Effective treatment of house dust mite–induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: Results from a randomized, double-blind, placebo-controlled phase III trial

Pascal Demoly, MD, PhD, a Waltraud Emminger, MD, b Dorte Rehm, PhD, c Vibeke Backer, MD, d Lene Tommerup, MSc, e and Jörg Kleine-Tebbe, MD e

From a the Department of Pulmonology, Division of Allergy, Hôpital Arnaud de Villeneuve, University Hospital of Montpellier, Paris; b the Allergy Outpatient Clinic, Renneville, Vienna; c ALK, Hørsholm; d the Department of Respiratory Medicine, Bispebjerg University Hospital, Copenhagen; and e Allergy & Asthma Center Westend, Outpatient Clinic & Research Center, Berlin. Supported by ALK, Hørsholm, Denmark.

Disclosure of potential conflict of interest: P. Demoly has received consultancy fees from ALK, Circassia, Stallergenes, Allergopharma, Thermo Fisher Scientific, and DBV; has received consultancy fees from Chiesi and Pierre Fabre Medicaments; and has received lecture fees from Menarini, MSD, AstraZeneca, and GlaxoSmithKline. W. Emminger has received consultancy fees and travel support from ALK. D. Rehm has stock/stock options in ALK. L. Tommerup was employed by ALK as a Clinical Project Manager for the trial. J. Kleine-Tebbe has received consultancy fees, travel support, participation fees, and speaker’s fees from ALK; is a board member for Leti; has received consultancy fees from Merck, Circassia, Leti, and Novartis; and has received lecture fees from ALK, Allergopharma, Benecard, HAL Allergy, Lofarma, Novartis, and Stallergenes. V. Backer declares no relevant conflicts of interest.

Received for publication January 19, 2015; revised June 16, 2015; accepted for publication June 17, 2015.

Available online August 17, 2015.

Corresponding author: Pascal Demoly, MD, PhD, Department of Pulmonology, Division of Allergy, Hôpital Arnaud de Villeneuve, University Hospital of Montpellier, 34295 Montpellier cedex 5, France and Sorbonne Universités, UPMC Paris 06, UMR-S 1136, IPELES, Equipe EPAR, 75013, Paris, France. E-mail: pascal.demoly@inserm.fr.

Allergic rhinitis (AR) is estimated to affect 17% to 29% of the population across Europe1 and is found in subjects of all ethnicities and ages. Allergy to house dust mite (HDM) is the most common inhalant allergy,2 with sensitization in 49% of subjects with a clinical diagnosis of AR in Western Europe.1 HDM-induced AR is also associated with an increased risk of asthma,3 and perennial exposure to HDM allergens might lead to more chronic and severe symptoms compared with other aeroallergens.4 In the European Community Respiratory Health Survey, including 1132 adults with current asthma, 48% had a positive skin prick test response to HDM allergens.5

HDM-induced AR can be treated with pharmacotherapy, including oral antihistamines and nasal steroids. However, investigations suggest that a substantial portion of patients’ symptoms are inadequately controlled,6 and allergen avoidance is not possible to an extent that relieves patients of their symptoms.7

Allergic rhinitis (AR) is estimated to affect 17% to 29% of the population across Europe1 and is found in subjects of all ethnicities and ages. Allergy to house dust mite (HDM) is the most common inhalant allergy,2 with sensitization in 49% of subjects with a clinical diagnosis of AR in Western Europe.1 HDM-induced AR is also associated with an increased risk of asthma,3 and perennial exposure to HDM allergens might lead to more chronic and severe symptoms compared with other aeroallergens.4 In the European Community Respiratory Health Survey, including 1132 adults with current asthma, 48% had a positive skin prick test response to HDM allergens.5

HDM-induced AR can be treated with pharmacotherapy, including oral antihistamines and nasal steroids. However, investigations suggest that a substantial portion of patients’ symptoms are inadequately controlled,6 and allergen avoidance is not possible to an extent that relieves patients of their symptoms.7

Allergy immunotherapy (AIT) is a treatment option that is complementary to pharmacotherapy and has a distinct mechanism of action. AIT modulates basic immunologic mechanisms of the allergic disease and is recognized as the only treatment option with the potential to provide long-term posttreatment benefits and alter the natural course of allergic disease.8 Subcutaneous AIT has been shown to decrease symptoms in patients with HDM-induced AR.9 10 11 However, sublingual allergy immunotherapy (SLIT) is more convenient because of home administration and is associated with fewer and less severe adverse events (AEs) than...
Abbreviations used

AE: Adverse event  
AR: Allergic rhinitis  
AIT: Allergy immunotherapy  
FAS: Full analysis set, observed data  
FAS-MI: Full analysis set with multiple imputation of missing data  
ICH: International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use  
ICS: Inhaled corticosteroid  
IMP: Investigational medicinal product  
LME: Linear mixed effect  
PP: Per protocol  
RQLQ: Rhinitis Quality of Life Questionnaire with Standardised Activities  
SLIT: Sublingual allergy immunotherapy  
TCRS: Total combined rhinitis score

A recent review of HDM SLIT trials concludes that reported results have been variable and that there is a need for more rigorous studies assessing standardized efficacy outcomes, treatment duration, and dose. Furthermore, there is a large variation in the quality and standardization of currently available SLIT products.

A recently published phase II trial with the SQ HDM SLIT-tablet (ALK, Hørsholm, Denmark) showed a beneficial effect on combined rhinitis symptom and medication scores in a subgroup of asthmatic patients with symptomatic AR at inclusion. Subsequently, the current phase III trial was initiated to confirm the efficacy of the highly standardized SQ HDM SLIT-tablet in subjects with moderate-to-severe AR.

METHODS

Ethics

The trial is identified by EudraCT number 2011-002277-38 and ClinicalTrials.gov Identifier NCT01454544. The trial was designed and conducted in accordance with the principles of the Declaration of Helsinki and conducted in compliance with the principles of the International Conference on Harmonization of Technical Requirement for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice.

