory reporting.
Reason for change:

Required by Clinical Trials Directive 2001/20/EC, ENTR/CT3 Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials.

2.30 Section 6.3.1, Follow-up on Non-Serious Adverse Events

Text has been changed to read as follows:

Cases of chronic conditions can after the subject has completed the trial be closed with the outcome “recovering” or “not recovered”.

Reason for change:

According to section 6.1.3 Adverse Event Assessment Definitions, “recovering” is not a possible outcome in this trial. Consequently, chronic conditions should be closed with the outcome “not recovered”.

2.31 Section 7, Data Management

Text has been changed to read as follows:

7 Data Management

7.1 Data Collection

7.1.1 Case Report Form (paper)

At the majority of trial centres, the investigator must enter the information required by the protocol in paper CRFs. The CRFs will be supplied as non carbon required (NCR) paper (1 original, 1 copy).

The monitor will review the CRFs for completeness and accuracy and instruct the personnel at the trial centre to make any required corrections or additions.

As soon as the CRFs are monitored and considered correctly completed the original CRFs are sent to ALK by the monitor. 1 copy of the CRF is retained at the trial centre.

Once the CRFs are received by ALK, their receipt is recorded and the original is forwarded to the responsible data management staff for processing.

7.1.2 Case Report Form (electronic)

At selected trial centres the investigator must enter the information required by the protocol in an electronic CRF (e-CRF). The electronic CRF is supplied by a CRO (Cyncron) as a zero-footprint web browser application.
The monitor will review the CRFs for completeness and accuracy and instruct the personnel at the trial centre to make any required corrections or additions.

At the end of the trial each trial centre will receive copies of all e-CRFs reported by the centre complete with an audit trail of any corrections made.

7.1.2 Electronic Diary

The electronic diary is dispatched as described in Section 5.10. Diary data will be entered by the subject and transferred to the vendor database on a daily basis. Once all electronic diary data has been collected the diary database will be closed and transferred from the vendor to ALK. The diary data will not be subject to data validation (query processing). Documentation of the data load from the vendor to ALK will be described in the data handling report.

7.1.3 Laboratory and Immunological Data

Results of laboratory assessments will be provided by the central laboratory selected by ALK and sent electronically to data management at ALK.

Immunology results will be provided from the research department at ALK and forwarded electronically to data management at ALK.

Documentation of data loads for laboratory and immunological data will be provided in the data handling report.

7.2 Data Processing

7.2.1 Case Report Form (paper)

Data items from the CRFs are entered into the trial database using double data entry with verification upon second entry. Text items (e.g. comments) are entered once.

Subsequently, the information entered into the database is systematically checked by data management staff, using error messages printed from validation programs and database listings. Errors or omissions will be entered on data clarification forms, which will be returned to the trial centre for resolution. A copy of the signed data clarification form is to be kept with the CRFs at the trial centre, and once the original is received by ALK the resolutions will be entered into the database.

7.2.2 Case Report Form (electronic)

Data items from the e-CRF are automatically entered into the trial database on entry by the trial centre.

The information entered into the database is systematically checked during data entry and subsequently by monitors and data management staff. Errors or omissions will generate a query in the e-CRF system. The progress of subject data entry and query resolution is followed through the e-CRF system.

7.2.3 Coding of Data

Concomitant medications entered into the database will be coded using the WHO Drug Reference List (version 2nd quarter 2003 or later).
Medical history and AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) (version 10.1 or later).

### 7.2.4 Release/Lock of Database

When the paper CRFs and e-CRFs have been signed off by the investigator, monitored, any queries resolved and the database has been declared to be complete and accurate, the database will be locked and data will be unblinded. Any changes to the database after that time can only be made by joint written agreement between the clinical project manager, the responsible statistician and the data manager.

**Reason for change:**

To introduce e-CRFs at selected sites, while maintaining paper CRFs at the others.

### 2.32 Section 8, Statistical Methods

Text has been changed to read as follows:

## 8 Statistical Methods

Statistical analyses will be carried out by ALK.

All computation will be performed using SAS® version 9.2 or above.

All analyses requiring significance testing will be two-sided at a 5% significance level, unless otherwise specified. All confidence intervals will be two-sided 95% confidence intervals.

Before unblinding, a separate statistical analysis plan (SAP) detailing the specifications given below will be prepared and agreed upon. This includes a detailed description of the full analysis set (FAS) and the per protocol (PP) analysis.

Any changes in the statistical methods compared to the final SAP will be documented in the integrated clinical trial report (ICTR). Post-hoc analyses, if any, will be clearly marked.

### 8.1 Sample Size and Power Considerations

The primary endpoint is time to first moderate or severe asthma exacerbation after ICS reduction and the treatment effect will be measured and estimated by the hazard ratio obtained from a Cox proportional hazards regression analysis.

**Multiplicity will be controlled by the following pre-specified order of the hypothesis to be tested:**

1. The first hypothesis to be tested is the hypothesis that all three groups (placebo, ALK HDM AIT 6DU, ALK HDM AIT 12DU) are equal

2. If and only if this hypothesis can be rejected at the 5% level each and all three pairwise comparisons can be tested at the 5% level
The sample size is based on power calculations for comparing hazard rates and the first hypothesis to be rejected is the hypothesis that the hazard rates are equal between groups. Then the main hypotheses of interest are the two comparisons of active treatment to placebo.

Maneechotesuwan et al. (19) found that 4 out of 12 (33%) placebo treated subjects did not have an asthma exacerbation during 12 weeks of complete withdrawal of ICS. The definition of an asthma exacerbation was very similar to the suggested definition in this protocol. The estimate may, however, be slightly overestimated because subjects who had an exacerbation during the 2-weeks ICS withdrawal run-in period were withdrawn.

In the present trial, the ICS reduction period consist of 3 months 50% ICS reduction followed by 3 months 100% ICS withdrawal. Therefore, based on the data from Maneechotesuwan et al. (19) an estimate of 35% in the placebo group not having an asthma exacerbation is considered to be a conservative overestimate, as subjects may experience asthma exacerbations already on 50% ICS reduction. Hence, it is assumed that about 65% of subjects in the placebo group will experience asthma exacerbations as defined in section 5.3.1.

Based on the MT-02 trial (doses of 1 DU, 3 DU and 6 DU) it is estimated that about 20% of the subjects in the placebo group may experience an asthma exacerbation during the first 3 months of period 3 (i.e. ICS 50% reduction). In a MT-02 subgroup (ACQ ≥ 1.0; 400 mcg ≤ ICS ≥ 800 mcg), about 20% (30/147) experienced 2 consecutive days with a 20% decrease in morning PEF compared to baseline during the ICS down-tapering and stable period (approximately 3 months). There was no difference between treatment groups. As more asthma exacerbations are expected to be observed during the first 3 months of period 3 than during the MT-02 ICS down-tapering period adjusting for control, 20% is considered a conservative underestimate. This is supported by the fact that the asthma exacerbation definition in the present trial also includes criteria on asthma symptoms, SABA use etc. It is also known, that the ICS dose could be reduced by more than 50% during the up to 3 months long ICS down-tapering period without loss of asthma control for about 40%-55% of subjects in the placebo group (20;21;27).

The power calculations for complete case analysis for comparing two groups at a 5% significance level, calculated for different differences to placebo based on both a Fisher's exact conditional test for two proportions as well as proportional hazards, and given that 65% of the subjects in the placebo group will experience an asthma exacerbation and that 240 subjects are included in each treatment group, is shown below (see Table 3).

<table>
<thead>
<tr>
<th>Assumptions</th>
<th>Difference between ALK HDM AIT and placebo</th>
<th>Power based on</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=240 per treatment group. ( \alpha = 5% ).</td>
<td>Absolute Hazard ratio Proportion Survival</td>
<td></td>
</tr>
<tr>
<td>20%</td>
<td>0.57</td>
<td>99%</td>
</tr>
<tr>
<td>16%</td>
<td>0.64</td>
<td>93%</td>
</tr>
<tr>
<td>15%</td>
<td>0.66</td>
<td>90%</td>
</tr>
<tr>
<td>13%</td>
<td>0.70</td>
<td>80%</td>
</tr>
<tr>
<td>10%</td>
<td>0.76</td>
<td>57%</td>
</tr>
</tbody>
</table>

In placebo group 65% of subjects experience asthma exacerbations.
For power based on survival proportional hazards are assumed.

<table>
<thead>
<tr>
<th></th>
<th>5%</th>
<th>0.87</th>
<th>18%</th>
<th>22%</th>
</tr>
</thead>
</table>

Below is illustrated fictive data for a placebo group that fulfils the assumption of 35% having no asthma exacerbations during the complete 6 months ICS reduction period and 80% during the first 3 months on 50% reduced ICS dose (Figure 2). Moreover, assumptions for the ALK HDM AIT 6 DU and 12 DU are absolute differences to reductions of hazard rates compared to placebo of 13.30% and 16.36%. The data follows proportional hazards. Based on 240 subjects per treatment group the overall power in this example to detect first a 16% difference between 12 DU and placebo and then to detect a 13% difference between 6 DU and placebo is 80% (=0.95x0.84x100%).

Figure 2 Proportion Free of Asthma Exacerbations after ICS Reduction

![Proportion Free of Asthma Exacerbations after ICS Reduction](image)

The treatment effect will be measured and estimated by the hazard ratio obtained from a Cox proportional hazards regression analysis. The analysis will be based on the full analysis set including all randomised subjects. Because discontinuation prior to period 3 is expected, data imputation will most likely be required for this analysis. A multiple imputation method will be applied. All subjects who discontinue during period 2, no matter their assigned randomised treatment group and for whatever reason for discontinuation, will be included in the primary analysis as if they were following the same distribution as the observed placebo group during the efficacy assessment period 3, i.e. as if they were having no treatment effect.

The power calculation is based on the following assumptions:

1. A total of 12% discontinuation during the trial period
   a. 8% during period 2
   b. 4% during period 3
2. Proportion of discontinuation is equal between groups

3. Analysis is performed based on multiple imputations, i.e. values for the estimated 8% of the subjects who discontinue during period 2 will be imputed as sampled from the observed placebo distribution of time to first moderate or severe asthma exacerbation during period 3

4. The estimated 4% of subjects who discontinue during period 3 will be included in the analysis with a right-censored event time following a constant hazard rate (of \(-\log(0.96)/6\)) over the 6 months period 3

5. Proportional hazard rates

6. The hazard rate for time to experiencing a moderate or severe asthma exacerbation in the placebo group is a constant hazard rate of 0.17 corresponding to 65% of the placebo group experience an asthma exacerbation (\(-\log(1-0.65)/6\))

7. Hypothesis testing strategy starting with the global null hypothesis of no difference between any of the three groups

8. Treatment effect compared to placebo is a hazard ratio of 0.70 for ALK HDM 6DU

9. Treatment effect compared to placebo is a hazard ratio of 0.64 for ALK HDM 12DU

The power to detect a hazard ratio of 0.70 for ALK HDM 6DU and 0.64 for ALK HDM 12DU corresponding to a 30% and 36% reduction of the hazard rate for time to first asthma exacerbation in the placebo group is presented in Table 4. The power calculations are performed with computer simulations (28).

Table 4  Power for statistical analysis based on imputation and assumptions

<table>
<thead>
<tr>
<th>Hypothesis and effect size</th>
<th>N=6</th>
<th>N=7</th>
<th>N=8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global null hypothesis: Placebo=6DU=12DU</td>
<td>8</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Detect either a hazard ratio of 0.70 for 6DU or 0.64 for 12DU compared to placebo</td>
<td>9</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

| Null hypothesis: Placebo=12DU | 8 | 9 | 9 |
| Detect a hazard ratio of 0.64 for 12DU compared to placebo | 7 | 1 | 3 |

| Null hypothesis: Placebo=6DU | 7 | 8 | 8 |
Detect a hazard ratio of 0.70 for 6DU compared to placebo & 5 0 3
placebo                  % % %
Both detect a hazard ratio of 0.70 for 6DU and 0.64 & 7 7 8
12DU compared to placebo. 3 8 2
                     % % %

A reduction in the hazard rate of approximately 30% corresponding to a hazard ratio of 0.70 is considered clinical relevant.

Based on the assumptions above it is estimated that 266 randomised subjects per treatment group (i.e. a total of 798 subjects) will provide at least 93% power to reject the global hypothesis of no difference between any of the treatment groups with a two-sided test at the 5% level of significance, see Table 4. In other words it can be detected if the hazard rate for 6DU is reduced by 30% or the hazard rate for 12DU is reduced by 36% compared to the hazard rate in placebo with a power of 93%. Furthermore, with a power of 91% a hazard ratio of 0.64 for ALK HDM AIT 12DU compared to placebo can be detected and with a power of 80% a hazard ratio of 0.70 for ALK HDM AIT 6DU compared to placebo can be detected. Finally, both hazard ratios of 0.70 and 0.64 for ALK HDM AIT 6DU and 12DU compared to placebo can be detected simultaneously with a power of 78% with a two-sided test at 5% significance level based on the assumptions above.

8.2 Analysis Data Sets

The total analysis set is all subjects who entered the trial. This analysis set includes screening failures. The total population will be used for listing reasons for screening failures and AEs before randomisation.

The FAS is all randomised subjects in accordance with the ICH intent-to-treat principle. This analysis set will be the primary set for all efficacy analyses. The FAS will be used for all baseline/demography tables, efficacy tables, safety tables and subject listings.

The PP analysis set is all subjects in the FAS with no major protocol violations which may influence the primary endpoint (please refer to the SAP for further details). The PP analysis set will be a supplementary set for selected efficacy analyses.

The safety analysis set is identical to the FAS.

8.3 Baseline Characteristics

Demographic and other baseline characteristics will be summarised by treatment group displaying number of subjects, mean, standard deviation, median, 25 and 75-percentiles, minimum and maximum for continuous variables and frequency tables for categorical variables.

8.4 Extent of Exposure

Extent of IMP exposure and IMP accountability will be summarised by treatment group.

8.5 Concomitant Therapy

Concomitant medication and illness will be summarised by means of descriptive statistics.
8.6 Endpoints

8.6.1 Primary Endpoint

The primary endpoint is the time to first moderate or severe asthma exacerbation during period 3 (ICS reduction).

Time to first asthma exacerbation is measured in days from start of period 3 (ICS reduction). The definition of asthma exacerbation used is that the subject must experience one or more of the criteria listed below.

At least one of the following criteria must be fulfilled and lead to a change in treatment to meet the definition of a moderate exacerbation:

a) Nocturnal awakening(s) due to asthma requiring SABA use for at least 2 consecutive nights or an increase of minimum 0.75 in daily symptom score from baseline value on at least 2 consecutive days.

b) An increase from 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 morning or evening PEF from baseline value on at least 2 consecutive days mornings or evenings or ≥ 20% decrease in FEV1 from baseline value.

d) Visit to the emergency room or unscheduled visit to the trial centre for asthma treatment not requiring systemic corticosteroids.

The baseline value is the mean values during the last 14 days of the screening period.

If the subject experience one of the following events, this will be characterised as a severe asthma 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.

8.6.2 Key Secondary Endpoints

Key secondary endpoints are:

\[\text{Time to first deterioration in asthma symptoms.} \]

Time in days from start of period 3 (ICS reduction) to the first asthma exacerbation fulfilling criterion a), see section 8.6.1.

\[\text{Immunology measured at end of trial in terms of specific IgE-blocking factor against HDM allergens.} \]

8.6.3 Other Secondary Endpoints

\[\text{Severe asthma exacerbation.} \]

\[\text{o Time to first severe asthma exacerbation.} \]

Time in days from start of period 3 to the first severe asthma exacerbation fulfilling criterion e) or f), see section 8.6.1.
Asthma exacerbations during period 3.
  o The frequency of asthma exacerbations (number/percentage of subjects) during period 3.

Asthma symptoms.
  o The average overall symptom score over the first asthma exacerbation free period during the first 3 months of period 3.
  o The average overall symptom score over the first asthma exacerbation free period during entire period 3.
  o Symptom free days during period 3.
    A symptom free day is defined as a day with:
    o No asthma symptoms (symptom score =0).
    o No need for SABA.
    o No increase in ICS or use of oral steroid.

Symptomatic medication.
  o Time to first increased use of SABA.
    Time in days from start of period 3 to the first asthma exacerbation fulfilling criterion b), see section 8.6.1.

Lung function.
  o The average morning PEF and diurnal variability over the first asthma exacerbation free period during first 3 months of period 3.
  o The average morning PEF and diurnal variability over the first asthma exacerbation free period during entire period 3.
  o Time to first deterioration in lung function.
    Time in days from start of period 3 to the first asthma exacerbation fulfilling criterion c), see section 8.6.1.
  o Change in FEV\textsubscript{1} from baseline to visit 9 (ICS reduction).

Asthma control.
  o The overall ACQ for the last week of period 2 (treatment maintenance) before period 3 (assessed at visit 9).

Asthma quality of life.
  o The overall AQLQ(s) for the last week of period 2 (treatment maintenance) before period 3 (assessed at visit 9).

Immunology.
  o Specific IgE, IgG4, and other immunological assessments.

Quality of Life and Pharmacoeconomics Assessments.
  o Development and changes in ACQ, AQLQ(s), SF-36, TSQM II and WPAI:ASTHMA.
  o Health care resource use and rate of hospitalisation.
Safety.

- AEs, SAEs, AE withdrawals, clinical lab tests, vital signs, physical examination.

8.7 Multiplicity

Multiplicity will be controlled by the pre-specified order of the hypothesis to be tested. The null hypotheses to be tested are the equality of active ALK HDM AIT to placebo. The order of hypothesis to be tested is:

1. The primary efficacy analysis of ALK HDM AIT 12 DU compared to placebo.
2. The primary efficacy analysis of ALK HDM AIT 6 DU compared to placebo.

The second hypothesis test will only be carried out if the first is statistically significant at the 5% level. If the first comparison is statistically significant (p < 0.05) then the second comparison is also tested at the 5% level.

**Multiplicity will be controlled for the multiple comparisons of the treatment groups on the primary endpoint.** Multiplicity will be controlled by the following pre-specified order of the hypothesis to be tested. The first hypothesis to be tested is the hypothesis that all three groups are equal. If and only if this hypothesis can be rejected at the 5% level, each of the three pairwise comparisons can be tested at the 5% level. No statistical conclusions can be based on any of the three pairwise comparisons unless the hypothesis of no difference between the three groups is rejected (p<0.05).

Additional endpoints and analyses are supportive in nature and will not be controlled for multiplicity.

8.8 Efficacy Analyses

8.8.1 Primary Efficacy Analysis

The primary efficacy analysis of the primary endpoint, time to first moderate or severe asthma exacerbation, will be performed with a Cox proportional hazards regression analysis. The model is stratified for trial centre and includes treatment group, trial centre, and baseline ICS dose as fixed effects and baseline ACQ score as a covariate factor. Depending on the number and size of trial centres, pooling of trial centres may be considered or trial centres may be replaced by regions or countries. Based on this model the comparison of each active dose against placebo will be conducted in a step-down method, starting with ALK HDM AIT 12 DU followed by ALK HDM AIT 6 DU. The hierarchical ordering of the comparisons implies that no statistical conclusions can be based on the second comparison (ALK HDM AIT 6 DU vs. placebo) unless the first comparison (ALK HDM AIT 12 DU vs. placebo) is statistically significant (p < 0.05). If and only if this hypothesis is rejected (p<0.05) the comparison of each active dose against placebo as well as the comparison of the two active dose groups can be...
tested at the 5% level. No statistical conclusions can be based on any of the three pairwise comparisons unless the hypothesis of no difference between the three groups is rejected (p<0.05).

For each active treatment group the estimated adjusted relative risk hazard ratio compared to placebo will be presented together with the two-sided 95% Wald confidence interval and a p-value. The hazard ratio for ALK HDM 12DU compared to ALK HDM 6DU will also be estimated and presented together with the two-sided 95% confidence interval and a p-value.

The primary analysis will be based on a multiple imputation method. This is because the analysis is based on the full analysis set (FAS) including all randomised subjects and because subjects may discontinue during the treatment maintenance period (period 2) prior to efficacy assessment of the primary endpoint.

All subjects who withdraw from the trial during period 2, no matter their assigned randomised treatment group and for whatever reason for withdrawal, will be included in the primary analysis as if they were following the same distribution as the observed placebo group during the efficacy assessment period (period 3), i.e. as if they were having no treatment effect. Thus, all subjects who withdraw during period 2 will be included as sampled from the placebo distribution of time to first asthma exacerbation during period 3.

This is a multiple imputation method that generates multiple copies of the original data set by replacing the missing values using the observed placebo distribution, analyse them as complete data sets and finally combine the different parameter estimates across the data sets to produce a unique point estimate and standard error taking into account the uncertainty of the imputation process.

Sensitivity analysis and model control will be conducted to assess the model assumption of non-informative drop-out withdrawal during period 3, and proportional hazards. Also the assumption of non-informative drop-out withdrawal during period 2 will be assessed and the drop-out withdrawal rate evaluated.

8.8.2 Key Secondary Efficacy Analyses

The key secondary event-time endpoints will be 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(s) evaluated are fulfilled.

IgE-blocking factor at end of trial will be analysed with a linear mixed effects model with treatment group, baseline IgE-blocking factor value as fixed effects and trial centre as a random effect.

8.8.3 Other Secondary Efficacy Analyses

Time to first severe asthma exacerbation will be analysed similar to the key secondary event-time endpoints.

Frequency of asthma exacerbations during period 3 will be analysed with a generalised linear model including treatment group as fixed effect and adjusting for covariates such as trial centre.
Other secondary efficacy endpoints including immunology will be analysed with a linear mixed effects model with treatment group and baseline value as fixed effects and trial centre as a random effect. For immunology data, also visit and treatment group by visit interaction will be included as fixed effects and a random subject effect.

8.9 Safety Analyses

8.9.1 Analyses of Adverse Events

AEs will be summarised by treatment group, system organ class and preferred term displaying number of subjects in treatment group, number and percentage of subjects having the event as well as number and percentage of events. Furthermore, the AEs will be summarised according to severity, relationship, outcome, action and seriousness. The analyses will be described further in the SAP.

8.9.2 Analyses of Other Safety Parameters

Laboratory assessments and vital signs will be summarised by treatment group displaying number of subjects, mean, standard deviation, median, 25 and 75-percentiles, minimum and maximum for continuous variables and frequency tables for categorical variables.

8.10 Interim Analysis

No interim analysis is planned.

8.11 Other Topics

For subjects who withdraw between visit 9 (ICS reduction) and visit 13 (end of trial), the time to asthma exacerbation is right-censored at the date of withdrawal. Handling of other missing data as well as additional sensitivity analysis will be described in the SAP.

8.12 Pharmacoeconomic Analyses

Information about the subject’s perception of quality of life and work impact during the course of the trial and health care resource use are collected.

Details for the evaluation of health care resource use, rate of hospitalisation, questionnaire data and derivation of subscales (scoring algorithms) including handling of missing observations will be described in the SAP.

Reasons for changes:

The MITRA trial has been postponed for one year in order to obtain scientific advice from the European Medicines Agency (EMA). The scientific advice from EMA, obtained in February 2011 (doc: EMA/CHMP/SAWP/97494/2011), supported the trial design but had some comments to the proposed statistical analyses. Therefore the section has been changed.

The concern from the EMA Scientific Advice Working Party (SAWP) was that the originally proposed analysis of the primary endpoint could result in a biased estimate of the treatment effect due to possible unbalanced withdrawals. The key concern was the 8 months period from treatment start to efficacy assessment and the possible unbalanced trial withdrawals due to
adverse events during that period of time (i.e. period 2). In the scientific advice it was recognised that the treatment maintenance phase is required in order for specific immunotherapy to have sufficient efficacy.

To account for this potential bias, a primary analysis with imputation of missing data was suggested. The approach approved by the EMA SAWP was an inclusion of subjects who withdrew due to adverse events as if they had an asthma exacerbation on day 1 of the efficacy assessment period (period 3). Withdrawals due to other reasons during period 2 would be included as ‘at risk’ on day 1 with a censored event-time, i.e. the subject would contribute to the efficacy data with 1 day with no exacerbation. This single imputation method replaces a missing data point with a single value and the analysis is conducted as if all the data was observed.

However, from a clinical point of view this may not be the most relevant imputation, as it is not taken into account if adverse events are considered IMP-related or not and as subjects withdrawing due to other reasons than adverse events (e.g. lost to follow-up or withdrawal of consent) will be included as having not exacerbated.

Further, if withdrawal due to adverse events turns out to be similar between groups but overall withdrawal is different, then the proposed analysis with imputation could be judged biased.

Therefore, ALK have proposed an alternative imputation for the MT-04 protocol, which also includes all randomised subjects in the analysis and is considered a conservative approach. It is proposed that all subjects who withdraw during period 2, no matter their assigned randomised treatment group and for whatever reason for withdrawal, will be included in the primary analysis as if they were following the same distribution as the observed placebo group during the efficacy assessment period (period 3), i.e. as if they were having no treatment effect. Thus, all subjects who discontinue during period 2 will be included as sampled from the placebo distribution of time to first asthma exacerbation during period 3.

As opposed to the above single imputation method, this is a multiple imputation method. This means that the method generates multiple copies of the original data set by replacing missing values using a stochastic model, analyse them as complete data sets and finally combine the different parameter estimates across the data sets to produce a unique point estimate and standard error taking into account the uncertainty of the imputation process (1).

This imputation will have an impact on the power of the trial and has led to a change of the testing strategy of the primary endpoint. Instead of hierarchical testing, a multiple hypotheses testing procedure will be applied, where the first test is whether there are any differences between any of the groups, i.e. the global null intersection hypothesis will be “no treatment effect in both 6DU and 12DU”. If this hypothesis is rejected at $\alpha=0.05$ then each of the three pairwise comparisons can then be tested at $\alpha=0.05$. This procedure is (as the hierarchical) based on the closed testing principle (2).

For the primary statistical analysis the model specification is changed by 1) stratifying for trial centre instead of adjusting by including as a covariate, and 2) avoiding including both baseline ICS and ACQ as covariates. The rationale is 1) by stratifying the model allows for variability between trial centres in a more flexible way than requiring proportional hazards, and 2) because the effect of the covariates on the primary outcome is unknown or not well established it is appropriate not to include them (3).
Reference List


2.33 Appendix 1, Investigator agreement on Protocol

Text has been changed to read as follows:

Investigator Agreement on Consolidated Clinical Trial Protocol incorporating General Amendment

TRIAL ID: 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.

Version: 10 April 2010 05 April 2011

I have read the consolidated clinical trial protocol incorporating general amendment and agree that it contains all the information required to conduct the trial. I agree to conduct the trial as set out in the protocol and amendment. In particular, I agree to adhere to the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, the guidelines on Good Clinical Practice, and applicable regulatory requirements.

Reason for change:
The consolidated protocol will be submitted to regulatory authorities and ethics committees for approval. Sites are expected to use the consolidated protocol as the working protocol, therefore investigators are asked to sign the consolidated protocol.
### 2.34 Appendix 2, Electronic Diary

Text has been changed to read as follows:

<table>
<thead>
<tr>
<th>#</th>
<th>Title</th>
<th>Text</th>
<th>Answer</th>
<th>Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Morning Diary</td>
<td>Good Morning&lt;br&gt;Please do the breathing test and fill in the questionnaire before taking your morning medicine.</td>
<td></td>
<td>A1M1+ subject’s instruction is inserted between “Good Morning screen” and M0</td>
</tr>
<tr>
<td>M0</td>
<td>Morning Diary</td>
<td>On the next screens you will be asked about how your asthma was during the night.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>Morning Diary</td>
<td>Please describe the severity of your <strong>worst</strong> asthma symptom (wheezing, coughing, shortness of breath, or chest tightness) during the night.</td>
<td>0 no symptoms 1 mild symptoms 2 moderate symptoms 3 severe symptoms</td>
<td>M1 to M2a if previous Evening Diary completed&lt;br&gt;M1 to M2b if previous Evening Diary missed</td>
</tr>
<tr>
<td>M2a</td>
<td>Morning Diary</td>
<td>How many puffs of <strong>bronchodilator</strong> did you use since you completed your Evening Diary?</td>
<td></td>
<td>Always M2a to M3</td>
</tr>
<tr>
<td>M2b</td>
<td>Morning Diary</td>
<td>How many puffs of <strong>bronchodilator</strong> did you use in the past 12 hours?</td>
<td></td>
<td>Always M2b to M3</td>
</tr>
<tr>
<td>M3</td>
<td>Morning Diary</td>
<td>How many times did you <strong>wake up</strong> due to asthma symptoms (wheezing, coughing, shortness of breath, or chest tightness)?</td>
<td>0-99</td>
<td>If &gt;0 then continue to M4&lt;br&gt; 0 then continue to “Thank you” screen&lt;br&gt; If M3 = 0 then continue to “Thank you” screen&lt;br&gt; If M3 &gt;0 and M1 ≠ 0 then continue to M4&lt;br&gt; If M3&gt;0 and M1=0 then continue to M3a</td>
</tr>
<tr>
<td>M3a</td>
<td>Morning Diary</td>
<td><strong>You have entered No symptoms but woke up due to asthma symptoms. Please review your responses.</strong></td>
<td>Next screen</td>
<td></td>
</tr>
<tr>
<td>M4</td>
<td>Morning Diary</td>
<td>When you woke up due to your asthma symptoms, <strong>did you use any bronchodilator?</strong></td>
<td>1Yes 2No</td>
<td>If “Yes” in M4 and 0 in M2a or M2b then the following prompt should appear: “You have entered 0 puffs but also reported using your bronchodilator when you woke up. Please review your responses.”&lt;br&gt; If M4 = Yes and M2a or M2b = 0 then continue to next screen&lt;br&gt; If M4 = Yes and M2a or M2b ≠ 0 then continue to M5 (if worsening) or thank you screen (if no worsening)</td>
</tr>
<tr>
<td>M4a</td>
<td>Morning Diary</td>
<td><strong>You have entered 0 puffs but also reported using your bronchodilator when you woke up. Please review your responses.</strong></td>
<td>otherwise go to M5 (if worsening) or thank you screen (if no worsening)</td>
<td></td>
</tr>
<tr>
<td>M5</td>
<td>Morning Diary</td>
<td>Your entries indicate that your asthma symptoms are worsening, please contact your study doctor now.</td>
<td></td>
<td>Appear only if Alert</td>
</tr>
</tbody>
</table>

| Thank you.<br>Remember to take the trial medicine together with your other asthma medicine. Please connect the LogPad to the charger for charging and transmission of data. | | |

---

**General Protocol Amendment no. 1**

**Trial ID:** MT-04  **EudraCT:** 2010-018621-19

**Version:** Final  **Date:** 05-April-2011
Reason for change:
If subjects first answer that they have not had any asthma symptoms during the night and later answers that they have woken up during the night due to asthma symptoms, subjects should have the opportunity to review their answers to avoid inconsistencies in data. The same applies when subjects first answer that they have not used any bronchodilator during the night, and then answers that they took bronchodilator when they woke up due to asthma symptoms.
2.35 Appendix 11, Treatment Satisfaction Questionnaire for Medication

New questionnaire has been added as follows:

Appendix 11 Treatment Satisfaction Questionnaire for Medication, Version II

TSQM (Version II)

Treatment Satisfaction Questionnaire for Medication

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical trial. We are interested in your evaluation of the effectiveness, side effects, and convenience of the medication over the last two to three weeks, or since you last used it. For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat the condition?

☐ 1. Extremely Dissatisfied
☐ 2. Very Dissatisfied
☐ 3. Dissatisfied
☐ 4. Somewhat Satisfied
☐ 5. Satisfied
☐ 6. Very Satisfied
☐ 7. Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves symptoms?

☐ 1. Extremely Dissatisfied
☐ 2. Very Dissatisfied
☐ 3. Dissatisfied
☐ 4. Somewhat Satisfied
☐ 5. Satisfied
☐ 6. Very Satisfied
☐ 7. Extremely Satisfied

3. As a result of taking this medication, do you experience any side effects at all?

☐ 1. Yes
0  No

4. How dissatisfied are you by side effects that interfere with your physical health and ability to function (e.g., strength, energy levels)?

1  Extremely Dissatisfied
2  Very Dissatisfied
3  Somewhat Dissatisfied
4  Slightly Dissatisfied
5  Not at all Dissatisfied
5  Not Applicable

5. How dissatisfied are you by side effects that interfere with your mental function (e.g., ability to think clearly, stay awake)?

1  Extremely Dissatisfied
2  Very Dissatisfied
3  Somewhat Dissatisfied
4  Slightly Dissatisfied
5  Not at all Dissatisfied
5  Not Applicable

6. How dissatisfied are you by side effects that interfere with your mood or emotions (e.g., anxiety/fear, sadness, irritation/anger)?

1  Extremely Dissatisfied
2  Very Dissatisfied
3  Somewhat Dissatisfied
4  Slightly Dissatisfied
5  Not at all Dissatisfied
5  Not Applicable

7. How satisfied or dissatisfied are you with how easy the medication is to use?

1  Extremely Dissatisfied
2  Very Dissatisfied
3  Dissatisfied
4  Somewhat Satisfied
5  Satisfied
6  Very Satisfied
7  Extremely Satisfied

8. How satisfied or dissatisfied are you with how easy it is to plan when you will use the medication each time?

1  Extremely Dissatisfied
9. How satisfied or dissatisfied are you by how often you are expected to use/take the medication?

☐ 1   Extremely Dissatisfied
☐ 2   Very Dissatisfied
☐ 3   Dissatisfied
☐ 4   Somewhat Satisfied
☐ 5   Satisfied
☐ 6   Very Satisfied
☐ 7   Extremely Satisfied

10. How satisfied are you that the good things about this medication outweigh the bad things?

☐ 1   Extremely Dissatisfied
☐ 2   Very Dissatisfied
☐ 3   Dissatisfied
☐ 4   Somewhat Satisfied
☐ 5   Satisfied
☐ 6   Very Satisfied
☐ 7   Extremely Satisfied

11. Taking all things into account, how satisfied or dissatisfied are you with this medication?

☐ 1   Extremely Dissatisfied
☐ 2   Very Dissatisfied
☐ 3   Dissatisfied
☐ 4   Somewhat Satisfied
☐ 5   Satisfied
☐ 6   Very Satisfied
☐ 7   Extremely Satisfied

**Reason for change:**

To measure patients’ satisfaction with the IMP treatment.
2.36 Appendix 12, General Protocol Amendment no. 1

Text has been added as follows:

**Appendix 12 General Protocol Amendment no. 1**

[General Protocol Amendment no. 1 appended as a new appendix]

**Reason for change:**

The changes described in General Protocol Amendment no. 1 are incorporated in Consolidated Clinical Trial Protocol incorporating General Protocol Amendment 1. The amendment itself will not be signed by investigators, but will be included as an appendix to the consolidated protocol, which will be signed by investigators and submitted to regulatory authorities and ethics committees for approval.
Clinical Trial Protocol Amendment
General Protocol Amendment no. 2

Trial ID: MT-04

Title of Trial: 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 (HDM) allergy immunotherapy tablet (AIT)

Development Phase: III
EudraCT no: 2010-018621-19
Sponsor: Global Clinical Development
ALK-Abelló A/S
DK-2970 Hørsholm
Phone: +45 4574 7576

Document status: Final
Date: 02-November-2011

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Approval of General Protocol Amendment no. 2 – ALK

Approved by ALK-Abelló:
General Protocol Amendment no. 2, dated 02-November-2011 to the Clinical Trial Protocol, dated 12-April-2010, and General Protocol Amendment no. 1, dated 05-April-2011, is approved by:

Amendment originator:  
Hanne H. Villesen  
Clinical Project Manager

[Signature]  
02 Nov 2011  
Date

On behalf of head of originating department:  
Ea Dige, MD  
EU QPPV, Director,  
Global Clinical Development

[Signature]  
2 Nov 2011  
Date
Approval of General Protocol Amendment no. 2 – International Coordinating Investigator

Approved by International Coordinating Investigator:
General Protocol Amendment no. 2, dated 02-November-2011 to the Clinical Trial Protocol, dated 12-April-2010, and General Protocol Amendment no. 1, dated 05-April-2011, is approved by:

International Coordinating Investigator:
Johann Christian Virchow
Prof. Dr. med.
Abteilung für Pneumologie / Internistische Intensivmedizin
Klinik I – Zentrum für Innere Medizin,
Universitätsklinikum Rostock,
Ernst-Heydemann-Str. 6,
18057 Rostock,
Germany

Signature

Date: 2.11.2011
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List of Appendices

Appendix 1: Investigator Agreement on Protocol Amendment
**List of Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>ACQ</td>
<td>Asthma Control Questionnaire</td>
</tr>
<tr>
<td>AIT</td>
<td>Allergy Immunotherapy Tablet</td>
</tr>
<tr>
<td>AQLQ(s)</td>
<td>Asthma Quality of Life Questionnaire with standardised activities</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>e-CRF</td>
<td>Electronic Case Report Form</td>
</tr>
<tr>
<td>ERS</td>
<td>European Respiratory Society</td>
</tr>
<tr>
<td>EudraCT</td>
<td>European Union Drug Regulating Authorities Clinical Trials database</td>
</tr>
<tr>
<td>EU QPPV</td>
<td>European Qualified Person Pharmacovigilance</td>
</tr>
<tr>
<td>FEV₁</td>
<td>Forced Expiratory Volume in one second</td>
</tr>
<tr>
<td>HDM</td>
<td>House Dust Mite</td>
</tr>
<tr>
<td>LABA</td>
<td>Long-Acting β2-Agonists</td>
</tr>
<tr>
<td>PEF</td>
<td>Peak Expiratory Flow</td>
</tr>
<tr>
<td>SABA</td>
<td>Short-Acting β2-Agonists</td>
</tr>
<tr>
<td>TSQM II</td>
<td>Treatment Satisfaction Questionnaire for Medication, Version II</td>
</tr>
<tr>
<td>WPAI:ASTHMA</td>
<td>Work Productivity and Activity Impairment – Asthma</td>
</tr>
</tbody>
</table>
1 Summary of Amendment

This amendment is prepared in order to:

- Simplify and correct the wording of inclusion criteria 6, 7 and 9.
- Inform that the 1983 table for FEV$_1$ from Coal and Steel is being replaced by updated formula by Quanjer et al1993.
- Inform that some of the procedures planned for visit 1 may be deferred to visit 2.
- Implement the use of a different dust sampling device than originally planned.
- Correct typing errors and important for the correct understanding of the protocol.

This amendment is a non-substantial protocol amendment because the suggested changes and updates do not affect the safety or physical or mental integrity of the subjects nor the scientific value of the trial.

2 Changes to the Protocol

Additions to the original protocol are listed below, with reference to the sections affected. Text deleted is marked with strike through, while added text is in bold italics.

All assessments will be performed as described in the original protocol. In cases where changes/additions have been made, the appropriate section has been included in this amendment. Repetition of otherwise unchanged sections have not been included in this amendment.

2.1 Section 1. Protocol synopsis

The protocol synopsis repeats elements of the protocol text. Changes to the protocol are changed both in the synopsis and relevant text sections of the consolidated protocol. However, in the present amendment the changes will be mentioned only in relation to the relevant protocol sections, and will, thus, not contain an amended protocol synopsis.
2.2 Section 2. Flow Chart

Text has been changed to read as follows:

<table>
<thead>
<tr>
<th>Trial Period</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
<th>End of trial</th>
<th>TC Follow-up</th>
<th>Unscheduled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit Title</td>
<td>Screening</td>
<td>Randomisation</td>
<td>Treatment maintenance</td>
<td>ICS reduction</td>
<td>ICS withdrawn</td>
<td></td>
</tr>
<tr>
<td></td>
<td>V1</td>
<td>V2</td>
<td>V3</td>
<td>V4</td>
<td>V5</td>
<td>V6</td>
</tr>
<tr>
<td>Timeframe</td>
<td>5wks+5days</td>
<td>0</td>
<td>0-4days</td>
<td>0-4days</td>
<td>0-4days</td>
<td>0-4days</td>
</tr>
</tbody>
</table>

| Informed consent  | X        |          |          | X X X X     | X X X X     | X X X X     | X X X X     |                             |
| ACQ             |          | X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X |
| AQLQ(s)         |          | X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X |
| SF-36           |          | X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X |
| MFAS/ASThma     |          | X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X |
| TSQM II         |          | X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X |
| Visits to GP/hospital | X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X |
| Demography and body measurements | X |          |          |          |          |          |          |                             |
| Medical History (incl. allergy, clinical and smoking history) | X |          |          |          |          |          |          |                             |
| Allergy and asthma medication history | X |          |          |          |          |          |          |                             |
| SPT             |          | X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X |
| Physical examination |          | X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X |
| Vital signs     |          | X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X |
| Spirometry - FEV1 |          | X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X |
| Reversibility test |          | X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X |

4 In the case of a withdrawal, the assessments listed at visit 13 (end of trial) must be performed at the last visit the subject attend.
5 Unscheduled visits or telephone contacts should be conducted as necessary. In case of an asthma exacerbation during Period 3 an unscheduled visit must take place in order to hand out an AQLQ(s). At a telephone contact 2-4 days after the visit, the subject should be reminded to fill in the AQLQ(s). Other evaluations/examinations stated should only be performed if deemed necessary by the investigator.
6 If the subject does not meet the target ACQ score between 1.0-1.5, visit 3 may, on an individual basis, and at investigators discretion, be rescheduled again a number of times with 2 weeks intervals, provided the deadline for randomisation can still be met.
7 To be obtained before any trial related procedures are performed.
8 Procedure may be deferred to visit 2 if the subject have taken SABA within the past 4 hours, LABA within the past 12 hours, or antihistamine within the last 3 days, see Appendix 13.
9 TSQM only to be performed in Germany and France.
10 Historical test performed within the last 2 years is accepted.
Reason for change

A footnote has been added to the procedures ACQ, spirometry - FEV₁, Reversibility test, and SPT on visit 1 stating: Procedure may be deferred to visit 2 if the subject have taken SABA within the past 4 hours, LABA within the past 12 hours, or antihistamines within the last 3 days, see Appendix 13.

