

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

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Background: The SQ HDM SLIT-tablet (ALK) has been developed for treatment of house dust mite (HDM)–induced respiratory allergic disease.

Objective: This trial investigated the efficacy and safety of the SQ HDM SLIT-tablet in adults with moderate-to-severe HDM-induced allergic rhinitis (AR).

Methods: The trial was a randomized, double-blind, placebo-controlled phase III trial conducted in 12 European countries including 992 adults with moderate-to-severe HDM-induced AR despite treatment with pharmacotherapy. Subjects were randomized 1:1:1 to 1 year of daily treatment with placebo, 6 SQ-HDM, or 12 SQ-HDM. The primary end point was the total combined rhinitis score (ie, the sum of rhinitis symptom and medication scores) during the efficacy assessment period (approximately the last 8 weeks of the treatment period). Key secondary end points were rhinitis symptoms, medication scores, quality of life, and the combined rhinoconjunctivitis score.

Results: Analysis of the primary end point (observed data) demonstrated absolute reductions in total combined rhinitis score of 1.18 ($P = .002$) and 1.22 ($P = .001$) compared with placebo for 6 SQ-HDM and 12 SQ-HDM, respectively. The statistically significant treatment effect was evident from

14 weeks of treatment onward. For all key secondary end points, efficacy was confirmed for 12 SQ-HDM, with statistically significant reductions of rhinitis symptoms and medication scores, improved quality of life, and a reduced combined rhinoconjunctivitis score in the efficacy assessment period compared with placebo. The treatment was well tolerated.

Conclusion: The trial confirmed the efficacy and favorable safety profile of both 6 SQ-HDM and 12 SQ-HDM in adults with HDM-induced AR. The treatment effect was present from 14 weeks of treatment onward. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Key words: Allergy immunotherapy, sublingual immunotherapy tablet, sublingual immunotherapy, allergen immunotherapy, allergy, allergic rhinitis, house dust mite, Rhinitis Quality of Life Questionnaire, rhinoconjunctivitis, total combined rhinitis score

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.⁹⁻¹¹ However, sublingual allergy immunotherapy (SLIT) is more convenient because of home administration and is associated with fewer and less severe adverse events (AEs) than subcutaneous AIT.¹² 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.¹³ Furthermore, there is a

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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
HDM:	House dust mite
ICH:	International Conference on Harmonization of Technical Requirement 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

large variation in the quality and standardization of currently available SLIT products.¹³

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.¹⁴ 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 Helsinki¹⁵ 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.¹⁶

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 at www.jacionline.org). 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 allergen extracts derived from 2 species of cultivated HDM (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*) 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 total 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.¹⁷

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.

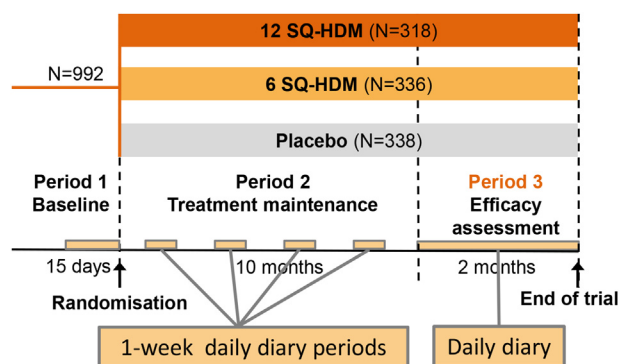


FIG 1. Overall trial design. Subjects were treated for approximately 12 months. The subjects filled in an electronic diary during 1 week after each visit and daily during the last 8 weeks of treatment (efficacy assessment period).