Trial design

This was a randomized, parallel-group, double-blind, placebo-controlled, multinational, multisite trial in Europe. The trial included 100 sites in 12 countries. In total, 992 subjects were randomized 1:1:1 to receive treatment with the SQ HDM SLIT-tablet in doses of 6 SQ-HDM or 12 SQ-HDM or with placebo for approximately 12 months. The trial design is shown in Fig 1.

Trial population

The trial population comprised adults 18 to 65 years of age with moderate-to-severe HDM-induced AR (with or without asthma and conjunctivitis) despite having received pharmacotherapy (further description of the trial population and main selection criteria can be found in the Methods section in this article’s Online Repository). Data on rhinitis symptoms and medication use were collected during the baseline period to confirm that subjects had moderate-to-severe HDM-induced AR. Moderate-to-severe HDM-induced AR symptoms were defined by a daily total rhinitis symptom score of at least 6 or a score of at least 5 with 1 severe symptom during at least 8 days of the 15-day baseline period. Furthermore, subjects should report use of pharmacotherapy for treatment of HDM-induced AR during at least 8 days of the 15-day baseline period. If the patient had asthma, daily use of inhaled corticosteroids (ICSs) during the baseline period should be 400 μg of budesonide or less or equivalent (ie, corresponding to Global Initiative for Asthma treatment steps 1 or 2). Subjects were allowed to increase this dose during the study, if needed.

Intervention medication

Each subject was randomly assigned to receive one of 2 active doses (SQ HDM SLIT-tablet) or placebo. The first dose was administered under medical supervision lasting at least 30 minutes after tablet intake. Subjects were instructed to take 1 tablet sublingually daily. The SQ HDM SLIT-tablet is a 1:1 mixture of allergens derived from 2 species of cultivated HDM (Dermatophagoidespteronyssinus and Dermatophagoidesfarinae) through a highly standardized production process, leading to a 1:1:1:1 ratio of the major allergens Der p 1, Der f 1, Der p 2, and Der f 2. The intervention medication was provided and manufactured by the trial sponsor (ALK). The placebo tablets were similar to the active intervention medication with regard to appearance, smell, and taste.

Pharmacotherapy for AR, conjunctivitis, or both (ie, antihistamine tablets and eye drops or nasal steroids) was provided by ALK to subjects at randomization as predefined open-label medication to be used freely in addition to the intervention medication to which the subjects had been randomized (details on pharmacotherapy can be found in the Methods section in this article’s Online Repository).

Randomization

Randomization was performed according to a sponsor-generated allocation schedule by a trial-independent statistician. Randomization was stratified by sites using block randomization. Details on randomization are provided in the Methods section in this article’s Online Repository.

End points and assessments

Subjects were instructed on how to complete symptom and medication assessments and record results in an electronic diary every morning during the baseline period (15 days), during 1 week after visits 3 to 6 (weeks 4, 14, 24, and 34), and during the efficacy assessment period (the last approximately 8 weeks of the 1 year treatment period, Fig 1). The efficacy assessment period took place between October 1 and March 15 to avoid overlapping symptoms caused by pollen allergy.

A total of 6 allergic symptoms, 4 rhinitis symptoms (runny nose, blocked nose, sneezing, and itchy nose), and 2 conjunctivitis symptoms (gritty feeling/red/itchy eyes and watery eyes) were measured on a scale from 0 to 3 (ie, no to severe symptoms). For the medication score, subjects reported their use of specific pharmacotherapy. The primary end point was the current combined rhinitis score (TCRS; ie, the sum of rhinitis symptom and medication score [range, 0-24]). Details of scoring scales are provided in Table E1 in this article’s Online Repository at www.jacionline.org.

Disease-specific quality of life was assessed by using the Rhinoconjunctivitis Quality of Life Questionnaire with Standardised Activities (RQLQ), which was included in the subject’s diary.

Immunologic parameters were assessed to confirm the diagnosis and evaluate the specific immunologic response to treatment (full results to be published separately). AEs were recorded from when the subjects signed the informed consent form until the last follow-up visit.

Statistical methodology

A sample size of 300 per treatment group was determined by using computer simulations (see Table E2 in this article’s Online Repository at www.jacionline.org for details of power calculation). The primary analysis compared treatment groups by using a linear mixed effects (LME) model, including the average AR symptoms score at baseline as a fixed effect and country as a random effect.

The full analysis set included all randomized subjects in accordance with the ICH intent-to-treat principle. The primary analysis set was the full analysis set with multiple imputations for missing data (FAS-MI), which conservatively treated all subjects with missing data as having no treatment effect.
Additional analyses for the primary end point were performed on the full analysis set, observed data (FAS), and on the per-protocol (PP) analysis set. Key secondary end points were similarly analyzed by means of LME models on FAS-MI and FAS. Multiplicity for the primary and key secondary analyses were controlled for by using the Fisher least significant difference procedure and a hierarchic testing strategy. All other statistical hypotheses were not controlled for multiplicity and are explorative in nature. An absolute difference in TCRS means between active treatment and placebo of 1 was predefined as the minimal clinically relevant difference based on what this difference could mean to the patient and further supported by results from previous trials with 2 authorized pollen SLIT-tablet products.18-23

Further details regarding statistical analyses are reported in the Methods section in this article’s Online Repository.

RESULTS
Population
An overview of subject disposition is shown in Fig 2. No overall differences were seen between groups in numbers of discontinuations. However, a slightly higher proportion of subjects discontinued because of AEs in the active groups (6 SQ-HDM, 3%; 12 SQ-HDM, 4%) compared with the placebo group (2%).

Subjects’ demographics and baseline characteristics are presented in Table I. The 3 treatment groups were similar with regard to sex distribution, different ethnic origin, and smoking history.