Subjects may take SABA within 4 hours of spirometry for the purpose of the ACQ score, however, it is not allowed within 4 hours of spirometry for the purpose of reversibility test or bronchial provocation tests (should these be applicable). If SABA has been taken within 4 hours before spirometry for reversibility/bronchial provocation test is to be performed, the reversibility/bronchial provocation test needs to be deferred to visit 2. Subjects should be instructed to not use SABA within 4 hours prior to visit 2.

Some subjects use LABA instead of SABA. In such cases the subject's ACQ score may be artificially low (as described in section 2.3 of this amendment), and result in the subject failing to meet the criterion of having an ACQ of at least 1.0 In order to have the ACQ filled in as intended, LABA should be switched to SABA before scoring the ACQ and hence the ACQ may be deferred to visit 2.

Subjects who have a positive SPT at visit 1 can immediately be switched to SABA and, if reversibility/bronchial provocation test needs to be done, instructed to not use the SABA within 4 hours prior to visit 2, where both the reversibility/provocation test (if applicable) and the ACQ will be done.

However, for subjects who have been using antihistamines within 3 days prior to visit 1, the SPT also needs to be deferred to visit 2 (prior to any regular visit 2 procedures). For these subjects, sites will need to await the positive IgE results from the lab before switching LABA to SABA, as we do not find it ethical to switch subjects from their usual medication without any evidence that they are actually sensitised to HDM.

All following footnotes are re-numbered.

2.3 Section 5.4.1.1. Inclusion criteria

Text has been changed to read as follows:

6. Documented reversible airway obstruction as judged by one of the following criteria:
   a) Improvement in absolute FEV₁ ≥ 12% and 200 ml after administration of SABA.
   b) Improvement in PEF > 20% after administration of SABA.
   c) Diurnal variability in PEF > 20% after administration of SABA.
   d) Bronchial provocation test:
      1. A decrease in FEV₁ > 15% after 6 min of sustained exercise.
      2. A decrease in FEV₁ ≥ 10% from baseline is recorded after a 6 minutes period of hyperpnea in dry air.
      3. A decrease in FEV₁ ≥ 15% from baseline or ≥ 10% from value obtained after the previous dose after mannitol inhalation challenge.
      4. A decrease in FEV₁ ≥ 20% from baseline after methacholine inhalation challenge.

Reason for change

Inclusion Criterion 6.c) is by error written in the clinical trial protocol and CRF as:
“Diurnal variability in PEF > 20% after administration of SABA”

The correct wording is as follows:

“Diurnal variability in PEF > 20%”

This error was discovered after printing the CRFs. Monitors will be instructed to strike through the last part of the sentence “Improvement in PEF > 20% after administration of SABA” in the Airway reversibility / responsiveness test section of the CRFs at the trial sites, so that it reads only “Improvement in PEF > 20%”. Revised CRF pages will not be printed.

As for the e-CRF (used in Denmark) the wording “after administration of SABA” will be deleted by the administrator.

As a footnote was added in Section 2. Flow Chart the footnote in this section is re-numbered.

2.4 Section 5.4.1.1. Inclusion criteria

Text has been changed to read as follows:

7. Asthma control level above or equal to 1.0 (ACQ ≥ 1.0) at visit 1 (screening).

Reason for change

Question no 6 in the ACQ is about the number of puffs/inhalations of SABA during the last week. If a subject is using LABA instead of SABA or is using a combination product, his/her response to this question will be "0" and the ACQ score may be artificially low and resulting in the subject failing to meet the criterion of having an ACQ of at least 1.0. In order to have the ACQ filled in as intended, LABA should be switched to SABA before scoring the ACQ and hence the ACQ may be deferred to visit 2.

The decision of deferring ACQ to visit 2 should be taken prior to assessing ACQ at visit 1 and be grounded on use of LABA or combination products and that it should not be interpreted as a second chance of assessing ACQ in case of an ACQ below 1.0 at visit 1.

The change is of pure technical character as both visit 1 and visit 2 are screening visits (as shown in section 2. Flow Chart). Monitors will be instructed to strike through the part of the sentence referring to “visit 1” in the Inclusion criteria sections of the CRFs at the trial sites, so that it reads only "7. Asthma control level above or equal to 1.0 (ACQ ≥ 1.0) at visit 1 (screening)”. Revised CRF pages will not be printed.

As for the e-CRF (used in Denmark) the wording including brackets “between visit 1 (…)” will be deleted by the administrator.

2.5 Section 5.4.1.1. Inclusion criteria

Text has been changed to read as follows:

9. Electronic diary compliance rate between visit 2 and visit 3 ≥ 80% at visit 3 (randomisation).

Reason for change
The electronic diary compliance is calculated based to the last 14 days prior to visit 3 (randomisation) and not over the whole period between visit 2 and visit 3.

This error was discovered after printing the CRFs. Monitors will be instructed to strike through the part of the sentence referring to the period in the Inclusion criteria sections of the CRFs at the trial sites, so that it reads only “i9. Electronic diary compliance rate ≥ 80% at visit 3 (randomisation)”.

Revised CRF pages will not be printed.

As for the e-CRF (used in Denmark) the wording “between visit 2 and visit 3” will be deleted by the administrator.

2.6 Section 5.4.1.1. Inclusion criteria

Text has been changed to read as follows:
10. FEV$_1$ ≥ 70% of predicted value$^{21,22}$

$^{22}$For predicted values, the European Community for Coal and Steel: Standardization of Lung Function Tests updated formula by Quanjer et al 1993 is to be used (1).

Reason for change

The 1983 report of the European Community for Coal and Steel was revised in 1993 with unchanged predicted values of lung indices. The 1993 report was officially adopted by the European Respiratory Society and is today regarded as the standard reference equations for use in Europe.

As a footnote was added in Section 2. Flow Chart the footnote in this section is re-numbered.

The reference is mentioned on page 14, 29, 49, and 82.


2.7 Section 5.6.1. Visit 1

Text has been changed to read as follows:
5.6.1. Visit 1 (Screening)
The following procedures will be performed:
- Obtain written informed consent before any trial procedures are performed.
- Issue and collect ACQ $^{26}$. This should preferably be completed before any other trial related activities.
- Demographic data and body measurements, see Section 5.8.5.1.
- Medical history, see Section 5.8.5.2.
- Physical examination, see Section 5.8.4.1.
- Vital signs, see Section 5.8.4.2.
- Measure FEV₁, see Section 5.8.5.6.
- Reversibility test, see Section 5.8.5.5.
- SPT, see Section 5.8.5.4.
- Urine pregnancy test (if appropriate), see Section 5.8.4.3.
- Assess compliance with inclusion and exclusion criteria, see Section 5.4.1.
- Safety laboratory assessments (blood and urine sampling), see Section 5.8.4.3.
- Blood sampling for specific IgE against Der pte or Der far, see Section 5.8.2.
- Blood sampling for immunology, see Section 5.8.2.
- Record AEs, see Section 6.
- Record previous and concomitant medication, see Section 5.5.6.2.
- Schedule date for visit 2.

---

28 Procedure may be deferred to visit 2 if the subject have taken SABA within the past 4 hours, LABA within the past 12 hours, or antihistamines within the last 3 days, see Appendix 13.

Reason for change

A footnote has been added to the procedures ACQ, spirometry - FEV1, Reversibility test, and SPT on visit 1 stating: Procedure may be deferred to visit 2 if the subject have taken SABA within the past 4 hours, LABA within the past 12 hours, or antihistamines within the last 3 days, see Appendix 13.

Subjects may take SABA within 4 hours of spirometry for the purpose of the ACQ score, however, it is not allowed within 4 hours of spirometry for the purpose of reversibility test or bronchial provocation tests (should these be applicable). If SABA has been taken within 4 hours before spirometry for reversibility/bronchial provocation test is to be performed, the reversibility/bronchial provocation test needs to be deferred to visit 2. Subjects should be instructed to not use SABA within 4 hours prior to visit 2.

Some subjects use LABA instead of SABA. In such cases the subject's ACQ score may be artificially low (as described in section 2.3 of this amendment), and result in the subject failing to meet the criterion of having an ACQ of at least 1.0 In order to have the ACQ filled in as intended, LABA should be switched to SABA before scoring the ACQ and hence the ACQ may be deferred to visit 2.

Subjects who have a positive SPT at visit 1 can immediately be switched to SABA and, if reversibility/bronchial provocation test needs to be done, instructed to not use the SABA within 4 hours prior to visit 2, where both the reversibility/provocation test (if applicable) and the ACQ will be done.

However, for subjects who have been using antihistamines within 3 days prior to visit 1, the SPT also needs to be deferred to visit 2 (prior to any regular visit 2 procedures). For these subjects, sites will need to await the positive IgE results from the lab before switching LABA to SABA, as we do not find it ethical to switch subjects from their usual medication without any evidence that they are actually sensitised to HDM.
All following footnotes are re-numbered.

As both visit 1 and visit 2 are screening visits the reference “(screening)” is deleted.

2.8 Section 5.6.2. Visit 2

Text has been changed to read as follows:

Prior to the visit, review results from laboratory assessment incl. specific IgE result. Cancel visit if subject is not eligible according to selection criteria, see Section 5.4.1.

The following procedures will be performed:

- **Issue and collect ACQ if this has been deferred from visit 1. The ACQ should preferably be completed before any other trial related activities.**
- **Measure FEV1 if this has been deferred from visit 1, see Section 5.8.1.6.**
- **Reversibility test if this has been deferred from visit 1, see Section 5.8.5.5.**
- **SPT if this has been deferred from visit 1, see Section 5.8.5.4.**
- Eligible subjects will be switched from their regular asthma controller medication to equivalent doses of ICS and SABA as needed, see Section 5.5.6.1.
- Dispense symptomatic medication, see Section 5.5.6.1.
- Issue individualised asthma action plan, see Section 6.1.5.
- Assess AEs, see Section 6.
- Record changes in concomitant medication, see Section 5.5.6.2.
- Record visits to general practitioner (GP), specialist or hospitals, see Section 5.8.3
- Issue and instruct the subject in use of electronic diary, see Section 5.10.
- Issue and instruct the subject in use of electronic peak flow meter, see Section 5.8.1.6.
- Issue and instruct the subject in collection of a dust sample, see Section 5.8.5.5.
- Schedule date for visit 3.

**Reason for change**

Please see “Reason for change” to section 2.7 in this document.

2.9 Section 5.8.1.1. Asthma Exacerbation.

Text has been changed to read as follows:

- **c) ≥ 20% decrease in morning or evening PEF from baseline value on at least 2 consecutive mornings or evenings days or ≥ 20% decrease in FEV1 from baseline value.**

**Reason for change**

It was clarified in the clinical trial protocol general amendment 1 dated 05-april-2011 that the specified changes in PEF only need to be either morning or evening measurements, not both. Due to an error this was not updated for section 5.8.1.1. Asthma Exacerbation.
2.10 Section 5.8.1.6. Lung Function

Text has been changed to read as follows:

Lung function will be measured by PEF and FEV\(_1\).

PEF measurement must be performed every morning and evening by the subject. The highest value of 3 consecutive measurements will transmitted to the electronic diary.

The FEV\(_1\) measurements will be performed with a spirometer available at the trial centre. The FEV\(_1\) is measured as 3 valid measurements and the highest value will be transcribed to the CRF. The predicted FEV\(_1\) will be calculated based on the statistics from the European Community for Coal and Steel: Standardization of Lung Function Tests (1) \textit{formula by Quanjer 1993} (1).

Reason for change

The 1983 report of the European Community for Coal and Steel was revised in 1993 with unchanged predicted values of lung indices. The 1993 report was officially adopted by the European Respiratory Society (ERS) and is today regarded as the standard reference equations for use in Europe.


2.11 Appendix 1 – Investigator Agreement

The investigator agreement has been updated with title and date of this document. The investigator agreement is attached as an appendix to this amendment.

2.12 Appendix 9 – Procedure for Collecting Dust Samples

Text has been changed to read as follows:

Procedure for Collecting Dust Samples

\textbf{Before collecting a dust sample}

You will need a vacuum cleaner with a tube attachment that will connect to the collection device. Before you start, please check to see that the provided sampling kit contains all of the following:

\begin{itemize}
  \item Filter dish with filter, preloaded into the collection device.
  \item Rubber O-ring for tight fitting on the vacuum tube.
  \item Plastic lid for the filter dish.
  \item Zip-lock plastic bag.
  \item Envelope and label.
\end{itemize}

\textbf{Attaching the collecting device}

Slide the flexible O-ring over the end of your vacuum tube. Then, fit the collection device on the end of the vacuum tube, using the O-ring to provide a tight seal.
Collecting a dust sample
Before vacuum your bed, remove any large particles such as food, small pieces of paper, or other extraneous material. Vacuum the entire top sheet, bottom sheet, pillowcase, mattress cover and mattress for about 5 minutes. IMPORTANT: Collect the sample before laundering the bed clothes. Check to see that an adequate volume of dust has been collected. The dust sample should appear to be about the size of a tablespoon of material. If the sample does not appear to be large enough, then repeat the dust collection procedure.

After collecting the dust sample
- Fill in the label.
- Hold the collection device with the nozzle pointing up and remove the vacuum tube.
- Detach the nozzle from the base of the collection device, by disengaging the side clips.
- Remove the filter dish with the filter, which now contains the sample. Be careful not to spill the dust sample.
- Fix the plastic lid securely over the filter dish and place the label on the lid.
- Seal the dish in the small zip-lock bag.
- Place the sample in the envelope and bring this for the next visit to your study doctor.

Before collecting a dust sample
You will need a vacuum cleaner with a tube attachment that will connect to the collection device. Before you start, please check to see that the provided sampling kit contains all of the following:

- **DUSTREAM™ collector + filter**
- **DUSTREAM™ adaptor**
- **2 caps for the DUSTREAM™ collector - one small and one large**
- **Ziploc plastic bag**

Attaching the collecting device
Insert the nylon filter into the DUSTREAM™ collector and attach the collector to the vacuum cleaner tube. If the collector does not fit the vacuum cleaner tube, attach the adaptor piece to the collector. Use the side of the adaptor which fits your vacuum cleaner.

Collecting a dust sample
• Before vacuum your bed, remove any large particles such as food, small pieces of paper, or other extraneous material.
• IMPORTANT: Collect the sample before laundering the bed-clothes.
• Turn on the vacuum cleaner and vacuum 4 separate areas (each the size of this sheet of paper) for 30 seconds (total vacuuming time is 2 minutes and the total area sampled ≈ 0.25sq meter).

After collecting the dust sample
• Place the caps on each end of the DUSTREAM™ collector.
• Place the whole DUSTREAM™ collector in the Ziploc bag.
• Bring the Ziploc bag with the dust sample for the next visit to your study doctor.

Reason for change
Another sampling device than originally planned will be used for collection of dust samples. The procedure for collecting dust samples is changed to instruct the subject in the use of the new device in accordance with the manufacturer’s product leaflet.
### 2.13 Appendix 13 – Guidance on When to Perform Visit 1 Procedures Depending on Subject’s Use of SABA, LABA and Antihistamines

Text has been changed to read as follows:

#### Guidance on When to Perform Visit 1 Procedures Depending on Subject’s Use of SABA, LABA and Antihistamines

<table>
<thead>
<tr>
<th>Visit</th>
<th>Scenario A: Subject has taken neither SABA, LABA nor antihistamines within the prohibited time frames before Visit 1</th>
<th>Scenario B: Subject has taken SABA within 4 hrs before Visit 1. No LABA. No antihistamines.</th>
<th>Scenario C: Subject has taken LABA within 12 hrs before Visit 1. No antihistamines.</th>
<th>Scenario D: Subject has taken antihistamines within 3 days before Visit 1. No SABA. No LABA.</th>
<th>Scenario E: Subject has taken SABA within 4 hrs and antihistamine within 3 days before Visit 1. No LABA.</th>
<th>Scenario F: Subject has taken LABA within 12 hrs and antihistamine within 3 days before Visit 1.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subject has taken SABA within 4 hrs before Visit 1. No LABA.</td>
<td>Subject has taken LABA within 12 hrs before Visit 1. No antihistamines.</td>
<td>Subject has taken antihistamines within 3 days before Visit 1. No SABA.</td>
<td>Subject has taken SABA within 4 hrs and antihistamine within 3 days before Visit 1.</td>
<td>Subject has taken LABA within 12 hrs and antihistamine within 3 days before Visit 1.</td>
<td>Subject has taken SABA within 4 hrs and antihistamine within 3 days before Visit 1.</td>
</tr>
<tr>
<td></td>
<td>Perform:</td>
<td>Perform:</td>
<td>Perform:</td>
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<td>Perform:</td>
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<td>SPT</td>
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<td>SPT</td>
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</tr>
<tr>
<td></td>
<td>ACQ</td>
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<td>ACQ</td>
<td>ACQ</td>
</tr>
<tr>
<td></td>
<td>Reversibility/bronchial provocation test (if applicable)</td>
<td>Reversibility/bronchial provocation test (if applicable)</td>
<td>Reversibility/bronchial provocation test (if applicable)</td>
<td>Reversibility/bronchial provocation test (if applicable)</td>
<td>Reversibility/bronchial provocation test (if applicable)</td>
<td>Reversibility/bronchial provocation test (if applicable)</td>
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<tr>
<td></td>
<td>All other Visit 1 procedures</td>
<td>All other Visit 1 procedures</td>
<td>All other Visit 1 procedures</td>
<td>All other Visit 1 procedures</td>
<td>All other Visit 1 procedures</td>
<td>All other Visit 1 procedures</td>
</tr>
<tr>
<td></td>
<td>Defer reversibility/bronchial provocation test (if applicable) to Visit 2</td>
<td>Instruct subject to withhold SABA for 4 hrs before Visit 2</td>
<td>Instruct subject to withhold SABA for 4 hrs before Visit 2</td>
<td>Instruct subject to withhold antihistamine for 3 days before Visit 2</td>
<td>Instruct subject to withhold SABA for 4 hrs and antihistamine for 3 days before Visit 2</td>
<td>Instruct subject to withhold antihistamine for 3 days before Visit 2</td>
</tr>
<tr>
<td></td>
<td>All other Visit 1 procedures</td>
<td>All other Visit 1 procedures</td>
<td>All other Visit 1 procedures</td>
<td>All other Visit 1 procedures</td>
<td>All other Visit 1 procedures</td>
<td>All other Visit 1 procedures</td>
</tr>
</tbody>
</table>

#### Between V1 and V2

- If lab report indicates IgE against HDM is Class 2, call the subject to instruct him/her to:
  - switch LABA to SABA and
  - withhold SABA for 4 hours before Visit 2

<table>
<thead>
<tr>
<th>Visit</th>
<th>Scenario A: Subject has taken neither SABA, LABA nor antihistamines within the prohibited time frames before Visit 1</th>
<th>Scenario B: Subject has taken SABA within 4 hrs before Visit 1. No LABA. No antihistamines.</th>
<th>Scenario C: Subject has taken LABA within 12 hrs before Visit 1. No antihistamines.</th>
<th>Scenario D: Subject has taken antihistamines within 3 days before Visit 1. No SABA. No LABA.</th>
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<th>Scenario F: Subject has taken LABA within 12 hrs and antihistamine within 3 days before Visit 1.</th>
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<td></td>
<td>Subject has taken SABA within 4 hrs before Visit 1. No LABA.</td>
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<td>Subject has taken SABA within 4 hrs and antihistamine within 3 days before Visit 1.</td>
<td>Subject has taken LABA within 12 hrs and antihistamine within 3 days before Visit 1.</td>
<td>Subject has taken SABA within 4 hrs and antihistamine within 3 days before Visit 1.</td>
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<td>Reversibility/bronchial provocation test (if applicable)</td>
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<td>Reversibility/bronchial provocation test (if applicable)</td>
</tr>
<tr>
<td></td>
<td>All other Visit 1 procedures</td>
<td>All other Visit 1 procedures</td>
<td>All other Visit 1 procedures</td>
<td>All other Visit 1 procedures</td>
<td>All other Visit 1 procedures</td>
<td>All other Visit 1 procedures</td>
</tr>
<tr>
<td></td>
<td>Defer reversibility/bronchial provocation test (if applicable) to Visit 2</td>
<td>Instruct subject to withhold SABA for 4 hrs before Visit 2</td>
<td>Instruct subject to withhold SABA for 4 hrs before Visit 2</td>
<td>Instruct subject to withhold antihistamine for 3 days before Visit 2</td>
<td>Instruct subject to withhold SABA for 4 hrs and antihistamine for 3 days before Visit 2</td>
<td>Instruct subject to withhold antihistamine for 3 days before Visit 2</td>
</tr>
<tr>
<td></td>
<td>All other Visit 1 procedures</td>
<td>All other Visit 1 procedures</td>
<td>All other Visit 1 procedures</td>
<td>All other Visit 1 procedures</td>
<td>All other Visit 1 procedures</td>
<td>All other Visit 1 procedures</td>
</tr>
</tbody>
</table>

#### Reason for change

Some procedures may be deferred from visit 1 to visit 2 depending whether subjects have been taken SABA, LABA and/or antihistamines. The guidance takes into account the different scenarios and what to do.
Appendix 1

TRIAL ID: MT-04

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

I have read and agree to comply in all respects with this General Protocol Amendment No. 2, dated 02-November-2011, and the Consolidated Clinical Trial Protocol incorporating General Amendment 1, dated 05-April-2011.

I agree to adhere to the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, the guidelines on Good Clinical Practice, and applicable regulatory requirements.

I understand that all documentation that has not previously been published will be kept in the strictest confidence. This documentation includes the Clinical Trial Protocol and Amendments, Investigator’s Brochure, Case Report Forms, and other scientific data.

Responsible Investigator at the local trial centre

<table>
<thead>
<tr>
<th>Location</th>
<th>Printed Name</th>
</tr>
</thead>
</table>

Date Signature
Clinical Trial Protocol Amendment
General Protocol Amendment no. 3

Trial ID: MT-04

Title of Trial: 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 (HDM) allergy immunotherapy tablet (AIT)

Development Phase: III
EudraCT no: 2010-018621-19
Sponsor: Global Clinical Development
ALK-Abelló A/S
DK-2970 Hørsholm
Phone: +45 4574 7576

Document status: Final
Date: 01-December-2011

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Approval of General Protocol Amendment no. 3 – ALK

Approved by ALK-Abelló:
General Protocol Amendment no. 3, dated 01-December-2011 to the Clinical Trial Protocol, dated 12-April-2010, General Protocol Amendment no. 1, dated 05-April-2011, and General Protocol Amendment no. 2, dated 02-November-2011, is approved by:

Amendment originator: Hanne H. Villesen
Clinical Project Manager

Signature: [Signature]
Date: 01 Dec 2011

On behalf of head of originating department:
Ea Dige, MD
EU QPPV, Director,
Global Clinical Development

Signature: [Signature]
Date: 01 Dec 2011
Approval of General Protocol Amendment no. 3 – International Coordinating Investigator

Approved by International Coordinating Investigator:
General Protocol Amendment no. 3, dated 01-December-2011 to the Clinical Trial Protocol, dated 12-April-2010, General Protocol Amendment no. 1, dated 05-April-2011, and General Protocol Amendment no. 2, dated 02-November-2011, is approved by:

International Coordinating Investigator:
Johann Christian Virchow
Prof. Dr. med.

Abteilung für Pneumologie / Internistische Intensivmedizin
Klinik I – Zentrum für Innere Medizin,
Universitätsklinikum Rostock,
Ernst-Heydemann-Str. 6,
18057 Rostock,
Germany

Signature

Date: 1/12/2011
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  2.3 Section 5.3. Discussion of Design ..............................................................................7
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Appendix 1: Investigator Agreement on Protocol Amendment
List of Abbreviations

AIT  Allergy Immunotherapy Tablet
DU   Development Unit
EudraCT  European Union Drug Regulating Authorities Clinical Trials database
EU QPPV European Qualified Person Pharmacovigilance
HDM  House Dust Mite
LABA Long-Acting ß2-Agonists
ICS  Inhaled corticosteroid
1 Summary of Amendment

This amendment is prepared in order to succeed with the recruitment of approximately 800 subjects to the MT-04 trial.

Until date the number of subjects recruited is lower than projected during the planning of the trial and it is foreseen with the current screening rate that the approximately 800 subjects planned to be randomized will be difficult to reach.

In order to increase the likelihood of reaching the estimated number of randomised subjects, period 1 (screening) will be extended with one month. As the period 3 (ICS reduction) is calendar fixed, some subjects may, due to the extended period 1 (screening), only receive treatment for 7 months prior to the efficacy assessment period.

Treatment duration prior to period 3 is in the MT-04 protocol defined to be minimum 8 months based on the wish of treating the subjects for as long as possible to ensure that the immunological modulations induced by AIT treatment are obtained.

As efficacy measurements are calendar fixed to ensure an optimised efficacy assessment period for the HDM AIT, and minimise bias from concomitant pollen allergies, the trial cannot be extended with another month.

It is judged that the risk of not reaching the estimated number of randomized subject will have a greater impact on the scientific value of the trial than one month less of treatment for a part of the included subjects. Therefore, minimum duration of period 2 will be 7 months.

2 Changes to the Protocol

Additions to the original protocol are listed below, with reference to the sections affected. Text deleted is marked with strike through, while added text is in **bold italics**.

All assessments will be performed as described in the original protocol. In cases where changes/additions have been made, the appropriate section has been included in this amendment. Repetition of otherwise unchanged sections have not been included in this amendment.

2.1 Section 3.3. Trial Rational

Text has been changed to read as follows:

In this trial, subjects will be randomised to 1 of 3 treatment groups (2 doses of ALK HDM AIT (6 DU or 12 DU) or placebo) and receive treatment for at least 78 months and up to 18 months.
2.2 Section 5.1. Overall Trial Design

Text has been changed to read as follows:

Figure 1 Trial Design

<table>
<thead>
<tr>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>Treatment Maintenance</td>
<td>ICS reduction</td>
</tr>
<tr>
<td>5 weeks</td>
<td>7-12 months</td>
<td>6 months</td>
</tr>
</tbody>
</table>

Randomisation | Treatment with AIT | End of trial

ICS 50% reduction | ICS 100% withdrawal

2.3 Section 5.3. Discussion of Design

Text has been changed to read as follows:

Treatment and efficacy measurements will be initiated outside major pollen seasons to minimize bias from other allergies. The duration of treatment is based on the results from MT-02, where a clear significant clinical effect was shown after 12 months. A clear increase in the immunological response was seen after 6 months of treatment and this was increasing over the next 6 months. As efficacy measurement are to be performed during the fall and winter where the concentration of HDM is considered higher than the rest of the year, treatment duration will be minimum 7-8 months.

3 Reason for changes

Until date the number of subjects recruited is lower than projected during the planning of the trial and it is foreseen with the current screening rate that the approximately 800 subjects planned to be randomized will be difficult to reach.

In order to increase the screening number and increase the likelihood of reaching the estimated number of randomised subjects, period 1 (screening) will be extended with one month. As the period 3 (ICS reduction) is calendar fixed, some subjects may due to the extended period 1 (screening) only receive treatment for 7 months prior to the efficacy assessment period.
Treatment duration prior to period 3 is in the MT-04 protocol defined to be minimum 8 months based on the wish of treating the subjects for as long as possible to ensure that the immunological modulations induced by AIT treatment are obtained. As efficacy measurements are calendar fixed to ensure an optimised efficacy assessment period for the HDM AIT, and minimise bias from concomitant pollen allergies, the trial cannot be extended with another month.

It is judged that the risk of not reaching the estimated number of randomized subject will have a greater impact on the scientific value of the trial than one month less of treatment for a part of the included subjects. Therefore, minimum duration of period 2 will be 7 months.
Appendix 1

TRIAL ID: MT-04

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

I have read and agree to comply in all respects with this General Protocol Amendment No. 3, dated 01-December-2011, and the Consolidated Clinical Trial Protocol incorporating General Amendment 1, dated 05-April-2011 as well as the General Protocol Amendment No. 2, dated 02-November-2011.

I agree to adhere to the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, the guidelines on Good Clinical Practice, and applicable regulatory requirements.

I understand that all documentation that has not previously been published will be kept in the strictest confidence. This documentation includes the Clinical Trial Protocol and Amendments, Investigator’s Brochure, Case Report Forms, and other scientific data.

Responsible Investigator at the local trial centre

Location

Printed Name

Date

Signature
Clinical Trial Protocol Amendment
General Protocol Amendment no. 4

Trial ID: MT-04

Title of Trial: 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 (HDM) allergy immunotherapy tablet (AIT)

Development Phase: III

EudraCT no: 2010-018621-19

Sponsor: Global Clinical Development
ALK-Abelló A/S
DK-2970 Hørsholm
Phone: +45 4574 7576

Document status: Final
Date: 28-June-2012

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Approval of Protocol Amendment – ALK

Approved by ALK-Abelló:
General Protocol Amendment No. 4, dated 28-June-2012 to the Clinical Trial Protocol, dated 12-April-2010, General Protocol Amendment no. 1, dated 05-April-2011, General Protocol Amendment no. 2, dated 02-November-2011, and General Protocol Amendment no. 3, dated 01-December-2011, is approved by:

Amendment originator:

Hanne H. Villesen
Clinical Project Manager

Signature: [Signature]
Date: 28 Jun 2012

Head of originating department:

Kreesten Melgaard Madsen
Vice President, Global Clinical Development

Signature: [Signature]
Date: 28 Jun 2012
Approval of Protocol Amendment – International Coordinating Investigator

Approved by International Coordinating Investigator:
General Protocol Amendment No. 4, dated 28-June-2012 to the Clinical Trial Protocol, dated 12-April-2010, General Protocol Amendment no. 1, dated 05-April-2011, General Protocol Amendment no. 2, dated 02-November-2011, and General Protocol Amendment no. 3, dated 01-December-2011, is approved by:

International Coordinating Investigator:

Johann Christian Virchow
Prof. Dr. med.

Abteilung für Pneumologie / Organische Innere Medizin, Klinik I – Zentrum für Innere Medizin, Universitätsklinikum Rostock, Ernst-Heydemann-Str. 6, 18057 Rostock, Germany

Signature: [Signature]
Date: 10.7.2012
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   2.2 5.6.15 Visit 13 (End of Trial) ................................................................ 7

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Appendix 1: Investigator Agreement on Amendment

List of Abbreviations

AE  Adverse event
DNA Deoxyribonucleic acid
1 Summary of Amendment

This amendment is prepared in order to obtain a blood sample for future pharmacogenetic studies from subjects already enrolled in the MITRA trial (MT04).

Pharmacogenetic studies can contribute to a greater understanding of inter-individual differences in the efficacy and safety of investigational drugs, and hereby improve the effectiveness and safety of drugs. Therefore, all patients in the MITRA trial will be asked to give a blood sample for pharmacogenetic analysis. If they consent to this, the samples will be drawn at the end of trial visit.

Exploratory pharmacogenetic studies may be performed on collected samples. These studies may include analyses for identifying e.g. genomic markers of atopic disease and treatment of allergy. Pharmacogenetic results may be compared to pharmacodynamics results or clinical outcomes. Any significant pharmacogenetic relationships to outcome will require validation in future clinical trials.

For pharmacogenomics testing, risk to the patient has been minimised. Risks include those associated with venepuncture to obtain blood sample. Data privacy concerns of the subject have been strictly protected against with ALK security, policies and procedures. It is necessary for subject-related data (i.e. ethnicity, diagnosis, drug therapy and dosage, age, toxicities etc.) to be re-associated to subject IDs at the time of analysis. No information concerning results obtained from genotyping or biomarker studies conducted with samples from the ALK research biobank will be entered into clinical records, nor will it be released to outside persons or agencies, in a way that could be tied to an individual patient. Unintentionally discovery of sensitive data such as risk of serious diseases is considered unlikely as testing will be focused on data related to allergic disease.

In the case that ALK publish results obtained from genotyping or biomarker studies based on pharmacogenetic samples obtained in the trial, results will be published in such a way that it cannot be tied to an individual subject.

There is no direct benefit for the subject by consenting to an additional blood sample. However, the pharmacogenetic research that may be conducted on these blood samples can contribute to a greater understanding of efficacy and safety of immunotherapy, and hereby improve the effectiveness and safety.

As the blood sample will be obtained at the end of trial visit, where blood sampling already is planned, the subject will only donate an extra blood sample (9 mL blood, thus in total at the end of trial visit the subject will donate 9 mL blood), no additional venepuncture is required.

Hence the risk-benefit assessment is considered neutral.

This request only includes sampling for pharmacogenetic tests and storage of the sample within the ALK research biobank, any results of future analyses will be reported separately and will not be included in MITRA trial. It is anticipated that data generated from processed samples collected during the course of this trial will be retained for an indefinite period. DNA specimens will be maintained for potential analyses for 15 years from the acquisition. Samples will be destroyed according to ALK policies and procedures and this destruction will be documented in the ALK research biobank.
2 Additions to the Protocol

Additions to the original protocol are listed below, with reference to the sections affected. Text deleted is marked with strike through, while added text is in italics.

All assessments will be performed as described in the original protocol. In cases where changes/additions have been made, the appropriate section has been included in this amendment. Repetition of otherwise unchanged sections have not been included in this amendment.

2.1 5.11 Pharmacogenetic Analysis

Text has been changed to read as follows:

The pharmacogenetic samples collected in the trial will be used to study various genetic causes for how subjects may respond to the treatment. The deoxyribonucleic acid (DNA) samples will be stored to provide a resource for future studies conducted by ALK focused on the study of how genes can affect drug absorption, distribution and removal from the body, and drug action in the body.

Exploratory pharmacogenetic studies may be performed on collected samples. These studies may include analyses for identifying e.g. genomic markers of atopic disease, efficacy of allergy treatment, AEs, or other genomic markers relevant for the atopic disease and treatment of allergy. Pharmacogenetic results may be compared to pharmacodynamic results or clinical outcomes. Any significant pharmacogenetic relationships to outcome will require validation in future clinical trials.

To obtain sufficient DNA for pharmacogenetic studies, a blood sample will be drawn at the end of trial visit. The subjects will be asked to consent specifically to a blood sampling for pharmacogenetic tests and storage of the sample within the ALK research biobank. The answer to this question will be recorded on an addendum to the informed consent form, the consent form for pharmacogenetic analysis, as well as in source documentation. The collection of pharmacogenetic sample is independent of the other procedures planned for the end of trial visit, thus if pharmacogenetic sampling and storage is not accepted by the subject, this extra blood sample will not be drawn and the other procedures will be performed as planned.

No information concerning results obtained from genotyping or biomarker studies conducted with samples from the trial will be entered into patient clinical records, nor will it be released to outside persons or agencies, in any way that could be tied to an individual subject.

Any results of pharmacogenetic analysis will be reported separately and will not be included in the ICTR. In the case that ALK publish results obtained from genotyping or biomarker studies based on pharmacogenetic samples obtained in the trial, results will be published in such a way that it cannot be tied to an individual subject.

Reason for change

Pharmacogenetic studies can contribute to a greater understanding of inter-individual differences in the efficacy and safety of investigational drugs, and hereby improve the effectiveness and safety of drugs.
As the blood sample will be obtained at the end of trial visit where blood sampling already is planned, the subject will only donate an extra blood sample, no additional venepuncture is required. Hence the risk-benefit assessment is considered neutral.

2.2 5.6.15 Visit 13 (End of Trial)

Text has been changed to read as follows:

5.6.15 Visit 13 (End of Trial)
The following procedures will be performed:

- Issue and collect ACQ, AQLQ(s), SF-36 and WPAI:ASTHMA, These should preferably be completed before any other trial related activities.
- In Germany and France only: Issue and collect TSQM II. This should preferably be completed before any other trial related activities.
- Review diary entries, see Section 5.10.
- Assess asthma exacerbation if necessary, see Section 5.8.1.1.
- Physical examination, see Section 5.8.4.1.
- Vital signs, see Section 5.8.4.2.
- Measure FEV₁, see Section 5.8.1.6.
- Safety laboratory assessments (blood and urine sampling), see Section 5.8.4.3.
- Blood sampling for immunology, see Section 5.8.2.
- *If the subject consents: Blood sampling for pharmacogenetic analysis, see Section 5.11.*
- Urine pregnancy test (if appropriate), see Section 5.8.4.3.
- Assess AEs, see Section 6.
- Record changes in concomitant medication, see Section 5.5.6.2.
- Record visits to GP, specialist or hospitals, see Section 5.8.3.
- Collect electronic diary and electronic peak flow meter, see Section 5.10.
- Collect dust sample, see Section 5.8.5.5.
- Collect empty and unused IMP and symptomatic medication packages incl. accountability, see Section 5.5.4 and 5.5.6.1.
- Schedule date for follow up telephone contact.

**Reason for change**

If the subject consents to the blood sampling for pharmacogenetic analysis, this blood sample should be taken at visit 13.
Clinical Trial Protocol Amendment
General Protocol Amendment no. 5

Trial ID: MT-04

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

Investigational Medicinal Product: ALK HDM AIT
Phase: III
EudraCT no: 2010-018621-19
Sponsor: Global Clinical Development
ALK-Abelló A/S
DK-2970 Hørsholm
Phone: +45 4574 7576

Document status: Final
Date: 01 May 2013

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Approval of Protocol Amendment – ALK

Approved by ALK:
General Protocol Amendment No. 5, dated 01-May-2013 to the Clinical Trial Protocol, dated 12-April-2010, General Protocol Amendment no. 1, dated 05-April-2011, General Protocol Amendment no. 2, dated 02-November-2011, General Protocol Amendment no. 3, dated 01-December-2011 and General Protocol Amendment No. 4, dated 28-June-2012 is approved by:

Amendment originator:
Hanne H. Villesen
Clinical Project manager

Signature
Date

Responsible statistician:
Christian Ljørring
Prinicipal statistician

Signature
Date

Head of originating department:
Kreesten Moldgaard Madsen
MD, VP, GCD

Signature
Date

General Protocol Amendment no. 5
Trial ID: MT-04
EudraCT: 2010-018621-19
Document status: Final
Date: 01-May-2013
Approval of Protocol Amendment – International Coordinating Investigator

Approved by International Coordinating Investigator:
General Protocol Amendment No. 5, dated 01-May-2013 to the Clinical Trial Protocol, dated 12-April-2010, General Protocol Amendment no. 1, dated 05-April-2011, General Protocol Amendment no. 2, dated 02-November-2011, General Protocol Amendment no. 3, dated 01-December-2011 and General Protocol Amendment No. 4, dated 28-June-2012 is approved by:

Johann Christian Virchow
Prof. Dr. med.

Abteilung für Pneumologie / Internistische Intensivmedizin
Klinik I – Zentrum für Innere Medizin,
Universitätsklinikum Rostock,
Ernst-Heydemann-Str. 6,
18057 Rostock,
Germany

Signature

Date: 02/05/2013
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List of Appendices

Appendix 1: Investigator Agreement on Amendment
List of Abbreviations

AIT  Allergy Immunotherapy Tablet
HDM  House Dust Mite
ICTR Integrated Clinical Trial Report
IgE  Immunoglobulin of isotype E
LABA Long-Acting $\beta_2$-Agonists
LAMA Long-Acting Muscarinic Antagonists
MAOIs Monoamine Oxidase Inhibitors
SPT  Skin Prick Test
1 Summary of Amendment

This non-substantial amendment is prepared in order to clarify storage and reporting of dust samples collected at visit 3 (randomisation) and visit 13 (end of trial).

The amendment is considered non-substantial as it will not impact patient safety or the scientific value of the trial.

Furthermore, the time point for when regular asthma controller medication was prohibited is corrected in Table 2 Prohibited Concomitant Medication.

2 Additions to the Protocol

Additions to the original protocol are listed below, with reference to the sections affected. Text deleted is marked with strike through, while added text is in bold italics.

All assessments will be performed as described in the original protocol. In cases where changes/additions have been made, the appropriate section has been included in this amendment. Repetition of otherwise unchanged sections have not been included in this amendment.

2.1 Changes to section 5.9, House Dust Mite Exposure

Text has been changed to read as follows:

5.9 House Dust Mite Exposure

Subjects will be asked to collect a dust sample by vacuum cleaning their bed. The specific procedure to be followed is described in Appendix 9.

The dust samples collected will be stored at ALK for up to 10 years after reporting of the integrated clinical trial report (ICTR). If it is decided to analyse the dust samples, results of analysis will be reported separately from the ICTR.

Reason for change

The timing of analysis and storage of dust samples were not been clearly specified in the clinical trial protocol. This amendment is written to clarify the timing of the analyses and that reporting of results will not be part of the ICTR.
2.2 Changes to section 5.5.6.3, Prohibited Concomitant Medication

Text has been changed to read as follows:

5.5.6.3 Prohibited Concomitant Medication

Prohibited concomitant medications are listed below.

