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Original Article

Title: House dust mite sublingual immunotherapy is safe in patients with mild-to-moderate, persistent asthma: a clinical trial.

Short title: Safety of HDM SLIT in asthma

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ABSTRACT

Background: The safety of allergen immunotherapy (AIT) in asthma has not always been sufficiently documented; accordingly, fear of asthma exacerbations has made physicians somewhat reluctant to prescribe AIT in this context. In a double-blind, placebo-controlled, randomized clinical trial, house dust mite (HDM) sublingual AIT was found to be efficacious in moderate, persistent asthma. The trial's safety results are now reported in detail.

Methods: Asthmatic adults were randomized 2:1 to twelve months of daily treatment with a sublingual solution of *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* extracts or a placebo. Adverse events (AEs) at least possibly related to the investigational product were classified by the investigators as adverse drug reactions (ADRs).

Results: Overall, the patients in the safety analysis set (n=484; active treatment: n=322; placebo: n=162) had mostly well-controlled, persistent asthma (mild in 290 patients (59.9%), moderate in 183 (37.8%) and severe in 11 (2.3%)). No treatment-related serious AEs were reported. Respectively 87.0% and 75.9% of the patients in the active and placebo groups experienced at least one AE (mostly mild), and 78.9% and 48.1% experienced an ADR (mostly mild or moderate oral reactions). The incidence of asthma exacerbations (symptoms requiring a short-course of oral corticosteroids) during the study was similar in the active treatment group (3.7%) and the placebo group (4.3%). There were no significant intergroup differences or intragroup changes over time in respiratory AEs, lung function or asthma-related quality of life.

Conclusions: HDM sublingual AIT was safe and well tolerated in adult patients with mild-to-moderate, persistent asthma (ClinicalTrials.gov: NCT00660452).

Key words: asthma, house dust mite, sublingual immunotherapy, safety

Introduction

Allergen immunotherapy (AIT) is an accepted treatment option for allergic respiratory disease, including allergic rhinitis (AR) and allergic asthma (1-6). Meta-analyses and systematic reviews show that sublingual immunotherapy (SLIT) and subcutaneous immunotherapy (SCIT) are efficacious in AR and allergic asthma in adults and children (5-11). However, with some notable exceptions (i.e. recent trials of house dust mite (HDM) SLIT tablet formulations), most of the data on the safety and efficacy of AIT in asthma gathered over the last few decades have come from trials performed on relatively low numbers of patients with concomitant AR and mild asthma (12,13). Although a recent Cochrane review on SLIT for asthma concluded that very few serious adverse events have been reported, most studies had included patients with intermittent or mild asthma; hence, it was not possible to comment on the safety of SLIT in patients with moderate or severe asthma (14). Furthermore, fear of serious adverse respiratory events (i.e. asthma attacks) even in controlled, mild-to-moderate asthma has made physicians reluctant to prescribe SLIT in this context.

To address these issues, we examined the efficacy and safety of HDM SLIT in a group of 484 adult patients with mild or moderate persistent allergic asthma (15). HDM SLIT was associated with significant clinical benefits (vs. placebo) in patients with moderate (but not mild) persistent asthma at baseline. One of the trial's objectives was to establish whether or not year-long treatment with HDM SLIT was safe and well tolerated in patients with mild or moderate persistent allergic asthma. The present article describes the trial's safety results in detail.