In accordance with the inclusion criteria, all subjects had moderate-to-severe HDM-induced AR. The proportion of polysensitized subjects was 68%, and main cosensitizations based on skin prick tests were as follows: grass pollen, 41%; cat, 41%; dog, 28%; and birch pollen, 22%. In addition, 46% of the population had concomitant HDM-induced allergic asthma. On average, the subjects had HDM-induced AR for 10 years, with no overall differences between groups. At baseline, the 3 groups were similar with regard to rhinitis, conjunctivitis, and rhinoconjunctivitis symptom scores (data not shown), as well as the extent and type of pharmacotherapy used (data not shown).

Efficacy in patients with AR
The primary end point was the TCRS averaged over the last 8 weeks of treatment. Results of the statistical analysis are shown in Table II.

For the FAS, the absolute reduction in the TCRS compared with the placebo group was 1.18 (P = .002) for the 6 SQ-HDM group and 1.22 (P = .001) for the 12 SQ-HDM group. The primary analysis on FAS-MI showed a statistically significant difference from placebo for both active groups, being greater than the prespecified clinical relevance criterion of an absolute difference of 1 compared with placebo. Relative differences from the placebo group in TCRS by using adjusted means and medians when analyzed on FAS and PP ranged from 18% to 22% (Table III). The difference from placebo was numerically higher for the 12 SQ-HDM group than for the 6 SQ-HDM group,
although the overall magnitudes of the absolute and relative differences were comparable between the 2 dose groups. The results were consistent regardless of analysis set and parameters used (adjusted means or medians). Post hoc subgroup analyses of the primary end point showed that there was no statistically significant difference between the treatment effect in patients with asthma versus no asthma and monosensitized versus polysensitized subjects (data not shown).
Fig 3 shows an analysis of the TCRS over the entire time course of the trial (FAS). For both active doses, a statistically significant difference from placebo of 1 or greater (prespecified criterion for clinical relevance) was seen from week 14 and throughout the 1-year treatment period. The analysis of the primary end point for each active dose group is represented by the point at 44 to 52 weeks with treatment.

Key secondary end points are AR symptom, AR medication, RQLQ, and total rhinoconjunctivitis scores averaged over the last 8 weeks of treatment. Analyses on FAS are presented in Table IV, whereas results based on FAS-MI are reported in Table E3 in this article’s Online Repository at www.jacionline.org. For 12 SQ-HDM, efficacy was confirmed for all 4 key secondary end points, whereas for 6 SQ-HDM, efficacy could only be confirmed for AR symptoms/medication scores.

Fig 4 shows the adjusted mean values of the individual components of the AR symptom and RQLQ scores. For all parameters, numerically lower scores were observed for the actively treated groups compared with the placebo group, and generally, a dose response was seen. For the 6 SQ-HDM group, the difference from placebo was statistically significant for blocked nose. For the 12 SQ-HDM group, the difference from placebo was statistically significant for all 4 individual AR symptoms and for 4 of the 7 RQLQ domains: nasal symptoms, nonnose/noneye symptoms, practical problems, and sleep impairment. Fig 3 shows the overall RQLQ score plotted versus time and by treatment group. The difference from placebo was more pronounced for the 12 SQ-HDM group compared with the 6 SQ-HDM group and was statistically significant at weeks 24 and 44 to 54. The change from baseline on overall RQLQ scores with the 12 SQ-HDM dose was 1.91 compared with 1.71 with placebo (P = .031).

Analysis of other secondary end points, including rhinoconjunctivitis symptom and medication scores, conjunctivitis scores, symptom-free days, and global evaluation during the efficacy assessment period, are shown in Tables E4 and E5 in this article’s Online Repository at www.jacionline.org. In general, the results were favorable for the actively treated groups compared with placebo in all these end points, with statistically significant differences from placebo seen in rhinoconjunctivitis symptom scores (12 SQ-HDM group), rhinoconjunctivitis medication scores (6 SQ-HDM group), symptom-free days (6 and 12 SQ-HDM groups), and global evaluations (6 SQ-HDM group).
Safety

In general, the intervention medication was well tolerated. Most AEs observed during the trial were mild local allergic reactions (an overview of AEs can be found in Table E6 in this article’s Online Repository at www.jacionline.org). The majority of these local allergic reactions occurred within the first few days, and each event typically subsided again within a few days or weeks with continued treatment depending on the type of local reaction. The most common AEs reported as being related to the investigational medicinal product (IMP) by the investigator were oral pruritus, throat irritation, and mouth edema (20%, 14%, and 8% of subjects on active treatment, respectively). Twelve serious adverse events were reported in 12 subjects during the trial: 8 subjects from the placebo group and 4 subjects from the 6 SQ-HDM group. None of the serious AEs were assessed as being related to the IMP by the investigator. One subject from the 6 SQ-HDM group received adrenaline after the first tablet because of mild laryngeal edema (palatine and oropharyngeal pruritus, followed by dysphonia, throat irritation, and dry cough). The subject subsequently continued and completed the trial without other AEs, except for mild oral pruritus (further description of this case can be found in the Results section in this article’s Online Repository at www.jacionline.org). No AEs were reported as systemic allergic reaction in any of the groups.