Table 2 Prohibited Concomitant Medication

<table>
<thead>
<tr>
<th>Drug</th>
<th>Time window</th>
<th>Excluded(^{25}) due to possible interference with</th>
</tr>
</thead>
<tbody>
<tr>
<td>An investigational drug</td>
<td>≤ 30 days before visit 1 and until end of trial</td>
<td>Efficacy, Safety reasons</td>
</tr>
<tr>
<td>Anti IgE treatment</td>
<td>&lt; 90 days before visit 1 and until end of trial</td>
<td>Efficacy</td>
</tr>
<tr>
<td>Antihistamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Oral or topical</td>
<td>For at least 3 days before SPT testing</td>
<td>SPT results</td>
</tr>
<tr>
<td>- Long-acting [astemizole]</td>
<td>≤ 90 days before SPT testing</td>
<td>SPT results</td>
</tr>
<tr>
<td>Antipsychotic medications with antihistaminic effects (i.e. chlorpromazine, levomepromazine, clozapine, olanzapine, tioridazine)</td>
<td>≤ 7 days before visit 1</td>
<td>SPT results</td>
</tr>
<tr>
<td>Glucocorticosteroid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Local application (on the skin area used for SPT)</td>
<td>≤ 21 days before SPT testing</td>
<td>SPT results</td>
</tr>
<tr>
<td>- Nasal</td>
<td>From visit 9 and until end of trial</td>
<td>Efficacy</td>
</tr>
<tr>
<td>- Oral(^{26})</td>
<td>≤ 60 days before SPT testing</td>
<td>SPT results</td>
</tr>
<tr>
<td>- Short-acting parenteral</td>
<td>≤ 30 days before SPT testing</td>
<td>SPT results</td>
</tr>
<tr>
<td>- Long-acting parenteral (intra-articular or intramuscular)</td>
<td>≤ 30 days before visit 1 and until end of trial</td>
<td>Efficacy</td>
</tr>
<tr>
<td>Immunotherapy with other allergens</td>
<td>From visit 1 and until end of trial</td>
<td>Efficacy</td>
</tr>
<tr>
<td>Inhaled, topical or oral nedocromil or cromolyn sodium</td>
<td>≤ 14 days before visit 1 and until end of trial</td>
<td>Efficacy</td>
</tr>
</tbody>
</table>

---

\(^{25}\) Excluded unless provided by ALK as symptomatic medication in the trial

\(^{26}\) Oral glucocorticosteroids in period 3 should be used exclusively for the treatment of asthma symptoms.
<table>
<thead>
<tr>
<th>Medication Type</th>
<th>Duration</th>
<th>Result Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukotriene antagonists / synthase inhibitors</td>
<td>≤ 30 days before visit 1 and until end of trial</td>
<td>Efficacy</td>
</tr>
<tr>
<td>Long-acting β₂-agonists (LABA)</td>
<td>From visit 1 to 2 and until end of trial</td>
<td>Efficacy</td>
</tr>
<tr>
<td>Long-acting muscarinic antagonist (LAMA)</td>
<td>From visit 1 to 2 and until end of trial</td>
<td>Efficacy</td>
</tr>
<tr>
<td>Mono amine oxidase inhibitors (MAOIs)</td>
<td>≤ 21 days before visit 1 and until end of trial</td>
<td>Adrenaline</td>
</tr>
<tr>
<td>Pizotifene</td>
<td>≤ 7 days before visit 1</td>
<td>SPT results</td>
</tr>
<tr>
<td>Theophyllin</td>
<td>From visit 1 to 2 and until end of trial</td>
<td>Efficacy</td>
</tr>
<tr>
<td>Tricyclic antidepressant medications</td>
<td>≤ 14 days before visit 1 and until end of trial</td>
<td>Adrenaline</td>
</tr>
<tr>
<td>Tricyclic antidepressant medications with antihistaminic effects (e.g., doxapine, mianserine)</td>
<td>≤ 14 days before visit 1</td>
<td>SPT results</td>
</tr>
</tbody>
</table>

**Reason for change**

The subjects were at visit 2 switched from their regular asthma controller medication (e.g., combination products) to equivalent doses of inhaled corticosteroid and short-acting β₂-agonist as needed. Thus, regular asthma controller medication (e.g., combination products) is not prohibited from visit 1.
Clinical Trial Protocol Amendment

Country Specific Protocol Amendment No. 1 - France

Trial ID: MT-04

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 (HDM) allergy immunotherapy tablet (AIT)

Development phase: III

EudraCT no: 2010-018621-19

Sponsor: Global Clinical Development
ALK-Abelló A/S
2970 Hørsholm
Denmark
Phone: +45 45747576

Document status: Final

Date: 14 May 2010

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Approval of Protocol Amendment – ALK-Abelló

Approved by ALK-Abelló:
Country Specific Protocol Amendment No. 1 - France, dated 14 May 2010, to the Clinical Trial Protocol, dated 12 April 2010, is approved by:

Head of Originating Department:
Kim Simonsen, MD
Senior Director
Group Clinical Development

[Signature] [19 May 2010]
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List of Appendices

Appendix 1: Investigator Agreement on Amendment

List of Abbreviations

AFSSAPS  Agence Française de Sécurité Sanitaire des Produits de Santé
SPT  Skin Prick Test
1 Summary of Amendment

1.1 Reason for Amendment

This amendment is prepared in order to comply with requirements issued by the Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS) on the Skin Prick Test (SPT).

Since some of the allergens extracts provided by ALK-Abello Danemark do not comply with local requirements, all the allergens extracts used in France for this trial will be provided by ALK France and will fulfill French requirements: the 17 allergens extracts used for this trial are included in the list of allergen extracts references authorized by the AFSSAPS (list dated on December 31st, 2007 and updated on December 22nd, 2008) or received a temporary authorization (authorization dated on December 23rd, 2009).

1.2 Changes to Protocol

Additions to the original protocol are listed below, with reference to the sections affected. Text deleted is marked with strikethrough, while added text is in italics blue.

All assessments will be performed as described in the original protocol. In cases where changes/additions have been made, the appropriate section has been included in this amendment. Repetition of otherwise unchanged sections have not been included in this amendment.

1.3 Changes to Section 5.8.5.4 (Skin Prick Test)

Original text:

SPT will be performed according to ALK procedure (see Appendix 8).

The panel of extracts for SPT include the following species:

- House Dust Mites – *Dermatophagoides pteronyssinus*.
- House Dust Mites – *Dermatophagoides farinae*.
- Moulds – *Alternaria alternate*.
- Moulds – *Cladosporium herbarium*.
- Animal hair/dander – Cat.
- Animal hair/dander – Dog.
- Animal hair/dander – Horse.
• Grass – *Phleum pratense*.
• Weed – *Artemisia vulgaris*.
• Tree - *Betula verrucosa*.
• Tree – *Cupressus* (depending upon region).
• Tree – *Corylus* (depending upon region).
• Tree – *Alnus* (depending upon region)
• Tree – *Fraxinus* (depending upon region)
• Tree – *Salix alba* (depending upon region)
• Tree – *Populus alba* (depending upon region)
• Weed – *Ambrosia artemisiifolia* (depending upon region).
• Weed – *Parietaria judaica* (depending upon region)
• Histamine (positive control).
• Saline (negative control).

The new text reads as follows:

SPT will be performed according to ALK procedure (see Appendix 8).

The panel of extracts for SPT include the following species:

• House Dust Mites – *Dermatophagoides pteronyssinus*.
• House Dust Mites – *Dermatophagoides farinae*.
• Moulds – *Alternaria alternate*.
• **Moulds – *Cladosporium herbarium*.
• Animal hair/dander – Cat.
• Animal hair/dander – Dog.
• Animal hair/dander – Horse.
• Grass – *Phleum pratense*.
• Weed – *Artemisia vulgaris*.
• Tree - *Betula verrucosa pendula Roth*. 
• Tree – *Cupressus* (depending upon region) *mix* (*Cupressus Arizona Greene + Cupressus sempervirens L.*).

• Tree – *Corylus* (depending upon region).

• Tree – *Alnus* (depending upon region)

• Tree – *Fraxinus* (depending upon region)

• Tree – *Salix alba* (depending upon region) *caprea L.*

• Tree – *Populus alba* (depending upon region)

• Weed – *Ambrosia artemisiifolia* (depending upon region).

• Weed – *Parietaria judaica* (depending upon region) *officinalis L.*

• Histamine (positive control).

• Saline (negative control).
Appendix 1

Investigator Agreement on Country Specific Protocol Amendment No. 1 - France

TRIAL ID: MT-04

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

I have read and agree to comply in all respects with this Country Specific Protocol Amendment No. 1 – France, dated 14 May 2010, and the Clinical Trial Protocol, dated 12 April 2010.

I agree to adhere to the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, the guidelines on Good Clinical Practice, and applicable regulatory requirements.

I understand that all documentation that has not previously been published will be kept in the strictest confidence. This documentation includes the Clinical Trial Protocol and Country Specific Protocol Amendment No. 1 – France, Case Report Forms, and other scientific data.

Responsible investigator at the local trial centre

Printed Name

Location

Signature

Date

To be signed on a separate page
Clinical Trial Protocol Amendment
Country Specific Amendment no. 1 - Germany

Trial ID: MT-04
Title of Trial: 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 (HDM) allergy immunotherapy tablet (AIT)
Development Phase: III
EudraCT no: 2010-018621-19
Sponsor: Global Clinical Development
ALK-Abelló A/S
DK-2970 Hørsholm
Phone: +45 4574 7576

Document status: Final
Date: 06 April 2011

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Approval of Country Specific Amendment no. 1 – Germany – ALK

Approved by ALK-Abelló:
Country Specific Amendment no. 1 - Germany, dated 06-April-2011 to the Clinical Trial Protocol, dated 12-April-2010, and General Protocol Amendment no. 1, dated 05-April-2011, is approved by:

Amendment originator:
Bente Tholstrup
Clinical Project Manager Expert

[Signature]
06 Apr 2011

Responsible statistician:
Christian Ljerring
Principal Statistician

[Signature]
11/4-2011

On behalf of head of originating department:
Ea Dige, MD
EU OPPV, Director, Global Clinical Development

[Signature]
12 Apr 2011
Approval of Country Specific Amendment no. 1 - Germany –
International Coordinating Investigator

Approved by International Coordinating Investigator:
Country Specific Amendment no. 1 - Germany, dated 06-April-2011 to the Clinical Trial Protocol,
dated 12-April-2010, and General Protocol Amendment no. 1, dated 05-April-2011, is approved
by:

International Coordinating
Investigator:

Johann Christian Virchow
Prof. Dr. med.
Abteilung für Pneumologie /
Internistische Intensivmedizin
Klinik I – Zentrum für Innere
Medizin,
Universitätsklinikum Rostock,
Ernst-Heydemann-Str. 6,
18057 Rostock,
Germany

Signature

Date 4. 2011
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## List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIT</td>
<td>Allergy Immunotherapy Tablet</td>
</tr>
<tr>
<td>Der far</td>
<td>Dermatophagoides farinae</td>
</tr>
<tr>
<td>Der pte</td>
<td>Dermatophagoides pteronyssinus</td>
</tr>
<tr>
<td>HDM</td>
<td>House Dust Mite</td>
</tr>
<tr>
<td>MITRA</td>
<td>House Dust Mite Treatment of Asthma</td>
</tr>
<tr>
<td>PEI</td>
<td>Paul-Ehrlich Institute</td>
</tr>
<tr>
<td>SPT</td>
<td>Skin Prick Test</td>
</tr>
</tbody>
</table>
1 Summary of Amendment

This amendment is prepared as a country specific amendment for Germany in order to implement commitments made to the Paul-Ehrlich Institute (PEI) during the protocol approval process.

The changes are as follows:

• In inclusion criterion 12, a special wording of the definition of a negative skin prick test (SPT) response has been made for Germany to exclude subjects with dermatographism. Furthermore, it has been clarified that subjects may be sensitised to both *Dermatophagoides pteronyssinus (Der pte)* and *Dermatophagoides farinae (Der far)*

• A new exclusion criterion (no. 18) has been added to exclude subjects with a history of alcohol or drug abuse

• Table 2 on prohibited concomitant medication is amended to exclude subjects in treatment with systemic and/or topical β-blockers during IMP treatment.

A commitment was also given during the approval process to add a footnote to Table 2, Prohibited Concomitant Medication, to specify that oral and parenteral corticosteroids in Period 3 should only be used for treatment of asthma symptoms. This commitment was dealt with in General Protocol Amendment no. 1, dated 1 April 2011.

2 Changes to the Protocol

Additions to the original protocol are listed below, with reference to the sections affected. Text deleted is marked with strike through, while added text is in *bold italics*.

All assessments will be performed as described in the original protocol. In cases where changes/additions have been made, the appropriate section has been included in this amendment. Repetition of otherwise unchanged sections have not been included in this amendment.
2.1 List of Appendices

Text has been changed to read as follows:

List of Appendices

Appendix 1: Investigator Agreement on Consolidated Clinical Trial Protocol - Germany incorporating General Protocol Amendment 1

Appendix 2: Electronic Diary Questions

Appendix 3: Asthma Control Questionnaire

Appendix 4: Asthma Quality of Life Questionnaire with standardised activities

Appendix 5: Short Form (36) Health Survey

Appendix 6: Work Productivity and Activity Impairment Questionnaire - Asthma version

Appendix 7: Standard Physical Examination

Appendix 8: Skin Prick Test Procedure

Appendix 9: Procedure for Collecting Dust Sample

Appendix 10: Asthma Action Plan

Appendix 11: Treatment Satisfaction Questionnaire for Medication, version II

Appendix 12: General Protocol Amendment no. 1

Reason for change

A new specific German protocol will be submitted to PEI and German ethics committees for approval. This specific German protocol will incorporate General Protocol Amendment 1 and the present country specific amendment. The appendix section is therefore updated to reflect the status as a specific German protocol and to omit protocol amendment(s) from the appendix section.

2.2 Section 1, Protocol Synopsis

The protocol synopsis repeats elements of the protocol text. Changes to protocol and previous amendment are changed both in the synopsis and relevant text sections of the consolidated protocol. However, in the present amendment the changes will be mentioned only in relation to the relevant protocol sections, and will, thus, not contain an amended protocol synopsis. For an amended protocol synopsis, please refer to the Clinical Trial Protocol – Germany, dated 06-Apr-2011.
2.3 Section 5.4.1.1, Inclusion Criteria

Text has been changed to read as follows:

12. Positive SPT response (wheal diameter ≥ 3 mm larger than the negative control) to Der pte and/or Der far. The negative control should be truly negative. Positive SPT response to Der pte and/or Der far is defined as wheal diameter ≥ 3 mm.

Reason for change:
PEI requirement.

2.4 Section 5.4.1.2, Exclusion Criteria

The following exclusion criteria have been added:
18. History of alcohol or drug abuse.

Reason for change:
PEI requirement.

2.5 Section 5.5.6.3, Prohibited Concomitant Medication

Text has been changed to read as follows:

Table 2 Prohibited Concomitant Medication

<table>
<thead>
<tr>
<th>Drug</th>
<th>Time window</th>
<th>Excluded due to possible interference with</th>
</tr>
</thead>
<tbody>
<tr>
<td>An investigational drug</td>
<td>≤ 30 days before visit 1 and until end of trial</td>
<td>Efficacy</td>
</tr>
<tr>
<td>Anti IgE treatment</td>
<td>&lt; 90 days before visit 1 and until end of trial</td>
<td>Efficacy</td>
</tr>
<tr>
<td>Antihistamine</td>
<td></td>
<td>Safety reasons</td>
</tr>
<tr>
<td>- Oral or topical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Long-acting [astemizole]</td>
<td>For at least 3 days before SPT testing</td>
<td>SPT results</td>
</tr>
<tr>
<td>- Glucocorticosteroid</td>
<td>≤ 90 days before SPT testing</td>
<td>SPT results</td>
</tr>
<tr>
<td>Antipsychotic medications with antihistaminic effects (i.e. chlorpromazine, levomepromazine, clozapine, olanzapine, tioridazine)</td>
<td>≤ 7 days before visit 1</td>
<td>SPT results</td>
</tr>
<tr>
<td>Glucocorticosteroid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Local application (on the skin)</td>
<td>≤ 21 days before SPT testing</td>
<td>SPT results</td>
</tr>
</tbody>
</table>
### Table

<table>
<thead>
<tr>
<th>Area used for SPT)</th>
<th>From visit 9 and until end of trial</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nasal</strong></td>
<td>≥ 60 days before SPT testing</td>
<td>SPT results</td>
</tr>
<tr>
<td><strong>Oral</strong></td>
<td>≥ 60 days before visit 1 and until end of trial</td>
<td>Efficacy</td>
</tr>
<tr>
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<td>≥ 90 days before visit 1 and until end of trial</td>
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<td>Immunotherapy with other allergens</td>
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<td>Efficacy</td>
</tr>
<tr>
<td>Inhaled, topical or oral nedocromil or cromolyn sodium</td>
<td>≤ 14 days before visit 1 and until end of trial</td>
<td>Efficacy</td>
</tr>
<tr>
<td>Leukotriene antagonists / synthase inhibitors</td>
<td>≤ 30 days before visit 1 and until end of trial</td>
<td>Efficacy</td>
</tr>
<tr>
<td>Long-acting β2-agonists (LABA)</td>
<td>From visit 1 and until end of trial</td>
<td>Efficacy</td>
</tr>
<tr>
<td>Long-acting muscarinic antagonist (LAMA)</td>
<td>From visit 1 and until end of trial</td>
<td>Efficacy</td>
</tr>
<tr>
<td>Mono amine oxidase inhibitors (MAOIs)</td>
<td>≤ 21 days before visit 1 and until end of trial</td>
<td>Adrenaline</td>
</tr>
<tr>
<td><strong>Systemic and/or topical β-blockers</strong></td>
<td>≤ 7 days before visit 3 and until end of trial</td>
<td>Adrenaline</td>
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<tr>
<td>Pizotifene</td>
<td>≤ 7 days before visit 1</td>
<td>SPT results</td>
</tr>
<tr>
<td>Theophyllin</td>
<td>From visit 1 and until end of trial</td>
<td>Efficacy</td>
</tr>
<tr>
<td>Tricyclic antidepressant medications</td>
<td>≤ 14 days before visit 1 and until end of trial</td>
<td>Adrenaline</td>
</tr>
<tr>
<td>Tricyclic antidepressant medications with antihistaminic effects (e.g., doxapine, mianserine)</td>
<td>≤ 14 days before visit 1</td>
<td>SPT results</td>
</tr>
</tbody>
</table>

25 Excluded unless provided by ALK as symptomatic medication in the trial
26 Oral glucocorticosteroids in period 3 should be used exclusively for treatment of asthma symptoms.

### Reason for change:

It has been a requirement from PEI to add an exclusion criterion on “Treatment with systemic and/or topical β-blockers”. An exclusion criterion on a specific medical treatment is not in line with the layout of this protocol. For all other prohibited medications, an exclusion criterion refers to Table 2 on Prohibited Concomitant Medication. To be in line with the protocol layout, systemic and/or topical β-blockers are therefore added to Table 2 as prohibited concomitant medication instead of adding it as a separate exclusion criterion.
2.6 Appendix 1, Investigator agreement on Protocol

Text has been changed to read as follows:

Investigator Agreement on Clinical Trial Protocol - Germany

TRIAL ID: 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.

Version: 01 April 2011 06 April 2011

I have read the clinical trial protocol – Germany, and agree that it contains all the information required to conduct the trial. I agree to conduct the trial as set out in the protocol and amendments. In particular, I agree to adhere to the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, the guidelines on Good Clinical Practice and applicable regulatory requirements.

Reason for change:
A specific German protocol incorporating General Protocol Amendment 1 and Country Specific Amendment 1 – Germany, will be submitted to PEI and German ethics committees for approval. German sites are expected to use the German consolidated protocol as the working protocol, therefore investigators are asked to sign the German consolidated protocol.

2.7 Appendix 8, Guideline for Skin Prick Testing, Double Determination

Text has been changed to read as follows:

4.2 Wheal sizes ≥ 3 mm (= W) are regarded as positive, provided that the wheal size of the negative control = 0 mm

NB! Please note that in case of dermografism, diameter of the wheal for Dermatophagoides pteronyssinus and/or Dermatophagoides farinae must be ≥ 3 mm greater than the saline control.

Reason for change:
PEI requirement.
Clinical Trial Protocol Amendment
Country Specific Amendment no. 1 -
the Netherlands

Trial ID: MT-04

Title of Trial: 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 (HDM) allergy immunotherapy tablet (AIT)

Development Phase: III
EudraCT no: 2010-018621-19

Sponsor: Global Clinical Development
ALK-Abelló A/S
DK-2970 Hørsholm
Phone: +45 4574 7576

Document status: Final

Date: 11 May 2011

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Approval of Protocol Amendment – ALK

Approved by ALK-Abelló:
Country Specific Amendment No. 1 - Netherlands, dated 11-May-2011 to the Clinical Trial Protocol, dated 12-April-2010, and General Protocol Amendment no. 1, dated 05-April-2011, is approved by:

Amendment originator: Bente Tholstrup
Clinical Project Manager Expert

Head of originating department: Ø. Ea Dige, MD
EU QPPV, Director, Global Clinical Development

Signature Date

11 May 2011
Approval of Protocol Amendment – National Coordinating Investigator

Approved by National Coordinating Investigator: Country Specific Amendment No. 1 - Netherlands, dated 11-May-2011 to the Clinical Trial Protocol, dated 12-April-2010, and General Protocol Amendment no. 1, dated 05-April-2011, is approved by:

Principal/Coordinating Investigator:
Dr. Frank W. J. M. Smeenk
MD, PhD (Pulmonologist)
Catharina Hospital
Michelangeloelaan 2,
5623 EJ Eindhoven,
The Netherlands

Signature

May 12, 2011

Date
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Appendix 1: Investigator Agreement on Protocol Amendment
List of Abbreviations

AIT Allergy Immunotherapy Tablet
EudraCT European Union Drug Regulating Authorities Clinical Trials database
EU QPPV European Qualified Person Pharmacovigilance
FEV₁ Forced Expiratory Volume in 1 Second
PEF Peak Expiratory Flow
SABA Short-Acting β-Agonist
HDM House Dust Mite
MITRA House Dust Mite Treatment of Asthma
1 Summary of Amendment

This amendment is prepared as a country specific amendment for the Netherlands to allow Dutch sites to use histamine instead of methacholine for inhalation challenge.

2 Changes to the Protocol

Additions to the original protocol are listed below, with reference to the sections affected. Text deleted is marked with strike through, while added text is in bold italics.

All assessments will be performed as described in the original protocol. In cases where changes/additions have been made, the appropriate section has been included in this amendment. Repetition of otherwise unchanged sections have not been included in this amendment.

2.1 Section 1, Protocol Synopsis

The protocol synopsis repeats elements of the protocol text. In the present amendment the changes will be mentioned only in relation to the relevant protocol sections, and will, thus, not contain an amended protocol synopsis.

2.2 Section 5.4.1.1, Inclusion Criteria

Text has been changed to read as follows:

6. Documented\textsuperscript{19} reversible airway obstruction as judged by one of the following criteria:
   a) Improvement in absolute FEV\textsubscript{1} ≥ 12% and 200 ml after administration of SABA.
   b) Improvement in PEF > 20% after administration of SABA.
   c) Diurnal variability in PEF > 20% after administration of SABA.
   d) Bronchial provocation test:
      1. A decrease in FEV\textsubscript{1} > 15% after 6 min of sustained exercise.
      2. A decrease in FEV\textsubscript{1} ≥ 10% from baseline is recorded after a 6 minutes period of hyperpnea in dry air.
      3. A decrease in FEV\textsubscript{1} ≥ 15% from baseline or ≥ 10% from value obtained after the previous dose after mannitol inhalation challenge.
      4. A decrease in FEV\textsubscript{1} ≥ 20% from baseline after methacholine (or, in the Netherlands, histamine) inhalation challenge.

\textsuperscript{19} Historical test performed within the last 2 years is accepted.

Reason for change:

In the Netherlands histamine inhalation challenges are used instead of methacholine inhalation challenges. In some Dutch clinics the histamine inhalation challenge is the only bronchial provocation test that is used routinely.
Statistical Analysis Plan

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

Clinical Trial ID: MT-04
EudraCT No.: 2010-018621-19
Investigational Medicinal Product: ALK house dust mite (HDM) allergy immunotherapy tablet (AIT)
Development Phase: III
Sponsor: Global Clinical Development
ALK-Abelló A/S
DK-2970 Hørsholm
Phone: +45 45747445
Document Status: Final
Date: 24 June 2013

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ALK Approval of Statistical Analysis Plan

Responsible Statistician: Christian Ljørring
Principal statistician

[Signature]

Date: 24/6-2013

Global Trial Manager: Hanne Hedegaard Villesen
Clinical Project Manager

[Signature]

Date: 24 June 2013

Medical Writer: Bente Riis
Senior Medical Writer

[Signature]

Date: 24 June 2013
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<tr>
<td>ACQ</td>
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1 Introduction

The MT-04 trial “Efficacy of ALK house dust mite allergy immunotherapy tablet in subjects with house dust mite induced asthma” is a randomised, parallel-group, double-blind, placebo-controlled, multi-national, multi-centre trial in Europe.

Section 8 "Statistical Methods" of the protocol (incorporating general protocol amendment 1, 2, 3, 4 and 5) describes the statistical analyses to be performed for the MT-04 trial.

This statistical analysis plan (SAP) provides all required further details in accordance with ICH-GCP guidelines(1) and ALK SOPs (in-house references). This SAP is written before database lock and unblinding.

In Appendix A, B and C, the layout of the tables (table shells), listings (list shells), and figures (figure shells) are presented. The table shells, list shells and figure shells together with the SAP form the detailed specification for analysis.

Text copied from the protocol is written in *italics* and placed within quotation marks. Text additions to the cited protocol text are marked in bold font and deletions are marked by strikethrough. Major changes and deletions are explained in section 7: Deviations from the Trial Protocol.
2 Trial Objectives

2.1 Primary Objective

"The primary objective of the trial is to evaluate the efficacy of the ALK HDM AIT (6 DU and 12 DU) given once daily compared to placebo in subjects with HDM induced asthma, as measured by reducing the risk for an asthma exacerbation."

2.2 Key Secondary Objectives

"The secondary objectives of the trial are to determine the effects of ALK HDM AIT on asthma symptoms and immunology."

2.3 Other Objectives

"Other secondary objectives include evaluating the effects of ALK HDM AIT on lung function, asthma control, safety, symptomatic medication, asthma quality of life, and pharmacoeconomics."
3 Trial Design

This section is selected text copied from section 5.1 of the protocol. "This trial is a randomised, parallel-group, double-blind, placebo-controlled, multi-national, multi-centre trial in Europe. The trial will be initiated when the major pollen seasons in Europe (e.g. grass) are over, and subjects will receive treatment for up to 18 months. Approximately 800 subjects will be randomised to receive treatment with either ALK HDM AIT 6 DU, 12 DU or placebo."

The trial design is shown in Panel 3-1.

Panel 3-1 Trial design

The duration of period 2B was approximately 4 weeks (the period between visit 8 and 9), while both periods 3A (50% ICS reduction) and 3B (ICS withdrawal) had duration of approximately 3 months.

Visit ID's of the flow chart are shown in Panel 3-2.
"During period 1 (screening period) eligible subjects will be switched from their regular asthma controller medication (e.g. combination products) to equivalent doses of inhaled corticosteroid (ICS) and SABA as needed."

"At randomisation and throughout period 2 (treatment maintenance period), the subject will receive investigational medicinal product (IMP) between 7 to 12 month in addition to ICS and SABA."

"Period 3 (ICS reduction period) will begin approximately October 2012. During this period, the subject will have the ICS reduced by 50% and after 3 months 100%, while continuing treatment with IMP for these 6 months. SABA will be provided for symptomatic use for the whole period."

"During period 3 (ICS reduction period) the primary efficacy objective of reducing the risk for an asthma exacerbation will be assessed by measuring time to first moderate or severe asthma exacerbation fulfilling the criteria of the protocol."

With respect to the electronic diary data the baseline period is defined as the last 14 days of the screening period prior to visit 3 (randomisation).

### 4 Trial Population

Four analysis sets are defined, the total analysis set, the full analysis set (FAS), the per protocol analysis set (PP) and the safety analysis set.

#### 4.1 Total Analysis Set

"The total analysis set is all subjects who entered the trial. This analysis set includes screening failures. The total population will be used for listing reasons for screening failures and AEs before randomisation."

#### 4.2 Full Analysis Set

"The FAS is all randomised subjects in accordance with the ICH intent-to-treat principle. This analysis set will be the primary set for all efficacy analyses. The FAS will be used for all baseline/demography tables, efficacy tables, safety tables and subject listings."
4.3 Per Protocol Analysis Set

"The PP analysis set is all subjects in the FAS with no major protocol violations which may influence the primary endpoint (please refer to the SAP for further details). The PP analysis set will be a supplementary set for selected efficacy analyses."

A supportive analysis using the PP analysis set will be performed for the primary efficacy analysis of the primary endpoint.

The final determination on protocol deviations, and thereby the composition of the PP analysis set, will be made prior to the final unblinding of the database and will be appropriately documented. A list of major protocol violators (i.e. subjects excluded from the PP analysis set) is provided in Appendix D.

4.4 Safety Analysis Set

"The safety analysis set is identical to the FAS."
5 Endpoints

5.1 Efficacy Endpoint

5.1.1 Primary endpoint

"The primary endpoint is the time to first moderate or severe asthma exacerbation during period 3 (ICS reduction).

Time to first asthma exacerbation is measured in days from start of period 3 (ICS reduction).
The definition of asthma exacerbation used is that the subject must experience one or more of the criteria listed below.

At least one of the following criteria must be fulfilled and lead to a change in treatment to meet the definition of a moderate exacerbation:

a) Nocturnal awakening(s) due to asthma requiring SABA use for at least 2 consecutive nights or an increase of minimum 0.75 in daily symptom score from baseline value on at least 2 consecutive days.
b) An increase from 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 PEF from baseline value on at least 2 consecutive mornings or evenings or ≥ 20% decrease in FEV1 from baseline value.
d) Visit to the emergency room or unscheduled visit to the trial centre for asthma treatment not requiring systemic corticosteroids.

The baseline value is the mean values during the last 14 days of the screening period.
If the subject experience one of the following events, this will be characterised as a severe asthma 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."

5.1.2 Key Secondary Endpoints

"The key secondary endpoints for this trial are:

- Time to first deterioration in asthma symptoms.
  Time in days from start of period 3 (ICS reduction) to the first asthma exacerbation fulfilling criterion a)
- Immunology measured as change from baseline to end of trial in terms of specific IgE-blocking factor IgG4 against HDM allergens."
- Proportion of subjects with minimal important difference (MID) change in ACQ controlled for change in ICS
- Proportion of subjects with MID change in AQLQ(s) controlled for change in ICS
5.1.3 Other Secondary Endpoints

- **"Severe asthma exacerbation.**
  - Time to first severe asthma exacerbation: Time in days from start of period 3 to the first severe asthma exacerbation fulfilling criterion e) or f).

- **Asthma exacerbations during period 3.**
  - The frequency of asthma exacerbations (number/percentage of subjects) during period 3.

- **Asthma symptoms.**
  - The average overall total asthma daytime symptom score over the first asthma exacerbation free period during the first 3 months of period 3.
  - The average overall total asthma daytime symptom score over the first asthma exacerbation free period during entire period 3.
  - Symptom free days during period 3.
  
  **A symptom free day is defined as a day with:**
  - No daytime asthma symptoms (daytime symptom score =0).
  - No daytime need for SABA.
  - No increase in ICS or
  - No use of oral steroid.
  
  - Symptom free nights during period 3.
  
  **A symptom free night is defined as a night with:**
  - No nocturnal asthma symptoms (worst nocturnal symptom score =0).
  - No nocturnal awakening due to asthma.
  - No nocturnal need for SABA.
  - No increase in ICS.
  - No use of oral steroid.
  
  - Symptom free 24-hour periods during period 3.
    
    **A symptom free 24-hour period is defined as:**
    
    - A symptom free night followed by a symptom free day.

- **Symptomatic medication.**
  - Time to first increased use of SABA: Time in days from start of period 3 to the first asthma exacerbation fulfilling criterion b).

- **Lung function.**
  - The average morning PEF and diurnal variability over the first asthma exacerbation free period during first 3 months of period 3.
  - The average morning PEF and diurnal variability over the first asthma exacerbation free period during entire period 3.
5.1.4 Derivation of Efficacy Endpoints

5.1.4.1 Primary endpoint

The primary endpoint consists of two variables, a time variable and an indicator variable indicating an event; i.e. whether an asthma exacerbation is observed or not.

For subjects who attend visit 9, data on a moderate or severe asthma exacerbation is collected from visit 9 (ICS reduction visit) on the asthma exacerbation CRF page.

The date of change in treatment due to asthma exacerbation is collected on the asthma exacerbation CRF page. Time to first asthma exacerbation is calculated as number of days from the date of visit 9 to the date of change in treatment due to asthma exacerbation. If an asthma exacerbation is observed at the visit 9 date then time to first asthma exacerbation is 0.

For subjects who do not experience asthma exacerbation (post visit 9) the time variable is calculated as number of days from the date of visit 9 to the date of trial completion or discontinuation and the indicator variable is indicating that no asthma exacerbation was observed.

For subjects who discontinue prior to visit 9, data on the primary endpoint is missing. Missing data for the primary endpoint is replaced by multiple imputations in the primary analysis, see section 6.1.2 and 6.5.2.

5.1.4.2 Time to first cause-specific component

Similar to the primary endpoint, the secondary endpoints:

- Time to first asthma exacerbation fulfilling criterion a)
- Time to first severe asthma exacerbation i.e. fulfilling criterion e) or f)
- Time to first asthma exacerbation fulfilling criterion b)
- Time to first asthma exacerbation fulfilling criterion c) consists of two variables, a time variable which equals the time variable of the primary endpoint (see section 5.1.4.1) and an indicator variable indicating whether the criteria in question are fulfilled or not.

5.1.4.3 Immunology
Specific IgE and IgG4 against *Dermatophagoides pteronyssinus* (*D. pteronyssinus*) and *Dermatophagoides farinae* (*D. farinae*) is measured in serum samples obtained at visits 1 (screening/baseline), 4, 6, 9, and 13/the end-of-trial visit.

All values of zero '0' will be replaced by the lowest observed value even if this is below the detection limit. All other non-missing values will be used as observed even if this is below the detection limit.

Change from baseline (visit 1) in both raw and logarithmic (log10) transformed values to visit 4, 6, 9 and 13/the end-of-trial visit is calculated for the immunological parameters.

5.1.4.4 Asthma exacerbations during period 3
For each subject who attend visit 9 (ICS reduction) the number of asthma exacerbations during period 3 is counted. For subjects who have not experienced an asthma exacerbation and who discontinue before end of trial the number of asthma exacerbation is 0.

Data on number of asthma exacerbations is missing for subjects who do not enter period 3.

5.1.4.5 Symptom free days, nights and 24-hour periods during period 3
For each subject the proportion of symptom free days, nights and 24-hour periods during period 3 is calculated as the number of symptom free days, nights and 24-hour periods during period 3 divided by the number of days from visit 9 to date of trial completion or discontinuation.

Data on symptom free days, nights and 24-hour periods is missing for subjects who do not enter period 3.

5.1.4.6 Asthma symptoms
A total of 4 daytime asthma symptoms are measured daily on a scale from 0 to 3 (0=no symptoms, 1=mild symptoms, 2=moderate symptoms, 3=severe symptoms). The 4 symptoms are

- Cough
- Wheeze
- Chest tightness/shortness of breath
- Exercise induced symptoms

Data on these daytime asthma symptoms is obtained from the evening diary in the electronic diary.

A total asthma daytime symptom score is calculated for each subject as the sum of the individual daily 4 asthma symptoms.

In the morning diary, subjects were asked to describe the severity (on a similar 0 to 3 scale) of their worst asthma symptom (wheezing, coughing, shortness of breath, or chest tightness) during the night. This is the asthma nocturnal symptom score.
For each subject entering period 3 a 'first asthma exacerbation free period' is defined. If the subject experiences an asthma exacerbation then 'first asthma exacerbation free period' is the period from visit 9 until the date of the first asthma exacerbation fulfilling the primary endpoint definition (see 5.1.1). If the subject does not experience an asthma exacerbation then 'first asthma exacerbation free period' is the period from visit 9 until the date of end-of-trial visit.

For each subject all non-missing observations of the total asthma daytime symptom score and the asthma nocturnal symptom score is averaged over the following periods:

- 14 days baseline period
- period 2B between visit 8 and 9
- first asthma exacerbation free period during period 3A
- first asthma exacerbation free period during the entire period 3 (3A+3B)

Moreover, weekly averages of the total asthma daytime and nocturnal symptom score are calculated for each subject for each week during the electronic diary assessment period between visit 8 and visit 13/the end-of-trial visit.

5.1.4.7 Lung function

PEF is measured and recorded in the diary by the subject every morning and evening during the baseline period, period 2B from visit 8 to visit 9 and during period 3 from visit 9 to visit 13/the end-of-trial visit.

For each subject all non-missing observations of the morning PEF, evening PEF and diurnal variation in PEF is averaged over the following periods:

- the 14 days baseline period
- period 2B between visit 8 and 9
- first asthma exacerbation free period during period 3A
- first asthma exacerbation free period during the entire period 3 (3A+3B)

(see 5.1.4.6 for definition of asthma exacerbation free period). The percentage diurnal variation in PEF is calculated for each subject as 100×(PEF evening – PEF morning)/(PEF evening).

The percentage of predicted FEV₁ is calculated for each subject for each visit. Also, changes from baseline (defined as FEV₁ at visit 3) in percentage of predicted FEV₁ is calculated for each subject to each visit.

5.1.4.8 Asthma control questionnaire - ACQ

The asthma control questionnaire ACQ consists of 7 questions referring to the previous week. 5 questions are related to symptoms (nocturnal wakening, morning symptoms, activity limitation, short of breath, wheeze), 1 question is about β₂-agonist use (SABA), and the last question is about lung function (percentage of predicted FEV₁). Each question is scored on a 7 point scale from 0 to 6 (the higher the worse). The overall ACQ score is the average of the 7 scores of the individual questions. The range of the overall ACQ score is 0 to 6.

From the paper CRF the overall ACQ score and individual ACQ question scores are calculated for each subject for each visit (1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13/the end-of-trial visit).

Change from baseline (visit 3) in overall ACQ is calculated for each subject to each visit 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13/the end-of-trial visit.
5.1.4.9 MID change in ACQ controlled for ICS
Change from baseline to visit 9, 11 and 13/the end-of-trial visit in overall ACQ is calculated for each subject and categorised into 1 of 3 possible categories according to the magnitude of the minimal important difference (MID) (2) (1: important improvement; 2: no important difference; 3: important deterioration; see Panel 5-1). Last observation is carried forward if overall ACQ for a visit is missing.

Panel 5-1 MID change in ACQ controlled for change in use of ICS

<table>
<thead>
<tr>
<th>Change in ACQ from baseline</th>
<th>Change in daily ICS from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;0</td>
</tr>
<tr>
<td>Improvement above MID (≤ -0.5)</td>
<td>+</td>
</tr>
<tr>
<td>No MID (&gt; -0.5 and &lt; 0.5)</td>
<td>+</td>
</tr>
<tr>
<td>Deterioration above MID (≥0.5)</td>
<td>-</td>
</tr>
</tbody>
</table>

MID: minimal important difference; light grey/+: meaningful improvement; dark grey/-: no meaningful improvement

Also change from prescribed ICS dose at baseline to most recent previously prescribed ICS dose at visit 9, 11 and 13/the end-of-trial visit is categorized to decrease (<0), no change (=0) or increase (>0) for each subject using last observation carried forward if missing.

The key secondary endpoint 'proportion of subjects with MID change in ACQ controlled for ICS' is defined as a binary variable ('0','1'). It is constructed based on change from baseline to visit 13/ the end-of-trial visit in ACQ and dose of ICS. The binary variable is set to '1' if change from baseline in ACQ corresponds to a meaningful improvement (≤-0.5) without increased use of ICS or if ICS is reduced compared to baseline (<0) without a deterioration in ACQ (≥0.5); otherwise the binary variable is set to '0' (see Panel 5-1). Last observation is carried forward if data is missing or for subjects who discontinue the trial. For ICS at end-of-trial it is the most recent previously prescribed ICS dose which is used.

5.1.4.10 Asthma quality of life questionnaire with standardised activities - AQLQ(S)
The AQLQ(S) has 32 questions in 4 domains, referring to the last two weeks. Each question is scored on a 7-point scale from 1 to 7 (worse to better). The 4 domains are symptoms (12 questions), activity limitation (11 questions), emotional function (5 questions) and environmental stimuli (4 questions). Overall AQLQ(S) score is the average of all items and domain score is the average of items within each domain.

Overall AQLQ(S) score and domain scores is calculated for each subject at visit 3, 6, 8, 9, 10, 11, 12 and 13/the end-of-trial visit.

For subjects experiencing asthma exacerbation during period 3 the AQLQ(S) is collected post this asthma exacerbation (2-4 days after). Overall AQLQ(S) score and domain scores is also calculated for these assessments and change from baseline (visit 3) in overall AQLQ(S) is calculated as well.

Change from baseline (visit 3) in overall AQLQ(S) is calculated for each subject to visit 6, 8, 9, 10, 11, 12 and 13/the end-of-trial visit.
5.1.4.11 MID change in AQLQ(S) controlled for ICS
The key secondary endpoint 'proportion of subjects with MID change (3) in AQLQ(S) score controlled for ICS' is defined and derived in the same way and at the same time-points as 'MID change in ACQ controlled for ICS' (see 5.1.4.9).

5.1.4.12 Other questionnaires and pharmacoconomics assessments

5.1.4.12.1 SF-36v2® Health survey
SF-36v2 is a generic questionnaire with 36 questions to measure functional health and well-being from the patient's point of view. It provides scores for 8 health domains, and additionally a psychometrically-based physical component summary (PCS) and a mental component summary (MCS) score.
SF-36v2 is assessed at visit 3, 6, 9, 10, 11, 12, 13/the end-of-trial visit.
Health domain scale scores (0-100) are calculated for each subject at each visit for each of the 8 health domains and the 2 summary scores (4).

5.1.4.12.2 Treatment satisfaction questionnaire for medication TSQM II
TSQM II has 11 questions in 4 domains (scales), to assess patient satisfaction with treatment, referring to the last 2 to 3 weeks. Patients are asked to rate their experiences of treatment between 'extremely dissatisfied' and 'extremely satisfied' on 5-point to 7-point scales. Higher TSQM II scores indicate higher satisfaction with treatment. The 4 domains are effectiveness (2 questions), side-effects (3 questions), convenience (3 questions) and global satisfaction (2 questions).
The TSQM-II questionnaire is assessed at visit 4, 8 and 13/the end-of-trial visit for subjects in Germany and France only.
Domain TSQM II scores is calculated at visit 4, 8 and 13/the end-of-trial visit.

5.1.4.12.3 Work productivity and activity impairment questionnaire
The work productivity and activity impairment questionnaire related to asthma, version 2.0 (WPAI: Asthma) consists of 6 questions referring to the previous week. The questions ask about the effect of the patient's asthma on ability to work and perform regular activities.
The questionnaire is collected at visit 3, 6, 9, 10, 11, 12 and 13/the end-of-trial visit.
WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes, as follow:
Questions: 1= currently employed; 2=hours missed due to specified problem; 3= hours missed other reason; 4= hours actually worked; 5=degree problem affected productivity while working; 6=degree problem affected regular activities.
Scores are multiplied by 100 to be expressed as percentages.
   a) Percent work time missed due to problem ('absenteeism'): Q2/(Q2+Q4)
   b) Percent impairment while working due to problem ('presenteeism'): Q5/10
   c) Percent overall work impairment due to problem ('work productivity loss'): Q2/(Q2+Q4)+[(1-Q2/(Q2+Q4))x(Q5/10)]
d) Percent activity impairment due to problem (activity impairment\(^\prime\)): Q6/10.