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,

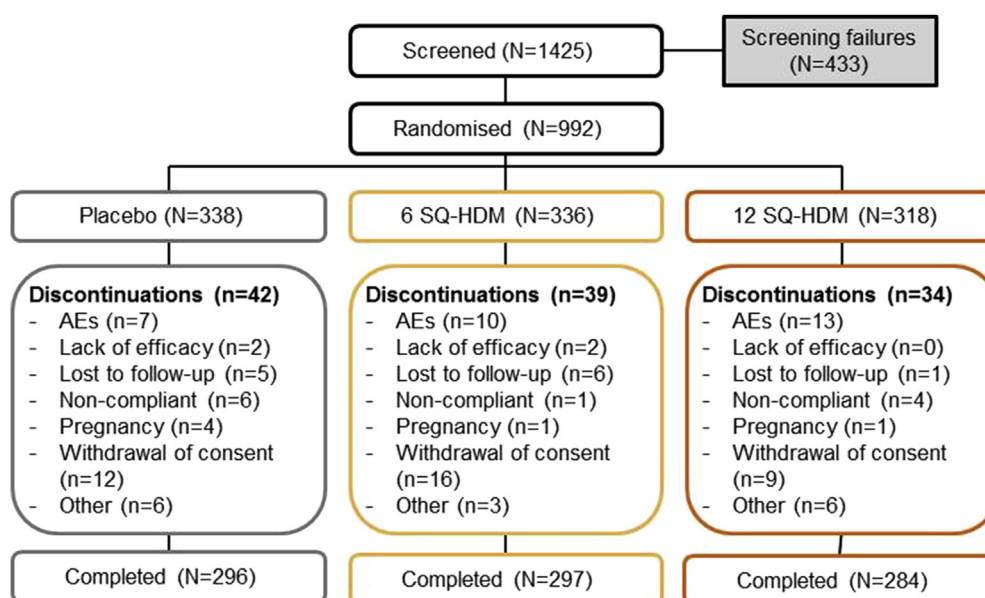


FIG 2. Subject disposition showing number of screened, randomized, and completed subjects, as well as reasons for discontinuations.

TABLE I. Baseline characteristics and demography

Treatment group	Placebo (n = 338)	6 SQ-HDM (n = 336)	12 SQ-HDM (n = 318)	Active all (n = 654)	Overall (n = 992)
HDM-induced AR, no. (%)	338 (100)	336 (100)	318 (100)	654 (100)	992 (100)
Years with HDM-induced AR, mean (SD)	10.0 (8.7)	10.0 (9.1)	9.8 (8.1)	9.9 (8.6)	9.9 (8.7)
HDM-induced allergic asthma, no. (%)	152 (45)	152 (45)	152 (48)	304 (46)	456 (46)
Sensitization status, no. (%)					
Monosensitized	106 (31)	98 (29)	109 (34)	207 (32)	313 (32)
Polysensitized	232 (69)	238 (71)	209 (66)	447 (68)	679 (68)
Sex, no. (%)					
Male	166 (49)	165 (49)	163 (51)	328 (50)	494 (50)
Female	172 (51)	171 (51)	155 (49)	326 (50)	498 (50)
Age (y)					
Mean (SD)	32.2 (10.9)	32.5 (11.2)	32.1 (10.6)	32.3 (10.9)	32.3 (10.9)
Median	29.0	30.0	30.0	30.0	30.0
Minimum-maximum	18.0-66.0	18.0-66.0	18.0-63.0	18.0-66.0	18.0-66.0
Ethnic origin, no. (%)					
White	331 (98)	330 (98)	314 (99)	644 (98)	975 (98)
Asian	1 (<1)	1 (<1)	1 (<1)	2 (<1)	3 (<1)
African	1 (<1)	1 (<1)	—	1 (<1)	2 (<1)
Hispanic	1 (<1)	—	1 (<1)	1 (<1)	2 (<1)
Other	4 (1)	4 (1)	2 (<1)	6 (<1)	10 (<1)
Smoking history, no. (%)					
Nonsmoker	272 (80)	275 (82)	261 (82)	536 (82)	808 (81)
Previous smoker	30 (9)	29 (9)	26 (8)	55 (8)	85 (9)
Smoker	36 (11)	32 (10)	31 (10)	63 (10)	99 (10)

TABLE II. Analysis of the primary end point

Analysis set	Treatment	No.	TCRS adjusted means	Difference from placebo (95% CI)	P value
FAS-MI		Global null hypothesis (placebo = 6 SQ-HDM = 12 SQ-HDM)			.003
	Placebo	338	6.81	—	—
	6 SQ-HDM	336	5.74	1.07 (0.34-1.80)	.004
	12 SQ-HDM	318	5.71	1.09 (0.35-1.84)	.004
FAS	Placebo	298	6.76	—	—
	6 SQ-HDM	297	5.58	1.18 (0.45-1.91)	.002
	12 SQ-HDM	284	5.53	1.22 (0.49-1.96)	.001

The prespecified criterion for clinical relevance was a difference from placebo of 1 or greater in TCRS.

TABLE III. Relative differences for the primary end point (TCRS) for the FAS and PP analysis set during the efficacy assessment period

Analysis set	Treatment	No.	TCRS	Absolute difference from placebo	Relative difference to placebo
PP set, adjusted means	Placebo	272	6.74	—	—
	6 SQ-HDM	269	5.53	1.20	18%
	12 SQ-HDM	264	5.38	1.36	20%
PP set, medians	Placebo	272	7.45	—	—
	6 SQ-HDM	269	5.91	1.54	21%
	12 SQ-HDM	264	5.79	1.66	22%
FAS, adjusted means	Placebo	298	6.76	—	—
	6 SQ-HDM	297	5.58	1.18	18%
	12 SQ-HDM	284	5.53	1.22	18%
FAS, medians	Placebo	298	7.54	—	—
	6 SQ-HDM	297	6.20	1.34	18%
	12 SQ-HDM	284	5.88	1.66	22%

The PP set indicates all subjects with no major protocol deviations (defined before unblinding).