DISCUSSION

This randomized, double-blind, placebo-controlled phase III trial with the SQ HDM SLIT-tablet revealed a statistically significant reduction in TCRSs in patients with moderate-to-severe HDM-induced AR, with simultaneous reductions of both symptoms and medication use. Consequently, the patients receiving active treatment had fewer symptoms, even though they used less pharmacotherapy to reduce them, an effect consistent across all analysis sets. The difference from placebo reached statistical significance and met the prespecified criterion for clinical relevance (TCRS ≥1) for both actively treated groups after 14 weeks of treatment. A statistically significant difference of greater than 1 was observed for all subsequent assessment points during the 1-year treatment period, with the magnitude of effect increasing until week 24, after which it remained constant. This supports the findings in 2 previous phase II trials with the SQ HDM SLIT-tablet. The first trial was a phase II in-field trial in which TCRSs were shown to be significantly reduced by 6 SQ-HDM in a post hoc analysis on a subgroup of asthmatic patients with mild-to-moderate HDM-induced AR. The second trial showed a significant dose-related reduction in total nasal symptom scores in patients with HDM-induced AR by using an experimental exposure chamber with statistically significant effect in the 12 SQ-HDM group already after 8 weeks of treatment. Despite differences in scoring scales, the presented results are also in accordance with what were found in a recently reported trial assessing the efficacy and safety of 2 doses of a different HDM SLIT-tablet in 509 subjects with moderate-to-severe HDM-induced AR. In this trial both tested doses significantly improved the primary end point of average adjusted symptom score (total symptoms score adjusted for pharmacotherapy use). In the current trial differences in both AR symptom and medication scores were statistically significant for both active doses compared with placebo, in contrast to the trial by Bergman et al., in which no significant difference could be seen for the medication score. The current trial only included patients that reported use of pharmacotherapy for treatment of HDM-induced AR during at least 8 days of the 15-day baseline period, which resulted in a population with a significantly higher medication score, indicating high disease severity.

It is widely acknowledged that the use of pharmacotherapy has an effect on symptom scores. Therefore the current trial uses a combined symptom and medication score (TCRS) in accordance with current guidelines. One potential weakness of medication scores is a lack of standardized measures for assessing daily medication use. The medication score used in the current trial is similar to what had been used in other trials with the SQ HDM SLIT-tablet and in trials with the authorized product Grazax (ALK). More recently, a European Academy of Allergy and Clinical Immunology position paper has been published, suggesting a more standardized model to score daily medication use, which could be considered in future trials.
The World Allergy Organization has suggested a minimum clinically relevant effect for immunotherapy as being 20% or greater of the relative difference from placebo.\(^{32}\) However, relative differences per se cannot be used as a sole measure of clinical relevance and need to be seen in context with the numeric size of the TCRS on which the relative differences are based. Thus relative differences depend not only on the absolute difference between groups but also on the absolute TCRS of the placebo group and hence on the disease severity of the investigated population. In the current trial the relative difference from placebo for 12 SQ-HDM was 22% for FAS by using medians (data not normally distributed), supporting the clinical relevance of the observed effect, especially when taking the high disease severity into account. All subjects had free access to pharmacotherapy in addition to the IMP. Therefore the effect measured in this trial provides an additional benefit to guided and free access to guideline-recommended pharmacotherapy. The added benefit provided by the SQ HDM SLIT-tablet is supported by the RQLQ results, which showed (1) an improvement from baseline to the end of treatment in the placebo group of more than 3 times the published minimal clinically important difference of 0.5 within a patient\(^{37}\) and (2) an additional improvement for 12 SQ-HDM compared with placebo. This effect was obtained even though patients also reduced their need for pharmacotherapy, which is not taken into account in the RQLQ.

Furthermore, the difference between 12 SQ-HDM and placebo was statistically significant for 4 of the 7 domains in the RQLQ: nasal symptoms, nonnose/noneye symptoms, practical problems, and impaired sleep. In addition, the 12 SQ-HDM group showed improvement in all 4 symptoms included in the AR symptom score: sneezing and blocked, itchy, and runny nose.

Regarding proper interpretation of the presented results, one will notice a reduction over time in TCRSs and RQLQ scores observed in all groups, including the placebo group (Fig 3), which is consistent with the literature on AIT in general.\(^{33}\) This might partially be caused by the free access to and personal guidance in the use of standard-of-care pharmacotherapy. This means that the improvement in the placebo group likely represents the maximum that can be achieved through these means. The differences from placebo in the active groups show that adding the SQ HDM SLIT-tablet provides substantial and consistent benefits not achieved by using standard-of-care pharmacotherapy or specialist advice alone. Another contributing factor explaining the observed reduction in the placebo group in addition to the interventional study effect in general and a possible “placebo effect” is the phenomenon of regression toward the mean. In this trial subjects were selected based on high symptom score and frequent use of pharmacotherapy at baseline. Interestingly, despite the debate on the effectiveness of AIT in polysensitized patients,\(^{17}\) this trial showed a statistically significant effect for both active doses regardless of sensitization status. This is consistent with a recent pooled post hoc analysis including several studies on the SQ grass SLIT-tablet, suggesting that the observed effects were not dependent on sensitization status.\(^{35}\) The presence of clinical symptoms to another perennial allergen to which the subject is regularly exposed was an exclusion criterion because other indoor sensitizations might interfere during efficacy assessment periods.

It is clear from this trial that the SQ HDM SLIT-tablet reduces HDM-induced AR symptoms and medication use, and in addition, a more general effect on HDM-induced respiratory disease can be expected. The SQ HDM SLIT-tablet has been shown to be effective in reducing ICS use and the risk of asthma exacerbations in patients with HDM-induced allergic asthma in a phase II asthma trial\(^{36}\) and in a recent phase III trial (Virchow et al, unpublished data), supporting the relevance of treating the underlying HDM-induced respiratory allergic disease with the SQ HDM SLIT-tablet, regardless of the dominant manifestation.

The potential for disease modification and long-term effect when treating the underlying cause of the disease is a unique feature for AIT compared with pharmacotherapy. The posttreatment effect has not been investigated in this trial, but the immunologic observations (to be published separately) are similar to those observed of the previously developed SQ grass SLIT-tablet, studies of which have confirmed the posttreatment effect in grass pollen–induced allergic rhinoconjunctivitis.\(^{37}\)

In conclusion, this trial confirmed the efficacy and favorable safety profile of both doses of the SQ HDM SLIT-tablet in adults with moderate-to-severe HDM-induced AR despite use of pharmacotherapy. Although efficacy was seen for both doses, the results were in general more robust for the 12 SQ-HDM dose. The predefined criterion for clinical relevance was met for both doses. Onset of action after 14 weeks and a sustained year-round treatment effect were demonstrated.