5.1.4.12.4 Health care resource use

At visit 1, data on days missed from work, numbers of visits to general practitioner (GP), specialist or emergency room (ER), hospitalisations and ≥3-day courses of systemic corticosteroids due to asthma during the previous 12 months are collected.

At each visit 2 to 13/the end-of-trial visit data on number of visits to a GP, specialist or ER is collected.

5.2 Safety endpoints

The safety endpoints used in this trial are:

- "AEs, SAEs, AE withdrawals discontinuations, clinical laboratory tests, vital signs, physical examination."

AEs are assessed at each visit. Clinical laboratory tests are analysed from samples taken at visit 1 and visit 13/the end-of-trial visit. Vital signs are measured at visits 1, 9, 11 and 13/the end-of-trial visit. Physical examinations are performed at visits 1, 9, 11 and 13/the end-of-trial visit.

5.3 Summary of all Endpoints

Panel 5-2 summarises the relation between endpoints and analysis sets.

Panel 5-2 Summary of all endpoints and analysis sets

<table>
<thead>
<tr>
<th></th>
<th>FAS-MI</th>
<th>FAS</th>
<th>PP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy Endpoints</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary (Time to first moderate or severe asthma exacerbation)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Key secondary endpoints</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other secondary endpoints</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Safety Endpoints</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAS-MI: Full analysis set with multiple imputations, see 6.5.2</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAS: Full analysis set based on available observed data. The safety analysis set is identical to FAS. PP: Per-protocol analysis set with available observed data.</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
6 Statistical Methods

The analyses and presentations described in this section, the table, lists and figure shells (Appendix A, B and C) specify the statistical analyses.

Statistical analyses will be carried out by ALK. All computation will be performed using SAS® version 9.3 or above.

6.1 General Considerations

“All analyses requiring significance testing will be two-sided at a 5% significance level, unless otherwise specified. All confidence intervals will be two-sided 95% confidence intervals.”

The null hypothesis is the hypothesis of no difference and the alternative to the null hypothesis is the hypothesis of difference.

Descriptive statistics will be presented by treatment group (placebo, HDM AIT 6DU and HDM AIT 12 DU), pooling the data from subjects who received active treatment and pooling all data (overall).

Descriptive statistics for numerical variables includes summary tables displaying mean, SD, median, 5%-percentile, 25%-percentile, 75%-percentile, 95%-percentile, minimum and maximum. Descriptive statistics for categorical variables includes frequencies tables that display numbers and percentage.

6.1.1 Sample Size and Power

All considerations on power and sample size are described in detail in section 8.1 of the protocol.

6.1.2 Handling of Missing Data

Text below is copied from section 8.8.1 of the protocol.

“The primary analysis will be based on a multiple imputation method. This is because the analysis is based on the full analysis set (FAS) including all randomised subjects and because subjects may discontinue during the treatment maintenance period (period 2) prior to efficacy assessment of the primary endpoint.

All subjects who withdraw from the trial during period 2, no matter their assigned randomised treatment group and for whatever reason for withdrawal, will be included in the primary analysis as if they were following the same distribution as the observed placebo group during the efficacy assessment period (period 3), i.e. as if they were having no treatment effect. Thus, all subjects who withdraw during period 2 will be included as sampled from the placebo distribution of time to first asthma exacerbation during period 3.

This is a multiple imputation method that generates multiple copies of the original data set by replacing the missing values using the observed placebo distribution, analyse them as complete data sets and finally combine the different parameter estimates across the data sets to produce a unique point estimate and standard error taking into account the uncertainty of the imputation process.”

This approach follows the EMA guideline on missing data (5).
Text below is copied from the protocol section 8.11.

“In the primary analysis subjects who withdraw between visit 9 (ICS reduction) and visit 13 (end of trial), the time to asthma exacerbation is right-censored at the date of withdrawal.”

For the two key secondary endpoints 'proportion of subjects with MID change in ACQ/AQLQ(s) controlled for ICS' last observation is carried forward. No other imputation of data will be carried out in case of missing data, but all available data will be used to its full extent. Thus for the other key secondary and other secondary endpoints imputation will not be performed.

6.1.3 Blinding
This trial is conducted as a double-blind, randomised placebo-controlled trial. The randomised allocation schedule is generated by an external and trial independent statistician.

The final database will not be unblinded until medical/scientific review has been performed, protocol violators have been identified, and data have been declared final and complete and the data base locked.

6.1.4 Multiple Comparison/Multiplicity
Text below is copied from section 8.7 of the protocol.

"Multiplicity will be controlled for the multiple comparisons of the treatment groups on the primary endpoint. Multiplicity will be controlled by the following pre-specified order of the hypothesis to be tested. The first hypothesis to be tested is the hypothesis that all three groups are equal. If and only if this hypothesis can be rejected at the 5% level, each of the three pairwise comparisons can be tested at the 5% level. No statistical conclusions can be based on any of the three pairwise comparisons unless the hypothesis of no difference between the three groups is rejected (p<0.05).

Additionally, the experiment-wise Type I error rate is strongly controlled for all key secondary hypotheses by hierarchical testing as described and illustrated below.

Other Additional endpoints and analyses are supportive in nature and will not be controlled for multiplicity."

The multiple hypothesis test strategy is illustrated in Panel 6-1. Hypotheses are rejected from top to bottom. The 4 hypotheses in the top concerning the primary endpoint are controlled by "Fisher's least significant difference procedure". This procedure is well known to preserve the experiment-wise type I error rate at the nominal level of significance, if (and only if) the number of treatment groups is three (6).

To further reject key secondary hypotheses the following sequentially rejective procedure is conducted.

If and only if the hypothesis of no difference between HDM AIT 12DU and placebo on the primary endpoint is rejected (p<0.05) the procedure continues in the hierarchical order:

1. 12DU versus placebo in change from baseline to visit 13/the end-of-trial visit in log_{10}(IgG_{4})
2. 12DU versus placebo in 'time to first asthma exacerbation fulfilling criterion a')
3. 12DU versus placebo in proportion with MID change in ACQ controlled for ICS
4. 12DU versus placebo in proportion with MID change in AQLQ(s) controlled for ICS
The procedure continues if a hypothesis is rejected (p<0.05) otherwise it stops with no further statistical conclusions allowed.

If all of the 4 key secondary hypotheses for the comparison of HDM AIT 12DU to placebo can be rejected (p<0.05); and if the hypothesis of no difference between HDM AIT 6DU and placebo on the primary endpoint is rejected (p<0.05) the procedure then continues in the following hierarchical order:

1. 6DU versus placebo in change from baseline to visit 13/the end-of-trial visit in log10(IgG4)
2. 6DU versus placebo in 'time to first asthma exacerbation fulfilling criterion a')
3. 6DU versus placebo in proportion with MID change in ACQ controlled for ICS
4. 6DU versus placebo in proportion with MID change in AQLQ(s) controlled for ICS

Panel 6-1  Multiple hypothesis testing strategy

- H1 & H2 & H3: Placebo = 6 DU = 12 DU (p<0.05)
  - H1: Placebo = 6 DU (p<0.05)
  - H2: Placebo = 12 DU (p<0.05)
  - H3: 6 DU = 12 DU

Hierarchy:
1. H2: Placebo = 12 DU; in change from baseline to visit 13/the end-of-trial visit in log10(IgG4)
2. H2: Placebo = 12 DU; in time to first asthma exacerbation fulfilling criterion a)
3. H2: Placebo = 12 DU; in proportion with MID change in ACQ controlled for ICS
4. H2: Placebo = 12 DU; in proportion with MID change in AQLQ(s) controlled for ICS

H1, H2, H2_1, H2_2, H2_3, and H2_4 are all rejected (p<0.05)
6.1.5 Interim Analysis
Text below is copied from section 8.10 of the protocol.
"No interim analysis is performed."

6.1.6 Adjustments for Covariates
Covariates that will be adjusted for includes country and baseline values.
The primary time-to-event analysis is stratified for country and the secondary time-to-event analyses are also stratified for country.
Country is included as a fixed categorical effect in the key secondary analyses of 'proportion of subjects with MID change in ACQ/AQLQ(s) controlled for ICS'.
Country is included as a random categorical effect in the linear mixed effects analyses including immunology.
Baseline is included as covariate in the statistical analyses when baseline data is collected and this also includes when analysing change from baseline.

6.1.7 Multicentre Trials
Variation between countries is expected and may result from variation in geography and thus HDM exposure, variation in standard treatment procedures and from possible differences in conduct of the trial protocol. Variation between sites is also expected but is assumed to be small compared to the variation between countries.
The trial is not powered to detect differences or interaction in treatment effect with countries or sites. Difference between countries will be adjusted for in the primary, key secondary and most of the secondary efficacy analyses by stratifying for country or including country as a covariate, please see section 6.5.

6.1.8 Model Assumptions
Text below is copied from section 8.8.1 of the protocol.
"Sensitivity analysis and model control will be conducted to assess the model assumption of non-informative withdrawal during period 3, and proportional hazards. Also withdrawals during period 2 will be assessed and the withdrawal rate evaluated."
The assumption of proportional hazards over time is assessed by visual inspection of Kaplan-Meier plots and plots of the estimated integrated hazards by treatment group.
The assumption of non-informative censoring is assessed by sensitivity analysis, see 6.5.2.
The assumption of normally distributed residuals underlying the parametric linear mixed effect (LME) model in the key secondary and secondary analyses will be evaluated by visual inspections of quantile-quantile (QQ) plots. If there is a poor approximation to the normal distribution, another transformation to the response variable will be applied if this improves the approximation to a normal distribution. If it is not possible (with or without transformation) to obtain a good approximation to the normal distribution, an appropriate non-parametric analysis as for example the Wilcoxon Rank Sum test will be applied.
6.1.9 Subgroup analysis

No formal statistical subgroup analyses are planned and the trial is not powered to detect treatment effect within a subgroup. However, summaries for the primary efficacy endpoint will be provided for the following subgroups:

- gender (male, female)
- allergen sensitisation type (mite only, mite + others)
- other indoor sensitisation\(^1\) (with, without)
- age group (<30 years, ≥30 years)

The descriptive summary of all first moderate or severe asthma exacerbations will be presented by treatment group.

Additionally, a forest plot will be provided for the estimated hazard ratio by the above subgroups. The plot will display the estimated hazard ratio to placebo (and corresponding confidence interval) for each subgroup by treatment. The estimated hazard ratio is calculated using the Cox regression stratified by country defined in section 6.5.2 and based on all observed data in FAS.

6.2 Subject Disposition

A table of subject disposition by treatment group displaying number and percentage of subjects screened, included in the FAS, included in the safety analysis set, included in the PP analysis set, discontinued and the primary reason for discontinuation will be presented. The number and percentage of subjects who discontinued during period 2, during period 3 and post-primary-endpoint is presented. The number and percentage of subjects who attended visit 9 (ICS reduction) and entered period 3 is also presented.

In addition a Kaplan-Meier plot of time to discontinuation by treatment group (all causes) and a Kaplan-Meier plot of time to discontinuation by treatment group due to AE will be generated.

6.3 Demographic and Baseline Characteristics

Text below is copied from the protocol section 8.3.

"Demographic and baseline characteristics will be summarised by treatment group displaying number of subjects, mean, SD, median, 5%-quantile, 25%-quantile, 75%-quantile, 95%-quantile, minimum and maximum for continues variables and frequency tables for categorical variables."

Baseline characteristics from the 14-days baseline period include average AM PEF, average PM PEF, average diurnal variability in PEF, average total (and separate) asthma daytime symptom score, average asthma nocturnal symptom score, average number of nocturnal awakenings as well as awakenings requiring SABA, average daily, nocturnal and 24-hour SABA intake.

The level of asthma control at the randomisation visit is classified into GINA 2010 levels of control by transforming the ACQ data according to the algorithm shown in Panel 6-2.

\(^1\) animal hair/dander + moulds (=cat, dog, horse, Cladosporium herbarium and Alternaria alternata)
Panel 6-2  Algorithm for translating ACQ questions to GINA 2010 control levels

<table>
<thead>
<tr>
<th>GINA</th>
<th>ACQ</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Controlled</strong></td>
<td></td>
</tr>
<tr>
<td>Nocturnal symptoms/ awakening</td>
<td>Nocturnal awakening Q1=0</td>
</tr>
<tr>
<td>None</td>
<td>Morning symptoms Q2=0</td>
</tr>
<tr>
<td>Limitations of activities</td>
<td>Activity limitations Q3=0</td>
</tr>
<tr>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Daytime symptoms</td>
<td>Shortness of breath Q4≤2, Q5≤2</td>
</tr>
<tr>
<td>Twice or less/week</td>
<td>Wheeze</td>
</tr>
<tr>
<td>Need for reliever/ rescue treatment</td>
<td>Puffs of short-acting β2- agonist Q6≤1</td>
</tr>
<tr>
<td>Lung function PEF or FEV₁</td>
<td>Predicted FEV₁ Q7≤2</td>
</tr>
<tr>
<td>Normal (&gt; = 80 predicted/ personal best)</td>
<td></td>
</tr>
<tr>
<td><strong>Partly controlled</strong>*</td>
<td></td>
</tr>
<tr>
<td>Nocturnal symptoms/ awakening</td>
<td>Nocturnal awakening Q1&gt;0</td>
</tr>
<tr>
<td>Any</td>
<td>Morning symptoms Q2&gt;0</td>
</tr>
<tr>
<td>Limitations of activities</td>
<td>Activity limitations Q3&gt;0</td>
</tr>
<tr>
<td>Any</td>
<td></td>
</tr>
<tr>
<td>Daytime symptoms</td>
<td>Shortness of breath Q4&gt;2, Q5&gt;2</td>
</tr>
<tr>
<td>More than twice or less/week</td>
<td>Wheeze</td>
</tr>
<tr>
<td>Need for reliever/ rescue treatment</td>
<td>Puffs of short-acting β2- agonist Q6&gt;1</td>
</tr>
<tr>
<td>Lung function PEF or FEV₁</td>
<td>Predicted FEV₁ Q7&gt;2</td>
</tr>
<tr>
<td>&lt;80% predicted/ personal best</td>
<td></td>
</tr>
<tr>
<td><strong>Uncontrolled</strong></td>
<td></td>
</tr>
<tr>
<td>≥3 features of partly controlled</td>
<td>≥3 out of 5 criteria for partly controlled fulfilled</td>
</tr>
</tbody>
</table>

*: any one of the items listed will categorise the patient as partly controlled.

Baseline characteristics also include from the randomisation visit the overall ACQ, percentage predicted FEV₁, and overall AQLQ(S) score. From visit 1 is included the duration of HDM allergic rhinitis and HDM induced asthma, skin prick test results (positive/negative result and skin sensitisation type) and HDM specific IgE class.

6.4  Extent of exposure

IMP accountability (number of daily doses used) is the difference between the number of daily doses dispensed and the number of daily doses returned.

IMP compliance is the number of daily doses used divided by the duration of IMP treatment period in days (number of days from IMP treatment start to IMP treatment stop) and multiplied with 100. A treatment year is the number of daily doses divided by 364.
Duration of IMP treatment period, IMP accountability, IMP compliance and treatment years will be displayed in summary tables by treatment group. For the purpose of summary tables, drug accountability above 100% without a corresponding report of IMP overdose, is set to 100%.

### 6.5 Efficacy Evaluation

This section describes the planned efficacy analysis. The primary efficacy analysis will be conducted based on the full analysis set with multiple imputations (FAS-MI) supported by FAS as well as PP analysis. All other efficacy analyses will be conducted based on FAS, see Table Shells, Appendix A and Figure Shells, Appendix B.

For the primary analysis all 3 pairwise comparisons between groups are performed. For all other analyses only the pairwise comparison between each active treatment group and placebo will be performed.

#### 6.5.1 Summary of analysis strategy

This section describes a brief summary of the analyses for this trial (see Panel 6-3).

**Panel 6-3 Strategy for primary efficacy analyses**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Statistical Method</th>
<th>Analysis Population</th>
<th>Missing data approach</th>
<th>Multiplicity control</th>
<th>Descriptive analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to first moderate or severe asthma exacerbation</td>
<td>Cox-model</td>
<td>FAS-MI</td>
<td>Multiple Imputation</td>
<td>F-LSD</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>FAS</td>
<td>Observed Data</td>
<td>KM-plot</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PP</td>
<td>Observed Data</td>
<td>KM-plot</td>
<td></td>
</tr>
</tbody>
</table>

F-LSD: Fisher's least significant difference (6)

KM: Kaplan-Meier

FAS-MI: Full analysis set with multiple imputations

FAS: Full analysis set

PP: Per protocol analysis set

#### 6.5.2 Primary Efficacy Analysis

Text below is copied from the protocol section 8.8.1.

"The primary efficacy analysis of the primary endpoint, time to first moderate or severe asthma exacerbation, will be performed with a Cox proportional hazards regression analysis. The model is stratified for country trial centre and includes treatment group as a factor. Depending on the number and size of trial centres, pooling of trial centres may be considered or trial centres may..."
be replaced by regions or countries. Based on this model the first hypothesis to be tested is the hypothesis of no difference between the three groups: placebo, ALK HDM AIT 6DU and ALK HDM AIT 12DU. Thus, this is the hypothesis that in each strata the hazard rate for time to first moderate or severe asthma exacerbation is equal between groups. The hypothesis is tested on 2 degrees of freedom.

If and only if this hypothesis is rejected ($p<0.05$) the comparison of each active dose against placebo as well as the comparison of the two active dose groups can be tested at the 5% level. No statistical conclusions can be based on any of the three pairwise comparisons unless the hypothesis of no difference between the three groups is rejected ($p<0.05$).

For each active treatment group the estimated hazard ratio compared to placebo will be presented together with the two-sided 95% Wald confidence interval and a p-value. The hazard ratio for ALK HDM 12DU compared to ALK HDM 6DU will also be estimated and presented together with the two-sided 95% confidence interval and a p-value.

The primary analysis will be based on a multiple imputation method. This is because the analysis is based on the full analysis set (FAS) including all randomised subjects and because subjects may discontinue during the treatment maintenance period (period 2) prior to efficacy assessment of the primary endpoint.

All subjects who withdraw from the trial during period 2, no matter their assigned randomised treatment group and for whatever reason for withdrawal, will be included in the primary analysis as if they were following the same distribution as the observed placebo group during the efficacy assessment period (period 3), i.e. as if they were having no treatment effect. Thus, all subjects who withdraw during period 2 will be included as sampled from the placebo distribution of time to first asthma exacerbation during period 3.

This is a multiple imputation method that generates multiple copies of the original data set by replacing the missing values using the observed placebo distribution, analysing them as complete data sets and finally combining the different parameter estimates across the data sets to produce a unique point estimate and standard error taking into account the uncertainty of the imputation process.

Sensitivity analysis and model control will be conducted to assess the model assumption of non-informative withdrawal during period 3, and proportional hazards. Also withdrawals during period 2 will be assessed and the withdrawal rate evaluated.*

The assumption of proportional hazards over time is assessed by visual inspection of Kaplan-Meier plots and estimated cumulative hazards by treatment group. In case of unacceptable violations of the assumption of time-constant proportionality, time period 3 may be broken down into two periods (first and last 3 months of period 3) or even 6 periods (each month of period 3).

In Panel 6-4 below, the SAS code for the primary analysis including imputation is specified.

Panel 6-4  SAS code for primary efficacy analysis including imputation

<table>
<thead>
<tr>
<th>SAS Code</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>FAS data set with one observation for each subject; data cox_data; ... /</em> missing_data: 1 if missing, 0 otherwise treat: 0=placebo, 1= 6DU, 2= 12DU treat_6du: 1 if 6DU, 0= otherwise</td>
</tr>
</tbody>
</table>
treat_12du:       1 if 12DU, 0 otherwise

time:             number of days from visit 9 to a) date of asthma exacerbation or
                   b) date of end of trial

censored:         1 if no asthma exacerbation, 0 otherwise

*/

keep subject site missing_data treat treat_6du treat_12du time censored;
run;

*What is the number of subjects with missing data?;
proc sql noprint;
   select sum(missing_data)
       into :n1
       from cox_data
quit;run;

*Impute missing values as sampled from the observed placebo distribution;
PROC SURVEYSELECT DATA=cox_data(where=(missing_data=0 and treat=0)) OUT=sample METHOD=URS
   SAMPSIZE=(&n1) outhits reps=50 SEED=2013 noprint;
RUN;

*Set together 50 copies of the observed data;
data cox_full;
   set cox_data;
   do _imputation_=1 to 50;
      time_imputed=time;
      censored_imputed=censored;
      output;
   end;
run;
proc sort data=cox_full; by _imputation_ subject; run;

*Extract subjects with no observed data;
data cox_missing;
   set cox_full;
   where missing_data=1;
run;

*rename variables;
data sample;
   set sample;
   _imputation_=replicate;
   time_imputed=time;
A descriptive summary of all first moderate or severe asthma exacerbations will be presented by treatment group and broken down by criteria, moderate only and severe.

All first moderate or severe asthma exacerbations will be summarised by treatment group and by all individual criteria and sub-criteria.
6.5.3 Key Secondary Efficacy Analysis

6.5.3.1 Specific IgG4 against HDM allergens

IgG4 will be log-transformed for this key-secondary analysis. The response variable is change from baseline in \( \log_{10}(\text{IgG4}) \) and the longitudinal analysis of \( \log_{10}(\text{IgG4}) \) is based on data from visit 4, visit 6, visit 9 and visit 13/the end-of-trial visit. The categorical variable ‘visit number’ is recoded to either 4, 6 or 9, for those samples obtained at ‘visit 13’ for which the visit is not a planned visit 13 but rather an end-of trial visit performed at discontinuation. The model is a linear mixed effects model with treatment group, baseline value (visit 1), visit and treatment group by visit interaction as fixed effects as well as a random country and subject effects. Different residual errors are specified for each treatment group. The difference in adjusted means between each treatment group and placebo will be presented including p-values and confidence limits. The p-value and 95% confidence limits for the absolute difference are obtained using Kenward-Roger calculations for the degrees of freedom. Adjusted means and relative differences in adjusted means with confidence intervals are also reported on the original scale (by taking the antilogarithm).

Covariance parameters are calculated using the method of restricted maximum likelihood (REML) method. LogLikelihood Ratio (LR) tests are used for testing the null hypothesis of equal residual variance for the treatment groups. The resulting p-values of the LR tests are reported.

Summary tables by treatment group and visit will be produced for raw data of IgG4 for both D. pteronyssinus and D. farinae. Also the change from baseline in IgG4 will be summarised for both D. pteronyssinus and D. farinae.

Samples from site 509 involving 31 subjects are all discarded and not included in the analysis because of uncertainty to whether samples may be swapped around.

6.5.3.2 Time to first deterioration in asthma symptoms

Thus, the event times are analysed with a Cox proportional hazards model stratifying for country and including treatment group as a factor. For each active treatment group the estimated hazard ratio compared to placebo will be presented together with the two-sided 95% confidence interval and a p-value. No comparison between the active groups HDM AIT 12DU and HDM AIT 6DU will be estimated. The analysis is performed on FAS without imputation.

This analysis of the hazard rate is accompanied by additional descriptive analyses. Cause-specific cumulative incidence functions (7) over time are presented by treatment group in plots and tables. This corresponds to estimating the cumulative proportion of subjects who experience the cause-specific event up to each time point.
Finally, a descriptive summary table is prepared to show how each and all specific components (criteria a-f) of the composite definition of an asthma exacerbation make up the first composite events.

6.5.3.3 MID change in ACQ controlled for ICS
An analysis of the odds for improvement in MID change in ACQ controlled for ICS is performed. Change is measured from baseline (visit 3) to visit 13/ the end-of-trial-visit.

The odds for improvement is analysed with a logistic regression analysis with treatment group and as categorical fixed effects and baseline ACQ and ICS as continuous fixed effects covariates. Country is included as a random effect.

For each active treatment group compared to placebo the estimated odds ratio and 95% confidence interval is presented including a p-value.

6.5.3.4 MID change in AQLQ(S) controlled for ICS
An analysis of the odds for improvement in MID change in AQLQ(S) controlled for ICS is performed similar to MID change in ACQ controlled for ICS (see section 6.5.3.3). Thus, change is measured from baseline (visit 3) to visit 13/ the end-of-trial-visit.

For each active treatment group compared to placebo the estimated odds ratio and 95% confidence interval is presented including a p-value.

6.5.4 Other Secondary Efficacy Analysis

6.5.4.1 Severe asthma exacerbation
Text is copied from protocol section 8.8.3.

"Time to first severe asthma exacerbation will be analysed similar to the key secondary event-time endpoints."

All the cause-specific analyses of the hazard rates (including time to first severe asthma exacerbation) are accompanied by two additional descriptive analyses.

First, cause-specific cumulative incidence functions (7) over time are presented by treatment group in plots and tables. This corresponds to estimating the cumulative proportion of subjects who experience the cause-specific event up to each time point.

Second, a descriptive summary table is prepared to show how each and all specific components (criteria a-f) of the composite definition of an asthma exacerbation make up the first composite events.

6.5.4.2 Asthma exacerbations during period 3
Text is copied from protocol section 8.8.3.

"Frequency of asthma exacerbations during period 3 will be analysed with a generalised linear model including treatment group as fixed effect and adjusting for covariates such as trial centre."

For each subject the binary response of whether asthma exacerbation was experienced or not is used in the analysis of the odds for asthma exacerbation during period 3.
Estimates are obtained from a logistic regression analysis with treatment group as categorical fixed effects and baseline ACQ and ICS as continuous fixed effects covariates. Country is included as a random effect.

Fisher's exact test for the binary response of whether asthma exacerbation was experienced or not is calculated for each active group compared to placebo.

Number or moderate or severe asthma exacerbations during period 3 will be summarised by treatment group and by criteria moderate only or severe.

6.5.4.3 Asthma symptoms
Both endpoints

- The average total asthma daytime symptom score over the first asthma exacerbations free period during period 3A
- The average total asthma daytime symptom score over the first asthma exacerbations free period during the entire period 3

are analysed in the same way with a LME model. The model includes treatment group and the average total asthma daily symptom score over the 14-days baseline period as fixed effects and country as a random effect. For each pairwise treatment group comparison all available data from all 3 treatment groups are included. Possible different error variance for each treatment group is adjusted for. The error variance is fitted as separate compound symmetry for each treatment group. Two-sided 95% confidence intervals for the adjusted mean differences will be presented as well as the p-values.

A descriptive summary by treatment group is prepared for both endpoints.

During period 2B (between visit 8 and visit 9) the average total asthma daytime symptom score, average nocturnal asthma symptoms score and average number of nocturnal awakenings (total and those requiring SABA) are summarised by treatment group.

The proportion of symptom free days, nights and 24-hour periods during period 3 is analysed similarly with a LME model. The proportion of symptom free days, nights or 24-hour period is the response variable and the model includes treatment group as fixed effect and country as a random effect. For each pairwise treatment group comparison, all available data from all 3 treatment groups are included. Possible different error variance for each treatment group is adjusted for. The error variance is fitted as separate compound symmetry for each treatment group. Two-sided 95% confidence intervals for the adjusted mean differences will be presented as well as the p-values.

The proportion of symptom free days, nights and 24-hour periods during period 3 are summarised by treatment group.

6.5.4.4 Symptomatic medication
Time to first increased use of SABA corresponding to time to first cause-specific component of criterion b) (see 5.1.4.2 ) is analysed and presented similar to the key secondary endpoint time to first deterioration in asthma symptoms (see 6.5.3.2).

Over period 2B (between visit 8 and visit 9) the average 24-hour, daytime and nocturnal SABA intake is summarised by treatment group.

6.5.4.5 Lung function
For both periods the endpoints
- The average morning and evening PEF and diurnal variability over the first asthma exacerbations free period during period 3A
- The average morning and evening PEF and diurnal variability over the first asthma exacerbations free period during the entire period 3

are analysed similarly with a LME model. The model includes treatment group and the average overall score over the 14-days baseline period as fixed effects and country as a random effect. For each pairwise treatment group comparison all available data from all 3 treatment groups are included. Possible different error variance for each treatment group is adjusted for. The error variance is fitted as separate compound symmetry for each treatment group. Two-sided 95% confidence intervals for the adjusted mean differences will be presented as well as the p-values.

A descriptive summary by treatment group is prepared for the endpoints for both periods.

Time to first deterioration in lung function corresponding to time to first cause-specific component of criterion c) (see 5.1.4.2 ) is analysed and presented in the same way as the key secondary endpoint time to first deterioration in asthma symptoms (see 6.5.3.2).

During period 2B (between visit 8 and visit 9) the average morning PEF, evening PEF and diurnal variability in PEF (l/min) are summarised by treatment group.

A LME model is used for the analysis of change from baseline (visit 3) in FEV₁ to each visit up to visit 9. The model is similar to the model described for IgG₄. Based on this analysis the adjusted means including standard error and the two-sided 95% confidence intervals for the adjusted mean differences compared to placebo will be presented together with the p-values.

Change from baseline (visit 3) in FEV₁ to each visit (4, 5, 6, 7, 8, 9, 10, 11, 12 and 13) is summarised by treatment group.

Also FEV₁ and predicted percentage of FEV₁ are summarised by each visit.

6.5.4.6 Asthma control - ACQ

A LME model is used for the analysis of the overall ACQ as well as change from baseline in overall ACQ at/to each visit (4, 5, 6, 7, 8 and 9) up to visit 9 with ACQ at visit 3 as baseline value. The model is similar to the model described for IgG₄. Based on this analysis the adjusted means including standard error and the two-sided 95% confidence intervals for the adjusted mean differences compared to placebo will be presented together with the p-values.

The overall ACQ score, individual ACQ question scores as well as change from baseline in overall ACQ to each visit is summarised by visit and presented in summary tables.

6.5.4.7 Asthma quality of life

Overall AQLQ(S) as well as change from baseline in overall AQLQ(S) at/to each visit (6, 8, and 9) up to visit 9 is analysed and presented similarly to the analysis of ACQ.

Also, the overall AQLQ(S) score, individual AQLQ(S) domain scores as well as change from baseline in overall AQLQ(S) score for each visit is summarised by visit and presented in summary tables as for ACQ.

For overall AQLQ(S) collected post asthma exacerbation a specific descriptive summary table is prepared.
6.5.4.8 MID change in ACQ/AQLQ(S) controlled for ICS
The MID change from baseline to visit 9 in overall ACQ and AQLQ(S) is summarised by treatment group.

The MID change from baseline in overall ACQ and AQLQ(S) is summarised by treatment group for each of the 3 subgroups (i.e. improvement >MID, no MID, deterioration >MID) defined by change from baseline in ICS.

Similarly, the MID change from baseline to visit 11 and 13/the end-of-trial visit in overall ACQ is summarised by treatment group for all and each of the 3 subgroups defined by change from baseline in ICS.

6.5.4.9 Immunology
Specific IgE against *D. pteronyssinus* and *D. farinae* is analysed and summarised similar to IgG4 (see Section 6.5.3.1).

6.5.4.10 Quality of life and pharmacoeconomics assessments
Text copied from section 8.12 of the protocol.

"Information about the subject’s perception of quality of life and work impact during the course of the trial and health care resource use are collected.

Details for the evaluation of health care resource use, rate of hospitalisation, questionnaire data and derivation of subscales (scoring algorithms) including handling of missing observations will be described in the SAP."

Descriptive analyses of the pharmacoeconomics assessments are performed. SF-36, TSQM II, WPAI:ASTHMA as well as health care resource use and rate of hospitalisation are summarised by treatment group displaying number of subjects, mean, SD, median, 5%-percentile, 25%-percentile, 75%-percentile, 95%-percentile, minimum and maximum for continues variables and frequency tables for categorical variables.

6.5.4.11 Prescribed ICS
The prescribed total daily dose of ICS (mcg/day) is summarised by visit.

For visit 9 (CS reduction), 11 (ICS withdrawal) and 13 (end-of-trial) the most recent previously prescribed total daily dose of ICS (mcg/day) is summarised.

A plot by treatment group and visit including both mean prescribed total daily dose of ICS and mean of the most recent previously prescribed of ICS at each visit will be prepared.

### 6.5.5 Sensitivity Analyses

As sensitivity analyses to assess the model assumption of non-informative censoring the following are conducted:

- Kaplan-Meier plot by treatment group of time to discontinuation (all causes) measured from randomisation
- Cause-specific cumulative incidence plot by treatment group of time to discontinuation (due to AE and 'not AE') measured from randomisation
- Time from visit 9 to first moderate or severe asthma exacerbation or discontinuation due to AEs is analysed similar to the primary analysis with imputation
6.6 Safety Evaluation

Text is copied from section 8.9.1 and 8.9.2 of the protocol.

"AEs will be summarised by treatment group, system organ class and preferred term displaying number of subjects in treatment group, number and percentage of subjects having the event as well as number and percentage of events. Furthermore, the AEs will be summarised according to severity, relationship, outcome, action and seriousness. The analyses will be described further in the SAP."

"Laboratory assessments and vital signs will be summarised by treatment group displaying number of subjects, mean, standard deviation, median, 25 and 75-percentiles, minimum and maximum for continuous variables and frequency tables for categorical variables."

Adverse events (AEs) are recorded from when the subjects sign the informed consent and until the last follow-up visit. Unless otherwise specified, the term ‘AE’ in this SAP refers to events occurring after the first IMP administration. If, due to partial dates, there is any doubt whether an AE has started prior to or after the first IMP administration, that event will be conservatively assumed to have started after the administration of first IMP dose.

IMP-related AEs are those not assessed ‘unlikely’ related.

All AEs and IMP-related AEs will be summarised by treatment group, MedDRA system organ class and preferred term displaying number subjects in treatment group, number and frequency of subjects having the event as well as number of events.

All AEs and IMP-related AEs will be broken down by severity (mild, moderate, severe) and summarised by treatment group displaying number of subjects in treatment group, number and frequency of subjects having the event as well as number of events.

AEs leading to IMP discontinuations/interruptions and SAEs will be summarised by SOC and treatment group in separate tables.

Most frequent AEs (defined as preferred term from MedDRA) are those that are present in ≥2% of subjects in any active treatment group. Most frequent AEs and most frequent IMP-related AEs will be summarised by SOC and treatment group in separate tables.

For most frequent AEs starting after first IMP intake on the first day of IMP, onset in minutes will be summarised by treatment group. For most frequent AEs onset in days will be summarised by treatment group. Onset of an AE is defined as time (e.g. in minutes or days) from first IMP intake to start of the first AE of a given preferred term. An onset of 1 day means that the AE has started on the day of first IMP intake.

Resolution of an AE is defined as days from start of the AE until the AE is resolved. E.g. recurrent AEs like oral pruritus that occurs every day for 1 minute on 5 days in a row will have a resolution of 5 days. Resolution will be summarised by treatment group for most frequent AEs.

All pre-IMP adverse events will be summarised by treatment group, SOC and preferred term for all randomised subjects.

All adverse events will be listed including events with onset before first IMP.

6.7 Post Hoc Analyses

All analyses performed after unblinding of the trial are considered exploratory post hoc analyses.
7 Deviations from the Trial Protocol

A secondary objective of the protocol is to determine the effects of ALK HDM AIT on immunology. In the statistical methods section 8.6.2 of the protocol "specific IgE-blocking factor" is stated as the parameter of interest. For laboratory technical reasons data on specific IgE-blocking factor cannot be provided. Instead of 'IgE-blocking factor', specific IgG4 is analysed and presented as the immunology parameter of key interest.

Because of ambiguity of the proposed secondary endpoint 'symptom free days during period 3' the endpoint is replaced by 3 separate endpoints; symptom free days, symptom free nights and symptom free 24-hour periods.

To align the terminology with other protocols the secondary endpoint 'overall asthma symptom score' is changed to 'total asthma daytime symptom score'.

The additional key secondary efficacy analyses of overall ACQ and ICS (as well as AQLQ and ICS) combined to a composite endpoint evaluating simultaneously change from baseline in both ACQ and ICS to end of trial were planned after the finalisation of the protocol. They are included in the multiple hypothesis testing strategy.

8 Discussion

As this trial is the first of its kind, both in terms of investigating time to asthma exacerbations in a specific immunotherapy trial, and in terms of the novel definition of a moderate asthma exacerbation, the clinically relevant effect size was not to be found in any literature when the protocol was written. However, based on the available literature on other asthma treatments and unpublished data from a previous HDM AIT trial (the MT-02 trial), a clinically relevant effect size was estimated in the protocol and formed the basis for the power calculations. A reduction in the hazard rate for time to first asthma exacerbation of approximately 30%, corresponding to a hazard ratio of 0.70, was considered clinical relevant. The corresponding 95% confidence intervals will be provided, as will the absolute and the relative reduction in exacerbations.

Due to the design of the trial, i.e. with ICS reduction from visit 9 and onwards, the trial is not made to show superiority for all the secondary endpoints separately per se. The secondary endpoints are primarily included to ensure, that the expected prolonged time to asthma exacerbation, is not occurring at the cost of a worsening in asthma control. Thus it is not considered relevant to define clinically relevant differences for each and every secondary endpoint.

Having said this, both lung function and asthma symptoms are included in the primary endpoint and therefore clinically relevant differences for these endpoints are covered by the primary endpoint.

For 2 of the secondary endpoints; ACQ (also including lung function and asthma symptoms) and AQLQ, the minimal important difference (MID) has been defined previously as 0.5 points (2;3). This difference is within patient, i.e. corresponding to measuring change from baseline.

As the protocol defines, that subjects experiencing an asthma exacerbation during period 3 should return to an ICS dose sufficient to maintain control, data on ACQ and ICS is combined to a composite endpoint evaluating simultaneously change from baseline in both ACQ and ICS to end of trial. Similarly, the corresponding composite of AQLQ and ICS is evaluated. To support the evidence of benefit for the subjects as measured by the primary endpoint, superiority on
these 2 key secondary composite endpoints (each evaluated as change from baseline to end-of-trial) should be observed in favour of active treatment compared to placebo.

The secondary event-time endpoints are analysed by analysis of the hazard rate in the same way as described for the primary efficacy endpoint, with the exception of right-censoring in case other criteria than the one(s) evaluated are fulfilled.

To evaluate and discuss a possible treatment effect on these cause-specific endpoints the analysis of the cause-specific hazard rates cannot stand alone but should be accompanied by the estimates of the cumulative incidence functions as well as the overall descriptive summary of how each and all specific components (criteria a-f) of the composite definition of an asthma exacerbation make up the first composite events (7).