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).

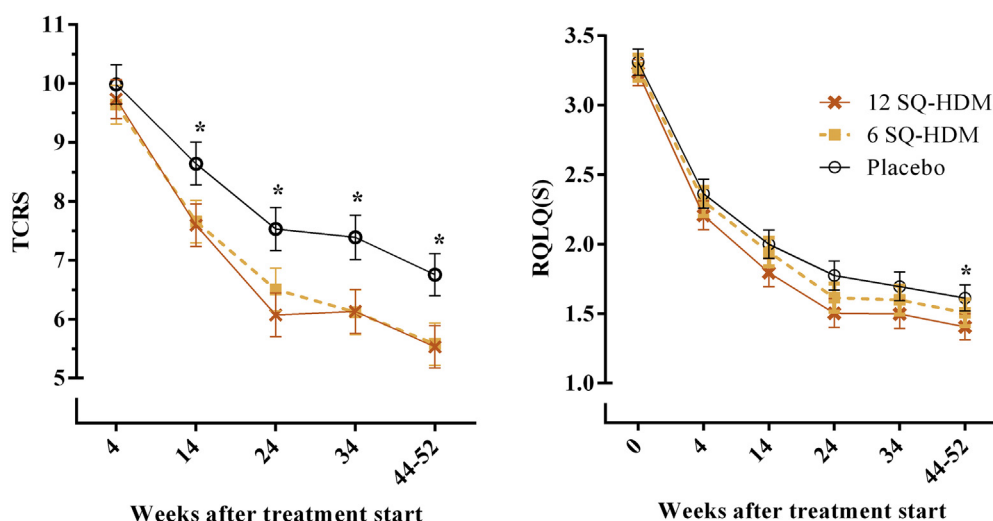


FIG 3. Adjusted means of the TCRS and overall RQLQ(s) score over time for the 3 treatment groups (FAS). Error bars represent pairwise comparisons between each of the active dose and placebo groups. Asterisks designate statistically significant differences from placebo.

TABLE IV. Key secondary results for FAS during the efficacy assessment period

Key secondary end point	Treatment	No.	Adjusted means	Absolute difference (95% CI)	P value
AR symptoms score	Placebo	298	3.30	—	—
	6 SQ-HDM	297	2.90	0.40 (0.03 to 0.76)	.032
	12 SQ-HDM	284	2.76	0.54 (0.18 to 0.89)	.003
AR medication score	Placebo	298	2.83	—	—
	6 SQ-HDM	297	2.13	0.69 (0.18 to 1.20)	.008
	12 SQ-HDM	284	2.22	0.60 (0.08 to 1.13)	.024
Overall RQLQ score	Placebo	240	1.58	—	—
	6 SQ-HDM	242	1.45	0.13 (−0.05 to 0.31)	.162
	12 SQ-HDM	229	1.38	0.19 (0.02 to 0.37)	.031
Combined rhinoconjunctivitis score	Placebo	257	9.12	—	—
	6 SQ-HDM	256	7.74	1.38 (0.32 to 2.45)	.011
	12 SQ-HDM	241	7.91	1.21 (0.13 to 2.28)	.029

Boldface numbers indicate a confirmatory result according to the multiplicity adjusting procedure.

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).