The trial was funded by ALK, and in this context we thank the clinical trial team at ALK for clinical project management, operational oversight, safety monitoring, data management and statistics. Brian Hansen, ALK, was responsible for medical writing, editorial, and journal submission assistance for this manuscript.

Clinical implications: Efficacy results indicate that the SQ HDM SLIT-tablet simultaneously reduces allergic rhinitis symptoms and pharmacotherapy use in patients with moderate-to-severe HDM-induced AR to a clinically relevant degree.

REFERENCES

1. Demoly P, V. Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Eu-
    variation in the prevalence of positive skin tests to environmental aeroallergens in
    The link between allergic rhinitis and allergic asthma: a prospective population-
    Virchow JC, et al. Respiratory allergy caused by house dust mites: what do we
    to airborne moulds and severity of asthma: cross sectional study from European
6. Canonica GW, Tarantini F, Compli E, Penagos M. Efficacy of desloratadine in
    the treatment of allergic rhinitis: a meta-analysis of randomized, double-blind,
7. Valovirta E, Myrseth SE, Palkonen S. The voice of the patients: allergic rhinitis is
    Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration
    with the World Health Organization, GA(2)LEN and AllerGen). Allergy 2008;
    63(suppl 86):8-160.
9. Pichler CE, Marquardsen A, Sparholt S, Lowenstein H, Bircher A, Bischof M,
    et al. Specific immunotherapy with Dermatophagoides pteronyssinus and D.
    fari-
    nae results in decreased bronchial hyperreactivity. Allergy 1997;52:274-83.
    and safety of a glutaraldehyde-modified house dust mite extract in allergic rhinitis.


METHODS

Trial population

Main selection criteria were as follows:

- 18 to 65 years of age, with a clinical history consistent with moderate-
to-severe persistent HDM-induced AR (with or without asthma) for at
least 1 year before trial entry, with AR symptoms despite having
received symptomatic treatment;
- moderate-to-severe HDM-induced AR symptoms during the baseline
period defined as a daily total rhinitis symptom score of at least 6 or
a score of at least 5 with 1 severe symptom during at least 8 days of
the 15-day baseline period;
- use of symptomatic medication for treatment of HDM-induced AR dur-
ing at least 8 days of the 15-day baseline period;
- presence of 1 or more of the following Allergic Rhinitis and its Impact
on Quality of Life (ARSIQ) quality-of-life items caused by HDM-induced AR during
the baseline period:
  1. sleep disturbance;
  2. impairment of daily activities, leisure, and/or sport; and
  3. impairment of school or work;
- daily use of RCSs should be 400 µg of budesonide or less or equivalent
if patient is asthmatic (ie, corresponding to Global Initiative for Asthma
treatment steps 1 or 2);
- positive skin prick test response (wheal diameter ≥3 mm) to D. pteronyssinus,
D. farinae, or both;
- positive specific IgE level against D. pteronyssinus, D. farinae, or both
(defined as IgE class ≥2 [ie, ≥0.70 kU/L]);
- no clinically relevant history of symptomatic seasonal allergic
rhinoconjunctivitis, asthma, or both caused by an allergen to which
the subject is regularly exposed and overlapping with the 8-week
efficacy assessment period;
- no reduced lung function (defined as FEV₁ <70% of predicted value
after adequate pharmacologic treatment); and
- no clinical history of uncontrolled asthma within 3 months before
screening.

Intervention medication

The following pharmacotherapy for AR, conjunctivitis, or both was
provided to the subjects at randomization.

For nasal symptoms, the subjects were provided with oral antihistamine
tablets (desloratadine tablets, 5 mg) or nasal corticosteroid spray (budesonide
64 µg per dose).

For conjunctivitis symptoms, the subjects were provided with antihista-
mide eye drops (azelastine 0.05% or lodoxamide tromethamine 0.1% [in
Croatia only]). No eye drops were provided in Serbia. Instead, oral
antihistamine tablets were provided for conjunctivitis symptoms in Serbia.

Maximum daily doses were 1 oral antihistamine tablet, 2 puffs per nostril of
nasal corticosteroid spray, and 2 drops per eye of antihistamine eye drops.

Randomization

The randomization list was divided into blocks of 6, with each block
comprising 2 sets of each of the 3 different treatments (ie, placebo, 6
SQ-HDM, or 12 SQ-HDM). In some cases the blocks were split when
distributed within countries.

End points and assessments

Primary and key secondary end points were daily scores averaged over the
8-week end-of-treatment efficacy assessment period.

Sample size

Power calculation was based on data from a previous trial of the SQ HDM
SLIT-tablet. The observed mean of the TCRS for placebo was 4.9, and the
observed pooled SD of the TCRS was 4.02, which corresponded to a
coefficient of variation (SD/mean) of 0.82.

Further assumptions for the power calculations were as follows:

1. Analysis is performed based on multiple imputations, and subjects who
do not contribute any diary data during the last 8 weeks of treatment
will be imputed as sampled from the observed placebo distribution
of the TCRS.
2. Equal proportion of 10% is imputed in each treatment group.
3. The global hypothesis is tested with an F test on 2 df at the 5% level of
significance.
4. The pairwise hypotheses are tested with a 2-sided t test at a 5% level of
significance.

Based on these assumptions, the power to detect a difference from placebo
for 6 SQ-HDM and 12 SQ-HDM is presented in Table E2. The power
calculations were performed with computer simulations.

Because the mean TCRS value for placebo was assumed to be 4.9, the
relative difference of 20% and 25% used in the power calculations
corresponded to an absolute difference of 0.98 and 1.22, respectively.

In conclusion, based on the assumptions above, it is estimated that 300
randomized subjects per treatment group (ie, a total of 900 subjects) will
provide about 90% power to reject the global hypothesis of no difference
between any of the treatment groups with an F test at a 5% level of significance
(Table E2). In other words, a difference between active treatment and placebo
can be detected with a power of about 90%.