Material and Methods

The study's design, sample size calculation, inclusion/exclusion criteria, efficacy endpoints and immunological endpoints have been described previously (15). In brief, this was a double-blind, placebo-controlled (DBPC), randomized, parallel-group study of AIT-naïve adult patients aged 16 to 50 (ClinicalTrials.gov identifier: NCT00660452). With regard to the primary efficacy criterion endpoint (well-controlled asthma, WCA) and using a randomization ratio of 2:1, we calculated that a sample size of 300 patients in the active treatment group and 150 patients in the placebo group would yield a power of 80% for detecting the expected difference in WCA at a 5% two-sided significance level. The study comprised a screening period, a 3-month baseline period and a 12-month treatment period (Figure 1). The study participants had suffered from mild or moderate persistent, HDM-induced asthma for at least the previous 12 months (a clinical history of HDM-induced allergic asthma with or without perennial allergic rhinitis for at least 1 year; sensitization to both *D. pte* and *D. far* (wheal diameter ≥ 4 mm in an SPT after washout of antihistamines, and specific IgE ≥ 0.70 kU/L); a bronchial reversibility test $\geq 12\%$ after inhalation of $\beta 2$ -agonist or a positive methacholine provocation test in the 12 months before the screening visit or at the screening visit). Sensitization to cat or dog allergens (a positive SPT diameter ≥ 4 mm and serum specific IgE ≥ 0.70 kU/L) and having a cat or a dog at home were study exclusion criteria, as was any cosensitization leading to clinically relevant allergic asthma and likely to significantly change the symptoms of the patient throughout the study. Mild, moderate and severe forms of asthma were respectively defined as daily budesonide doses of 200 to 400 μg , 401 to 800 μg and >800 μg required for acceptable asthma control according to the seven-item Asthma Control Questionnaire™ (ACQ) (16-18). The ACQ score ranges from 0 (totally controlled asthma) to 6 (extremely poorly controlled asthma). An ACQ score of below

0.75 means that the patient's asthma is very likely to be well controlled, and a score of 1.5 or more means that the asthma is not well controlled (18). The only authorized medications were budesonide dry powder 100 µg (for controlling asthma), salbutamol (in a metered dose inhaler), prednisolone 5 mg tablets (for asthma exacerbations), loratadine 10 mg tablets (for AR) and antibiotics (for asthma exacerbations with concomitant bacterial infections).

Reporting and analysis of safety data.

Study participants recorded safety, concomitant medication data and adverse events (AEs) on a daily record card. Participants were also invited to report AEs spontaneously at study visits.

Adverse events were defined as any untoward medical occurrence in a patient receiving a pharmaceutical product, including prior occurrences that recurred or worsened during the study; they were subsequently coded by system-organ class (SOC) and preferred term using version 12.0 of the Medical Dictionary for Regulatory Activities (<http://www.meddra.org>). The investigator had to note the AE's start date, end date (if applicable) and severity (mild, moderate or severe) and whether the AE was intermittent or continuous. The investigator rated the severity of AEs with regard to the following clinical criteria. For mild AEs, signs and symptoms were easily tolerated. The symptoms could be ignored, disappeared when the patient was distracted, did not interfere with the patient's daily life and were not clinically relevant. In moderate AEs, symptoms caused discomfort but were tolerable; they could not be ignored and did affect concentration. The symptoms may have interfered with the daily activities and may have been clinically relevant. In severe AEs, symptoms affected usual daily activity and were clinically relevant. Lastly, the investigator had to assess the relationship between the investigational product (whether active or placebo) and the AE. Adverse events that were possibly, probably or

certainly related to the investigational product (in the investigator's opinion) were classified as adverse drug reactions (ADRs). An asthma exacerbation was defined as the presence of symptoms requiring a short course of oral corticosteroid (prednisolone). Asthma exacerbations were further classified as being associated (or not) with an infection requiring the concomitant intake of antibiotics. A transient worsening of asthma not requiring oral corticosteroids was not classified as an SAE. For each patient, the number of exacerbations was normalized against a one-year period (since the treatment duration for a given patient was unlikely to be exactly 12 months).

Participants completed the ACQ and the Asthma Quality of Life Questionnaire (AQLQ) on a regular basis (Figure 1) (18,19). Lung function testing was also performed on a regular basis (Figure 1), and included measurement of the forced expiratory volume in one second (FEV_1) and the forced vital capacity (FVC). For each patient, standard haematological and other laboratory parameters were categorized as “low”, “within normal range” or “high”. The numbers of patients whose values shifted from one category to another between the first and last visits were calculated and analyzed.

The safety analysis set (SAS) included all randomized patients having received at least one dose of the investigational product. The full analysis set (FAS) included all randomized patients having received at least one dose of the investigational product and with at least 16 assessable weeks during the treatment period. A linear model for repeated measures was used to assess the change over time in FEV_1 . The incidences of AEs in the active treatment and placebo groups were compared in a chi-squared test or Fisher's exact test. The latter test was performed using

GraphPad Prism[®] software (version 5.01, GraphPad Software Inc., San Diego, CA, USA). All other statistical analyses were performed using SAS[®] software (version 9.1.3, SAS Inc., Cary, NC, USA).