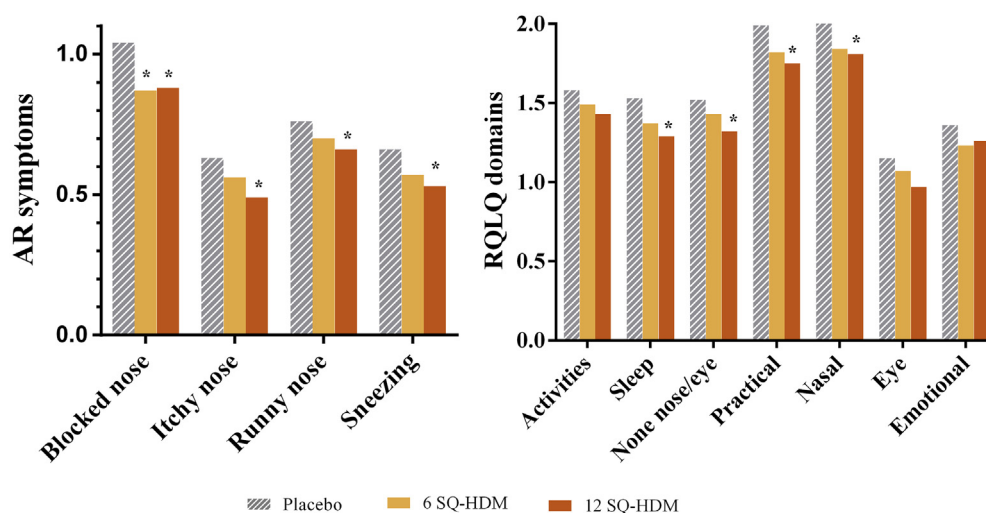


FIG 4. Individual components of the AR symptom and RQLQ(S) scores in the efficacy assessment period. Scores are shown as adjusted means. Asterisks designate statistically significant differences from placebo.

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 12 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.²⁴ 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.²⁵ 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.²⁶ In this trial both tested doses significantly improved the primary end point of average adjusted symptom score (total symptoms score adjusted for pharmacotherapy use).²⁶ 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,²⁶ 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.^{27,28} One potential weakness of medication scores is a lack of standardized measures for assessing daily medication use.^{29,30} 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,³¹ 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 patient¹⁷ 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,³⁴ 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 trial³⁶ 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.

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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.

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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 during at least 8 days of the 15-day baseline period;
- presence of 1 or more of the following Allergic Rhinitis and its Impact on Asthma 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 ICSs should be 400 μ g 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 rhinitis symptoms, the subjects were provided with oral antihistamine tablets (desloratadine tablets, 5 mg) or nasal corticosteroid spray (budesonide 64 μ g per dose).

For conjunctivitis symptoms, the subjects were provided with antihistamine 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.^{E1} 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^{E2} by using a multiple imputation strategy for missing data by Rubin (data set denoted FAS-MI).^{E3} 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^{E2} 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 difference 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 comparisons 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.

Multiplicity 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.

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TABLE E1. Construction of scores used in the trial

	TCRS	AR symptom score	AR medication score	Conjunctivitis symptom score	Conjunctivitis medication score	Total combined conjunctivitis score	Total combined rhinoconjunctivitis score
Runny nose	0-3	0-3					0-3
Blocked nose	0-3	0-3					0-3
Sneezing	0-3	0-3					0-3
Itchy nose	0-3	0-3					0-3
Red/itchy eyes				0-3		0-3	0-3
Watery eyes				0-3		0-3	0-3
Oral antihistamine	0-4		0-4		0-2	0-2	0-6
Ocular antihistamine					0-6	0-6	0-6
Nasal steroid	0-8		0-8				0-8
Total	0-24	0-12	0-12	0-6	0-8	0-14	0-38

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

Hypotheses to be rejected	Difference from placebo to be detected		No. total	Power to reject
	6 SQ-HDM	12 SQ-HDM		
$H_{0,1}$: placebo = 6SQ-HDM = 12 SQ-HDM	20%	25%	900	90%
$H_{0,1}$: placebo = 6SQ-HDM = 12 SQ-HDM and $H_{0,2}$: placebo = 12 SQ-HDM	20%	25%	900	88%
$H_{0,1}$: placebo = 6 SQ-HDM = 12 SQ-HDM and $H_{0,3}$: placebo = 6 SQ-HDM	20%	25%	900	75%
$H_{0,1}$: placebo = 6 SQ-HDM = 12 SQ-HDM and $H_{0,2}$: placebo = 12 SQ-HDM and $H_{0,3}$: placebo = 6 SQ-HDM	20%	25%	900	73%

TABLE E3. Key secondary results for FAS-MI during the efficacy assessment period

Key secondary end point	Treatment	No.	Adjusted means	Absolute difference (95% CI)	P value
AR symptom score	Placebo	338	3.31	—	—
	6 SQ-HDM	336	2.94	0.38 (0.01-0.74)	.042
	12 SQ-HDM	318	2.84	0.47 (0.11-0.82)	.001
AR medication score	Placebo	338	2.86	—	—
	6 SQ-HDM	336	2.23	0.63 (0.11-1.15)	.017
	12 SQ-HDM	318	2.32	0.54 (0.01-1.07)	.045

Boldface numbers indicate a confirmatory result according to the multiplicity adjusting procedure.

TABLE E4. Secondary end points on rhinoconjunctivitis and conjunctivitis in the efficacy assessment period (FAS)

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

*Antihistamine eye drops were unavailable in 2 countries and thus not scored.