Statistical methodology

All statistical tests were performed with SAS version 9.3 software (SAS
Institute, Cary, NC) with a 5% significance level, and all tests and 95% CIs
were 2-sided. The full analysis set represents all randomized subjects in
accordance with the ICH intent-to-treat principle.

The primary efficacy analysis was based on an LME model and performed
on the FAS by using a multiple imputation strategy for missing data by Rubin
(data set denoted FAS-MI). Missing data in all treatment groups were
sampled from the observed data of the primary end point in the placebo
group by using the method of unrestricted random sampling with replacement.

The response variable in the LME was the square root of the TCRS, and
covariates included the average AR symptom score at baseline and country.
The primary outcome was the pairwise comparison between all 3 treatment
groups by using a t test in the LME model. The resulting P values were
reported together with the associated difference in (back-transformed) adjusted
means with 95% CIs.

The Fisher least significant difference procedure was used to control for
multiplicity in the primary efficacy analysis. By using an F test in the LME
model, the first hypothesis to be tested was the global hypothesis of no differ-
ence in means between the 3 groups: placebo, 6 SQ-HDM, and 12 SQ-HDM. If
and only if this global hypothesis was rejected (P <.05), all pairwise compar-
isons between treatment groups were performed (12 SQ-HDM vs placebo, 6
SQ-HDM vs placebo, and 12 SQ-HDM vs 6 SQ-HDM).

Additional analyses of the primary end point included analyses using the
same LME model on subjects in the full analysis set with observations
(denoted FAS), on the PP set, and on FAS-MI by using the method of last
observation carried forward.

Multiplicty for the key secondary end points was controlled for by
hierarchic testing in the following order:

1. average total AR symptom score during the efficacy assessment period;
2. average total AR medication score during the efficacy assessment period;
3. average overall RQLQ score during the efficacy assessment period; and
4. average total combined allergic rhinoconjunctivitis score during the
efficacy assessment period.

The 4 key secondary hypotheses were first to be tested for 12 SQ-HDM and
then, if all were statistically significant, for 6 SQ-HDM. The key secondary
efficacy analyses were based on LME models and performed on the FAS-MI
for key secondary end points 1 and 2 and on FAS for all of the key secondary
end points.
Secondary end points were analyzed on FAS. The statistical methods used were LME models for continuous end points and generalized linear mixed effect models for binary end points.

An absolute difference of 1 in TCRS means between the active treatment and placebo groups was predefined as the minimal clinically relevant difference.

RESULTS
The results of the analysis of the primary end point (FAS-MI, FAS, and PP) and the key secondary end points (FAS) are presented in the main article. Table E3 shows the results of statistical analysis for the 2 key secondary end points AR symptom score and AR medication score based on FAS-MI.

Other secondary end points on rhinoconjunctivitis and conjunctivitis
For all parameters, numerically lower scores were observed for the actively treated groups compared with the placebo group. The difference from placebo was statistically significant for the 12 SQ-HDM group for the rhinoconjunctivitis symptom score and for the 6 SQ-HDM group for the rhinoconjunctivitis medication score.

Summary statistics for the individual conjunctivitis symptoms showed a lower raw mean score for the 12 SQ-HDM group than for the placebo group for both conjunctivitis symptoms.

Binary secondary end points
Two binary end points were prespecified. One was the proportion of symptom-free days during the efficacy assessment period (ie, the last 8 weeks of the 1-year treatment period). A symptom-free day was defined as a day with use of no antihistamines (oral or ocular) and a rhinoconjunctivitis symptom score of 0. Nasal steroid was allowed because one recommended use is as a daily controller.

The other binary end point was the proportion of subjects responding “better” or “much better” to the end-of-treatment global evaluation question on the comparison of rhinitis symptoms during the year with treatment with symptoms in the previous year. The odds for being in the “improved” category in the global evaluation were numerically higher in the active groups than in the placebo group, and this was statistically significant for the 6 SQ-HDM group. The odds for having a symptom-free day were statistically significantly higher in the actively treated groups than in the placebo group, but the overall proportion of symptom-free days was low.

Safety: Summary of adrenaline case
One subject from the 12 SQ-HDM group received adrenaline after the first tablet because of a mild local allergic reaction. Within 5 minutes of the first administration of the IMP, the subject experienced laryngeal edema (reported by the investigator as very mild laryngeal edema, no vital risk). Treatment included adrenaline, methylprednisolone, and desloratadine. All symptoms abated after 30 minutes. The subject subsequently continued and completed the trial without other AEs, except for mild oral pruritus.

REFERENCES
<table>
<thead>
<tr>
<th>Symptom</th>
<th>TCRS</th>
<th>AR symptom score</th>
<th>AR medication score</th>
<th>Conjunctivitis symptom score</th>
<th>Conjunctivitis medication score</th>
<th>Total combined conjunctivitis score</th>
<th>Total combined rhinoconjunctivitis score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Runny nose</td>
<td>0-3</td>
<td>0-3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0-3</td>
</tr>
<tr>
<td>Blocked nose</td>
<td>0-3</td>
<td>0-3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0-3</td>
</tr>
<tr>
<td>Sneezing</td>
<td>0-3</td>
<td>0-3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0-3</td>
</tr>
<tr>
<td>Itchy nose</td>
<td>0-3</td>
<td>0-3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0-3</td>
</tr>
<tr>
<td>Red/itchy eyes</td>
<td>0-3</td>
<td>0-3</td>
<td></td>
<td></td>
<td>0-3</td>
<td>0-3</td>
<td>0-3</td>
</tr>
<tr>
<td>Watery eyes</td>
<td>0-3</td>
<td>0-3</td>
<td></td>
<td>0-3</td>
<td></td>
<td></td>
<td>0-3</td>
</tr>
<tr>
<td>Oral antihistamine</td>
<td>0-4</td>
<td>0-4</td>
<td></td>
<td>0-2</td>
<td>0-2</td>
<td>0-6</td>
<td></td>
</tr>
<tr>
<td>Ocular antihistamine</td>
<td></td>
<td></td>
<td></td>
<td>0-6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal steroid</td>
<td>0-8</td>
<td>0-8</td>
<td></td>
<td>0-8</td>
<td>0-8</td>
<td>0-8</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>0-24</td>
<td>0-12</td>
<td>0-12</td>
<td>0-6</td>
<td>0-8</td>
<td>0-14</td>
<td>0-38</td>
</tr>
</tbody>
</table>