Results

The study population

All 484 randomized participants received at least one dose of product (active treatment: n=322 patients) or placebo (n=162) and were thus included in the SAS (Figure 2, Table 1). When considering either the SAS or the FAS, there were no significant differences between the active and placebo groups in terms of demographic characteristics, time since onset of asthma, asthma exacerbations in the previous year, ICS dose, asthma medication prior to study enrolment, the ACQ score and the AQLQ score (Table 1). Although all study participants were classified as having mild-to-moderate asthma at inclusion, some improved or worsened between inclusion and randomization. At randomization, 290 patients had mild asthma (59.9% of the SAS), 183 (37.8%) had moderate asthma and 11 (2.3%) had severe asthma. Of the patients with mild asthma, 46 (9.5% of the SAS) had very mild disease because they required less than 200 µg/day of budesonide for asthma control immediately prior to randomization. Treatment compliance (based on counts of used and unused boxes and vials of investigational product) over a rigorous, 12-month period of daily dosing was high. For the SAS, the median (interquartile range) level of compliance was 93.1% (87.4-98.3) in the active group and 94.1% (87.7-98.9) in the placebo group.

Adverse events and adverse drug reactions

Overall, more patients in the active treatment group experienced at least one AE (87.0% in the active treatment group vs. 75.9% in the placebo group, $p=0.0029$), and respectively 78.9% and 48.1% ($p<0.0001$) experienced at least one ADR (Table 2). There were 751 ADRs in 254 patients in the active treatment group and 184 ADRs in 78 patients in the placebo group. AEs prompted premature study discontinuation in 8 (2.5%) patients in the active treatment group and 1 (0.6%) patient in the placebo group. The 8 AEs that led to discontinuation in the active treatment group were (as reported using preferred terms) abdominal pain ($n=3$), cough ($n=1$), rash ($n=1$), abdominal pain upper ($n=1$), abdominal pain, nausea and vomiting ($n=1$), and oral pruritus, rhinitis, abdominal pain, palpitation and oedema mouth ($n=1$). The AE that led to discontinuation in the placebo group was worsening of asthma. None of the AEs that led to discontinuation were classified as ADRs.

In terms of severity, most AEs were mild (affecting 80.4% of the participants in the active treatment group and 62.3% of the placebo group; $p<0.0001$) or moderate (affecting 46.3% of the active treatment group and 38.9% of the placebo group; $p=n.s.$) (Table 3). Similarly, most ADRs (i.e. AEs that were possibly, probably or certainly related to the investigational product) were mild or moderate (Table 3). The proportion of participants with at least one mild ADR was significantly higher in the active treatment group than in the placebo group. The same was true for moderate ADRs (Table 3). Severe ADRs occurred in 3.1% of the patients in the active treatment group and 1.9% in patients in the placebo group ($n.s.$). Ten patients in the active treatment group had a total of 12 severe ADRs: abdominal pain ($n=3$ events), abdominal pain upper ($n=1$ event), nausea ($n=1$ event), swollen tongue ($n=5$ event), tongue oedema ($n=1$ event)

and cough (n=1). Three patients in the active treatment group had a total of 3 severe ADRs: rhinitis (n=1), asthma (n=1) and cough (n=1). Most of the moderate-intensity ADRs (n=24 patients) in the placebo group were due to rhinitis (n=12 patients) or asthma (n=8 patients).

In terms of seriousness, five patients (four in the active treatment group and one in the placebo group) reported treatment-emergent SAEs (Table 4). None of these AEs were classified as ADRs and all resolved during the study. Hence, there were no life-threatening ADRs, serious allergic reactions or deaths in either treatment group.