9 Software

The statistical computations will be performed using the computer software package SAS® version 9.3.
10 Reference List


Statistical Analysis Plan – Appendix A

Table Shells

Trial ID: MT-04

Efficacy of ALK house dust mite allergy immunotherapy tablet in subjects with house dust mite induced asthma

Investigational Medicinal Product: ALK HDM AIT 6 DU and 12 DU

Development phase: III

EudraCT no: 2010-018621-19

Sponsor: Group Clinical Development
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<td>6.11</td>
<td>All severe IMP related adverse events by SOC (Safety set)</td>
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<tr>
<td>6.12</td>
<td>All serious IMP related adverse events by SOC (Safety set)</td>
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<td>6.13</td>
<td>Number of treatment emergent adverse events per subject for subjects with events (Safety set)</td>
</tr>
<tr>
<td>6.14</td>
<td>Number of treatment emergent adverse events per subject (Safety set)</td>
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6.15 Most frequent TEAEs (≥2% in any active group) by SOC (Safety set) 100
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## 1 Subject disposition and baseline characteristics

### 1.1 Subjects disposition (total analysis set)

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<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active All (N=XXX)</th>
<th>Overall (N=XXX)</th>
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<tbody>
<tr>
<td>n (%n)</td>
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<td>n (%n)</td>
<td>n (%n)</td>
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<td>XXX (100%)</td>
<td>XXX (100%)</td>
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<td>XXX (XXX%)</td>
<td>XXX (XXX%)</td>
<td>XXX (XXX%)</td>
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<tr>
<td>Per protocol set (PP)</td>
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<tr>
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<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
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<td>during period 2a</td>
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<td>XX (XX%)</td>
<td>XX (XX%)</td>
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<td>post primary endpoint+</td>
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<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
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<td>XX (XX%)</td>
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<td></td>
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<td>XX (XX%)</td>
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<tr>
<td></td>
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<tr>
<td></td>
<td>Lost to follow-up</td>
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<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
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<td>Non-compliance</td>
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</tbody>
</table>

Reason for discontinuation:
- Withdrawal of consent
- Pregnancy
- Lack of efficacy
- Lost to follow-up
- Non-compliance
- Protocol
- Adverse event
- Other

Subjects entering period 3#

Subjects completed

---

<table>
<thead>
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<tr>
<td>Subjects completed</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
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</table>

---

Explanation:
- # = number of subjects (FAS), n = number of subjects with event, %n = percentage of subjects in treatment group of FAS with the event
- a: Subjects who have not attended visit 9.
- A: Subjects discontinued in the period after fulfilling the primary endpoint of a moderate or severe asthma exacerbation.
- #: Subjects who have attended visit 9.
### 1.2 Demography and baseline characteristics – I (FAS)

<table>
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<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active All (N=XXX)</th>
<th>Overall (N=XXX)</th>
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<td>XX (XX%)</td>
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<td>XX (XX%)</td>
<td>XX (XX%)</td>
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<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
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<td>XX (XX%)</td>
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<td>XX (XX%)</td>
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<tr>
<td>Lithuania</td>
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<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
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<td>XX (XX%)</td>
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<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Spain</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
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<td>XX (XX%)</td>
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<td>XX (XX%)</td>
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<td>XX (XX%)</td>
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<tr>
<td><strong>Smoking history</strong></td>
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<td></td>
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<tr>
<td>Non-smoker</td>
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<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
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<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Smoker</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
</tbody>
</table>

- N = number of subjects (Full analysis set), n = number of subjects with event, %n = percentage of subjects in treatment group of Full analysis set with the event

---

**Note:** The table above contains demographic and baseline characteristic data for the trial MT-04. The data is provided as a summary for the full analysis set (FAS). Each row represents a different category of data, such as sex, ethnic origin, country, smoking history, etc., and the columns show the counts and percentages for each category across different treatment groups. The data is presented in a structured format, allowing for easy comparison and analysis. The table includes placeholders for numerical values (e.g., XX) and percentages (%n), indicating that the actual numbers and percentages are to be filled in based on the data collected during the trial.
### 1.3 Demography and baseline characteristics – II (FAS)

<table>
<thead>
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<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active All (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (year)</strong></td>
<td>n</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XXX</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
</tr>
<tr>
<td>Median</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
<tr>
<td>P25%-P75%</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
</tr>
<tr>
<td>Min-Max</td>
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<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>n</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
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</tr>
<tr>
<td>Mean (SD)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
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<td>XX.X</td>
<td>XX.X</td>
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<td>XX.X</td>
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<tr>
<td>P25%-P75%</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
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<td>Min-Max</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td>n</td>
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<td>XX</td>
<td>XX</td>
<td>XXX</td>
</tr>
<tr>
<td>Mean (SD)</td>
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<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
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<td>XX.X</td>
<td>XX.X</td>
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<tr>
<td>P25%-P75%</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
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<tr>
<td>Min-Max</td>
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<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
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<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
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<td>XX.X</td>
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<td>XX.X</td>
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<tr>
<td>P25%-P75%</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
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<tr>
<td>Min-Max</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
</tr>
</tbody>
</table>

- N = number of subjects (Full analysis set), n = number of subjects with observations, SD = standard deviation, P25% = 25% percentile, P75% = 75%, P5% = 5% percentile, P95% = 95% percentile
### 1.4 PEF (l/min) during baseline (FAS)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active All (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average AM PEF</td>
<td>n</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XXX</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>XX. X (XX.X)</td>
<td>XX. X (XX.X)</td>
<td>XX. X (XX.X)</td>
<td>XX. X (XX.X)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
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<td>XX. X</td>
<td>XX. X</td>
<td>XX. X</td>
</tr>
<tr>
<td></td>
<td>P25%–P75%</td>
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<td>XX. X – XX. X</td>
<td>XX. X – XX. X</td>
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<tr>
<td></td>
<td>Min–Max</td>
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<td>XX. X – XX. X</td>
<td>XX. X – XX. X</td>
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<td>XX. X</td>
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<td></td>
<td>P25%–P75%</td>
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</tr>
</tbody>
</table>

N = number of subjects (Full analysis set), n = number of subjects with observations, SD = standard deviation, P25% = 25% percentile, P75% = 75%, P5% = 5% percentile, P95% = 95% percentile. The baseline period is the 14-day period prior to randomisation. Data is obtained from the morning and the evening diary data.
1.5 Average asthma daytime symptom score over the baseline period (FAS)

<table>
<thead>
<tr>
<th>Total asthma daytime symptom score</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active AII (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
</tr>
<tr>
<td>Median</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
<tr>
<td>P25%-P75%</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
</tr>
<tr>
<td>Min-Max</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
</tr>
</tbody>
</table>

Cough

| n                                 | XX              | XX                        | XX                        | XX                | XXX             |
| Mean (SD)                         | XX.X (XX.X)     | XX.X (XX.X)               | XX.X (XX.X)               | XX.X (XX.X)      | XX.X (XX.X)     |
| Median                            | XX.X            | XX.X                     | XX.X                      | XX.X              | XX.X            |
| P25%-P75%                         | XX.X – XX.X     | XX.X – XX.X               | XX.X – XX.X               | XX.X – XX.X      | XX.X – XX.X     |
| Min-Max                           | XX.X – XX.X     | XX.X – XX.X               | XX.X – XX.X               | XX.X – XX.X      | XX.X – XX.X     |

Wheeze

| n                                 | XX              | XX                        | XX                        | XX                | XXX             |
| Mean (SD)                         | XX.X (XX.X)     | XX.X (XX.X)               | XX.X (XX.X)               | XX.X (XX.X)      | XX.X (XX.X)     |
| Median                            | XX.X            | XX.X                     | XX.X                      | XX.X              | XX.X            |
| P25%-P75%                         | XX.X – XX.X     | XX.X – XX.X               | XX.X – XX.X               | XX.X – XX.X      | XX.X – XX.X     |
| Min-Max                           | XX.X – XX.X     | XX.X – XX.X               | XX.X – XX.X               | XX.X – XX.X      | XX.X – XX.X     |

Chest tightness/shortness of breath

... ...

Exercise induced symptoms

... ...

- n = number of subjects (full analysis set), n = number of subjects with observations, SD = standard deviation, P25% = 25% percentile, P75% = 75%, P5% = 5% percentile, P95% = 95% percentile. The baseline period is the 14-day period prior to randomisation. Data is obtained from the evening diary data. The overall symptom score is the total asthma daily symptom score.
### 1.6 Average asthma nocturnal symptom score over the baseline period (FAS)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active All (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma nocturnal symptom score</td>
<td>XX (X.X)</td>
<td>XX (X.X)</td>
<td>XX (X.X)</td>
<td>XX (X.X)</td>
<td>XX (X.X)</td>
</tr>
<tr>
<td>n</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
<tr>
<td>Median</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
<tr>
<td>P25%-P75%</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
</tr>
<tr>
<td>P5%-P95%</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
</tr>
</tbody>
</table>

N = number of subjects (Full analysis set), n = number of subjects with observations, SD = standard deviation, P25% = 25% percentile, P75% = 75%, P5% = 5% percentile, P95% = 95% percentile. The baseline period is the 14-day period prior to randomisation. The asthma nocturnal symptom score is the severity of the worst nocturnal asthma symptom (wheezing, coughing, shortness of breath or chest tightness) obtained from the morning diary.
### 1.7 Average number of nocturnal awakenings during the baseline period (FAS)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM All 6 DU (N=XXX)</th>
<th>ALK HDM All 12 DU (N=XXX)</th>
<th>Active All (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nocturnal awakening#</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XXX</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
</tr>
<tr>
<td>Median</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
<tr>
<td>P25%-P75%</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
</tr>
<tr>
<td>P5%-P95%</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
</tr>
<tr>
<td>Min-Max</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
</tr>
</tbody>
</table>

| Nocturnal awakening requiring SABA intake |                 |                          |                           |                   |                 |
| n                   | XX              | XX                       | XX                        | XX                | XXX             |
| Mean (SD)           | XX.X (XX.X)     | XX.X (XX.X)              | XX.X (XX.X)               | XX.X (XX.X)      | XX.X (XX.X)    |
| Median              | XX.X            | XX.X                     | XX.X                      | XX.X              | XX.X            |
| P25%-P75%           | XX.X – XX.X     | XX.X – XX.X              | XX.X – XX.X               | XX.X – XX.X      | XX.X – XX.X    |
| P5%-P95%            | XX.X – XX.X     | XX.X – XX.X              | XX.X – XX.X               | XX.X – XX.X      | XX.X – XX.X    |
| Min-Max             | XX.X – XX.X     | XX.X – XX.X              | XX.X – XX.X               | XX.X – XX.X      | XX.X – XX.X    |

N = number of subjects (Full analysis set), n = number of subjects with observations, SD = standard deviation, P25% = 25% percentile, P75% = 75%, P5% = 5% percentile, P95% = 95% percentile. The baseline period is the 14-day period prior to randomisation.

#: For each subject the average number of nocturnal awakenings over the 14-day baseline period.

* For each subject the average number of nocturnal awakenings with SABA intake over the 14-day baseline period.
### 1.8 Average SABA intake during the baseline period (FAS)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active All (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-hour SABA intake</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XXX</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
</tr>
<tr>
<td>Median</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
<tr>
<td>P25%-P75%</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
</tr>
<tr>
<td>Min-Max</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
</tr>
<tr>
<td>Daytime SABA intake</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XXX</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
</tr>
<tr>
<td>Median</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
<tr>
<td>P25%-P75%</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
</tr>
<tr>
<td>Min-Max</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
</tr>
<tr>
<td>Nocturnal SABA intake</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XXX</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
</tr>
<tr>
<td>Median</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
<tr>
<td>P25%-P75%</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
</tr>
<tr>
<td>Min-Max</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
</tr>
</tbody>
</table>

N = number of subjects (Full analysis set), n = number of subjects with observations, SD = standard deviation, P25% = 25% percentile, P75% = 75%, P5% = 5% percentile, P95% = 95% percentile. The baseline period is the 14-day period prior to randomisation.
1.9 Baseline skin prick test (FAS)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK NAB AIT 12 DU (N=XXX)</th>
<th>ALK NAB AIT 12 DU (N=XXX)</th>
<th>Active All (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Tree - Betula verrucosa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Negative</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Missing</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Grass - Phleum pratense</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Negative</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Missing</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Negative control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Negative</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Missing</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
</tbody>
</table>

N = number of subjects (Full analysis set), n = number of subjects with event, %n = percentage of subjects of treatment group in Full analysis set with the event
### 1.10 Number of other sensibilities (positive SPT) screening visit (FAS)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active All (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%n)</td>
<td>n (%n)</td>
<td>n (%n)</td>
<td>n (%n)</td>
<td>n (%n)</td>
</tr>
<tr>
<td>No other</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>One other</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Two other</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Three other</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Four other</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Five other</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Six other</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Seven other</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Eight other</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
</tbody>
</table>

n = number of subjects (full analysis set), n = number of subjects with event, %n = percentage of subjects of treatment group in full analysis set with the event excluding tests for HDM, positive and negative controls.

Statistical Analysis Plan – Appendix A – Table Shells

Trial ID: MT-04
Version: Final
Date: 24-June-2013
### 1.11 Specific IgE against Der p and/or Der f (FAS)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active all (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>(%)</td>
<td>n</td>
<td>(%)</td>
<td>n</td>
</tr>
<tr>
<td><strong>Der p</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgE class 1</td>
<td>XX</td>
<td>(XX%)</td>
<td>XX</td>
<td>(XX%)</td>
<td>XX</td>
</tr>
<tr>
<td>IgE class 2</td>
<td>XX</td>
<td>(XX%)</td>
<td>XX</td>
<td>(XX%)</td>
<td>XX</td>
</tr>
<tr>
<td>IgE class 3</td>
<td>XX</td>
<td>(XX%)</td>
<td>XX</td>
<td>(XX%)</td>
<td>XX</td>
</tr>
<tr>
<td>IgE class 4</td>
<td>XX</td>
<td>(XX%)</td>
<td>XX</td>
<td>(XX%)</td>
<td>XX</td>
</tr>
<tr>
<td>IgE class 5</td>
<td>XX</td>
<td>(XX%)</td>
<td>XX</td>
<td>(XX%)</td>
<td>XX</td>
</tr>
<tr>
<td>IgE class 6</td>
<td>XX</td>
<td>(XX%)</td>
<td>XX</td>
<td>(XX%)</td>
<td>XX</td>
</tr>
<tr>
<td><strong>Der f</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgE class 1</td>
<td>XX</td>
<td>(XX%)</td>
<td>XX</td>
<td>(XX%)</td>
<td>XX</td>
</tr>
<tr>
<td>IgE class 2</td>
<td>XX</td>
<td>(XX%)</td>
<td>XX</td>
<td>(XX%)</td>
<td>XX</td>
</tr>
<tr>
<td>IgE class 3</td>
<td>XX</td>
<td>(XX%)</td>
<td>XX</td>
<td>(XX%)</td>
<td>XX</td>
</tr>
<tr>
<td>IgE class 4</td>
<td>XX</td>
<td>(XX%)</td>
<td>XX</td>
<td>(XX%)</td>
<td>XX</td>
</tr>
<tr>
<td>IgE class 5</td>
<td>XX</td>
<td>(XX%)</td>
<td>XX</td>
<td>(XX%)</td>
<td>XX</td>
</tr>
<tr>
<td>IgE class 6</td>
<td>XX</td>
<td>(XX%)</td>
<td>XX</td>
<td>(XX%)</td>
<td>XX</td>
</tr>
<tr>
<td>IgE class of maximum of specific IgE against Der p and Der f:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgE class 1</td>
<td>XX</td>
<td>(XX%)</td>
<td>XX</td>
<td>(XX%)</td>
<td>XX</td>
</tr>
<tr>
<td>IgE class 2</td>
<td>XX</td>
<td>(XX%)</td>
<td>XX</td>
<td>(XX%)</td>
<td>XX</td>
</tr>
<tr>
<td>IgE class 3</td>
<td>XX</td>
<td>(XX%)</td>
<td>XX</td>
<td>(XX%)</td>
<td>XX</td>
</tr>
<tr>
<td>IgE class 4</td>
<td>XX</td>
<td>(XX%)</td>
<td>XX</td>
<td>(XX%)</td>
<td>XX</td>
</tr>
<tr>
<td>IgE class 5</td>
<td>XX</td>
<td>(XX%)</td>
<td>XX</td>
<td>(XX%)</td>
<td>XX</td>
</tr>
<tr>
<td>IgE class 6</td>
<td>XX</td>
<td>(XX%)</td>
<td>XX</td>
<td>(XX%)</td>
<td>XX</td>
</tr>
</tbody>
</table>

N = number of subjects (Full analysis set), n = number of subjects with event, %n = percentage of subjects of treatment group in Full analysis set with the event.

Trial ID: Initials DM & Initials STAT\Date of run
1.12 Allergy medical history (FAS)

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active all (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>House dust mite induced asthma</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>House dust mite induced rhinitis</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
</tbody>
</table>

N = number of subjects (Full analysis set), n = number of subjects with event, %n = percentage of subjects of treatment group in Full analysis set with the event
### Clinical Characteristics

#### 1.13 Years with house dust mite induced allergic asthma and rhinitis (FAS)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active all (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Years HDM induced asthma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
</tr>
<tr>
<td>Median</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
<tr>
<td>P25%-P75%</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
</tr>
<tr>
<td>Min-Max</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
</tr>
</tbody>
</table>

| **Years HDM induced rhinitis** | | | | | |
| N               | XX              | XX                       | XX                        | XX                 | XX             |
| Mean (SD)       | XX.X (XX.X)     | XX.X (XX.X)              | XX.X (XX.X)               | XX.X (XX.X)       | XX.X (XX.X)   |
| Median          | XX.X            | XX.X                     | XX.X                      | XX.X               | XX.X           |
| P25%-P75%       | XX.X – XX.X     | XX.X – XX.X              | XX.X – XX.X               | XX.X – XX.X       | XX.X – XX.X   |
| Min-Max         | XX.X – XX.X     | XX.X – XX.X              | XX.X – XX.X               | XX.X – XX.X       | XX.X – XX.X   |

HDM= House dust mite  
N = number of subjects (Full analysis set), n = number of subjects with observations, SD = standard deviation, P25% = 25% percentile, P75% = 75% percentile, P5% = 5% percentile, P95% = 95% percentile
### 1.14 Other medical history by SOC (FAS)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active all (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred term</td>
<td>n (%n)</td>
<td>n (%n)</td>
<td>n (%n)</td>
<td>n (%n)</td>
<td>n (%n)</td>
</tr>
<tr>
<td>Any other medical history</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>System Organ Class 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Preferred Term 1.1</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Preferred Term 1.2</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Preferred Term 1.3</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
</tbody>
</table>

N = number of subjects (Full analysis set), n = number of subjects with event, %n = percentage of subjects of treatment group in Full analysis set with the event

---

Trial ID\file name.sas\Initials DM & Initials STAT\Date of run
### 1.15 Previous and concomitant medication (FAS)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active all (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = number of subjects (Full analysis set), n = number of subjects with event, %n = percentage of subjects of treatment group in Full analysis set with the event</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**WHO Drug Code n (%n) n (%n) n (%n) n (%n) n (%n)**

- All allergy/asthma medication
  - XX (XX%)
  - XX (XX%)
  - XX (XX%)
  - XX (XX%)
  - XX (XX%)
- WHO Drug Code 1
  - XX (XX%)
  - XX (XX%)
  - XX (XX%)
  - XX (XX%)
  - XX (XX%)
- WHO Drug Code 2
  - XX (XX%)
  - XX (XX%)
  - XX (XX%)
  - XX (XX%)
  - XX (XX%)
- WHO Drug Code 3
  - XX (XX%)
  - XX (XX%)
  - XX (XX%)
  - XX (XX%)
  - XX (XX%)
- WHO Drug Code 4
  - XX (XX%)
  - XX (XX%)
  - XX (XX%)
  - XX (XX%)
  - XX (XX%)
- WHO Drug Code 5
  - XX (XX%)
  - XX (XX%)
  - XX (XX%)
  - XX (XX%)
  - XX (XX%)

Trial ID: file name.sas\Initials DM & Initials STAT\Date of run
### 1.16 Number of oral steroid courses – total and by trial period (FAS)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placbo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active All (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%n)</td>
<td>e</td>
<td>n (%n)</td>
<td>e</td>
<td>n (%n)</td>
</tr>
<tr>
<td>All steroid courses</td>
<td>XX (XX%)</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>During period 2</td>
<td>XX (XX%)</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX (XX%)</td>
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<tr>
<td>During period 3A</td>
<td>XX (XX%)</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>During period 3B</td>
<td>XX (XX%)</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX (XX%)</td>
</tr>
</tbody>
</table>

N = number of subjects (FAS), n = number of subjects with events, \( \% n \) = percent of subjects in treatment group of FAS with events, e = number of events.

Number of steroid courses lasting at least 3 days.
### 1.17 GINA asthma control level at randomisation (FAS)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active all (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GINA control</td>
<td>n (n%)</td>
<td>n (n%)</td>
<td>n (n%)</td>
<td>n (n%)</td>
<td>n (n%)</td>
</tr>
<tr>
<td>Controlled</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Partly controlled</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
</tbody>
</table>

Controlled, if all of the following during the week prior to randomisation visit:
- Daytime symptoms (twice or less/week)
- Limitations of activities (none)
- Nocturnal symptoms/awakening (none)
- Need for reliever/rescue treatment (twice or less/week)
- Lung function (normal, predicted FEV1 >=80%)

Partly controlled, if any of the following present:
- Daytime symptoms (more than twice/week)
- Limitations of activities (any)
- Nocturnal symptoms/awakening (any)
- Need for reliever/rescue treatment (more than twice/week)
- Lung function (predicted FEV1 <80%)

Uncontrolled, if three or more features of partly controlled asthma present.

Data is based on the ACQ questionnaire obtained from CRF.
2 IMP accountability, exposure, compliance and visit dates

2.1 IMP accountability (FAS)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XX)</th>
<th>ALK HDM AIT 6 DU (N=XX)</th>
<th>ALK HDM AIT 12 DU (N=XX)</th>
<th>Active all (N=XX)</th>
<th>Overall (N=XX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX (XX)</td>
<td>XX (XX)</td>
<td>XX (XX)</td>
<td>XX (XX)</td>
<td>XX (XX)</td>
</tr>
<tr>
<td>Median</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td>P25% - P75%</td>
<td>XX - XX</td>
<td>XX - XX</td>
<td>XX - XX</td>
<td>XX - XX</td>
<td>XX - XX</td>
</tr>
<tr>
<td>P5% - P95%</td>
<td>XX - XX</td>
<td>XX - XX</td>
<td>XX - XX</td>
<td>XX - XX</td>
<td>XX - XX</td>
</tr>
<tr>
<td>Min - Max</td>
<td>XX - XX</td>
<td>XX - XX</td>
<td>XX - XX</td>
<td>XX - XX</td>
<td>XX - XX</td>
</tr>
</tbody>
</table>

N= number of subjects (FAS), n = number of subjects with observations, SD = standard deviation, P25% = 25% percentile, P75% = 75% percentile, P5% = 5% percentile, P95% = 95% percentile

The IMP accountability (number of daily doses used) is the difference between the number of daily doses dispensed and the number of daily doses returned.
### 2.2 Duration of IMP treatment period in days (FAS)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo ( (N=XX) )</th>
<th>ALK HDM AIT 6 DU ( (N=XX) )</th>
<th>ALK HDM AIT 12 DU ( (N=XX) )</th>
<th>Active all ( (N=XX) )</th>
<th>Overall ( (N=XX) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n )</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX (XX)</td>
<td>XX (XX)</td>
<td>XX (XX)</td>
<td>XX (XX)</td>
<td>XX (XX)</td>
</tr>
<tr>
<td>Median</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td>( P25% - P75% )</td>
<td>XX - XX</td>
<td>XX - XX</td>
<td>XX - XX</td>
<td>XX - XX</td>
<td>XX - XX</td>
</tr>
<tr>
<td>( P5% - P95% )</td>
<td>XX - XX</td>
<td>XX - XX</td>
<td>XX - XX</td>
<td>XX - XX</td>
<td>XX - XX</td>
</tr>
<tr>
<td>Min - Max</td>
<td>XX - XX</td>
<td>XX - XX</td>
<td>XX - XX</td>
<td>XX - XX</td>
<td>XX - XX</td>
</tr>
</tbody>
</table>

\( N \) = number of subjects (FAS), \( n \) = number of subjects with observations, SD = standard deviation, \( P25\% \) = 25\% percentile, \( P75\% \) = 75\% percentile, \( P5\% \) = 5\% percentile, \( P95\% \) = 95\% percentile

Duration of IMP treatment period is the number of days from IMP treatment start to IMP treatment stop.
### 2.3 Exposure in treatment years (FAS)

The table below shows the exposure in treatment years (FAS) for different treatment groups. The treatment years are calculated as the number of daily doses used divided by 364. The values are presented as follows:

- **n**: Number of subjects (FAS)
- **Mean (SD)**: Mean and standard deviation
- **Median**: Median
- **P25% - P75%**: 25% to 75% percentile
- **P5% - P95%**: 5% to 95% percentile
- **Min - Max**: Minimum and maximum

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XX)</th>
<th>ALK HDM AIT 6 DU (N=XX)</th>
<th>ALK HDM AIT 12 DU (N=XX)</th>
<th>Active all (N=XX)</th>
<th>Overall (N=XX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX (XX)</td>
<td>XX (XX)</td>
<td>XX (XX)</td>
<td>XX (XX)</td>
<td>XX (XX)</td>
</tr>
<tr>
<td>Median</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td>P25% - P75%</td>
<td>XX - XX</td>
<td>XX - XX</td>
<td>XX - XX</td>
<td>XX - XX</td>
<td>XX - XX</td>
</tr>
<tr>
<td>P5% - P95%</td>
<td>XX - XX</td>
<td>XX - XX</td>
<td>XX - XX</td>
<td>XX - XX</td>
<td>XX - XX</td>
</tr>
<tr>
<td>Min - Max</td>
<td>XX - XX</td>
<td>XX - XX</td>
<td>XX - XX</td>
<td>XX - XX</td>
<td>XX - XX</td>
</tr>
</tbody>
</table>

**N** = number of subjects (FAS), **n** = number of subjects with observations, **SD** = standard deviation, **P25% = 25% percentile**, **P75% = 75% percentile**, **P5% = 5% percentile**, **P95% = 95% percentile**

Treatment years is the number of daily doses used divided by 364.
## 2.4 IMP compliance (FAS)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XX)</th>
<th>ALK HDM AIT 6 DU (N=XX)</th>
<th>ALK HDM AIT 12 DU (N=XX)</th>
<th>Active all (N=XX)</th>
<th>Overall (N=XX)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IMP Compliance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX (XX)</td>
<td>XX (XX)</td>
<td>XX (XX)</td>
<td>XX (XX)</td>
<td>XX (XX)</td>
</tr>
<tr>
<td>Median</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td>P25% – P75%</td>
<td>XX – XX</td>
<td>XX – XX</td>
<td>XX – XX</td>
<td>XX – XX</td>
<td>XX – XX</td>
</tr>
<tr>
<td>P5% – P95%</td>
<td>XX – XX</td>
<td>XX – XX</td>
<td>XX – XX</td>
<td>XX – XX</td>
<td>XX – XX</td>
</tr>
<tr>
<td>Min – Max</td>
<td>XX – XX</td>
<td>XX – XX</td>
<td>XX – XX</td>
<td>XX – XX</td>
<td>XX – XX</td>
</tr>
</tbody>
</table>

N = number of subjects (FAS), n = number of subjects with observations, SD = standard deviation, P25% = 25% percentile, P75% = 75% percentile, P5% = 5% percentile, P95% = 95% percentile

IMP compliance is the number of daily doses used (IMP accountability) divided by the number of days with IMP treatment and multiplied with 100. IMP accountability is set to 100% for subjects with IMP accountability above 100% without a corresponding report of IMP overdose.
## 2.5 Summary of selected visit dates (FAS)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active All (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1</td>
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<tr>
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<tr>
<td>Median</td>
<td>ddmmyy</td>
<td>ddmmyy</td>
<td>ddmmyy</td>
<td>ddmmyy</td>
<td>ddmmyy</td>
</tr>
<tr>
<td>P25%-P75%</td>
<td>ddmmyy - ddmmyy</td>
<td>ddmmyy - ddmmyy</td>
<td>ddmmyy - ddmmyy</td>
<td>ddmmyy - ddmmyy</td>
<td>ddmmyy - ddmmyy</td>
</tr>
<tr>
<td>P5%-P95%</td>
<td>ddmmyy - ddmmyy</td>
<td>ddmmyy - ddmmyy</td>
<td>ddmmyy - ddmmyy</td>
<td>ddmmyy - ddmmyy</td>
<td>ddmmyy - ddmmyy</td>
</tr>
<tr>
<td>Min-Max</td>
<td>ddmmyy - ddmmyy</td>
<td>ddmmyy - ddmmyy</td>
<td>ddmmyy - ddmmyy</td>
<td>ddmmyy - ddmmyy</td>
<td>ddmmyy - ddmmyy</td>
</tr>
<tr>
<td>Visit 3 (randomisation)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
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<td>Median</td>
<td>ddmmyy</td>
<td>ddmmyy</td>
<td>ddmmyy</td>
<td>ddmmyy</td>
<td>ddmmyy</td>
</tr>
<tr>
<td>P25%-P75%</td>
<td>ddmmyy - ddmmyy</td>
<td>ddmmyy - ddmmyy</td>
<td>ddmmyy - ddmmyy</td>
<td>ddmmyy - ddmmyy</td>
<td>ddmmyy - ddmmyy</td>
</tr>
<tr>
<td>P5%-P95%</td>
<td>ddmmyy - ddmmyy</td>
<td>ddmmyy - ddmmyy</td>
<td>ddmmyy - ddmmyy</td>
<td>ddmmyy - ddmmyy</td>
<td>ddmmyy - ddmmyy</td>
</tr>
<tr>
<td>Min-Max</td>
<td>ddmmyy - ddmmyy</td>
<td>ddmmyy - ddmmyy</td>
<td>ddmmyy - ddmmyy</td>
<td>ddmmyy - ddmmyy</td>
<td>ddmmyy - ddmmyy</td>
</tr>
<tr>
<td>Visit 4</td>
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<tr>
<td>Visit 13+</td>
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</tr>
<tr>
<td>n</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
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<tr>
<td>Median</td>
<td>ddmmyy</td>
<td>ddmmyy</td>
<td>ddmmyy</td>
<td>ddmmyy</td>
<td>ddmmyy</td>
</tr>
<tr>
<td>P25%-P75%</td>
<td>ddmmyy - ddmmyy</td>
<td>ddmmyy - ddmmyy</td>
<td>ddmmyy - ddmmyy</td>
<td>ddmmyy - ddmmyy</td>
<td>ddmmyy - ddmmyy</td>
</tr>
<tr>
<td>P5%-P95%</td>
<td>ddmmyy - ddmmyy</td>
<td>ddmmyy - ddmmyy</td>
<td>ddmmyy - ddmmyy</td>
<td>ddmmyy - ddmmyy</td>
<td>ddmmyy - ddmmyy</td>
</tr>
<tr>
<td>Min-Max</td>
<td>ddmmyy - ddmmyy</td>
<td>ddmmyy - ddmmyy</td>
<td>ddmmyy - ddmmyy</td>
<td>ddmmyy - ddmmyy</td>
<td>ddmmyy - ddmmyy</td>
</tr>
</tbody>
</table>

N = number of subjects (Full analysis set), n = number of subjects with observations, P25% = 25% percentile, P75% = 75%, P5% = 5% percentile, P95% = 95% percentile.

Trial ID:\file name.sas\Initials DM & Initials STAT\Date of run
### 3 Efficacy – summary

#### 3.1 First moderate or severe asthma exacerbation (FAS)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 1 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active all (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%n)</td>
<td>n (%n)</td>
<td>n (%n)</td>
<td>n (%n)</td>
<td>n (%n)</td>
</tr>
<tr>
<td>First moderate or severe asthma exacerbation</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>First moderate asthma exacerbation#</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>First severe asthma exacerbation#</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
</tbody>
</table>

### Notes

- Moderate asthma exacerbation: one or more of criterion a) to d) fulfilled, but without fulfillment of criteria e) and/or f).
- Severe asthma exacerbation: Criterion e) and/or f)

- a: Nocturnal awakening(s) due to asthma requiring SABA use on at least 2 consecutive nights or an increase in minimum 0.75 in daily symptom score from baseline value on at least 2 consecutive days
- b: An increase from 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 PEF from baseline value on at least 2 consecutive mornings or evenings or 20% decrease in FEVi1 from baseline
- d: Visit to the emergency room or unscheduled visit to the trial site for asthma treatment not requiring systemic corticosteroids
- 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.
### 3.2 First moderate or severe asthma exacerbation, by criteria (FAS)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active all (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>First moderate or severe asthma exacerbation</td>
<td>XX (YY%)</td>
<td>XX (YY%)</td>
<td>XX (YY%)</td>
<td>XX (YY%)</td>
<td>XX (YY%)</td>
</tr>
<tr>
<td>Single and multiple criteria*:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>a &amp; b</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>a &amp; b &amp; c</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>. . .</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>b</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>b &amp; c</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>. . .</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>a &amp; b &amp; c &amp; d &amp; e &amp; f</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
</tbody>
</table>

*a: Nocturnal awakening(s) due to asthma requiring SABA use on at least 2 consecutive nights or an increase of minimum 0.75 in daily symptom score from baseline value on at least 2 consecutive days
b: An increase from baseline value in occasions of SABA use on at least 2 consecutive days (a minimum increase of 4 puffs per day)
c: 220s decrease in PEF from baseline value on at least 2 consecutive mornings or evenings or 520s decrease in FEV1 from baseline
d: Visit to the emergency room or unscheduled visit to the trial site for asthma treatment not requiring systemic corticosteroids
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.

---

**Trial ID**: MT-04
**Version**: Final
**Date**: 24-June-2013
### 3.3 First asthma exacerbation with deterioration in asthma symptoms (FAS)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active all (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Nocturnal awakening or daily symptoms a)≥</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Nocturnal awakening a1)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>daily symptoms a2)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Nocturnal awakening a1) &amp; daily symptoms a2)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
</tbody>
</table>

≥: All first moderate or severe asthma exacerbations for which criterion a) is fulfilled.

a: Nocturnal awakening(s) due to asthma requiring SABA use on at least 2 consecutive nights or an increase of minimum 0.75 in daily symptom score from baseline value on at least 2 consecutive days.
3.4 *First asthma exacerbation with increased use of SABA (FAS)*

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active all (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
</tbody>
</table>

*SABA rescue medication b)*

XX (XX%) XX (XX%) XX (XX%) XX (XX%) XX (XX%)

*: All first moderate or severe asthma exacerbations for which criterion b) is fulfilled.

b: An increase from baseline value in occasions of SABA use on at least 2 consecutive days (a minimum increase of 4 puffs per day)
### 3.5 First asthma exacerbation with deterioration in lung function (FAS)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active all (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%n)</td>
<td>n (%n)</td>
<td>n (%n)</td>
<td>n (%n)</td>
<td>n (%n)</td>
<td>n (%n)</td>
</tr>
<tr>
<td>Peak Flow or FEV1 c)×</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>220% decrease in PEF c1)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>220% decrease in FEV1 c2)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>220% decrease in PEF c1) &amp; 220% decrease in FEV1 c2)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
</tbody>
</table>

×: All first moderate or severe asthma exacerbations for which criterion c) is fulfilled.

c: 220% decrease in PEF from baseline value on at least 2 consecutive mornings or evenings or 220% decrease in FEV1 from baseline

---

Statistical Analysis Plan – Appendix A – Table Shells

Trial ID: MT-04

Version: Final

Date: 24-June-2013
3.6 First severe asthma exacerbation (FAS)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active all (N=XXX)</th>
<th>Overall (N=XXX)</th>
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</thead>
<tbody>
<tr>
<td>First severe exacerbation#</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Need of systemic corticosteroids e)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Emergency visit - systemic corticosteroids f)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Systemic corticosteroids e) &amp; emergency visit f)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
</tbody>
</table>

#: All first severe asthma exacerbations for which criterion e) and/or f) is fulfilled.

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
### 3.7 KM-estimates of the proportion free of moderate or severe asthma exacerbation (FAS)

<table>
<thead>
<tr>
<th>Time in days since ICS reduction at visit 9:</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active All (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>120</td>
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<tr>
<td>150</td>
<td></td>
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</tr>
<tr>
<td>180</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N = number of subjects in FAS, KM = Kaplan-Meier estimate, LCL = Pointwise 95% lower confidence limit, UCL = Pointwise 95% upper confidence limit.
### 3.8 Cumulative proportion of first moderate asthma exacerbation (FAS)

<table>
<thead>
<tr>
<th>Time in days since ICS reduction at visit</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active All (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0 XXX</td>
<td>0 XXX</td>
<td>0 XXX</td>
<td>0 XXX</td>
<td>0 XXX</td>
</tr>
<tr>
<td>30</td>
<td>0.XX XXX</td>
<td>0.XX XXX</td>
<td>0.XX XXX</td>
<td>0.XX XXX</td>
<td>0.XX XXX</td>
</tr>
<tr>
<td>60</td>
<td>0.XX XXX</td>
<td>0.XX XXX</td>
<td>0.XX XXX</td>
<td>0.XX XXX</td>
<td>0.XX XXX</td>
</tr>
<tr>
<td>90</td>
<td>0.XX XX</td>
<td>0.XX XX</td>
<td>0.XX XX</td>
<td>0.XX XX</td>
<td>0.XX XX</td>
</tr>
<tr>
<td>120</td>
<td>0.XX XX</td>
<td>0.XX XX</td>
<td>0.XX XX</td>
<td>0.XX XX</td>
<td>0.XX XX</td>
</tr>
<tr>
<td>150</td>
<td>0.XX XX</td>
<td>0.XX XX</td>
<td>0.XX XX</td>
<td>0.XX XX</td>
<td>0.XX XX</td>
</tr>
<tr>
<td>180</td>
<td>0.XX XX</td>
<td>0.XX XX</td>
<td>0.XX XX</td>
<td>0.XX XX</td>
<td>0.XX XX</td>
</tr>
</tbody>
</table>

CIF: The estimated cause-specific cumulative incidence function is the probability of experiencing the cause-specific event before time t.
3.9 Cumulative proportion of first severe asthma exacerbation (FAS)
as Table 3.8
3.10 Cumulative proportion of first asthma exacerbation with deterioration in asthma symptoms (FAS)

As Table 3.8

All first moderate or severe asthma exacerbations for which criterion a) is fulfilled.

a: Nocturnal awakening(s) due to asthma requiring SABA use on at least 2 consecutive nights or an increase of minimum 0.75 in daily symptom score from baseline value on at least 2 consecutive days
3.11 Cumulative proportion of first asthma exacerbation with increased use of SABA (FAS)

As Table 3.8

All first moderate asthma exacerbations for which criterion b) is fulfilled.

b: An increase from baseline value in occasions of SABA use on at least 2 consecutive days (a minimum increase of 4 puffs per day)
3.12 Cumulative proportion of first asthma exacerbation with deterioration in lung function (FAS)

As table 3.8

All first moderate asthma exacerbations for which criterion c) is fulfilled.

c: 220% decrease in PEF from baseline value on at least 2 consecutive mornings or evenings or 220% decrease in FEV1 from baseline
### 3.13 Summary of number of moderate or severe asthma exacerbation during period 3 (FAS)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active All (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%n) e</td>
<td>n (%n) e</td>
<td>n (%n) e</td>
<td>n (%n) e</td>
<td>n (%n) e</td>
</tr>
<tr>
<td>All moderate or severe</td>
<td>XX (XX%) XX</td>
<td>XX (XX%) XX</td>
<td>XX (XX%) XX</td>
<td>XX (XX%) XX</td>
<td>XX (XX%) XX</td>
</tr>
<tr>
<td>All moderate #</td>
<td>XX (XX%) XX</td>
<td>XX (XX%) XX</td>
<td>XX (XX%) XX</td>
<td>XX (XX%) XX</td>
<td>XX (XX%) XX</td>
</tr>
<tr>
<td>All severe¤</td>
<td>XX (XX%) XX</td>
<td>XX (XX%) XX</td>
<td>XX (XX%) XX</td>
<td>XX (XX%) XX</td>
<td>XX (XX%) XX</td>
</tr>
</tbody>
</table>

N = number of subjects (FAS), n = number of subjects with visits, % n = percent of subjects in treatment group of FAS with events, e = number of events.

# Moderate asthma exacerbation: One or more of criterion a) to d) fulfilled, but without fulfilment of criteria e) and/or f).

¤ Severe asthma exacerbation: Criterion e) and/or f).

a: Nocturnal awakening(s) due to asthma requiring SABA use on at least 2 consecutive nights or an increase of minimum 0.75 in daily symptom score from baseline value on at least 2 consecutive days
b: An increase from baseline value in occasions of SABA use on at least 2 consecutive days (a minimum increase of 4 puffs per day)
c: 220% decrease in PEF from baseline value on at least 2 consecutive mornings or evenings or 220% decrease in FEVI from baseline
d: Visit to the emergency room or unscheduled visit to the trial site for asthma treatment not requiring systemic corticosteroids
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
3.14 Summary of overall ACQ by visit (FAS)

3.15 Summary of change from baseline in overall ACQ by visit (FAS)

3.16 Summary of individual ACQ items by visit (FAS)

3.17 Summary of overall AQLQ by visit (FAS)

3.18 Summary of change from baseline in overall AQLQ by visit (FAS)

3.19 Summary of domain AQLQ scores by visit (FAS)
### 3.20 Summary of SF36v2 health domain scales (0-100) scores by visit (FAS)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALR HDM AIT 6 DU (N=XXX)</th>
<th>ALR HDM AIT 12 DU (N=XXX)</th>
<th>Active all (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Visit 3</strong> (randomisation)</td>
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<td></td>
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</tr>
<tr>
<td><strong>Physical Functioning (PF)</strong></td>
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</tr>
<tr>
<td>n</td>
<td>XX</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX.X</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
</tr>
<tr>
<td>Median</td>
<td>XX.X</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
</tr>
<tr>
<td>P5%-P95%</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
</tr>
<tr>
<td><strong>Role Physical (RP)</strong></td>
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<td></td>
</tr>
<tr>
<td>n</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX.X</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
</tr>
<tr>
<td>Median</td>
<td>XX.X</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
</tr>
<tr>
<td>P5%-P95%</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
</tr>
<tr>
<td><strong>Mental Health (MH)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX.X</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
</tr>
<tr>
<td>Median</td>
<td>XX.X</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
</tr>
<tr>
<td>P5%-P95%</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
</tr>
</tbody>
</table>

N = number of subjects (Full analysis set), n = number of subjects with observations, SD = standard deviation, P25% = 25% percentile, P75% = 75% percentile, P5% = 5% percentile, P95% = 95% percentile
### 3.2.1 Summary of WPAI: ASTHMA by visit (FAS)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active all (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline (visit 3)</strong></td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
</tr>
<tr>
<td>Percent work time missed due to asthma</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
</tr>
<tr>
<td>Min–Max</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
<tr>
<td>Percent impairment while working due to asthma</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
</tr>
<tr>
<td>Min–Max</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
<tr>
<td>Percent activity impairment due to asthma</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
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<tr>
<td>Visit 6</td>
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<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
</tr>
<tr>
<td>...</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
</tr>
<tr>
<td>Percent activity impairment due to asthma</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
</tr>
<tr>
<td>Visit 9</td>
<td>XX.X (XXX.X)</td>
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<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
</tr>
<tr>
<td>...</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
</tr>
<tr>
<td>Percent activity impairment due to asthma</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
</tr>
<tr>
<td>Visit 13</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
</tr>
<tr>
<td>...</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
<td>XX.X (XXX.X)</td>
</tr>
</tbody>
</table>

- N = number of subjects (full analysis set), n = number of subjects with observations, SD = standard deviation, P25% = 25% percentile, P75% = 75%, P5% = 5% percentile, P95% = 95% percentile.
### 3.22 Summary of TSQM II by visit (FAS: Germany, France)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XX)</th>
<th>ALK HDM AIT 6 DU (N=XX)</th>
<th>ALK HDM AIT 12 DU (N=XX)</th>
<th>Active all (N=XX)</th>
<th>Overall (N=XX)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Visit 4</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effectiveness</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XXX</td>
</tr>
<tr>
<td>n</td>
<td></td>
<td>XX (XX.X)</td>
<td>XX (XX.X)</td>
<td>XX (XX.X)</td>
<td>XX (XX.X)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX.X</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
</tr>
<tr>
<td>Median</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
<tr>
<td>P5e-P95e</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
</tr>
<tr>
<td>Min-Max</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
</tr>
<tr>
<td>Side-effects</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XXX</td>
</tr>
<tr>
<td>n</td>
<td></td>
<td>XX (XX.X)</td>
<td>XX (XX.X)</td>
<td>XX (XX.X)</td>
<td>XX (XX.X)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX.X</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
</tr>
<tr>
<td>Median</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
<tr>
<td>P5e-P95e</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
</tr>
<tr>
<td>Min-Max</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
</tr>
</tbody>
</table>

**Convenience**

"..."

**Global satisfaction**

"...

**Visit 13**

"...