Symptom scores: 0, no; 1, mild; 2, moderate; and 3, severe. Rhinitis medication scores: oral antihistamine (desloratadine tablets, 5 mg): 4 per tablet, nasal steroid (budesonide nasal spray, 64 μg/dose), 2 per puff. Conjunctivitis medication score: oral antihistamine (desloratadine tablets, 5 mg): 2 per tablet, ocular antihistamine (azelastine eye drops, 0.05%): 1.5 per drop. Maximum daily medication use: 1 oral antihistamine tablet, 2 puffs per nostril of nasal corticosteroid spray, 2 antihistamine eye drops per eye.
### TABLE E2. Power for statistical analysis based on imputation

<table>
<thead>
<tr>
<th>Hypotheses to be rejected</th>
<th>Difference from placebo to be detected</th>
<th>6 SQ-HDM</th>
<th>12 SQ-HDM</th>
<th>No. total</th>
<th>Power to reject</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₀₁: placebo = 6SQ-HDM = 12 SQ-HDM</td>
<td>20% 25%</td>
<td>900</td>
<td>90%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H₀₁: placebo = 6SQ-HDM = 12 SQ-HDM and H₀₂: placebo = 12 SQ-HDM</td>
<td>20% 25%</td>
<td>900</td>
<td>88%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H₀₁: placebo = 6 SQ-HDM = 12 SQ-HDM and H₀₃: placebo = 6 SQ-HDM</td>
<td>20% 25%</td>
<td>900</td>
<td>75%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H₀₁: placebo = 6 SQ-HDM = 12 SQ-HDM and H₀₂: placebo = 12 SQ-HDM and H₀₃: placebo = 6 SQ-HDM</td>
<td>20% 25%</td>
<td>900</td>
<td>73%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Key secondary end point</td>
<td>Treatment</td>
<td>No.</td>
<td>Adjusted means</td>
<td>Absolute difference (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-----------</td>
<td>------</td>
<td>----------------</td>
<td>-----------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>AR symptom score</td>
<td>Placebo</td>
<td>338</td>
<td>3.31</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>6 SQ-HDM</td>
<td>336</td>
<td>2.94</td>
<td>0.38 (0.01-0.74)</td>
<td>.042</td>
</tr>
<tr>
<td></td>
<td>12 SQ-HDM</td>
<td>318</td>
<td>2.84</td>
<td>0.47 (0.11-0.82)</td>
<td>.001</td>
</tr>
<tr>
<td>AR medication score</td>
<td>Placebo</td>
<td>338</td>
<td>2.86</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>6 SQ-HDM</td>
<td>336</td>
<td>2.23</td>
<td>0.63 (0.11-1.15)</td>
<td>.017</td>
</tr>
<tr>
<td></td>
<td>12 SQ-HDM</td>
<td>318</td>
<td>2.32</td>
<td>0.54 (0.01-1.07)</td>
<td>.045</td>
</tr>
</tbody>
</table>

Boldface numbers indicate a confirmatory result according to the multiplicity adjusting procedure.
<table>
<thead>
<tr>
<th>End point</th>
<th>Treatment group</th>
<th>No.</th>
<th>Adjusted mean</th>
<th>Absolute difference (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinoconjunctivitis symptom score (n = 879)</td>
<td>Placebo</td>
<td>298</td>
<td>4.24</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>6 SQ-HDM</td>
<td>297</td>
<td>3.84</td>
<td>0.40 (−0.10 to 0.89)</td>
<td>.118</td>
</tr>
<tr>
<td></td>
<td>12 SQ-HDM</td>
<td>284</td>
<td>3.56</td>
<td>0.68 (0.19 to 1.17)</td>
<td>.006</td>
</tr>
<tr>
<td>Rhinoconjunctivitis medication score (n = 754)*</td>
<td>Placebo</td>
<td>257</td>
<td>3.87</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>6 SQ-HDM</td>
<td>256</td>
<td>2.95</td>
<td>0.92 (0.19 to 1.65)</td>
<td>.013</td>
</tr>
<tr>
<td></td>
<td>12 SQ-HDM</td>
<td>241</td>
<td>3.23</td>
<td>0.65 (−0.12 to 1.41)</td>
<td>.097</td>
</tr>
<tr>
<td>Combined conjunctivitis score (n = 754)*</td>
<td>Placebo</td>
<td>257</td>
<td>1.98</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>6 SQ-HDM</td>
<td>256</td>
<td>1.76</td>
<td>0.21 (−0.13 to 0.55)</td>
<td>.220</td>
</tr>
<tr>
<td></td>
<td>12 SQ-HDM</td>
<td>241</td>
<td>1.79</td>
<td>0.19 (−0.15 to 0.53)</td>
<td>.279</td>
</tr>
<tr>
<td>Conjunctivitis symptom score (n = 879)</td>
<td>Placebo</td>
<td>298</td>
<td>0.76</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 SQ-HDM</td>
<td>297</td>
<td>0.75</td>
<td>0.01 (−0.15 to 0.17)</td>
<td>.898</td>
</tr>
<tr>
<td></td>
<td>12 SQ-HDM</td>
<td>284</td>
<td>0.63</td>
<td>0.13 (−0.02 to 0.29)</td>
<td>.087</td>
</tr>
<tr>
<td>Conjunctivitis medication score (n = 754)*</td>
<td>Placebo</td>
<td>257</td>
<td>0.90</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 SQ-HDM</td>
<td>256</td>
<td>0.71</td>
<td>0.19 (−0.01 to 0.39)</td>
<td>.065</td>
</tr>
<tr>
<td></td>
<td>12 SQ-HDM</td>
<td>241</td>
<td>0.72</td>
<td>0.19 (−0.02 to 0.39)</td>
<td>.077</td>
</tr>
</tbody>
</table>