TABLE E5. Binary secondary end points in the efficacy assessment period (FAS)

End point	Treatment group	No.	Estimated probability (% [95% CI])	Odds ratio (active over placebo [95% CI])	P value
Symptom-free days	Placebo	298	0.7% (0.4% to 1.3%)	—	—
	6 SQ-HDM	297	1.6% (0.9% to 2.9%)	2.33 (1.32 to 4.13)	.004
	12 SQ-HDM	284	1.6% (0.9% to 2.9%)	2.28 (1.28 to 4.07)	.005
Global evaluation (% improved)	Placebo	299	68.0% (56.9% to 77.3%)	—	—
	6 SQ-HDM	300	76.1% (66.3% to 83.8%)	1.50 (1.04 to 2.16)	.029
	12 SQ-HDM	284	75.1% (65.0% to 83.0%)	1.42 (0.98 to 2.05)	.062

TABLE E6. Overview of AEs in the trial

Treatment group	Placebo (n = 338)		6 SQ-HDM (n = 336)		12 SQ-HDM (n = 318)		Active all (n = 654)		Overall (n = 992)	
	No. (%)	E (%)	No. (%)	E (%)	No. (%)	E (%)	No. (%)	E (%)	No. (%)	E (%)
All AEs	154 (46)	327 (100)	212 (63)	678 (100)	213 (67)	681 (100)	425 (65)	1359 (100)	579 (58)	1686 (100)
Causality										
Unlikely	128 (38)	231 (71)	128 (38)	277 (41)	121 (38)	224 (33)	249 (38)	501 (37)	377 (38)	732 (43)
Possible	50 (15)	96 (29)	161 (48)	401 (59)	167 (53)	457 (67)	328 (50)	858 (63)	378 (38)	954 (57)
Severity of all AEs										
Mild	119 (35)	235 (72)	186 (55)	509 (75)	184 (58)	505 (74)	370 (57)	1014 (75)	489 (49)	1249 (74)
Moderate	56 (17)	82 (25)	83 (25)	157 (23)	78 (25)	168 (25)	161 (25)	325 (24)	217 (22)	407 (24)
Severe	10 (3)	10 (3)	10 (3)	12 (2)	7 (2)	8 (1)	17 (3)	20 (1)	27 (3)	30 (2)
Severity of IMP-related AEs										
Mild	41 (12)	77 (80)	147 (44)	351 (88)	149 (47)	364 (80)	296 (45)	715 (83)	337 (34)	792 (83)
Moderate	13 (4)	19 (20)	27 (8)	47 (12)	37 (12)	87 (19)	64 (10)	134 (16)	77 (8)	153 (16)
Severe	—	—	3 (<1)	3 (<1)	5 (2)	6 (1)	8 (1)	9 (1)	8 (<1)	9 (<1)
Seriousness										
Serious	8 (2)	8 (2)	4 (1)	4 (<1)	—	—	4 (<1)	4 (<1)	12 (1)	12 (<1)
Nonserious	151 (45)	319 (98)	212 (63)	674 (>99)	213 (67)	681 (100)	425 (65)	1355 (>99)	576 (58)	1674 (>99)
Change to IMP										
None	135 (40)	277 (85)	194 (58)	596 (88)	195 (61)	595 (87)	389 (59)	1191 (88)	524 (53)	1468 (87)
Temporary interruption	29 (9)	42 (13)	45 (13)	68 (10)	38 (12)	59 (9)	83 (13)	127 (9)	112 (11)	169 (10)
Discontinued	7 (2)	8 (2)	10 (3)	14 (2)	13 (4)	27 (4)	23 (4)	41 (3)	30 (3)	49 (3)
Outcome										
Recovered	150 (44)	308 (94)	209 (62)	659 (97)	211 (66)	671 (99)	420 (64)	1330 (98)	570 (57)	1638 (97)
Recovered with sequelae	1 (<1)	1 (<1)	—	—	—	—	—	—	1 (<1)	1 (<1)
Not recovered	13 (4)	15 (5)	14 (4)	18 (3)	6 (2)	8 (1)	20 (3)	26 (2)	33 (3)	41 (2)
Unknown	3 (<1)	3 (<1)	1 (<1)	1 (<1)	2 (<1)	2 (<1)	3 (<1)	3 (<1)	6 (<1)	6 (<1)
Leading to discontinuation										
Yes	7 (2)	8 (2)	10 (3)	14 (2)	13 (4)	28 (4)	23 (4)	42 (3)	30 (3)	50* (3)
No	151 (45)	319 (98)	205 (61)	664 (98)	207 (65)	653 (96)	412 (63)	1317 (97)	563 (57)	1636 (97)

E, Number of events.

*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.