---

n = number of subjects (FAS), n = number of subjects with observations, SD = standard deviation, P25 = 25% percentile, P75 = 75%, P5 = 5% percentile, P95 = 95% percentile
### 3.23 Summary of visits to GP, Specialist or hospital (FAS)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active All (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit due to asthma worsening</td>
<td>n (%)</td>
<td>v</td>
<td>n (%)</td>
<td>v</td>
<td>n (%)</td>
</tr>
<tr>
<td>Visit 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit to GP or specialist</td>
<td>XX (XXX%)</td>
<td>XX</td>
<td>XX (XXX%)</td>
<td>XX</td>
<td>XX (XXX%)</td>
</tr>
<tr>
<td>Visit to emergency room</td>
<td>XX (XXX%)</td>
<td>XX</td>
<td>XX (XXX%)</td>
<td>XX</td>
<td>XX (XXX%)</td>
</tr>
<tr>
<td>visit 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visits to GP or specialist</td>
<td>XX (XXX%)</td>
<td>XX</td>
<td>XX (XXX%)</td>
<td>XX</td>
<td>XX (XXX%)</td>
</tr>
<tr>
<td>Visit to emergency room</td>
<td>XX (XXX%)</td>
<td>XX</td>
<td>XX (XXX%)</td>
<td>XX</td>
<td>XX (XXX%)</td>
</tr>
<tr>
<td>...</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>visit 13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visits to GP or specialist</td>
<td>XX (XXX%)</td>
<td>XX</td>
<td>XX (XXX%)</td>
<td>XX</td>
<td>XX (XXX%)</td>
</tr>
<tr>
<td>Visit to emergency room</td>
<td>XX (XXX%)</td>
<td>XX</td>
<td>XX (XXX%)</td>
<td>XX</td>
<td>XX (XXX%)</td>
</tr>
</tbody>
</table>

N = number of subjects (safety set), n = number of subjects with visits, % n = percent of subjects in treatment group of safety set with visits, v = number of visits, GP = General practitioner.

---

Trial ID: MT-04
Version: Final
Date: 24-June-2013

Statistical Analysis Plan – Appendix A – Table Shells
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3.24 Summary of the average asthma daytime symptom score over the first asthma exacerbation free period during period 3A (FAS)

3.25 Summary of the average asthma daytime symptom score over the first asthma exacerbation free period during the entire period 3 (FAS)

3.26 Summary of the proportion of symptom free days, nights and 24-hour periods during period 3 (FAS)

3.27 Summary of average morning and evening PEF and diurnal variability over the first asthma exacerbation free period during period 3A (FAS)

3.28 Summary of average morning and evening PEF and diurnal variability over the first asthma exacerbation free period during entire period 3 (FAS)

3.29 Summary of change from baseline in FEV1 by visit (FAS)
### 3.3.0 Summary of FEV1 and percentage predicted FEV1 by visit (FAS)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>Active 1 (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active all (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomisation visit: FEV1 result (l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>XX (XX.X)</td>
<td>XX (XX.X)</td>
<td>XX (XX.X)</td>
<td>XX (XX.X)</td>
<td>XXX (XX.X)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX.X ± XX.X</td>
<td>XX.X ± XX.X</td>
<td>XX.X ± XX.X</td>
<td>XX.X ± XX.X</td>
<td>XX.X ± XX.X</td>
</tr>
<tr>
<td>P25%-P75%</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
</tr>
<tr>
<td>P5%-P95%</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
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<tr>
<td>FEV1 % predicted</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>XX (XX.X)</td>
<td>XX (XX.X)</td>
<td>XX (XX.X)</td>
<td>XX (XX.X)</td>
<td>XXX (XX.X)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX.X ± XX.X</td>
<td>XX.X ± XX.X</td>
<td>XX.X ± XX.X</td>
<td>XX.X ± XX.X</td>
<td>XX.X ± XX.X</td>
</tr>
<tr>
<td>P25%-P75%</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
</tr>
<tr>
<td>P5%-P95%</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
</tr>
</tbody>
</table>

Visit 4:
. . .
Visit 5:
. . .

n = number of subjects (Full analysis set), n = number of subjects with observations, SD = standard deviation, P25% = 25% percentile, P75% = 75%, P5% = 5% percentile, P95% = 95% percentile.
### 3.31 Summary of PEF (l/min) data over the last 4 weeks before visit 9 (FAS)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active All (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Average AM PEF</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>n</td>
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<td>XX</td>
<td>XX</td>
<td>XXX</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
</tr>
<tr>
<td>Median</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
</tr>
<tr>
<td>P25%-P75%</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
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<tr>
<td>Min-Max</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
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<tr>
<td><strong>Average PM PEF</strong></td>
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<tr>
<td>n</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XXX</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
</tr>
<tr>
<td>Median</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
</tr>
<tr>
<td>P25%-P75%</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
</tr>
<tr>
<td>Min-Max</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
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<td><strong>Average diurnal variability in PEF</strong></td>
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<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XXX</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
</tr>
<tr>
<td>Median</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
</tr>
<tr>
<td>P25%-P75%</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
</tr>
<tr>
<td>Min-Max</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
</tr>
</tbody>
</table>

- **n** = number of subjects (Full analysis set), **n** = number of subjects with observations, **SD** = standard deviation, **P25%** = 25% percentile, **P75%** = 75%, **P5%** = 5% percentile, **P95%** = 95% percentile.
- Data is obtained from the morning and the evening diary data during the last 4 weeks before visit 9.
### 3.32 Average asthma daytime symptom score over period 2B (FAS)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active All (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
</tr>
<tr>
<td>Median</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
<tr>
<td>P5%–P95%</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
</tr>
</tbody>
</table>

#### Cough

| n               | XX              | XX                       | XX                        | XX                 | XX              |
| Mean (SD)       | XX.X (XX.X)     | XX.X (XX.X)              | XX.X (XX.X)               | XX.X (XX.X)        | XX.X (XX.X)    |
| Median          | XX.X            | XX.X                     | XX.X                      | XX.X               | XX.X            |
| P5%–P95%        | XX.X – XX.X     | XX.X – XX.X              | XX.X – XX.X               | XX.X – XX.X        | XX.X – XX.X    |

#### Wheeze

| n               | XX              | XX                       | XX                        | XX                 | XX              |
| Mean (SD)       | XX.X (XX.X)     | XX.X (XX.X)              | XX.X (XX.X)               | XX.X (XX.X)        | XX.X (XX.X)    |
| Median          | XX.X            | XX.X                     | XX.X                      | XX.X               | XX.X            |
| P5%–P95%        | XX.X – XX.X     | XX.X – XX.X              | XX.X – XX.X               | XX.X – XX.X        | XX.X – XX.X    |

#### Chest tightness/shortness of breath

|                  | XX              | XX                       | XX                        | XX                 | XX              |

#### Exercise induced symptoms

|                  | XX              | XX                       | XX                        | XX                 | XX              |

---

* n = number of subjects (full analysis set), SD = standard deviation, P25% = 25% percentile, P75% = 75%, P5% = 5% percentile, P95% = 95% percentile.

Data is obtained from the evening diary data during the period 2B between visit 8 and visit 9.
### 3.33 Average asthma nocturnal symptom score over period 2B (FAS)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo</th>
<th>ALK HDM AIT 6 DU</th>
<th>ALK HDM AIT 12 DU</th>
<th>Active ALI</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma nocturnal symptom score</td>
<td>(N=XXX)</td>
<td>(N=XXX)</td>
<td>(N=XXX)</td>
<td>(N=XXX)</td>
<td>(N=XXX)</td>
</tr>
<tr>
<td>n</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XXX</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
</tr>
<tr>
<td>Median</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
<tr>
<td>P95%–P95%</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
</tr>
</tbody>
</table>

n = number of subjects (Full analysis set), n = number of subjects with observations, SD = standard deviation, P25% = 25% percentile, P75% = 75%, P95% = 5% percentile, P99% = 95% percentile.

The asthma nocturnal symptom score is the severity of the worst nocturnal asthma symptom (wheezing, coughing, shortness of breath or chest tightness) obtained from the morning diary.
### 3.34 Average number of nocturnal awakenings during period 2B (FAS)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active All (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nocturnal awakening#</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
</tr>
<tr>
<td>Median</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
<tr>
<td>P25%-P75%</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
</tr>
<tr>
<td>Min-Max</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
</tr>
</tbody>
</table>

| Nocturnal awakening requiring SABA intake¤ | XX.X (XX.X) | XX.X (XX.X) | XX.X (XX.X) | XX.X (XX.X) | XX.X (XX.X) |
| Mean (SD) | XX.X - XX.X | XX.X - XX.X | XX.X - XX.X | XX.X - XX.X | XX.X - XX.X |
| Median | XX.X | XX.X | XX.X | XX.X | XX.X |
| P25%-P75% | XX.X - XX.X | XX.X - XX.X | XX.X - XX.X | XX.X - XX.X | XX.X - XX.X |
| Min-Max | XX.X - XX.X | XX.X - XX.X | XX.X - XX.X | XX.X - XX.X | XX.X - XX.X |

N = number of subjects (Full analysis set), n = number of subjects with observations, SD = standard deviation, P25% = 25% percentile, P75% = 75%, P5% = 5% percentile, P95% = 95% percentile.

# : For each subject the average number of nocturnal awakenings over period 2B between visit 8 and visit 9.

¤ : For each subject the average number of nocturnal awakenings with SABA intake over period 2B between visit 8 and visit 9.

---

**Trial ID**: MT-04  
**Version**: Final  
**Date**: 24-June-2013
3.35 Average SABA intake during period 2B (FAS)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo</th>
<th>ALK HDM AIT 6 DU</th>
<th>ALK HDM AIT 12 DU</th>
<th>Active All</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=XXX)</td>
<td>(S=XXX)</td>
<td>(S=XXX)</td>
<td>(S=XXX)</td>
<td>(S=XXX)</td>
</tr>
<tr>
<td>24-hour SABA intake</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XXX</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
</tr>
<tr>
<td>Median</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
<tr>
<td>P5%–P95%</td>
<td>XX.X–XX.X</td>
<td>XX.X–XX.X</td>
<td>XX.X–XX.X</td>
<td>XX.X–XX.X</td>
<td>XX.X–XX.X</td>
</tr>
<tr>
<td>Daytime SABA intake</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
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<td>XX</td>
<td>XX</td>
<td>XXX</td>
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<tr>
<td>Mean (SD)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
</tr>
<tr>
<td>Median</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
<tr>
<td>P5%–P95%</td>
<td>XX.X–XX.X</td>
<td>XX.X–XX.X</td>
<td>XX.X–XX.X</td>
<td>XX.X–XX.X</td>
<td>XX.X–XX.X</td>
</tr>
<tr>
<td>Nocturnal SABA intake</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XXX</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
</tr>
<tr>
<td>Median</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
<tr>
<td>P5%–P95%</td>
<td>XX.X–XX.X</td>
<td>XX.X–XX.X</td>
<td>XX.X–XX.X</td>
<td>XX.X–XX.X</td>
<td>XX.X–XX.X</td>
</tr>
</tbody>
</table>

N = number of subjects (Full analysis set), n = number of subjects with observations, SD = standard deviation, P25% = 25% percentile, P75% = 75%, P5% = 5% percentile, P95% = 95% percentile.
### 3.36 Prescribed total daily dose of ICS (mcg) by visit (FAS)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active All (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XXX</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX,X (XX,X)</td>
<td>XX,X (XX,X)</td>
<td>XX,X (XX,X)</td>
<td>XX,X (XX,X)</td>
<td>XX,X (XX,X)</td>
</tr>
<tr>
<td>Median</td>
<td>XX,X</td>
<td>XX,X</td>
<td>XX,X</td>
<td>XX,X</td>
<td>XX,X</td>
</tr>
<tr>
<td>P25% – P75%</td>
<td>XX,X – XX,X</td>
<td>XX,X – XX,X</td>
<td>XX,X – XX,X</td>
<td>XX,X – XX.X</td>
<td>XX,X – XX.X</td>
</tr>
<tr>
<td>Min-Max</td>
<td>XX,X – XX,X</td>
<td>XX,X – XX,X</td>
<td>XX,X – XX,X</td>
<td>XX,X – XX,X</td>
<td>XX,X – XX.X</td>
</tr>
</tbody>
</table>

Visit 3 (randomisation)

| n               | XX              | XX                        | XX                        | XX                | XXX             |
| Mean (SD)       | XX,X (XX,X)    | XX,X (XX,X)               | XX,X (XX,X)               | XX,X (XX,X)      | XX,X (XX,X)    |
| Median          | XX,X           | XX,X                      | XX,X                      | XX,X              | XX,X            |
| P25% – P75%     | XX,X – XX,X    | XX,X – XX,X               | XX,X – XX,X               | XX,X – XX.X      | XX,X – XX.X    |
| Min-Max         | XX,X – XX,X    | XX,X – XX,X               | XX,X – XX,X               | XX,X – XX,X      | XX,X – XX.X    |

Visit 4

| n               | XX              | XX                        | XX                        | XX                | XXX             |
| Mean (SD)       | XX,X (XX,X)    | XX,X (XX,X)               | XX,X (XX,X)               | XX,X (XX,X)      | XX,X (XX,X)    |
| Median          | XX,X           | XX,X                      | XX,X                      | XX,X              | XX,X            |
| P25% – P75%     | XX,X – XX,X    | XX,X – XX,X               | XX,X – XX,X               | XX,X – XX.X      | XX,X – XX.X    |
| Min-Max         | XX,X – XX,X    | XX,X – XX,X               | XX,X – XX,X               | XX,X – XX,X      | XX,X – XX.X    |

. . .

Visit 13

| n               | XX              | XX                        | XX                        | XX                | XXX             |
| Mean (SD)       | XX,X (XX,X)    | XX,X (XX,X)               | XX,X (XX,X)               | XX,X (XX,X)      | XX,X (XX,X)    |
| Median          | XX,X           | XX,X                      | XX,X                      | XX,X              | XX,X            |
| P25% – P75%     | XX,X – XX,X    | XX,X – XX,X               | XX,X – XX,X               | XX,X – XX.X      | XX,X – XX.X    |
| Min-Max         | XX,X – XX,X    | XX,X – XX,X               | XX,X – XX,X               | XX,X – XX,X      | XX,X – XX.X    |

N = number of subjects (Full analysis set), n = number of subjects with observations, SD = standard deviation, P25% = 25% percentile, P75% = 75%, P5% = 5% percentile, P95% = 95% percentile. The prescribed dose at each visit is the dose to be used onwards. E.g. the prescribed dose at visit 9 (ICS reduction) is the reduced dose which the subject should proceed with.
### 3.37 Most recent previously prescribed total daily dose of ICS (mcg) at selected visits (FAS)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active All (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Visit 9</strong></td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>n</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XXX</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
</tr>
<tr>
<td>Median</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
<tr>
<td>Min-Max</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
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<tr>
<td><strong>Visit 11</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>n</td>
<td>XX</td>
<td>XX</td>
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<td>XX</td>
<td>XXX</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
</tr>
<tr>
<td>Median</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
<tr>
<td>Min-Max</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
</tr>
<tr>
<td><strong>Visit 13</strong></td>
<td></td>
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</tr>
<tr>
<td>n</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XXX</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
</tr>
<tr>
<td>Median</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
<tr>
<td>Min-Max</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
</tr>
</tbody>
</table>

- **n** = number of subjects (Full analysis set), **n** = number of subjects with observations, **SD** = standard deviation, **P25%** = 25% percentile, **P75%** = 75%, **P5%** = 5% percentile, **P95%** = 95% percentile.

The most recent previously prescribed dose at each visit is the dose which has been prescribed to be used up until now. E.g. the most recent previously prescribed dose at visit 9 (ICS reduction) is the dose which the subject was prescribed to use up until visit 9.
<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo</th>
<th>ALK HDM AIT 6 DU</th>
<th>ALK HDM AIT 12 DU</th>
<th>Active All</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=XXX)</td>
<td>(N=XXX)</td>
<td>(N=XXX)</td>
<td>(N=XXX)</td>
<td>(N=XXX)</td>
</tr>
<tr>
<td>Change from baseline in overall ACQ</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Improvement above MID (&lt;=-0.5)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>No MID (-0.5c &lt;-0.5)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Deterioration above MID (&gt;=0.5)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Decreased ICS compared to baseline (&lt;0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Improvement above MID (&lt;=-0.5)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>No MID (-0.5c &lt;-0.5)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Deterioration above MID (&gt;=0.5)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>No change from baseline in ICS (=0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Improvement above MID (&lt;=-0.5)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>No MID (-0.5c &lt;-0.5)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Deterioration above MID (&gt;=0.5)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Increased ICS compared to baseline (&gt;0)</td>
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<td></td>
</tr>
<tr>
<td>All</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Improvement above MID (&lt;=-0.5)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>No MID (-0.5c &lt;-0.5)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Deterioration above MID (&gt;=0.5)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
</tbody>
</table>

- n = number of subjects (Full analysis set), n = number of subjects with event, %n = percentage of subjects in treatment group of full analysis set with the event, MID = minimal important difference.

Last observation is carried forward (LOCF) for both ACQ and ICS if data is missing at visit 9. For all subjects ICS dose at visit 9 is defined as the most recently previously prescribed dose at visit 9 (LOCF to visit 9).
3.39 Change from baseline to visit 9 in overall AQLQ for all and by change in ICS (FAS)
As Table 3.38

3.40 Change from baseline to visit 11 in overall ACQ for all and by change in ICS (FAS)
As Table 3.38

3.41 Change from baseline to visit 11 in overall AQLQ for all and by change in ICS (FAS)
As Table 3.38

3.42 Change from baseline to visit 13 in overall ACQ for all and by change in ICS (FAS)
As Table 3.38

3.43 Change from baseline to visit 13 in overall AQLQ for all and by change in ICS (FAS)
As Table 3.38
### 3.44 Change from baseline to visit 9, 11 or 13 in proportion of subjects with MID change in ACQ controlled for ICS (FAS)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active All (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Visit 9:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favourable (Yes)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Unfavourable (No)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Visit 11:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favourable (Yes)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Unfavourable (No)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Visit 13:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favourable (Yes)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td>Unfavourable (No)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
</tbody>
</table>

N = number of subjects (Full analysis set), n = number of subjects with event, %n = percentage of subjects in treatment group of Full analysis set with the event, MID = minimal important difference.

Last observation is carried forward (LOCF) for both ACQ and ICS if data is missing at the visit. For all subjects the ICS dose is the most recent previously prescribed dose.
3.45 Change from baseline to visit 9, 11 or 13 in proportion of subjects with MID change in AQoL(s) controlled for ICS (FAS) as Table 3.44.
# Efficacy – analysis

## 4.1 Primary efficacy analysis of time to first moderate or severe asthma exacerbation (FAS-MI)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Treatment Effect</th>
<th>Hazard Ratio</th>
<th>95% CI for Hazard Ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global null hypothesis: Placebo=6DU=12DU</td>
<td>x.xxx</td>
<td>[x.xxx ; x.xxx]</td>
<td>x.xxx</td>
<td></td>
</tr>
<tr>
<td>12DU versus Placebo</td>
<td>x.xxx</td>
<td>[x.xxx ; x.xxx]</td>
<td>x.xxx</td>
<td></td>
</tr>
<tr>
<td>6DU versus Placebo</td>
<td>x.xxx</td>
<td>[x.xxx ; x.xxx]</td>
<td>x.xxx</td>
<td></td>
</tr>
<tr>
<td>12DU versus 6DU</td>
<td>x.xxx</td>
<td>[x.xxx ; x.xxx]</td>
<td>x.xxx</td>
<td></td>
</tr>
</tbody>
</table>

Data included in each imputation:

<table>
<thead>
<tr>
<th></th>
<th>N Total</th>
<th>N Observed</th>
<th>N Imputed</th>
</tr>
</thead>
<tbody>
<tr>
<td>12DU</td>
<td>(xxx)</td>
<td>(xxx)</td>
<td>(xxx)</td>
</tr>
<tr>
<td>6DU</td>
<td>(xxx)</td>
<td>(xxx)</td>
<td>(xxx)</td>
</tr>
<tr>
<td>Placebo</td>
<td>(xxx)</td>
<td>(xxx)</td>
<td>(xxx)</td>
</tr>
</tbody>
</table>

Cox regression analysis stratified for country. This analysis is based on multiple imputations. Multiple copies of the original data set are generated and analysed as complete data sets (50 imputations). The different parameter estimates across the data sets are combined to produce a unique point estimate and standard error. FAS-MI refers to the Full Analysis Set with Multiple Imputations.

- N Total = Total number of subjects in each copy of the data set analysed
- N Observed = Number of subjects in each copy of the data set contributing with observed data
- N Imputed = Number of subjects in each copy of the data set contributing with an imputed value
### 4.2 Efficacy analysis of time to first moderate or severe asthma exacerbation (FAS)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Active N Total</th>
<th>Active N Events</th>
<th>Placebo N Total</th>
<th>Placebo N Events</th>
<th>Hazard Ratio</th>
<th>95% CI for Hazard Ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>12DU versus Placebo (XXX) (100%)</td>
<td>(xx) (xx%)</td>
<td>(xxx) (100%)</td>
<td>(xx) (xx%)</td>
<td>x.xx</td>
<td>[x.xx ; x.xx]</td>
<td>x.xxx</td>
<td></td>
</tr>
<tr>
<td>6DU versus Placebo (XXX) (100%)</td>
<td>(xx) (xx%)</td>
<td>(xxx) (100%)</td>
<td>(xx) (xx%)</td>
<td>x.xx</td>
<td>[x.xx ; x.xx]</td>
<td>x.xxx</td>
<td></td>
</tr>
</tbody>
</table>

Cox regression analysis stratified for country. The analysis is based on FAS.

* N Total = Total number of subjects included in analysis
* N Events = Number of subjects with an event
4.3 Efficacy analysis of time to first moderate or severe asthma exacerbation (PP)

As Table 4.2 but for PP
## 4.4 Efficacy analysis of time to first asthma exacerbation with deterioration in asthma symptoms\(^\#\) (FAS)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Active</th>
<th>Placebo</th>
<th>Treatment Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Total</td>
<td>N Events</td>
<td>N Total</td>
</tr>
<tr>
<td>12DU versus Placebo</td>
<td>(xxx) (100%)</td>
<td>(xx) (xx%)</td>
<td>(xxx) (100%)</td>
</tr>
<tr>
<td>6DU versus Placebo</td>
<td>(xxx) (100%)</td>
<td>(xx) (xx%)</td>
<td>(xxx) (100%)</td>
</tr>
</tbody>
</table>

Cox regression analysis stratified for country.

N Total = Total number of subjects included in analysis
N Events = Number of subjects with an event

\(^\#\): All first moderate or severe asthma exacerbations for which criterion a) is fulfilled.

a: Nocturnal awakening[s] due to asthma requiring SABA use on at least 2 consecutive nights or an increase of minimum 0.75 in daily symptom score from baseline value on at least 2 consecutive days
### 4.5 Efficacy analysis of time to first severe asthma exacerbation (FAS)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Active</th>
<th>Placebo</th>
<th>Treatment Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Total</td>
<td>N Events</td>
<td>N Total</td>
</tr>
<tr>
<td>12DU versus Placebo</td>
<td>(XXX) (100%)</td>
<td>(xx) (xx%)</td>
<td>(xxx) (100%)</td>
</tr>
<tr>
<td>6DU versus Placebo</td>
<td>(XXX) (100%)</td>
<td>(xx) (xx%)</td>
<td>(xxx) (100%)</td>
</tr>
</tbody>
</table>

Cox regression analysis stratified for country.

N Total = Total number of subjects included in analysis
N Events = Number of subjects with an event

### Notes
- **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.
### 4.6 Efficacy analysis of time to first asthma exacerbation with increased use of SABA\(\textsuperscript{c}\) (FAS)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Active</th>
<th>Placebo</th>
<th>Treatment Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Total</td>
<td>N Events</td>
<td>N Total</td>
</tr>
<tr>
<td>12DU versus Placebo</td>
<td>(XXX)</td>
<td>(100%)</td>
<td>(xx)</td>
</tr>
<tr>
<td>6DU versus Placebo</td>
<td>(XXX)</td>
<td>(100%)</td>
<td>(xx)</td>
</tr>
</tbody>
</table>

Cox regression analysis stratified for country.

N Total - Total number of subjects included in analysis
N Events - Number of subjects with an event
\(\textsuperscript{c}\): All moderate or severe asthma exacerbations for which criterion b) is fulfilled.
b: An increase from baseline value in occasions of SABA use on at least 2 consecutive days (a minimum increase of 4 puffs per day)
### 4.7 Efficacy analysis of time to first asthma exacerbation with deterioration in lung function* (FAS)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Active N Total</th>
<th>Active N Events</th>
<th>Placebo N Total</th>
<th>Placebo N Events</th>
<th>Treatment Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hazard Ratio</td>
</tr>
<tr>
<td>12DU versus Placebo</td>
<td>(XXX) (100%)</td>
<td>(xx) (xx%)</td>
<td>(xxx) (100%)</td>
<td>(xx) (xx%)</td>
<td>x.xx [x.xx; x.xx]</td>
</tr>
<tr>
<td>6DU versus Placebo</td>
<td>(XXX) (100%)</td>
<td>(xx) (xx%)</td>
<td>(xxx) (100%)</td>
<td>(xx) (xx%)</td>
<td>x.xx [x.xx; x.xx]</td>
</tr>
</tbody>
</table>

Cox regression analysis stratified for country.

- N Total = Total number of subjects included in analysis
- N Events = Number of subjects with an event

* All moderate or severe asthma exacerbation for which criterion c) is fulfilled.

** c: 220% decrease in PEF from baseline value on at least 2 consecutive mornings or evenings or 220% decrease in FEV1 from baseline

---

Trial ID\file name.sas\Initials DM & Initials STAT\Date of run
4.8 Efficacy analysis of odds for asthma exacerbation during period 3 (FAS)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Adjusted odds</th>
<th>N</th>
<th>N</th>
<th>Adjusted odds</th>
<th>N</th>
<th>N</th>
<th>Adjusted Odds Ratio</th>
<th>95% CI for adjusted odds Ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>12DU versus Placebo</td>
<td>x.xx</td>
<td>XXX</td>
<td>xx</td>
<td>(xx%)</td>
<td>x.xx</td>
<td>XXX</td>
<td>xx (xx%)</td>
<td>[x.xx ; x.xx]</td>
<td>x.xxx</td>
</tr>
<tr>
<td>6DU versus Placebo</td>
<td>x.xx</td>
<td>XXX</td>
<td>xx</td>
<td>(xx%)</td>
<td>x.xx</td>
<td>XXX</td>
<td>xx (xx%)</td>
<td>[x.xx ; x.xx]</td>
<td>x.xxx</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Estimated proportion</th>
<th>Estimated proportion</th>
<th>Difference</th>
<th>95% CI for difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>12DU versus Placebo</td>
<td>0.xx</td>
<td>0.xx</td>
<td>[0.xx ; 0.xx]</td>
</tr>
<tr>
<td>6DU versus Placebo</td>
<td>0.xx</td>
<td>0.xx</td>
<td>[0.xx ; 0.xx]</td>
</tr>
</tbody>
</table>

N Total = Total number of subjects included in analysis
N Events = Number of subjects with an event

Estimates are obtained from a logistic regression analysis with treatment group, ACQ and ICS at baseline as fixed effects. Country is included as a random effect.

#: Fisher's exact test.
4.9 Efficacy analysis of the average total asthma daytime symptom score over the first asthma exacerbation free period during period 3A (FAS)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Active Adjusted Mean (se)</th>
<th>Active N</th>
<th>Placebo Adjusted Mean (se)</th>
<th>Placebo N</th>
<th>Difference (se)</th>
<th>95% CI for difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 DU versus Placebo</td>
<td>xxx.x (xx.x)</td>
<td>xxx</td>
<td>xxx.x (xx.x)</td>
<td>xxx</td>
<td>xxx.x (xx.x)</td>
<td>[xxx.x ; xxx.x]</td>
<td>x.xxx</td>
</tr>
<tr>
<td>5 DU versus Placebo</td>
<td>xxx.x (xx.x)</td>
<td>xxx</td>
<td>xxx.x (xx.x)</td>
<td>xxx</td>
<td>xxx.x (xx.x)</td>
<td>[xxx.x ; xxx.x]</td>
<td>x.xxx</td>
</tr>
</tbody>
</table>

The estimates are based on a linear mixed model including all available data from all 3 treatment groups for each pairwise comparison. Treatment group and the baseline value are included as fixed effects and country is included as a random effect. Possible different error variance for each treatment group is adjusted for. The error variance is fitted as separate compound symmetry for each treatment group.
4.10 Efficacy analysis of the average total asthma daytime symptom score over the first asthma exacerbation free period during the entire period 3 (FAS) as table 4.9
4.11 Efficacy analysis of the proportion of symptom free days during period 3 (FAS) as table 4.9, but without baseline value in the model
4.12 Efficacy analysis of the proportion of symptom free nights during period 3 (FAS) as table 4.9, but without baseline value in the model
4.13 Efficacy analysis of the proportion of symptom free 24-hour periods during period 3 (FAS) as table 4.9, but without baseline value in the model
4.14 Efficacy analysis of the average morning PEF over the first asthma exacerbation free period during period 3A (FAS) as table 4.9
4.15 Efficacy analysis of the average PEF diurnal variability over the first asthma exacerbation free period during period 3A (FAS) as table 4.9
4.16 Efficacy analysis of the average morning PEF over the first asthma exacerbation free period during the entire period 3 (FAS) as table 4.9
4.17 Efficacy analysis of the average PEF diurnal variability over the first asthma exacerbation free period during entire period 3 (FAS) as table 4.9
4.18 Efficacy analysis of change from baseline to visit 9 in FEV1 (FAS) as table 4.20
### 4.19 Efficacy analysis of overall ACQ (FAS)

| Visit | Comparison | Active | | | | | Placebo | | | | | | Treatment Effect | | | |
|-------|------------|--------|---|---|---|---|--------|---|---|---|---|---|---|---|---|---|---|
|        |            | Adjusted Mean | (se) | N | Adjusted Mean | (se) | N | Difference | (se) | 95% CI for difference | p-value |
| Visit 4 | 12 DU versus Placebo | xxx.xxx (xxx.xx) | xxx.xxx | xxx.xxx (xxx.xx) | xxx.xxx (xxx.xx) | [xxx.xxx ; xxx.xxx] | x.xxx |
|         | 6 DU versus Placebo | xxx.xxx (xxx.xx) | xxx.xxx | xxx.xxx (xxx.xx) | xxx.xxx (xxx.xx) | [xxx.xxx ; xxx.xxx] | x.xxx |
| Visit 5 | 12 DU versus Placebo | xxx.xxx (xxx.xx) | xxx.xxx | xxx.xxx (xxx.xx) | xxx.xxx (xxx.xx) | [xxx.xxx ; xxx.xxx] | x.xxx |
|         | 6 DU versus Placebo | xxx.xxx (xxx.xx) | xxx.xxx | xxx.xxx (xxx.xx) | xxx.xxx (xxx.xx) | [xxx.xxx ; xxx.xxx] | x.xxx |
|        |            | xxx.xxx (xxx.xx) | xxx.xxx | xxx.xxx (xxx.xx) | xxx.xxx (xxx.xx) | [xxx.xxx ; xxx.xxx] | x.xxx |
| Visit 8 | 12 DU versus Placebo | xxx.xxx (xxx.xx) | xxx.xxx | xxx.xxx (xxx.xx) | xxx.xxx (xxx.xx) | [xxx.xxx ; xxx.xxx] | x.xxx |
|         | 6 DU versus Placebo | xxx.xxx (xxx.xx) | xxx.xxx | xxx.xxx (xxx.xx) | xxx.xxx (xxx.xx) | [xxx.xxx ; xxx.xxx] | x.xxx |
| Visit 9 | 12 DU versus Placebo | xxx.xxx (xxx.xx) | xxx.xxx | xxx.xxx (xxx.xx) | xxx.xxx (xxx.xx) | [xxx.xxx ; xxx.xxx] | x.xxx |
|         | 6 DU versus Placebo | xxx.xxx (xxx.xx) | xxx.xxx | xxx.xxx (xxx.xx) | xxx.xxx (xxx.xx) | [xxx.xxx ; xxx.xxx] | x.xxx |

A mixed model including as fixed effect the baseline value (visit 3), treatment group, visit and treatment group by visit interaction. For each pairwise comparison all available data from all 3 treatment groups are included. To allow correlation of observations on the same patient a random subject effect is included in the model and moreover possible different error variance for each treatment group is adjusted for. The error variance is fitted as separate compound symmetry for each treatment group.
### 4.20 Efficacy analysis of change from baseline in overall ACQ (FAS)

<table>
<thead>
<tr>
<th>Visit</th>
<th>Comparison</th>
<th>Active Adjusted Mean [se] N</th>
<th>Active Adjusted Mean [se] N</th>
<th>Placebo Adjusted Mean [se] N</th>
<th>Placebo Adjusted Mean [se] N</th>
<th>Difference [se] N</th>
<th>95% CI for difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>12 DU versus Placebo</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x]</td>
<td>[xxx.x ; xxx.x]</td>
<td>x.xxx</td>
</tr>
<tr>
<td></td>
<td>6 DU versus Placebo</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x]</td>
<td>[xxx.x ; xxx.x]</td>
<td>x.xxx</td>
</tr>
<tr>
<td>5</td>
<td>12 DU versus Placebo</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x]</td>
<td>[xxx.x ; xxx.x]</td>
<td>x.xxx</td>
</tr>
<tr>
<td></td>
<td>6 DU versus Placebo</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x]</td>
<td>[xxx.x ; xxx.x]</td>
<td>x.xxx</td>
</tr>
<tr>
<td>6</td>
<td>12 DU versus Placebo</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x]</td>
<td>[xxx.x ; xxx.x]</td>
<td>x.xxx</td>
</tr>
<tr>
<td></td>
<td>6 DU versus Placebo</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x]</td>
<td>[xxx.x ; xxx.x]</td>
<td>x.xxx</td>
</tr>
<tr>
<td>7</td>
<td>12 DU versus Placebo</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x]</td>
<td>[xxx.x ; xxx.x]</td>
<td>x.xxx</td>
</tr>
<tr>
<td></td>
<td>6 DU versus Placebo</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x]</td>
<td>[xxx.x ; xxx.x]</td>
<td>x.xxx</td>
</tr>
<tr>
<td>8</td>
<td>12 DU versus Placebo</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x]</td>
<td>[xxx.x ; xxx.x]</td>
<td>x.xxx</td>
</tr>
<tr>
<td></td>
<td>6 DU versus Placebo</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x] xxx</td>
<td>xxx.x [xx.x]</td>
<td>[xxx.x ; xxx.x]</td>
<td>x.xxx</td>
</tr>
</tbody>
</table>

A mixed model including as fixed effect the baseline value (visit 3), treatment group, visit and treatment group by visit interaction. For each pairwise comparison all available data from all 3 treatment groups are included. To allow correlation of observations on the same patient a random subject effect is included in the model and moreover possible different error variance for each treatment group is adjusted for. Country is included as a random categorical effect and the error variance is fitted as separate compound symmetry for each treatment group.
4.21 Efficacy analysis of overall AQLQ (FAS)  
as Table 4.20

4.22 Efficacy analysis of change from baseline in overall AQLQ (FAS)  
as Table 4.20
### 4.23 Efficacy analysis of the proportion of subjects with a MID change in ACQ controlled for ICS (FAS)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Active</th>
<th></th>
<th></th>
<th>Placebo</th>
<th></th>
<th></th>
<th>Treatment Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted odds</td>
<td>N Total</td>
<td>N Events</td>
<td>Adjusted odds</td>
<td>N Total</td>
<td>N Events</td>
<td>Adjusted Odds Ratio</td>
</tr>
<tr>
<td>12DU versus Placebo</td>
<td>x.xx</td>
<td>XXX xx (xx%)</td>
<td>x.xx</td>
<td>XXX xx (xx%)</td>
<td>x.xx</td>
<td>[x.xx ; x.xx]</td>
<td>x.xxx</td>
</tr>
<tr>
<td>6DU versus Placebo</td>
<td>x.xx</td>
<td>XXX xx (xx%)</td>
<td>x.xx</td>
<td>XXX xx (xx%)</td>
<td>x.xx</td>
<td>[x.xx ; x.xx]</td>
<td>x.xxx</td>
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</table>

**Estimated proportion**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Active</th>
<th></th>
<th></th>
<th>Placebo</th>
<th></th>
<th></th>
<th>Treatment Effect</th>
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<tr>
<td></td>
<td>Estimated</td>
<td>proportion</td>
<td></td>
<td>Estimated</td>
<td>proportion</td>
<td>Difference</td>
<td>95% CI for difference</td>
</tr>
<tr>
<td>12DU versus Placebo</td>
<td>0.xx</td>
<td></td>
<td>0.xx</td>
<td></td>
<td>0.xx</td>
<td>[x.xx ; x.xx]</td>
<td></td>
</tr>
<tr>
<td>6DU versus Placebo</td>
<td>0.xx</td>
<td></td>
<td>0.xx</td>
<td></td>
<td>0.xx</td>
<td>[x.xx ; x.xx]</td>
<td></td>
</tr>
</tbody>
</table>

- **N Total** = Total number of subjects included in analysis
- **N Events** = Number of subjects with an event

A binary variable ('0','1') is constructed based on change from baseline to visit 13/ the end-of-trial visit in ACQ and dose of ICS. The binary variable is set to '1' if change from baseline in ACQ corresponds to a meaningful improvement (<= -0.5) without increased use of ICS or if ICS is reduced compared to baseline (<0) without a deterioration in ACQ (>=0.5); otherwise the binary variable is set to '0'. Last observation is carried forward for subjects who discontinue the trial.