*Antihistamine eye drops were unavailable in 2 countries and thus not scored.
<table>
<thead>
<tr>
<th>End point</th>
<th>Treatment group</th>
<th>No.</th>
<th>Estimated probability (% [95% CI])</th>
<th>Odds ratio (active over placebo [95% CI])</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom-free days</td>
<td>Placebo</td>
<td>298</td>
<td>0.7% (0.4% to 1.3%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>6 SQ-HDM</td>
<td>297</td>
<td>1.6% (0.9% to 2.9%)</td>
<td>2.33 (1.32 to 4.13)</td>
<td>.004</td>
</tr>
<tr>
<td></td>
<td>12 SQ-HDM</td>
<td>284</td>
<td>1.6% (0.9% to 2.9%)</td>
<td>2.28 (1.28 to 4.07)</td>
<td>.005</td>
</tr>
<tr>
<td>Global evaluation (% improved)</td>
<td>Placebo</td>
<td>299</td>
<td>68.0% (56.9% to 77.3%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>6 SQ-HDM</td>
<td>300</td>
<td>76.1% (66.3% to 83.8%)</td>
<td>1.50 (1.04 to 2.16)</td>
<td>.029</td>
</tr>
<tr>
<td></td>
<td>12 SQ-HDM</td>
<td>284</td>
<td>75.1% (65.0% to 83.0%)</td>
<td>1.42 (0.98 to 2.05)</td>
<td>.062</td>
</tr>
</tbody>
</table>
### TABLE E6. Overview of AEs in the trial

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo (n = 338)</th>
<th>6 SQ-HDM (n = 336)</th>
<th>12 SQ-HDM (n = 318)</th>
<th>Active all (n = 654)</th>
<th>Overall (n = 992)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>E (%)</td>
<td>No. (%)</td>
<td>E (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>All AEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Causality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unlikely</td>
<td>128 (38)</td>
<td>231 (71)</td>
<td>128 (38)</td>
<td>277 (41)</td>
<td>121 (38)</td>
</tr>
<tr>
<td>Possible</td>
<td>50 (15)</td>
<td>96 (29)</td>
<td>161 (48)</td>
<td>401 (59)</td>
<td>167 (53)</td>
</tr>
<tr>
<td>Severity of all AEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>119 (35)</td>
<td>235 (72)</td>
<td>186 (55)</td>
<td>509 (75)</td>
<td>184 (58)</td>
</tr>
<tr>
<td>Moderate</td>
<td>56 (17)</td>
<td>82 (25)</td>
<td>83 (25)</td>
<td>157 (23)</td>
<td>78 (25)</td>
</tr>
<tr>
<td>Severe</td>
<td>10 (3)</td>
<td>10 (3)</td>
<td>10 (3)</td>
<td>12 (2)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Severity of IMP-related AEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>41 (12)</td>
<td>77 (80)</td>
<td>147 (44)</td>
<td>351 (88)</td>
<td>149 (47)</td>
</tr>
<tr>
<td>Moderate</td>
<td>13 (4)</td>
<td>19 (20)</td>
<td>27 (8)</td>
<td>47 (12)</td>
<td>37 (12)</td>
</tr>
<tr>
<td>Severe</td>
<td>—</td>
<td>—</td>
<td>3 (&lt;1)</td>
<td>3 (&lt;1)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Seriousness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious</td>
<td>8 (2)</td>
<td>8 (2)</td>
<td>4 (1)</td>
<td>4 (&lt;1)</td>
<td>—</td>
</tr>
<tr>
<td>Nonserious</td>
<td>151 (45)</td>
<td>319 (98)</td>
<td>212 (63)</td>
<td>674 (&gt;99)</td>
<td>213 (67)</td>
</tr>
<tr>
<td>Change to IMP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>135 (40)</td>
<td>277 (85)</td>
<td>194 (58)</td>
<td>596 (88)</td>
<td>195 (61)</td>
</tr>
<tr>
<td>Temporary interruption</td>
<td>29 (9)</td>
<td>42 (13)</td>
<td>45 (13)</td>
<td>68 (10)</td>
<td>38 (12)</td>
</tr>
<tr>
<td>Discontinued</td>
<td>7 (2)</td>
<td>8 (2)</td>
<td>10 (3)</td>
<td>14 (2)</td>
<td>13 (4)</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recovered</td>
<td>150 (44)</td>
<td>308 (94)</td>
<td>209 (62)</td>
<td>659 (97)</td>
<td>211 (66)</td>
</tr>
<tr>
<td>Recovered with sequelae</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Not recovered</td>
<td>13 (4)</td>
<td>15 (5)</td>
<td>14 (4)</td>
<td>18 (3)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (&lt;1)</td>
<td>3 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Leading to discontinuation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7 (2)</td>
<td>8 (2)</td>
<td>10 (3)</td>
<td>14 (2)</td>
<td>13 (4)</td>
</tr>
<tr>
<td>No</td>
<td>151 (45)</td>
<td>319 (98)</td>
<td>205 (61)</td>
<td>664 (98)</td>
<td>207 (65)</td>
</tr>
</tbody>
</table>

*One of the AEs leading to discontinuation from the trial was concomitantly reported by the investigator as leading to a temporary interruption of IMP. Thus this AE is only included in the number of AEs leading to discontinuation from the trial and not in the number of AEs leading to a discontinuation of IMP.

E, Number of events.