Estimates are obtained from a logistic regression analysis with treatment group as a categorical fixed effect and baseline ACQ and ICS as continuous fixed effects covariates. Country is included as a categorical random effect.
4.24 Efficacy analysis of the proportion of subjects with a MID change in AQLQ(s) controlled for ICS (FAS) as table 4.23
5 Immunology

5.1 Summary of specific IgE against Der p (FAS)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active all (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (visit 1)</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
</tr>
<tr>
<td>Median</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
<tr>
<td>P25%-P75%</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
</tr>
<tr>
<td>P5%-P95%</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
</tr>
<tr>
<td>Min-Max</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
</tr>
<tr>
<td>Geo. Mean</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
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<tr>
<td>Geo. SD</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
<tr>
<td>Visit 4</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
</tr>
<tr>
<td>Median</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
<tr>
<td>P25%-P75%</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
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<tr>
<td>P5%-P95%</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
</tr>
<tr>
<td>Min-Max</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
<td>XX.X - XX.X</td>
</tr>
<tr>
<td>Geo. Mean</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
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<tr>
<td>Geo. SD</td>
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<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
</tbody>
</table>

N = number of subjects (Full analysis set), n = number of subjects with observations, SD = standard deviation, P25% = 25% percentile, P75% = 75%, P95% = 95% percentile, Geo. Mean = geometric mean, Geo. SD = geometric standard deviation
5.2 Summary of specific IgE against Der f (FAS)

As Table 5.1
### 5.3 Summary of change from baseline in specific IgE against Der p (FAS)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active all (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Visit 4</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute difference</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
</tr>
<tr>
<td>Median</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
<tr>
<td>P25%-P75%</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
</tr>
<tr>
<td>Min-Max</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
<td>XX.X – XX.X</td>
</tr>
<tr>
<td>Relative difference</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geo. Mean</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
<tr>
<td>Geo. SD</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
</tbody>
</table>

---

### End of trial (visit 13)

| Absolute difference |                  |                          |                          |                   |                 |
| N               | XX              | XX                       | XX                       | XX                | XX              |
| Mean (SD)       | XX.X (XX.X)     | XX.X (XX.X)              | XX.X (XX.X)              | XX.X (XX.X)      | XX.X (XX.X)    |
| Median          | XX.X            | XX.X                     | XX.X                     | XX.X              | XX.X            |
| P25%-P75%       | XX.X – XX.X     | XX.X – XX.X              | XX.X – XX.X              | XX.X – XX.X      | XX.X – XX.X    |
| Min-Max         | XX.X – XX.X     | XX.X – XX.X              | XX.X – XX.X              | XX.X – XX.X      | XX.X – XX.X    |
| Relative difference |                |                          |                          |                   |                 |
| Geo. Mean       | XX.X            | XX.X                     | XX.X                     | XX.X              | XX.X            |
| Geo. SD         | XX.X            | XX.X                     | XX.X                     | XX.X              | XX.X            |

N = number of subjects (Full analysis set), n = number of subjects with observations, SD = standard deviation, P25% = 25% percentile, P75% = 75%, P5% = 5% percentile, P95% = 95% percentile, Geo. Mean = geometric mean, Geo. SD = geometric standard deviation.
5.4 Summary of change from baseline in specific IgE against Der f (FAS)
As Table 5.3

5.5 Summary of specific IgG4 against Der p (FAS)
As Table 5.1

5.6 Summary of specific IgG4 against Der f (FAS)
As Table 5.1

5.7 Summary of change from baseline in specific IgG4 against Der p (FAS)
As Table 5.3

5.8 Summary of change from baseline in specific IgG4 against Der f (FAS)
As Table 5.3
### 5.9 Analysis of change from baseline in log10(IgE) against Der p (FAS)

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Test/Effect</th>
<th>DF</th>
<th>Estimate</th>
<th>95% CL</th>
<th>Prob</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statistical test</td>
<td>Fixed effect</td>
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<tr>
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<td>Visit</td>
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<td>Baseline</td>
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<tr>
<td>Random effect</td>
<td>Subject</td>
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<td>Different residual</td>
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</tr>
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</table>

#### Adjusted means (in log\(_{10}\))

<table>
<thead>
<tr>
<th>Visit</th>
<th>Placebo</th>
<th>ALK HMD AIT 12 DU</th>
<th>ALK HMD AIT 6 DU</th>
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</thead>
<tbody>
<tr>
<td>4</td>
<td>XXX</td>
<td>XXX</td>
<td>[XXX:XXX]</td>
</tr>
<tr>
<td>6</td>
<td>XXX</td>
<td>XXX</td>
<td>[XXX:XXX]</td>
</tr>
<tr>
<td>9</td>
<td>XXX</td>
<td>XXX</td>
<td>[XXX:XXX]</td>
</tr>
</tbody>
</table>

DF=degrees of freedom, CL=confidence limit

---

Trial ID: MT-04
Version: Final
Date: 24-June-2013
### Analysis of change from baseline in log10(IgE) against Der. p – continued (FAS)

<table>
<thead>
<tr>
<th>Analysis</th>
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<th>95% CL</th>
<th>Prob</th>
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<tbody>
<tr>
<td>Absolute difference in log10</td>
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<td>Placebo-ALK HDM 12DU</td>
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<td>[XXX:XXX]</td>
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<td></td>
</tr>
<tr>
<td></td>
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<td>XXX</td>
<td>[XXX:XXX]</td>
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<td></td>
</tr>
<tr>
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<td>XXX</td>
<td>[XXX:XXX]</td>
<td>X.XX</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo-ALK HDM 6DU</td>
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<td>[XXX:XXX]</td>
<td>X.XX</td>
<td></td>
</tr>
<tr>
<td>Visit 9</td>
<td>Placebo-ALK HDM 12DU</td>
<td>XXX</td>
<td>[XXX:XXX]</td>
<td>X.XX</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo-ALK HDM 6DU</td>
<td>XXX</td>
<td>[XXX:XXX]</td>
<td>X.XX</td>
<td></td>
</tr>
<tr>
<td>Visit 13</td>
<td>Placebo-ALK HDM 12DU</td>
<td>XXX</td>
<td>[XXX:XXX]</td>
<td>X.XX</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo-ALK HDM 6DU</td>
<td>XXX</td>
<td>[XXX:XXX]</td>
<td>X.XX</td>
<td></td>
</tr>
<tr>
<td>Backtransferred adjusted means</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit 4</td>
<td>Placebo</td>
<td>XXX</td>
<td>[XXX:XXX]</td>
<td>X.XX</td>
<td></td>
</tr>
<tr>
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<td>ALK HMD AIT 12 DU</td>
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<td>[XXX:XXX]</td>
<td>X.XX</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ALK HMD AIT 6 DU</td>
<td>XXX</td>
<td>[XXX:XXX]</td>
<td>X.XX</td>
<td></td>
</tr>
<tr>
<td>Visit 6</td>
<td>Placebo</td>
<td>XXX</td>
<td>[XXX:XXX]</td>
<td>X.XX</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ALK HMD AIT 12 DU</td>
<td>XXX</td>
<td>[XXX:XXX]</td>
<td>X.XX</td>
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</tr>
<tr>
<td></td>
<td>ALK HMD AIT 6 DU</td>
<td>XXX</td>
<td>[XXX:XXX]</td>
<td>X.XX</td>
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</tr>
<tr>
<td>Visit 9</td>
<td>Placebo</td>
<td>XXX</td>
<td>[XXX:XXX]</td>
<td>X.XX</td>
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<tr>
<td></td>
<td>ALK HMD AIT 12 DU</td>
<td>XXX</td>
<td>[XXX:XXX]</td>
<td>X.XX</td>
<td></td>
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<tr>
<td></td>
<td>ALK HMD AIT 6 DU</td>
<td>XXX</td>
<td>[XXX:XXX]</td>
<td>X.XX</td>
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<td></td>
<td>ALK HMD AIT 12 DU</td>
<td>XXX</td>
<td>[XXX:XXX]</td>
<td>X.XX</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ALK HMD AIT 6 DU</td>
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<td>[XXX:XXX]</td>
<td>X.XX</td>
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</tr>
</tbody>
</table>

DF=degrees of freedom, CL=confidence limit
### Analysis Test/Effect

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Test/Effect</th>
<th>DF</th>
<th>Estimate</th>
<th>95% CL</th>
<th>P Val</th>
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</thead>
<tbody>
<tr>
<td>Backtransferred relative difference</td>
<td>Visit 4 100*(ALK HDM 12DU-Placebo)/Placebo</td>
<td>XXX</td>
<td>XXX</td>
<td>[XXX:XXX]</td>
<td>X.XX</td>
</tr>
<tr>
<td></td>
<td>100*(ALK HDM 6DU-Placebo)/Placebo</td>
<td>XXX</td>
<td>XXX</td>
<td>[XXX:XXX]</td>
<td>X.XX</td>
</tr>
<tr>
<td></td>
<td>Visit 6 100*(ALK HDM 12DU-Placebo)/Placebo</td>
<td>XXX</td>
<td>XXX</td>
<td>[XXX:XXX]</td>
<td>X.XX</td>
</tr>
<tr>
<td></td>
<td>100*(ALK HDM 6DU-Placebo)/Placebo</td>
<td>XXX</td>
<td>XXX</td>
<td>[XXX:XXX]</td>
<td>X.XX</td>
</tr>
<tr>
<td></td>
<td>Visit 9 100*(ALK HDM 12DU-Placebo)/Placebo</td>
<td>XXX</td>
<td>XXX</td>
<td>[XXX:XXX]</td>
<td>X.XX</td>
</tr>
<tr>
<td></td>
<td>100*(ALK HDM 6DU-Placebo)/Placebo</td>
<td>XXX</td>
<td>XXX</td>
<td>[XXX:XXX]</td>
<td>X.XX</td>
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<tr>
<td></td>
<td>Visit 13 100*(ALK HDM 12DU-Placebo)/Placebo</td>
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<td>XXX</td>
<td>[XXX:XXX]</td>
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<tr>
<td></td>
<td>100*(ALK HDM 6DU-Placebo)/Placebo</td>
<td>XXX</td>
<td>XXX</td>
<td>[XXX:XXX]</td>
<td>X.XX</td>
</tr>
</tbody>
</table>

**DF=degrees of freedom, CL=confidence limit**

Change from baseline of log10(IgE) is analysed using a LME model. Change from baseline of log10(IgE) is response variable, visit, treatment and their two-factor interaction categorical variables, log10(IgE) at baseline is a regression variable and subject is a random variable. Different residual errors are specified for each treatment group. The primary outcome is the difference in adjusted means between each treatment group and placebo with coherent p-values and confidence limits. The p-value and 95% confidence limits for the absolute difference are obtained using Kenward-Roger calculations for the degrees of freedom. Adjusted means and relative differences in adjusted means with confidence intervals are also reported on the original scale (by taking the antilogarithm).

Covariance parameters are calculated using the REML method. LogLikelihood Ratio (RL) tests are used for testing the null hypothesis of equal residual variance for the treatment groups. The resulting p-values of the LR tests are reported.
5.10 Analysis of change from baseline in log10(IgE) against Der f (FAS) as table 5.9

5.11 Analysis of change from baseline in log10(IgG4) against Der p (FAS) as table 5.9

5.12 Analysis of change from baseline in log10(IgG4) against Der f (FAS) as table 5.9
6 Safety evaluation

6.1 Summary of treatment emergent adverse events (Safety set)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active All (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>e (%)</td>
<td>n (%)</td>
<td>e (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>All events</td>
<td>XXX (XXX%)</td>
<td>XXX (100%)</td>
<td>XXX (XXX%)</td>
<td>XXX (100%)</td>
<td>XXX (XXX%)</td>
</tr>
<tr>
<td>Causality</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Unlikely</td>
<td>XXX (XXX%)</td>
<td>XXX (XXX%)</td>
<td>XXX (XXX%)</td>
<td>XXX (XXX%)</td>
<td>XXX (XXX%)</td>
</tr>
<tr>
<td>Possible</td>
<td>XXX (XXX%)</td>
<td>XXX (XXX%)</td>
<td>XXX (XXX%)</td>
<td>XXX (XXX%)</td>
<td>XXX (XXX%)</td>
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<tr>
<td>Severity</td>
<td></td>
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<tr>
<td>Mild</td>
<td>XXX (XXX%)</td>
<td>XXX (XXX%)</td>
<td>XXX (XXX%)</td>
<td>XXX (XXX%)</td>
<td>XXX (XXX%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>XXX (XXX%)</td>
<td>XXX (XXX%)</td>
<td>XXX (XXX%)</td>
<td>XXX (XXX%)</td>
<td>XXX (XXX%)</td>
</tr>
<tr>
<td>Severe</td>
<td>XXX (XXX%)</td>
<td>XXX (XXX%)</td>
<td>XXX (XXX%)</td>
<td>XXX (XXX%)</td>
<td>XXX (XXX%)</td>
</tr>
<tr>
<td>By worst case</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>XXX (XXX%)</td>
<td>XXX (XXX%)</td>
<td>XXX (XXX%)</td>
<td>XXX (XXX%)</td>
<td>XXX (XXX%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>XXX (XXX%)</td>
<td>XXX (XXX%)</td>
<td>XXX (XXX%)</td>
<td>XXX (XXX%)</td>
<td>XXX (XXX%)</td>
</tr>
<tr>
<td>Severe</td>
<td>XXX (XXX%)</td>
<td>XXX (XXX%)</td>
<td>XXX (XXX%)</td>
<td>XXX (XXX%)</td>
<td>XXX (XXX%)</td>
</tr>
</tbody>
</table>

N = number of subjects (safety set), n = number of subjects with events, % n = percent of subjects in treatment group of safety set with events, e = number of events, % e = percent of all events in treatment group of safety set

An adverse event is considered to be a treatment emergent adverse event (TEAE) if the AE start time is equal to or after the time of the first IMP intake.

e and e% are not applicable for "By worst case".
### 6.1 Summary of treatment emergent adverse events (Safety set)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALR HDM AIT 6 DU (N=XXX)</th>
<th>ALR HDM AIT 12 DU (N=XXX)</th>
<th>Active All (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%) n (%)</td>
<td>e (%) n (%)</td>
<td>e (%) n (%)</td>
<td>e (%) n (%)</td>
<td>e (%) n (%)</td>
</tr>
<tr>
<td><strong>Seriousness</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-serious</td>
<td>XXX (XX%) XXX (XX%)</td>
<td>XXX (XX%) XXX (XX%)</td>
<td>XXX (XX%) XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%) XXX (XX%) XXX (XX%) XXX (XX%)</td>
</tr>
<tr>
<td>Serious</td>
<td>XXX (XX%) XXX (XX%)</td>
<td>XXX (XX%) XXX (XX%)</td>
<td>XXX (XX%) XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%) XXX (XX%) XXX (XX%) XXX (XX%)</td>
</tr>
<tr>
<td><strong>Action taken</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>XXX (XX%) XXX (XX%)</td>
<td>XXX (XX%) XXX (XX%)</td>
<td>XXX (XX%) XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%) XXX (XX%) XXX (XX%) XXX (XX%)</td>
</tr>
<tr>
<td>Temporary interrupted</td>
<td>XXX (XX%) XXX (XX%)</td>
<td>XXX (XX%) XXX (XX%)</td>
<td>XXX (XX%) XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%) XXX (XX%) XXX (XX%) XXX (XX%)</td>
</tr>
<tr>
<td>IMP discontinued</td>
<td>XXX (XX%) XXX (XX%)</td>
<td>XXX (XX%) XXX (XX%)</td>
<td>XXX (XX%) XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%) XXX (XX%) XXX (XX%) XXX (XX%)</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not recovered</td>
<td>XXX (XX%) XXX (XX%)</td>
<td>XXX (XX%) XXX (XX%)</td>
<td>XXX (XX%) XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%) XXX (XX%) XXX (XX%) XXX (XX%)</td>
</tr>
<tr>
<td>Fatal</td>
<td>XXX (XX%) XXX (XX%)</td>
<td>XXX (XX%) XXX (XX%)</td>
<td>XXX (XX%) XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%) XXX (XX%) XXX (XX%) XXX (XX%)</td>
</tr>
<tr>
<td>Recovered with sequelae</td>
<td>XXX (XX%) XXX (XX%)</td>
<td>XXX (XX%) XXX (XX%)</td>
<td>XXX (XX%) XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%) XXX (XX%) XXX (XX%) XXX (XX%)</td>
</tr>
<tr>
<td>Not known</td>
<td>XXX (XX%) XXX (XX%)</td>
<td>XXX (XX%) XXX (XX%)</td>
<td>XXX (XX%) XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%) XXX (XX%) XXX (XX%) XXX (XX%)</td>
</tr>
<tr>
<td><strong>Event leading to withdrawal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>XXX (XX%) XXX (XX%)</td>
<td>XXX (XX%) XXX (XX%)</td>
<td>XXX (XX%) XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%) XXX (XX%) XXX (XX%) XXX (XX%)</td>
</tr>
<tr>
<td>No</td>
<td>XXX (XX%) XXX (XX%)</td>
<td>XXX (XX%) XXX (XX%)</td>
<td>XXX (XX%) XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%) XXX (XX%) XXX (XX%) XXX (XX%)</td>
</tr>
</tbody>
</table>

N = number of subjects (Safety set), n = number of subjects with events, % n = percent of subjects in treatment group of safety set with events, e = number of events, % e = percent of all events in treatment group of safety set.

An adverse event is considered to be a treatment emergent adverse event (TEAE) if the AE start time is equal to or after the time of the first IMP intake.

---

**Trial ID**: MT-04  
**Version**: Final  
**Date**: 24-June-2013
### 6.2 All treatment emergent adverse events by SOC (Safety set)

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Treatment group</th>
<th>n (%n) e</th>
<th>n (%n) e</th>
<th>n (%n) e</th>
<th>n (%n) e</th>
<th>n (%n) e</th>
</tr>
</thead>
<tbody>
<tr>
<td>All events</td>
<td>Placebo (N=XXX)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td></td>
<td>ALK HDM AIT 6 DU (N=XXX)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td></td>
<td>ALK HDM AIT 12 DU (N=XXX)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td></td>
<td>Active All (N=XXX)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
<tr>
<td></td>
<td>Overall (N=XXX)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
<td>XX (XX%)</td>
</tr>
</tbody>
</table>

N = number of subjects (Safety set), n = number of subjects with events, 
% n = percent of subjects in treatment group of safety set with events, 
e = number of events

An adverse event is considered to be a treatment emergent adverse event (TEAE) if the AE start time is equal to or after the time of the first IMP intake.

Preferred term is coded in MedDRA version 15.0
6.3 All mild treatment emergent adverse events by SOC (Safety set)

As table 6.2

An adverse event is considered to be a treatment emergent adverse event (TEAE) if the AE start time is equal to or after the time of the first IMP intake.

Preferred term is coded in MedDRA version 15.0
6.4 All moderate treatment emergent adverse events by SOC (Safety set)

As Table 6.2

An adverse event is considered to be a treatment emergent adverse event (TEAE) if the AE start time is equal to or after the time of the first IMP intake.

Preferred term is coded in MedDRA version 15.0
6.5 All severe treatment emergent adverse events by SOC (Safety set)

As Table 6.2

An adverse event is considered to be a treatment emergent adverse event (TEAE) if the AE start time is equal to or after the time of the first IMP intake.

Preferred term is coded in MedDRA version 15.0
6.6 All serious treatment emergent adverse events by SOC (Safety set)

As Table 6.2

An adverse event is considered to be a treatment emergent adverse event (TEAE) if the AE start time is equal to or after the time of the first IMP intake.

Preferred term is coded in MedDRA version 15.0
### 6.7 Summary of all IMP related adverse events (Safety set)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active All (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%n)</td>
<td>e (%e)</td>
<td>n (%n)</td>
<td>e (%e)</td>
<td>n (%n)</td>
</tr>
<tr>
<td>All events</td>
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<td>XXX (100%)</td>
<td>XXX (XXX)</td>
<td>XXX (100%)</td>
<td>XXX (XXX)</td>
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<td>Severity</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>XXX (XXX)</td>
<td>XXX (XXX)</td>
<td>XXX (XXX)</td>
<td>XXX (XXX)</td>
</tr>
<tr>
<td>Moderate</td>
<td>XXX (XXX)</td>
<td>XXX (XXX)</td>
<td>XXX (XXX)</td>
<td>XXX (XXX)</td>
<td>XXX (XXX)</td>
</tr>
<tr>
<td>Severe</td>
<td>XXX (XXX)</td>
<td>XXX (XXX)</td>
<td>XXX (XXX)</td>
<td>XXX (XXX)</td>
<td>XXX (XXX)</td>
</tr>
<tr>
<td>By worst case</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>XXX (XXX)</td>
<td>-</td>
<td>XXX (XXX)</td>
<td>-</td>
<td>XXX (XXX)</td>
</tr>
<tr>
<td>Moderate</td>
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<td>-</td>
<td>XXX (XXX)</td>
<td>-</td>
<td>XXX (XXX)</td>
</tr>
<tr>
<td>Severe</td>
<td>XXX (XXX)</td>
<td>-</td>
<td>XXX (XXX)</td>
<td>-</td>
<td>XXX (XXX)</td>
</tr>
<tr>
<td>Seriousness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-serious</td>
<td>XXX (XXX)</td>
<td>XXX (XXX)</td>
<td>XXX (XXX)</td>
<td>XXX (XXX)</td>
<td>XXX (XXX)</td>
</tr>
<tr>
<td>Serious</td>
<td>XXX (XXX)</td>
<td>XXX (XXX)</td>
<td>XXX (XXX)</td>
<td>XXX (XXX)</td>
<td>XXX (XXX)</td>
</tr>
</tbody>
</table>

N = number of subjects (Safety set), n = number of subjects with events, 
% n = percent of subjects in treatment group of safety set with events, 
% e = percent of all events in treatment group of safety set

IMP related adverse events are those not assessed 'Unlikely' related (possibly related + unknown). 
e and e% are not applicable for "By worst case".

---

Trial ID\file name.sas\Initials DM & Initials STAT\Date of run: page 1 of 2
### 6.7 Summary of all IMP related adverse events (Safety set)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (n=XXX)</th>
<th>ALK HDM AIT 6 DU (n=XXX)</th>
<th>ALK HDM AIT 12 DU (n=XXX)</th>
<th>Active All (n=XXX)</th>
<th>Overall (n=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%n)</td>
<td>e (%e)</td>
<td>n (%n)</td>
<td>e (%e)</td>
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<tr>
<td>Action taken</td>
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<td></td>
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<tr>
<td>None</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
</tr>
<tr>
<td>Temporary interrupted</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
</tr>
<tr>
<td>IMP discontinued</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not recovered</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
</tr>
<tr>
<td>Fatal</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
</tr>
<tr>
<td>Recovered with sequelae</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
</tr>
<tr>
<td>Recovered</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
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<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
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<tr>
<td>Event leading to withdrawal</td>
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<td></td>
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</tr>
<tr>
<td>Yes</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
</tr>
<tr>
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<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
<td>XXX (XX%)</td>
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</tr>
</tbody>
</table>

N = number of subjects (Safety set), n = number of subjects with events,
% n = percent of subjects in treatment group of safety set with events,
e = number of events, % e = percent of all events in treatment group of safety set

IMP related adverse events are those not assessed 'Unlikely' related (possible related + unknown).
### 6.8 All IMP related adverse events by SOC (Safety set)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placibo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active All (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>System organ class</strong></td>
<td><strong>Preferred term</strong></td>
<td><strong>n (%)</strong></td>
<td><strong>e</strong></td>
<td><strong>n (%)</strong></td>
<td><strong>e</strong></td>
</tr>
<tr>
<td>All events</td>
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<td></td>
<td></td>
</tr>
<tr>
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<td>All</td>
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<td></td>
</tr>
<tr>
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<td>Preferred term 1.3</td>
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<td><strong>System organ class 2</strong></td>
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<tr>
<td>All</td>
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<tr>
<td>Preferred term 2.3</td>
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</tr>
</tbody>
</table>

N = number of subjects (Safety set), n = number of subjects with events, 
% n = percent of subjects in treatment group of safety set with events, 
e = number of events, % e = percent of all events in treatment group of safety set

IMP related adverse events are those not assessed 'Unlikely' related (possible related + unknown).

Preferred term is coded in MedDRA version 15.0
6.9 All mild IMP related adverse events by SOC (Safety set)

As table 6.8

IMP related adverse events are those not assessed 'Unlikely' related (possible related + unknown).

Preferred term is coded in MedDRA version 15.0
6.10 All moderate IMP related adverse events by SOC (Safety set)

As table 6.8

IMP related adverse events are those not assessed 'unlikely' related (possible related + unknown).

Preferred term is coded in MedDRA version 15.0
6.11 All severe IMP related adverse events by SOC (Safety set)

As table 6.8

IMP related adverse events are those not assessed ‘Unlikely’ related (possible related + unknown).

Preferred term is coded in MedDRA version 15.0
6.12 All serious IMP related adverse events by SOC (Safety set)

As table 6.8

IMP related adverse events are those not assessed 'Unlikely' related ('Possible related' + 'Unknown').
Preferred term is coded in MedDRA version 15.0
### 6.13 Number of treatment emergent adverse events per subject for subjects with events (Safety set)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active All (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX (XX)</td>
<td>XX (XX)</td>
<td>XX (XX)</td>
<td>XX (XX)</td>
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</tr>
<tr>
<td>Median</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td>P25% - P75%</td>
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<td>XX - XX</td>
<td>XX - XX</td>
<td>XX - XX</td>
<td>XX - XX</td>
</tr>
<tr>
<td>P5% - P95%</td>
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<td>XX - XX</td>
<td>XX - XX</td>
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<td>XX - XX</td>
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<tr>
<td>Min - Max</td>
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<td>XX - XX</td>
<td>XX - XX</td>
<td>XX - XX</td>
<td>XX - XX</td>
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</tbody>
</table>

Only subjects in safety set with AEs are included

An adverse event is considered to be a treatment emergent adverse event (TEAE) if the AE start time is equal to or after the time of the first IMP intake.

IMP related adverse events are those not assessed 'Unlikely' related ('Possible related' + 'Unknown').
6.14 Number of treatment emergent adverse events per subject (Safety set)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active All (N=XXX)</th>
<th>Overall (N=XXX)</th>
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</thead>
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<tr>
<td>All TEAEs</td>
<td>n</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX (XX)</td>
<td>XX (XX)</td>
<td>XX (XX)</td>
<td>XX (XX)</td>
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</tr>
<tr>
<td>Median</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td>P25% - P75%</td>
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<td>XX - XX</td>
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<tr>
<td>P25% - P75%</td>
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<td>XX - XX</td>
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<tr>
<td>P5% - P95%</td>
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</table>

N = number of subjects (Safety set), n = number of subjects with observations, SD = standard deviation, P25% = 25% percentile, P75% = 75% percentile, P5% = 5% percentile, P95% = 95% percentile

An adverse event is considered to be a treatment emergent adverse event (TEAE) if the AE start time is equal to or after the time of the first IMP intake.

IMP related adverse events are those not assessed 'Unlikely' related ('Possible related' + 'Unknown').
6.15 Most frequent TEAEs (>=2% in any active group) by SOC (Safety set)

As table 6.8

An adverse event is considered to be a treatment emergent adverse event (TEAE) if the AE start time is equal to or after the time of the first IND intake.
### 6.16 Onset in days after first IMP intake of most frequent TEAEs (Safety set)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
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<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active All (N=XXX)</th>
<th>Overall (N=XXX)</th>
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<tr>
<td>Mean (SD)</td>
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<td>XX</td>
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<td>XX</td>
</tr>
<tr>
<td>P25% - P75%</td>
<td>XX - XX</td>
<td>XX - XX</td>
<td>XX - XX</td>
<td>XX - XX</td>
<td>XX - XX</td>
</tr>
<tr>
<td>P5% - P95%</td>
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<td>Min - Max</td>
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</table>

N = number of subjects (safety set), n = number of subjects with events, SD = standard deviation, P25% = 25% percentile, P75% = 75% percentile, P5% = 5% percentile, P95% = 95% percentile

Onset of an AE is defined as days from first IMP intake to start of the first AE of a given preferred term. An onset of 1 day means that the AE has started on the day of first IMP intake.

An adverse event is considered to be a treatment emergent adverse event (TEAE) if the AE start time is equal to or after the time of the first IMP intake.

Most frequent TEAEs are defined by 2% of subjects in any active treatment group having the same TEAE (defined as preferred term from MedDRA).
### 6.17 Onset in minutes after first IMP intake on the first day of IMP of most frequent TEAEs (Safety set)

<table>
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<td>P25% – P75%</td>
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<td>XX – XX</td>
<td>XX – XX</td>
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$N =$ number of subjects (safety set), $n =$ number of subjects with events, SD = standard deviation, P25% = 25% percentile, P75% = 75% percentile, P5% = 5% percentile, P95% = 95% percentile

Onset of an AE is defined as minutes from first IMP intake to start of the first AE of a given preferred term.

An adverse event is considered to be a treatment emergent adverse event (TEAE) if the AE start time is equal to or after the time of the first IMP intake.

Most frequent TEAEs are defined by 25% of subjects in any active treatment group having the same TEAE (defined as preferred term from MedDRA).
### 6.18 Resolution in days of most frequent treatment emergent adverse events by SOC (Safety set)

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<td>XX - XX</td>
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<tr>
<td>P5% - P95%</td>
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</table>

N = number of subjects (safety set), n = number of subjects with events,
SD = standard deviation, P25% = 25% percentile, P75% = 75% percentile,
P5% = 5% percentile, P95% = 95% percentile

Resolution of an AE is defined as days from start of the AE until the AE is resolved.

An adverse event is considered to be a treatment emergent adverse event (TEAE) if the AE start time is equal to or after the time of the first IMP intake.

Most frequent TEAEs are defined by that ≥2% of subjects in any active treatment group has the same TEAE (defined as preferred term from MedDRA).
6.19 IMP discontinuations/interruptions due to adverse events by SOC (Safety set)

As table 6.8
### 6.20 Physical examination – shift table (Safety set)

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</table>

#### Head (Ears,Eyes,Nose,Throat)
- **Baseline M**
  - M = Missing
  - N = Normal
  - Ab Not CR = Abnormal not clinically relevant
  - Ab CR = Abnormal clinically relevant

<table>
<thead>
<tr>
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#### Oral inspection
- **Baseline M**
- **Follow-up**
- **N**
- **Ab Not CR**
- **Ab CR**

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#### Respiratory
- **Baseline M**
- **Follow-up**
- **N**
- **Ab Not CR**
- **Ab CR**

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*N = Normal
Ab Not CR = Abnormal not clinically relevant
Ab CR = Abnormal clinically relevant
M = Missing

Follow-up is the physical examination performed most recently after last IMP intake – End of trial visit 13
Baseline is the visit closest to randomisation (Visit 3)
### 6.21 Laboratory data – Haematology, shift table (Safety set)

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Follow-up is the blood sample taken closest after the last IMP intake – End of trial visit 13

N = Normal
L = Low
H = High
M = Missing

Trial ID:\file name.sas\Initials DM & Initials STAT\Date of run
6.22 Laboratory data - Blood chemistry, shift table (Safety set)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
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<td>X X X X X X X X X X X X X X</td>
<td>X X X X X X X X X X X X X X</td>
<td>X X X X X X X X X X X X X X</td>
</tr>
</tbody>
</table>

H = Normal
L = Low
H = High
M = Missing

Follow-up is the blood sample taken closest after the last IMP intake - End of trial visit 13
### 6.23 Laboratory data - pH in urinalysis, shift table (Safety set)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active AIT (n=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>Follow-up</td>
<td>Follow-up</td>
<td>Follow-up</td>
<td>Follow-up</td>
<td>Follow-up</td>
</tr>
<tr>
<td>Missing</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Low</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Normal</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>High</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

M = Normal  
L = Low  
H = High  
M = Missing  

Follow-up is the urine sample taken closest after the last IMP intake - End of trial visit 13
### 6.24 Laboratory data - Urinalysis, shift table (Safety set)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active All (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>Pos</td>
<td>Neg</td>
<td>M</td>
<td>Pos</td>
</tr>
<tr>
<td><strong>Bacteria</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Missing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Positive</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Bilirubin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Missing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Positive</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Blood</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Missing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Positive</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

N = Number of subjects in treatment group of FAS
M = Missing
Pos = Positive
Neg = Negative

Follow-up is the urine sample taken closest after the last IMP intake - End of trial visit 13
### 6.25 Vital signs (safety set)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active All (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic BP [mmHg]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
</tr>
<tr>
<td>Median</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
<td>XX.X (XX.X)</td>
</tr>
<tr>
<td>Median</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
</tbody>
</table>

| **Diastolic BP [mmHg]** | | | | | |
| **Baseline** | | | | | |
| Mean (SD) | XX.X (XX.X) | XX.X (XX.X) | XX.X (XX.X) | XX.X (XX.X) | XX.X (XX.X) |
| Median | XX.X | XX.X | XX.X | XX.X | XX.X |

- N = number of subjects (safety set), n = number of subjects with observations, SD = standard deviation, P25% = 25% percentile, P75% = 75%, P5% = 5% percentile, P95% = 95% percentile
- Follow-up is the measurement performed closest after last IMP intake – End of trial visit 13
- Baseline is the visit closest to randomisation (Visit 1)

---

Statistical Analysis Plan – Appendix A – Table Shells

**Trial ID:** MT-04
**Version:** Final
**Date:** 24-June-2013
### 6.26 Pregnancy test (Safety set)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (N=XXX)</th>
<th>ALK HDM AIT 6 DU (N=XXX)</th>
<th>ALK HDM AIT 12 DU (N=XXX)</th>
<th>Active all (N=XXX)</th>
<th>Overall (N=XXX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potential childbearing</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td>Positive</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td>Negative</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td>Missing</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td>Follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potential childbearing</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td>Positive</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td>Negative</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td>Missing</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
</tbody>
</table>

N = number of subjects (safety set), n = number of subjects with event

Baseline is the visit closest to randomisation (visit 3). Follow-up is the last pregnancy test performed for the subject - after start of IMP treatment.
6.27 All adverse events occurred prior to first IMP administration by SOC (Safety set)

As Table 6.2

An adverse event is considered to be pre-IMP if the AE start time is before the time of the first IMP intake.
Statistical Analysis Plan – Appendix B – List Shells

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

The MITRA Trial

Clinical Trial ID: MT-04
EudraCT No.: 2010-018621-19
Investigational Medicinal Product: ALK house dust mite (HDM) allergy immunotherapy tablet (AIT)
Development Phase: III
Sponsor: Global Clinical Development
ALK-Abelló A/S
DK-2970 Hørsholm
Phone: +45 45747445
Document Status: Final
Date: 24 June 2013

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   Listing 1-3  Subject disposition (FAS)  7
   Listing 1-4  Discontinuations (FAS)  8
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### 1. Subject details and baseline characteristics

**Listing 1-1  Reason for screening failures (list includes screening failures only)**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Site</th>
<th>Country</th>
<th>Date of informed consent</th>
<th>Late subject left the trial</th>
<th>Non-fulfilment of inclusion or exclusion criteria</th>
<th>Withdrawal of consent</th>
<th>Other reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>XXXX</td>
<td>XXXX</td>
<td>XXXXXX</td>
<td>XX.XX.XX</td>
<td>XX.XX.XX</td>
<td>XX/XX/XXX</td>
<td>Y/N</td>
<td>XXXXXXXXXXXXX</td>
</tr>
</tbody>
</table>

Sorted by site and subject.
### Listing 1-2  Inclusion and exclusion criteria (FAS)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Site</th>
<th>Subject</th>
<th>Visit</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>XXX</td>
<td>XXXX</td>
<td>1</td>
<td>Y/N/N/Y/N/Y/N</td>
<td>Y/N/Y/N/Y/N/NA</td>
</tr>
<tr>
<td>DU/12DU</td>
<td>3</td>
<td></td>
<td></td>
<td>Y/N/Y/N/Y/N</td>
<td>Y/N/Y/N/Y/N/NA</td>
</tr>
</tbody>
</table>

Sorted by treatment, site, subject and visit.
### Listing 1-3  Subject disposition (FAS)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Subject Random number</th>
<th>PP</th>
<th>Attended visit 9</th>
<th>Completed study</th>
<th>Discontinued post primary endpoint</th>
<th>Withdrawal reason</th>
<th>Explanation if reason &quot;other&quot;</th>
<th>Completion/withdrawal date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/ 6OS/12DU</td>
<td>XXXX XXXX</td>
<td>Y/N</td>
<td>Y/N</td>
<td>Y/N</td>
<td>XXXXXXXXXX</td>
<td>XXXXXXXXXX</td>
<td>XX.xx.xx</td>
<td></td>
</tr>
</tbody>
</table>

Sorted by treatment and subject
## Listing 1-4 Discontinuations (FAS)

<table>
<thead>
<tr>
<th>Treatment Subject</th>
<th>Discontinued Withdrawal post primary initiated by endpoint</th>
<th>Withdrawal reason</th>
<th>AE number if reason &quot;AE&quot;</th>
<th>Explanation if reason &quot;other&quot;</th>
<th>Withdrawal date</th>
<th>First IMP date</th>
<th>Last IMP date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/6DU/12DU</td>
<td>XXXX</td>
<td>1/M</td>
<td>XX</td>
<td>XXXXXXXXXX</td>
<td>XX.XX.XX</td>
<td>XX.XX.XX</td>
<td>XX.XX.XX</td>
</tr>
</tbody>
</table>

Sorted by treatment and subject.
### Listing 1-5  Demography and other baseline characteristics (FAS)

<table>
<thead>
<tr>
<th>Treatment Subject</th>
<th>Date of Birth</th>
<th>Age</th>
<th>Sex</th>
<th>Ethnic origin</th>
<th>Specification if ethnic origin &quot;other&quot;</th>
<th>Height(cm)</th>
<th>Weight(kg)</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/ XXXX</td>
<td>XX.XX.XXXX</td>
<td>XX</td>
<td>F/M</td>
<td>Caucasian/Asian/African/Hispanic/Other</td>
<td>XXX</td>
<td>XXX</td>
<td>XXX</td>
<td></td>
</tr>
<tr>
<td>6DU/12DU</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>African/Hispanic/Other</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sorted by treatment and subject
### Listing 1-6  Skin prick test (FAS)

<table>
<thead>
<tr>
<th>Treatment Country Subject</th>
<th>Tree</th>
<th>Grass</th>
<th>Weed</th>
<th>Ani</th>
<th>Ani</th>
<th>HDM</th>
<th>Mould</th>
<th>Mould</th>
<th>Control</th>
<th>Control</th>
<th>Weed</th>
<th>Tree</th>
<th>Tree</th>
<th>Tree</th>
<th>Tree</th>
<th>Weed</th>
</tr>
</thead>
<tbody>
<tr>
<td>6DU/12DU</td>
<td>XXXX</td>
<td>XXXX</td>
<td>XXXX</td>
<td>XXXX</td>
<td>XXXX</td>
<td>XXXX</td>
<td>XXXX</td>
<td>XXXX</td>
<td>XXXX</td>
<td>XXXX</td>
<td>XXXX</td>
<td>XXXX</td>
<td>XXXX</td>
<td>XXXX</td>
<td>XXXX</td>
<td>XXXX</td>
</tr>
<tr>
<td>[11] = Tree, populus alba</td>
<td>[12]</td>
<td>[13]</td>
<td>[14]</td>
<td>[15]</td>
<td>[16]</td>
<td>[17]</td>
<td>[18]</td>
<td>[19]</td>
<td>[20]</td>
<td>[21]</td>
<td>[22]</td>
<td>[23]</td>
<td>[24]</td>
<td>[25]</td>
<td>[26]</td>
<td>[27]</td>
</tr>
</tbody>
</table>
| Sorted by treatment, country and subject; *+* = positive SPT; *-* = negative SPT

| Placebo/            | XXXX | XXXX  | XXXX | XXXX| XXXX| XXXX | XXXX  | XXXX  | XXXX    | XXXX    | XXXX | XXXX | XXXX | XXXX | XXXX | XXXX |
| 6DU/12DU            | XXXX | XXXX  | XXXX | XXXX| XXXX| XXXX | XXXX  | XXXX  | XXXX    | XXXX    | XXXX | XXXX | XXXX | XXXX | XXXX | XXXX |
| [11] = Tree, populus alba | [12] | [13]  | [14] | [15]| [16]| [17]| [18]  | [19]  | [20]    | [21]    | [22] | [23] | [24] | [25] | [26] | [27] |
| Sorted by treatment, country and subject; *+* = positive SPT; *-* = negative SPT

= Positive control
= Negative control

---

**Statistical Analysis Plan**

**Trial ID:** MT-04  
**EudraCT:** 2010-018621-19

**Version:** Final  
**Date:** 24-June-2013
### Listing 1-7  Specific IgE class against HDM, number of other sensibilities and GINA control level at baseline (FAS)

<table>
<thead>
<tr>
<th>Treatment Subject</th>
<th>D.pteronyssinus</th>
<th>D.farinae</th>
<th>Number of other sensibilities</th>
<th>GINA control level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IgE (KU/L)</td>
<td>IgE class</td>
<td>No other/1 other/2 other/3 other/4 other/5 other/6 other/7 other/8 other/+8 other</td>
<td></td>
</tr>
<tr>
<td>Placebo/XXXXX</td>
<td>A.XX</td>
<td>Class 1/ Class 2/ No other</td>
<td>Controlled/Partly Uncontrolled</td>
<td></td>
</tr>
<tr>
<td>6DU/12DU</td>
<td>Class 3/ Class 4/ 3 other/ 4 other/ 5 other/ controlled/Uncontrolled</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*: based on ACM data; ¤: D.pteronyssinus, D.farinae, positive and negative controls are excluded; #: based on ACQ data from visit 3

Sorted by treatment and subject
### Listing 1-8  Vital signs at screening, randomisation and end of trial (FAS)

<table>
<thead>
<tr>
<th>Treatment Subject</th>
<th>Systolic / Diastolic (mmHg)</th>
<th>Heart rate (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/ 6DU/12DU</td>
<td>XXX/XXX XXX/XXX XXX/XXX XXX/XXX</td>
<td>XXX/XXX XXX/XXX XXX/XXX XXX/XXX</td>
</tr>
</tbody>
</table>
| UV = unscheduled visit  
Sorted by treatment and subject |
### Listing 1-9  History of reversible airway obstruction (FAS)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Subject</th>
<th>Inc. in FEV1</th>
<th>Inc. in PEF</th>
<th>Variability in PEF</th>
<th>Red. after exercise</th>
<th>Red. after dry air</th>
<th>Red. after mannitol</th>
<th>Red. after methacholine*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/ 6DU/12DU</td>
<td>XXXXX</td>
<td>ND/Y/N</td>
<td>ND/Yes/No</td>
<td>ND/Yes/No</td>
<td>ND/Yes/No</td>
<td>ND/Yes/No</td>
<td>ND/Yes/No</td>
<td>ND/Yes/No</td>
</tr>
</tbody>
</table>

*Or in the Netherlands, histamine; ND = not done; Inc. = increased; Red. = reduced

Sorted by treatment and subject
### Listing 1-10  Smoking history (FAS)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Smoking habits</th>
<th>Age at starting smoking</th>
<th>Age at smoking cessation</th>
<th>Numbers smoked per week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/6DU/12DU</td>
<td>Non-smoker/Previous smoker/Smoker</td>
<td>ND/XX/XX</td>
<td>ND/XX/ND</td>
<td>ND/XX/ND</td>
</tr>
</tbody>
</table>

Sorted by treatment and subject.
### Listing 1-11 Medical history (FAS)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Subject No.</th>
<th>Verbatim</th>
<th>PT</th>
<th>Start Date</th>
<th>Stop Date</th>
<th>Ongoing</th>
<th>If ongoing: is medication given?</th>
<th>Years with disease*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/</td>
<td>XXXX</td>
<td>HDM induced asthma</td>
<td>XXXXXX</td>
<td>XX.XX.XX NA</td>
<td>NA</td>
<td>Yes</td>
<td>Yes/No</td>
<td>XX</td>
</tr>
<tr>
<td>6DS/12DU</td>
<td>XXXX</td>
<td>HDM induced rhinitis</td>
<td>XXXXXX</td>
<td>XX.XX.XX NA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes/No</td>
<td>XX</td>
</tr>
<tr>
<td></td>
<td>XXXX</td>
<td>XXXXXXXXX</td>
<td>XX.XX.XX/NA</td>
<td>Yes/No</td>
<td>Yes/No</td>
<td>XX</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*: if ongoing, years from start date to visit 1

Sorted by treatment, subject and number (no.)
| Treatment Subject No. | Medication        | Drug code | Indication | Dose Unit | Frequency Route | Start       | Stop       | Ongoing First IMP date | Start date | Stop date | Ongoing date | IMP date | First IMP date | Placebo/ XXXX | XXXXXXXXX | XXXXXXX | XXXXX | XXXX | XXXX | XXXX | XXXX | Yes/No | XX.XX.XX |
|-----------------------|-------------------|-----------|------------|-----------|-----------------|-------------|------------|------------------------|-------------|------------|---------------|-----------|----------------|----------------|-----------|----------|--------|------|------|------|------|------|--------|--------|---------|
| Placebo/ XXXX         | XXXXXXXXX         | XXXXXXXXX| XXXXXXXXX | XXXXXXXXX | XXXXXXXXX       | XXXXXXXXX   | XXXXXXXXX | XXXXXXXXX             |             |            |               |           |                |                | XXXXXXXXX | XXXXXXX | XXXXX | XXXX | XXXX | XXXX | XXXX | Yes/No | XX.XX.XX |

Sorted by treatment, subject and number (no.)
### Listing 1-13  OCS courses (FAS)

<table>
<thead>
<tr>
<th>Treatment Subject</th>
<th>All OCS courses</th>
<th>OCS during period 2</th>
<th>OCS during period 3A</th>
<th>OCS during Period 3B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/ 6DU/12DU</td>
<td>XXXX</td>
<td>XXXX</td>
<td>XXXX</td>
<td>XXXX</td>
</tr>
</tbody>
</table>

OCS = oral corticosteroid; course = OCS for at least 3 days
Sorted by treatment and subject
## Listing 1-14  Physical examination at screening, randomisation and end of trial (FAS)

<table>
<thead>
<tr>
<th>Treatment Subject</th>
<th>Visit</th>
<th>Head</th>
<th>Oral inspection</th>
<th>Respiratory</th>
<th>Heart</th>
<th>Abdomen</th>
<th>Urogenital</th>
<th>Musculoskeletal</th>
<th>Neurological</th>
<th>Lymph</th>
<th>Skin</th>
<th>Other abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/ 6DS/12DU</td>
<td>XXXX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Visit 1</td>
<td>Normal/</td>
<td>Normal/</td>
<td>Normal/</td>
<td>Normal/</td>
<td>Normal/</td>
<td>Normal/</td>
<td>Normal/</td>
<td>Normal/</td>
<td>Normal/</td>
<td>Normal/</td>
<td>Normal/</td>
</tr>
<tr>
<td></td>
<td>Visit 9</td>
<td>nor/</td>
<td>nor/</td>
<td>nor/</td>
<td>nor/</td>
<td>nor/</td>
<td>nor/</td>
<td>nor/</td>
<td>nor/</td>
<td>nor/</td>
<td>nor/</td>
<td>nor/</td>
</tr>
<tr>
<td></td>
<td>Visit 11</td>
<td>cr/</td>
<td>cr/</td>
<td>cr/</td>
<td>cr/</td>
<td>cr/</td>
<td>cr/</td>
<td>cr/</td>
<td>cr/</td>
<td>cr/</td>
<td>cr/</td>
<td>cr/</td>
</tr>
<tr>
<td></td>
<td>Visit 13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

nor = abnormal, not clinically relevant, cr = abnormal, clinically relevant, ND = not done
Sorted by treatment and subject
### Listing 1-15 Abnormal laboratory findings (FAS)

<table>
<thead>
<tr>
<th>Treatment Subject</th>
<th>Assessment</th>
<th>Visit</th>
<th>Visit Date</th>
<th>Result</th>
<th>Unit</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/6DU/12DU</td>
<td>Haematology/XXXXX</td>
<td>Visit 1/visit</td>
<td>XX.XX.XX</td>
<td>XXX</td>
<td>XXX-XXX</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chemistry/XXXXX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urinalysis/XXXXX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Only clinically significant laboratory assessments are displayed; UV = unscheduled visit
Sorted by treatment, subject and visit
### 2. IMP accountability, IMP exposure, ICS prescribed, visit dates and diary compliance

**Listing 2-1 IMP exposure (FAS)**

<table>
<thead>
<tr>
<th>Treatment Subject</th>
<th>IMP dispensed*</th>
<th>IMP returned¤</th>
<th>IMP used</th>
<th>First IMP date</th>
<th>Last IMP date</th>
<th>Days with IMP Exposure in TY</th>
<th>IMP compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/6DU/12DU</td>
<td>XXX</td>
<td>XXX</td>
<td>XXXXXXX/NA</td>
<td>X.X.X.X</td>
<td>X.X.X.X</td>
<td>XX</td>
<td>XX%</td>
</tr>
</tbody>
</table>

* cumulative number from visits 3, 6, 8, 10, and unscheduled visits
¤ cumulative number from visits 6, 8, 10, 13, and unscheduled visits
TY = treatment years (number of IMP used/364); IMP compliance = IMP used/days with IMP×100
Sorted by treatment and subject
### Listing 2-2  ICS prescribed (FAS)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Subject</th>
<th>Visit No.</th>
<th>Total daily dose ICS prescribed (μg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>XXXXX</td>
<td>TC XX/</td>
<td>UTC XX/</td>
</tr>
<tr>
<td>6DU/12DU</td>
<td></td>
<td>UV XX/</td>
<td>UTC XX/</td>
</tr>
</tbody>
</table>

TC = telephone contact; UV = unscheduled visit; UTC = unscheduled telephone contact
Sorted by treatment, subject and number (No.)
### Listing 2-3  Subject visit dates – Visits 1-8 (FAS)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Subject Random number</th>
<th>Informed consent</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Visit 4</th>
<th>Visit 5</th>
<th>Visit 6</th>
<th>Visit 7*</th>
<th>Visit 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/ 6DU/12DU</td>
<td>XXXXX XXXX</td>
<td>XX.XX.XX XX.XX.XX XX.XX.XX XX.XX.XX XX.XX.XX XX.XX.XX XX.XX.XX XX.XX.XX/ND XX.XX.XX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Visit 7 was only applicable for subjects randomized before 01 January 2012; ND = not done.

Sorted by treatment and subject.
### Listing 2-4 Subject visit dates – Visits 9-End-of-trial (FAS)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Subject Random number</th>
<th>Visit 9</th>
<th>TC1</th>
<th>Visit 10</th>
<th>Visit 11</th>
<th>TC2</th>
<th>Visit 12</th>
<th>Visit 13</th>
<th>TC Follow up</th>
<th>UV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/ 6DU/12DU</td>
<td>XXXXX</td>
<td>XX.XX.XX</td>
<td>XX.XX.XX</td>
<td>XX.XX.XX</td>
<td>XX.XX.XX</td>
<td>XX.XX.XX</td>
<td>XX.XX.XX</td>
<td>XX.XX.XX</td>
<td>XX.XX.XX</td>
<td>XX.XX.XX/XX.XX/…</td>
</tr>
</tbody>
</table>

TC = telephone contact; UV = unscheduled visit
Sorted by treatment and subject
## Listing 2-5  Diary compliance (FAS)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Subject</th>
<th>PP</th>
<th>N(days)</th>
<th>N(records)</th>
<th>% diary compliance</th>
<th>N(days)</th>
<th>N(records)</th>
<th>% diary compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/6DU</td>
<td>XXXX</td>
<td>Yes/No</td>
<td>XXX</td>
<td>XXX</td>
<td>XXX</td>
<td>XXX</td>
<td>XXX</td>
<td>XXX</td>
</tr>
</tbody>
</table>

PP = per protocol; N(days) = number of days in period; N(records) = number of days with any diary records
Sorted by treatment and subject
### 3. Efficacy data

#### Listing 3-1 Primary endpoint data (FAS)

<table>
<thead>
<tr>
<th>Treatment Subject</th>
<th>Visit 9</th>
<th>Asthma exacerbation</th>
<th>Discontinuation</th>
<th>Trial completion</th>
<th>Time to*: trial completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/XXXXX</td>
<td>XXXX</td>
<td>XX,XX,XX/NA</td>
<td>XX/NA</td>
<td>XX/NA</td>
<td>XX/NA</td>
</tr>
<tr>
<td>6DU/12DU</td>
<td>XXXX</td>
<td>XX,XX,XX/NA</td>
<td>XX/NA</td>
<td>XX/NA</td>
<td>XX/NA</td>
</tr>
</tbody>
</table>

*Time to* = days from visit 9 to: ... ; NA = not applicable

Sorted by treatment, subject and number (no.)
### Listing 3-2  All asthma exacerbations (FAS: subjects with asthma exacerbation)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Subject</th>
<th>Asthma exacerbation no.</th>
<th>Visit 9 date</th>
<th>Date of change in treatment due to asthma exacerbation</th>
<th>Time to* related con. med. number</th>
<th>Related ICS prescribed number</th>
<th>Severity of exacerbations</th>
<th>SAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/6DU/12DU</td>
<td>XXXXX</td>
<td>X</td>
<td>XX.XX.XX</td>
<td>XX.XX.XX</td>
<td>XX</td>
<td>XX/NA</td>
<td>XX/NA</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

* Time to = days from visit 9 to asthma exacerbation; Moderate asthma exacerbation = criterion a, b, c and/or d fulfilled, but without fulfillment of criterion e or f; Severe asthma exacerbation = criterion e and/or f fulfilled

con. med. = concomitant medication; NA = not applicable

Sorted by treatment, subject and number (no.)
### Listing 3-3  Asthma exacerbation criteria fulfilled (FAS)

<table>
<thead>
<tr>
<th>Treatment Subject</th>
<th>Asthma exacerbation no.</th>
<th>Nocturnal symptom awakening score</th>
<th>SABA use</th>
<th>Decrease in PEF</th>
<th>Decrease in FEV₁</th>
<th>Visit to ER/UV -CS</th>
<th>ER + SCS Hospitalisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/XXXXX 600/1200</td>
<td>XXXX</td>
<td>Yes/No/NA</td>
<td>Yes/No/NA</td>
<td>Yes/No/NA</td>
<td>Yes/No/NA</td>
<td>Yes/No/NA</td>
<td>Yes/No/NA</td>
</tr>
</tbody>
</table>

ER = emergency room; UV = unscheduled visit; SCS = systemic corticosteroid; NA = not applicable; NK = not known

Sorted by treatment, subject and number (no.)
<table>
<thead>
<tr>
<th>Treatment Subject</th>
<th>Visit 1</th>
<th>Visit 2&lt;sup&gt;*&lt;/sup&gt;</th>
<th>Visit 3</th>
<th>Visit 4</th>
<th>Visit 5</th>
<th>Visit 6</th>
<th>Visit 7</th>
<th>Visit 8</th>
<th>Visit 9</th>
<th>Visit 10</th>
<th>Visit 11</th>
<th>Visit 12</th>
<th>Visit 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/ 6DU/12DU</td>
<td>X.X</td>
<td>X.X/X.X/X.X</td>
<td>X.X</td>
<td>X.X</td>
<td>X.X</td>
<td>X.X</td>
<td>X.X</td>
<td>X.X</td>
<td>X.X</td>
<td>X.X</td>
<td>X.X</td>
<td>X.X</td>
<td>X.X</td>
</tr>
</tbody>
</table>

<sup>*</sup>: some subjects may have more than one value for "before visit 3"; baseline value is the last visit 3 value

Sorted by treatment and subject
### Listing 3-5  ACQ item scores (FAS)

<table>
<thead>
<tr>
<th>Treatment Subject</th>
<th>Items #</th>
<th>Visit 1</th>
<th>Visit 3*</th>
<th>Visit 4</th>
<th>Visit 5</th>
<th>Visit 6</th>
<th>Visit 7</th>
<th>Visit 8</th>
<th>Visit 9</th>
<th>Visit 10</th>
<th>Visit 11</th>
<th>Visit 12</th>
<th>Visit 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/XXXXX</td>
<td>Awakenings</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>6DU/12DU</td>
<td>Symptoms</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Limitations</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>SOB</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Wheeze</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
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<td>X</td>
</tr>
<tr>
<td></td>
<td>SABA</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>FEV1</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

#: all items are scored on a 0-6 scale; *: some subjects may have more than one value for "before visit 3"; baseline value if the last value

SOB: shortness of breath

Sorted by treatment and subject
**Listing 3-6  Average asthma daytime symptoms (FAS)**

<table>
<thead>
<tr>
<th>Treatment Subject</th>
<th>Period</th>
<th>Total asthma daytime symptom score</th>
<th>Cough</th>
<th>Wheeze</th>
<th>Chest tightness/shortness of breath</th>
<th>Exercise induced symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/6 XXXXX</td>
<td>Baseline</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
<tr>
<td>DU/12DU</td>
<td>Period 2B</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
<tr>
<td></td>
<td>Period 3A+</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
<tr>
<td></td>
<td>Period 3A+3B*</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
</tbody>
</table>

* during the first asthma exacerbation free period of the period
Sorted by treatment and subject
## Listing 3-7  Numbers of asthma symptom free days, nights, 24-hour periods during period 3 (FAS)

<table>
<thead>
<tr>
<th>Treatment Subject</th>
<th>Duration, period 3*</th>
<th>Asthma symptom free days</th>
<th>Symptom free days/duration</th>
<th>Asthma symptom free nights</th>
<th>Symptom free nights/duration</th>
<th>Asthma symptom free 24-hour periods</th>
<th>Symptom free 24-hour periods/duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/6 XXXXX</td>
<td>XX</td>
<td>XX</td>
<td>XX.X</td>
<td>XX</td>
<td>XX.X</td>
<td>XX</td>
<td>XX.X</td>
</tr>
<tr>
<td>06/1226</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* days from visit 9 to visit 13/discontinuation date
Sorted by treatment and subject
## Listing 3-8  PEF, nocturnal awakenings and SABA use (FAS)

<table>
<thead>
<tr>
<th>Treatment Subject</th>
<th>Period</th>
<th>AN PEF</th>
<th>PM PEF</th>
<th>PEF diurnal variability</th>
<th>Asthma nocturnal symptom score</th>
<th>Nocturnal awakenings</th>
<th>Nocturnal awakenings requiring SABA use</th>
<th>24-hour SABA use</th>
<th>SABA use</th>
<th>SABA use</th>
<th>SABA use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/6 XXXXX</td>
<td>Baseline</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
<tr>
<td>2G/1DO</td>
<td>Period 2B</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
<tr>
<td></td>
<td>Period 3A</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
<tr>
<td></td>
<td>Period 3A³B³</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
<td>XX.X</td>
</tr>
</tbody>
</table>

* during the first asthma exacerbation free period of the period

Sorted by treatment and subject
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Subject</th>
<th>Visit 1</th>
<th>Visit 3</th>
<th>Visit 4</th>
<th>Visit 5</th>
<th>Visit 6</th>
<th>Visit 7</th>
<th>Visit 8</th>
<th>Visit 9</th>
<th>Visit 10</th>
<th>Visit 11</th>
<th>Visit 12</th>
<th>Visit 13</th>
<th>UV X/ UV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/6</td>
<td>XXXX</td>
<td>X.XX</td>
<td>X.XX</td>
<td>X.XX</td>
<td>X.XX</td>
<td>X.XK</td>
<td>X.XK</td>
<td>X.XK</td>
<td>X.XK</td>
<td>X.XK</td>
<td>X.XK</td>
<td>X.XK</td>
<td>X.XK</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND = not done; UV = unscheduled visit
Sorted by treatment and subject
# Listing 3-10  FEV₁ in % of predicted (FAS)

<table>
<thead>
<tr>
<th>Treatment Subject</th>
<th>Visit 1</th>
<th>Visit 3</th>
<th>Visit 4</th>
<th>Visit 5</th>
<th>Visit 6</th>
<th>Visit 7</th>
<th>Visit 8</th>
<th>Visit 9</th>
<th>Visit 10</th>
<th>Visit 11</th>
<th>Visit 12</th>
<th>Visit 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/6DU/12DU</td>
<td>XXXX</td>
<td>XXXX</td>
<td>XXXX</td>
<td>XXXX</td>
<td>XXXX</td>
<td>XXXX</td>
<td>XXXX</td>
<td>XXXX</td>
<td>Yes/No</td>
<td>XXXX</td>
<td>Yes/No</td>
<td>XXXX</td>
</tr>
</tbody>
</table>

Sorted by treatment and subject.
4. Quality of life and pharmacoeconomic data

Listing 4-1 Average and domain AQLQ (FAS)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Subject</th>
<th>AQLQ overall</th>
<th>Visit 3</th>
<th>Visit 6</th>
<th>Visit 8</th>
<th>Visit 9</th>
<th>Visit 10</th>
<th>Visit 11</th>
<th>Visit 13</th>
<th>UV</th>
<th>UV related to asthma exacerbation number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/</td>
<td>XXXX</td>
<td>XXX</td>
<td>XXX</td>
<td>XXX</td>
<td>XXX</td>
<td>XXX</td>
<td>XXX</td>
<td>XXX</td>
<td>XXX</td>
<td>UV</td>
<td>XXX/NA</td>
</tr>
<tr>
<td>6DU/12DU</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

 UV: unscheduled visit; NA: not applicable; Visit 3 corresponds to baseline value
Sorted by treatment and subject
### Listing 4-2  Pharmacoeconomic questions asked at visit 1, relating to past 12 months (FAS)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Subject</th>
<th>Days missed from work*</th>
<th>Visits to GP</th>
<th>Visits to ER</th>
<th>Hospitalisations</th>
<th>Courses of SCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/</td>
<td>XXXX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td>6DU/12DU</td>
<td>XXXX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
</tbody>
</table>

* Only to be answered if subject was employed in the past 12 months

GP = general practitioner; ER = emergency room; SCS = systemic corticosteroid
Sorted by treatment and subject
### Listing 4-3  Pharmacoeconomic questions relating to period since last visit (FAS)

<table>
<thead>
<tr>
<th>Treatment Subject</th>
<th>Assessments</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Visit 4</th>
<th>Visit 5</th>
<th>Visit 6</th>
<th>Visit 7</th>
<th>Visit 8</th>
<th>Visit 9</th>
<th>Visit 10</th>
<th>Visit 11</th>
<th>Visit 12</th>
<th>Visit 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/6DU/12DU</td>
<td></td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
</tbody>
</table>

GP = general practitioner (or specialist other than trial site); ER = emergency room
Sorted by treatment, subject and visit
### Listing 4-4  
**SF-36 component scores (FAS)**

<table>
<thead>
<tr>
<th>Treatment Subject</th>
<th>SF-36 Component Scores</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Visit 4</th>
<th>Visit 5</th>
<th>Visit 6</th>
<th>Visit 7</th>
<th>Visit 8</th>
<th>Visit 9</th>
<th>Visit 10</th>
<th>Visit 11</th>
<th>Visit 12</th>
<th>Visit 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/6DU/12DU</td>
<td>Physical component summary (PCS)</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td></td>
<td>Mental component summary (MCS)</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td></td>
<td>Physical functioning (PF)</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td></td>
<td>Role-physical (RP)</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td></td>
<td>Bodily pain (BP)</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td></td>
<td>General health (GH)</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td></td>
<td>Vitality (VT)</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td></td>
<td>Social functioning (SF)</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td></td>
<td>Role-emotional (RE)</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td></td>
<td>Mental health (MH)</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
</tbody>
</table>

PCS is composed of PF, RP, BP, and GH; MCS is composed of VT, SF, RE and MH.

Sorted by treatment and subject.
### Listing 4-5  WPAI:Asthma scores (FAS)

<table>
<thead>
<tr>
<th>Treatment Subject</th>
<th>WPAI:Asthma scores</th>
<th>Visit 3</th>
<th>Visit 6</th>
<th>Visit 9</th>
<th>Visit 10</th>
<th>Visit 11</th>
<th>Visit 12</th>
<th>Visit 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/XXXXX</td>
<td>Absenteeism (work time missed)</td>
<td>XX%/ND</td>
<td>XX%/ND</td>
<td>XX%/ND</td>
<td>XX%/ND</td>
<td>XX%/ND</td>
<td>XX%/ND</td>
<td>XX%/ND</td>
</tr>
<tr>
<td>6DU/12DU</td>
<td>Presenteesism (impairment at work)</td>
<td>XX%/ND</td>
<td>XX%/ND</td>
<td>XX%/ND</td>
<td>XX%/ND</td>
<td>XX%/ND</td>
<td>XX%/ND</td>
<td>XX%/ND</td>
</tr>
<tr>
<td></td>
<td>Work productivity loss*</td>
<td>XX%/ND</td>
<td>XX%/ND</td>
<td>XX%/ND</td>
<td>XX%/ND</td>
<td>XX%/ND</td>
<td>XX%/ND</td>
<td>XX%/ND</td>
</tr>
<tr>
<td></td>
<td>Activity Impairment</td>
<td>XX%</td>
<td>XX%</td>
<td>XX%</td>
<td>XX%</td>
<td>XX%</td>
<td>XX%</td>
<td>XX%</td>
</tr>
</tbody>
</table>

* absenteeism plus presenteesism; ND = absenteeism, presenteesism and work productivity are only done for subjects currently employed (Yes to question 1)

Sorted by treatment and subject
### Listing 4-6  TSQM II scores (FAS: Germany and France)

<table>
<thead>
<tr>
<th>Treatment Subject</th>
<th>TSQM II Domains</th>
<th>Visit 4</th>
<th>Visit 8</th>
<th>Visit 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/6DU/12DU</td>
<td>Effectiveness</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td></td>
<td>Side effects</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td></td>
<td>Convenience</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td></td>
<td>Overall satisfaction</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
</tbody>
</table>

Sorted by treatment and subject

Effectiveness: Q1-Q2; Side effects: Q3-Q6; Convenience: Q7-Q9; Overall satisfaction: Q10-Q11
### 5. Pharmacodynamic data

#### Listing 4-1 Specific immunology

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Subject</th>
<th>HDM</th>
<th>Visit 1</th>
<th>Visit 4</th>
<th>Visit 6</th>
<th>Visit 9</th>
<th>Visit 13</th>
<th>Visit 1</th>
<th>Visit 4</th>
<th>Visit 6</th>
<th>Visit 9</th>
<th>Visit 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/</td>
<td>XXXXX</td>
<td>DP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>XXXX/12</td>
<td>DP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DP = D.pteronyssinus, DF = D.farinae
Sorted by treatment and subject
6. Safety data

Listing 6-1 All adverse events occurring prior to first IMP administration (all subjects)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Subject</th>
<th>PT</th>
<th>Description</th>
<th>AE start</th>
<th>AE stop</th>
<th>Severity</th>
<th>Outcome</th>
<th>Med. given</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF/Place</td>
<td>XXXX</td>
<td>XXXXX</td>
<td></td>
<td>XXXX.XX.XX</td>
<td>XXXX.XX.XX</td>
<td>Mild/</td>
<td>Recovered/Recovered with sequelae/Not recovered/Fatal/Unknown</td>
<td>Yes/No</td>
</tr>
<tr>
<td></td>
<td>XXXX</td>
<td>XXXXX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SF = screening failures; PT = preferred term; events are coded in MedDRA 15.0
Sorted by treatment, subject and AE no.
### Listing 6-2  All AEs* (safety analysis set)

| Treatment | Subject | AE no. | PT | AE start | AE stop | Relation to IMP | Severity | Change to IMP | Outcome | Med. given | SAE |
|-----------|---------|--------|----|----------|---------|-----------------|----------|---------------|---------|------------|-----|------|
| Placebo/6 | XXXXX   | X:XX   | X:XX,XX | X:XX,XX,XX | Unlikely/Possible/None | Temporarily interrupted/IMP discontinued | Mild/Moderate/Severe | Yes/No | Yes/No | Yes/No | Yes/No |

* AEs are referring to events occurring after the first IMP administration; PT = preferred term; events are coded in MedDRA 15.0. Sorted by treatment, subject and AE No.
### Listing 6-3  All AEs* descriptions (safety analysis set)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Subject</th>
<th>AE no.</th>
<th>SOC</th>
<th>PT</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/6</td>
<td>Xxxxx</td>
<td>Xx</td>
<td>Xxxxxx</td>
<td>Xxxxxx</td>
<td>Xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx</td>
</tr>
</tbody>
</table>

* AEs are referring to events occurring after the first IMP administration; SOC = system organ class; PT = preferred terms; events are coded in MedDRA 15.0

Sorted by treatment, subject, and AE no.
### Listing 6-4 All SAEs (safety analysis set)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Subject</th>
<th>AE No.</th>
<th>PT</th>
<th>AE start</th>
<th>AE stop</th>
<th>Relation to IMP</th>
<th>Severity</th>
<th>Change to IMP</th>
<th>Outcome</th>
<th>Med. given</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/6</td>
<td>XXXX</td>
<td>XX</td>
<td>XXXXXXXXX XX.XX.AX XX.XX.AX</td>
<td>Unlikely/ Possible</td>
<td>Mild/None</td>
<td>Temporarily interrupted/ IMP discontinued</td>
<td>Recovered/Recovered with sequelae/Not recovered/Fatal/Unknown</td>
<td>Yes/No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** PT = preferred terms are coded in MedDRA 15.0

Sorted by treatment, subject, and AE no.
## Listing 6-5  Onset and resolution of AEs* (safety analysis set)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Subject</th>
<th>AE no.</th>
<th>PT</th>
<th>IMP start</th>
<th>AE start</th>
<th>AE stop</th>
<th>Onset since first IMP, in minutes</th>
<th>Onset since first IMP, in days¤</th>
<th>Resolution of AE, in days#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/6</td>
<td>XXX</td>
<td>XXXX</td>
<td>XX</td>
<td>XXXXXXXX</td>
<td>XX.XX.XX</td>
<td>XX:XX</td>
<td>NA/NA</td>
<td>NA/NA</td>
<td>NA/NA</td>
</tr>
</tbody>
</table>

* AEs are referring to events occurring after the first IMP administration; ¤: An onset of 1 day means that the AE has started on the day of first IMP intake; #: Resolution of an AE is defined as days from start of the AE until the AE is resolved; SOC = system organ class; PT = preferred term; events are coded in MedDRA 15.0

Sorted by treatment, subject, and AE no.
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Subject</th>
<th>AE no.</th>
<th>PT</th>
<th>AE start</th>
<th>AE stop</th>
<th>Relation to IMP</th>
<th>Severity</th>
<th>Outcome</th>
<th>Med. given</th>
<th>SAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>6</td>
<td>XXXXX</td>
<td>XX</td>
<td>XXXXX</td>
<td>XXXX</td>
<td>Unlikely/Mild/Moderate</td>
<td>Severe</td>
<td>Recovered/Recovered with sequelae/Not recovered/Fatal/Unknown</td>
<td>Yes/No</td>
<td>Yes/No</td>
</tr>
<tr>
<td>DU 12</td>
<td>DU</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*: AEs are referring to events occurring after the first IMP administration; PT = preferred term; events are coded in MedDRA 15.0.

Sorted by treatment, subject, and AE no.
### Listing 6-7  Pregnancy test (safety analysis set: all subjects with childbearing potential)

<table>
<thead>
<tr>
<th>Treatment Subject</th>
<th>Visit</th>
<th>Date</th>
<th>Result of urine pregnancy test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/ XXXXX</td>
<td>Visit 1</td>
<td>XX,XX,XX</td>
<td>Positive/Negative/ND</td>
</tr>
<tr>
<td>6DU/12DU</td>
<td>Visit 3</td>
<td>XX,XX,XX</td>
<td>Positive/Negative/ND</td>
</tr>
<tr>
<td></td>
<td>Visit 13</td>
<td>XX,XX,XX</td>
<td>Positive/Negative/ND</td>
</tr>
</tbody>
</table>

ND = not done

Sorted by treatment, subject and visit
Statistical Analysis Plan – Appendix C

Figure Shells

Trial ID: MT-04

Efficacy of ALK house dust mite allergy immunotherapy tablet in subjects with house dust mite induced asthma

Investigational Medicinal Product: ALK HDM AIT 6 DU and 12 DU

Development phase: III

EudraCT no: 2010-018621-19

Sponsor: Group Clinical Development
ALK-Abelló A/S
DK-2970 Hørsholm, Denmark
Phone: +45 45747445

Document status: Final

Date: 24 June 2013

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Efficacy - Figures

1.1 Kaplan-Meier plot of time to first moderate or severe asthma exacerbation (FAS)

(Fictive data)
1.2 Cumulative hazards of time to first moderate or severe asthma exacerbation (FAS) by treatment group.
1.3 Cumulative proportion of first moderate - and first severe asthma exacerbation (FAS)

Cause-specific cumulative incidence functions.

(Fictive Data)
1.4 **Cumulative proportion of first asthma exacerbation with deterioration in symptoms (FAS)**

Similar to figure 1.2, but incidence functions are plotted for both:

a) All moderate or severe asthma exacerbations for which criterion a) is fulfilled

b) All moderate or severe asthma exacerbations for which criterion a) is *not* fulfilled

1.5 **Cumulative proportion of first asthma exacerbation with increased use of SABA (FAS)**

Similar to figure 1.2, but incidence functions are plotted for both:

c) All moderate or severe asthma exacerbations for which criterion b) is fulfilled

d) All moderate or severe asthma exacerbations for which criterion b) is *not* fulfilled

1.6 **Cumulative proportion of first asthma exacerbation with deterioration in lung function (FAS)**

Similar to figure 1.2, but incidence functions are plotted for both:

e) All moderate or severe asthma exacerbations for which criterion c) is fulfilled

f) All moderate or severe asthma exacerbations for which criterion c) is *not* fulfilled
1.7 Mean total daily dose of ICS (mcg) by visit (FAS)

A plot of the treatment group mean (95% confidence interval) versus the visit number (3, 4, 5, 6, 7, 8, -9, 9+, 10, -11, 11+, 12, -13, 13+). Note that, for visit 9, 11 and 13 both the most recent previously prescribed dose as well as the prescribed dose at the visit is presented. This corresponds two presenting the mean dose at visit entry as well as at the time-point of leaving the visit.

1.8 Distribution of the total daily dose of ICS (mcg) at baseline and visit 9 (FAS)

A histogram of the ICS dose (mcg) for each treatment group presented at baseline and at visit 9 (ICS reduction visit). Baseline visit is visit 3 and the dose at baseline is the prescribed total daily dose at visit 3. At visit 9 the dose presented is the most recent previously prescribed total daily dose of ICS at visit 9. This corresponds to the dose of ICS at entry to visit 9.

1.9 Mean predicted FEV1 by visit (FAS)

A plot of the treatment group mean (95% confidence interval) versus the visit number (3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13).

1.10 Mean overall ACQ by visit (FAS)

A plot of the treatment group mean (95% confidence interval) versus the visit number (3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13).

1.11 Mean change from baseline in overall ACQ by visit (FAS)

A plot of the treatment group mean (95% confidence interval) versus the visit number (4, 5, 6, 7, 8, 9, 10, 11, 12, 13).

1.12 Mean overall AQLQ by visit (FAS)

A plot of the treatment group mean (95% confidence interval) versus the visit number (3, 6, 8, 9, 10, 11, 12, 13).
1.13 Mean change from baseline in overall AQLQ by visit (FAS)

A plot of the treatment group mean (95% confidence interval) versus the visit number (6, 8, 9, 10, 11, 12, 13).

1.14 Mean overall daytime asthma symptoms score (FAS)

A plot of the treatment group mean (95% confidence interval) of the weekly average overall asthma daytime symptoms versus the baseline, the 4 weeks between visit 8 and visit 9, and then weekly from visit 9 to visit 13.

1.15 Mean change from baseline in log10-transformed specific IgE against Der p (FAS)

A plot of the treatment group mean (95% confidence interval) versus the visit number (4, 6, 9, 13).

1.16 Mean change from baseline in log10-transformed specific IgE against Der f (FAS)

A plot of the treatment group mean (95% confidence interval) versus the visit number (4, 6, 9, 13).

1.17 Mean change from baseline in log10-transformed specific IgG4 against Der p (FAS)

A plot of the treatment group mean (95% confidence interval) versus the visit number (4, 6, 9, 13).

1.18 Mean change from baseline in log10-transformed specific IgG4 against Der f (FAS)

A plot of the treatment group mean (95% confidence interval) versus the visit number (4, 6, 9, 13).
2 Safety - Figures

2.1 Kaplan-Meier plot of time to discontinuation - all causes (FAS)

2.2 Kaplan-Meier plot of time to discontinuation due to AE (FAS)
Statistical Analysis Plan – Appendix D – PP analysis set

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

Clinical Trial ID: MT-04
EudraCT No.: 2010-018621-19
Investigational Medicinal Product: ALK house dust mite (HDM) allergy immunotherapy tablet (AIT)
Development Phase: III
Sponsor: Global Clinical Development
ALK-Abelló A/S
DK-2970 Hørsholm
Phone: +45 45747445

Document Status: Final
Date: 24 June 2013
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1 Criteria for PP analysis set

The PP analysis set comprises subjects who did not have major protocol deviations that influence the primary endpoint. Consequently, it has been decided that the PP analysis set comprises subjects according to criteria listed in Table 1-1 and Table 1-2.

Table 1-1: Deviations from inclusion/exclusion criteria

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Comment</th>
<th>Incl. in PP</th>
<th>Excl. from PP</th>
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<tr>
<td><strong>Inclusion criteria</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I3 (HDM asthma)</td>
<td>Required that subjects have relevant disease</td>
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<td>X</td>
</tr>
<tr>
<td>I5 (recent ICS use)</td>
<td>Required that subjects have relevant disease severity</td>
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<td>X</td>
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<tr>
<td>I6 (reversibility)</td>
<td>Acceptable if test is &gt;2 years at randomisation</td>
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<tr>
<td></td>
<td>Not acceptable if test is not available or test is negative prior randomisation</td>
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<td>X</td>
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<tr>
<td>I7 (ACQ, visit 1)</td>
<td>Not acceptable if ACQ is &lt;1 at visit 1</td>
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<td>X</td>
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<tr>
<td>I8 (ACQ, visit 3)</td>
<td>Acceptable if ACQ is &gt;1.5 at visit 3</td>
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<tr>
<td></td>
<td>Not acceptable if ACQ is &lt;1 at visit 3</td>
<td></td>
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<tr>
<td>I11 (rhinitis)</td>
<td>Required that subjects have relevant disease</td>
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<tr>
<td>I12 (SPT)</td>
<td>Required that subjects have relevant disease</td>
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<tr>
<td>I13 (IgE)</td>
<td>Required that subjects have relevant disease</td>
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<tr>
<td>I14 (pregnancy)</td>
<td>Excluded from trial and thus also from PP</td>
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<tr>
<td>I15 (willingness to comply)</td>
<td>Required that subjects were willing to comply with protocol</td>
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<td><strong>Exclusion criteria</strong></td>
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<tr>
<td>E1 (other persistent allergy)</td>
<td>Potentially interferes with primary endpoint</td>
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<td>X</td>
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<tr>
<td>E2 (seasonal allergy)</td>
<td>Potentially interferes with primary endpoint</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>E3 (previous HDM SIT)</td>
<td>Potentially interferes with primary endpoint</td>
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<td>X</td>
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<tr>
<td>E6 (prohibited medication)</td>
<td>See Table 1-2</td>
<td></td>
<td>X</td>
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<tr>
<td>E15 (immunosuppressive disease)</td>
<td>Potentially interferes with primary endpoint</td>
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<td>Deviation</td>
<td>Comment</td>
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<td>----------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
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<td>---------------</td>
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<tr>
<td>No visit 9</td>
<td>Only subjects attending visit 9 is included</td>
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<td>50% ICS reduction</td>
<td>Acceptable if reduced between visit 9 and 10</td>
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<td>Not acceptable if not reduced at all</td>
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<td>Acceptable if dose reduced less than 50% (e.g. from 600 mcg to 400 mcg)</td>
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<tr>
<td>IMP compliance</td>
<td>IMP compliance &lt;75%</td>
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<tr>
<td>Use of prohibited medications with influence on baseline diary data during the last 14 days prior to randomisation</td>
<td>Other IMP/anti-IgE/oral or parenteral steroid/LABA/LAMA/theophylline/cromoglicic acid</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Use of prohibited medications with influence on primary endpoint from V9 until first asthma exacerbation</td>
<td>Other IMP/anti-IgE/nasal, oral or parenteral steroid/LABA/LAMA/theophylline/cromoglicic acid</td>
<td>X</td>
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<tr>
<td>Wrong IMP administered</td>
<td>Subject 50261 received wrong IMP-number from visit 8 until 30 Nov 2012 (app. 3 months)</td>
<td>X</td>
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</tr>
<tr>
<td>Change in treatment without asthma exacerbation criteria fulfilled</td>
<td>Subject 50736 had a change in ICS during period 3 due to increased symptoms without meeting the cut off for an exacerbation</td>
<td>X</td>
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</tbody>
</table>
2 Subjects excluded from PP analysis set

The FAS includes 834 subjects.

Table 2-1 lists the subjects who are excluded from the PP analysis set (PP=0). In total, 170 subjects (20.4%) are excluded from the PP analysis set.

78 of the subjects excluded from the PP analysis set attended visit 9 and are thus providing data to the primary efficacy analysis. A number of the subjects excluded had >1 major protocol deviation that were considered to influence the primary endpoint.

2.1 Exclusions based on trial inclusion criteria

2.1.1 I3
Subjects that significantly violate inclusion criterion I3 are defined as subjects with a clinical history of HDM allergic rhinitis of less than 12 months at start of screening. No subjects are excluded from the PP analysis set due to violation of I3.

2.1.2 I5
Subjects that significantly violate inclusion criterion I5 are defined as subjects using 400-1200 μg budesonide at randomisation. 3 subjects are excluded from the PP analysis set due to violation of I5.

2.1.3 I6
Subjects that significantly violate inclusion criterion I6 are defined as subjects who did not have a reversibility test (neither historic nor performed during screening) or had a negative reversibility test at visit 1 (despite a positive historical test). For supporting the diagnosis of asthma it is defined as acceptable that the historical test is 2 years and some months. 9 subjects are excluded from the PP analysis set due to violation of I6.

2.1.4 I7 or I8
Subjects that significantly violate inclusion criterion I7 or I8 are defined as subjects who had an ACQ value of <1 at visit 1 or visit 3. These subjects are well-controlled and therefore not part of the target population to assess improved control in terms of prolonged time to asthma exacerbation. 8 subjects are excluded from the PP analysis set due to violation of I7 and 5 subjects are excluded due to violation of I8.

2.1.5 I11, I12 or I13
Subjects that significantly violate inclusion criterion I11, I12 or I13 are defined as subjects who do not have a clinical history of HDM-induced rhinitis (I11), a positive SPT to HDM (I12) or a positive specific IgE to HDM (I13). That is subjects that do not necessarily have the relevant disease for this treatment. No subjects are excluded from the PP analysis set due to violations of I11, I12, or I13.
2.1.6 I14
No subjects are excluded from the PP analysis set due to violation of I14 (pregnancy).

2.1.7 I15
No subjects are excluded from the PP analysis set due to violation of I15 (willingness to comply with trial regimen).

2.2 Exclusions based on trial exclusion criteria

2.2.1 E1 or E2
Subjects that significantly violate exclusion criterion E1 and E2 are defined as subjects with a clinical history of other symptomatic respiratory allergies, persistent or intermittent, during the efficacy assessment period. No subjects are excluded from the PP analysis set due to violation of E1 while 2 subjects are excluded due to violation of E2.

2.2.2 E3
Subjects that significantly violate exclusion criterion E3 are defined as subjects with previous treatment with immunotherapy with HDM allergen for >1 months during the previous 5 years. 1 subject is excluded from the PP analysis set due to violation of E3.

2.2.3 E6
Subjects that significantly violate exclusion criterion E6 are defined as subjects using prohibited medication influencing baseline assessments (other IMP/anti-IgE/oral or parenteral steroid/LABA/LAMA/theophylline/cromoglicic acid) during the baseline period (the last 14 days prior to visit 3). 9 subjects are excluded from the PP analysis set due to violation of E6.

2.2.4 E15
Subjects that significantly violate exclusion criterion E15 are defined as subjects using immunosuppressive treatment (ATC code L04 or L01) within 3 months prior to screening (except for steroids for allergic symptoms). No subjects are excluded from the PP analysis set due to violation of E15.

2.3 Exclusions based on other criteria

2.3.1 No visit 9
To be included in the primary efficacy analysis, it is required that subjects attend visit 9. Thus subjects discontinuing the trial prior to visit 9 are not part of the PP analysis set. 92 subjects are excluded from the PP analysis set due to violation of the visit 9 criterion.

2.3.2 50% ICS reduction at visit 9
It is of major influence on the primary endpoint that subjects are reduced in ICS use around visit 9. Further, visit 9 is ‘time=0’ for all subjects for the primary efficacy analysis.
Subjects that significantly violate the criterion of 50% reduction at visit 9 are defined as subjects attending visit 9, which were not reduced in ICS no later than visit 10. 8 subjects are excluded from the PP analysis set due to violation of the 50% ICS reduction at visit 9 criterion.

2.3.3 IMP compliance

Subjects that significantly violate the IMP compliance criterion are defined as subjects attending visit 9 and having a compliance of <75% from visit 3 to end of trial. IMP compliance is calculated as the number of tablets used (dispensed-returned) divided by the number of days from first IMP to last IMP (or in case of missing last IMP date, to end of trial date) and multiplied by 100%.

10 subjects are excluded from the PP analysis set due to violation of the IMP compliance criterion.

2.3.4 Use of prohibited medication

Subjects that significantly violate the use of prohibited medication criterion are defined as subjects using prohibited medication during the last 14 days prior to randomisation (PM1: other IMP/ anti-IgE/ oral or parenteral steroid/ LABA/ LAMA/ theophylline/ cromoglicic acid) or from visit 9 until first asthma exacerbation (PM3: other IMP/ anti-IgE/ nasal, oral or parenteral steroid/ LABA/ LAMA/ theophylline/ cromoglicic acid).

5 subjects are excluded from the PP analysis set due to violation of the PM1 criterion and 31 subjects are excluded due to violation of the PM3 criterion.

2.3.5 Other reasons

1 subject (# 50261) received wrong IMP from visit 8 until 30 Nov 2012 (app. 3 months) and is therefore excluded from the PP analysis set.

1 subject (#50736) had a change in ICS prescription during period 3 due to increased symptoms without meeting the cut off for an exacerbation. This subject is excluded from the PP analysis set.
## Table 2-1: Subjects excluded from PP analysis set

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<th>Subject Number</th>
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**Table notes:**
- I8-pp: ACQ>=1
- V9: Attend visit 9
- V9-ICS: ICS reduction at visit 9
- IMP-C: Attend visit 9 and IMP compliance >=75%
- W-IMP: No wrong IMP administered
- ANC: Asthma exacerbation with no criteria fulfilled
- PM-1: Prohibited medication period 1
- PM-3: Prohibited medication during period 3
- 1=yes, 0=no, .=not applicable
- Sorted by subject number
- Program: Listing_pp_set.sas/ChL/24JUN13
Subjects excluded from PP analysis set

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I8-pp: ACQ>=1
V9: Attend visit 9
V9-IQS: ICS reduction at visit 9
IMP-C: Attend visit 9 and IMP compliance >=75%
W-IMP: No wrong IMP administered
ANC: Asthma exacerbation with no criteria fulfilled
PM-1: Prohibited medication period 1
PM-3: Prohibited medication during period 3
1=yes, 0=no, =not applicable
Sorted by subject number

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I8-pp: ACQ>=1  
V9: Attend visit 9  
V9-ICS: ICS reduction at visit 9  
IMP-C: Attend visit 9 and IMP compliance =>75%  
W-IMP: No wrong IMP administered  
ANC: Asthma exacerbation with no criteria fulfilled  
PM-1: Prohibited medication period 1  
PM-3: Prohibited medication during period 3  
1=yes, 0=no, .=not applicable  
Sorted by subject number  
Program: Listing_pp_set.sas/ChL/24JUN13
Subjects excluded from PP analysis set

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I8-pp: ACQ=>1
V9: Attend visit 9
V9-ICS: ICS reduction at visit 9
IMP-C: Attend visit 9 and IMP compliance =>75%
W-IMP: No wrong IMP administered
ANC: Asthma exacerbation with no criteria fulfilled
PM-1: Prohibited medication period 1
PM-3: Prohibited medication during period 3
1=yes, 0=no, .=not applicable
Sorted by subject number
Program: Listing_pp_set.sas/ChL/24JUN13
Subjects excluded from PP analysis set

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I8-pp: ACQ>=1
V9: Attend visit 9
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PM-3: Prohibited medication during period 3
1=yes, .no, .=not applicable

Sorted by subject number

Program: Listing_pp_set.sas/ChL/24JUN13
Subjects excluded from PP analysis set

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