When analyzed by SOC, the most frequent ADRs were gastrointestinal disorders (affecting 74.2% and 35.8% of the patients in the active treatment and placebo groups, respectively; $p<0.0001$) (Table 5). Abdominal pain was the most frequent non-oral gastrointestinal ADR (affecting 25.2% of the active treatment group and 10.5% of the placebo groups $p<0.0001$). In each group, fewer than 5% of patients were affected by ADRs related to nausea, diarrhoea and vomiting. The ADRs of abdominal pain in the active treatment group were almost always mild or moderate: only 2.8% of these episodes were severe. Apart from abdominal pain, the most frequent ADRs were oral local reactions (mainly tongue swelling, oral pruritus, glossitis, cheilitis and edema of mouth), the incidence of which was significantly higher in the active treatment group than in the placebo group (Table 5).

The incidence of asthma exacerbation during the study was similar in the active treatment group (3.7% in the SAS) and the placebo group (4.3% in the SAS) - despite the fact that actively treated patients with moderate (but not mild) asthma had a greater mean absolute decrease in budesonide dose than those in the placebo group (218.5 µg and 126.2 µg, respectively, in the FAS; $p=0.004$). Likewise, the incidences of exacerbations requiring oral corticosteroids with antibiotics were also similar in the active treatment group (1.6%) and the placebo group (2.5%).

In the FAS, the mean $\pm$ SD [95% confidence interval] number of asthma exacerbations standardized over a year in the active treatment group (0.06 ± 0.38 [0.02; 0.11]) did not differ significantly from that recorded in the placebo group (0.04 ± 0.24) [0.01; 0.08]).

Overall, the mean FEV₁ (% predicted, calculated for the FAS) remained above 75% during the treatment period in both the active treatment and placebo groups (data not shown). In subgroups of patients with mild or moderate asthma, *post-hoc* analyses of FEV₁ measured at each visit and the changes in FEV₁ between V5 and the last visit did not reveal any active vs. placebo differences (data not shown).

Although QoL is not a safety parameter *per se*, it is related to tolerability. There were no statistically significant differences between the active and placebo groups in terms of the change in the overall AQLQ score for the FAS (from baseline to V12) (Supplementary Table 1).

In the FAS, the active treatment and placebo groups did not differ significantly in terms of the proportion of patients lacking well-controlled asthma (i.e. an ACQ score ≥ 1.5) at V5, V9 and V10.

There were no significant differences between the treatment groups in terms of laboratory test results, vital signs or physical signs.

Discussion

With 484 randomized participants, this was one of the largest DBPC studies of SLIT to have been performed in adult patients with HDM-induced asthma. A post-hoc analysis of the efficacy data revealed a significant active vs. placebo difference in both well-controlled asthma and totally controlled asthma in patients with moderate (but not mild) persistent asthma (15).

The investigational HDM SLIT product was well tolerated, and the overall safety profile was consistent with data from previous clinical trials and post-marketing studies of SLIT in general (5,6,20) and aqueous HDM SLIT formulations in particular (21-23), with mainly mild, local, transient adverse events. Encouragingly, we did not observe any significant differences in the proportion of patients with asthma exacerbations (i.e. events requiring oral corticoids). The low mean annualized number of asthma exacerbations in the SLIT group did not differ significantly from that recorded in the placebo group. The small changes over time in FEV₁% were similar in the active treatment and placebo groups. However, these changes were observed in a context of ICS dose reductions. We observed a high incidence of abdominal pain in both active treatment and placebo groups (albeit not associated with vomiting or diarrhoea); this was surprising because abdominal pain is not a particularly frequent feature of SLIT in the literature (5,6,20).

We found that respectively 87.0% and 75.9% of the patients in the active and placebo groups experienced at least one AE (mostly mild), and 78.9% and 48.1% experienced an ADR (mostly mild or moderate oral reactions). The ADR rate of 48.1% in the placebo group was unexpectedly high; almost two-thirds of the AEs in the placebo group were judged to be at least possibly linked to administration of the placebo. By way of an indirect comparison, the percentage of placebo-group patients with ADRs was 15% in Demoly et al.'s study of SQ HDM SLIT-tablets in adults with allergic rhinitis (24). Similarly, a recent, large, placebo-controlled study of three dose levels of an HDM SLIT tablet by Mosbech et al. (published after the present study had been designed) (12) reported that a similar percentage of AEs in the placebo group were probably or possibly related to the study drug.

However, we suspect that the high percentage of ADRs in the placebo group was related to the investigators' concern for safety (notably respiratory AEs) and the frequency of study visits. Given that this study was (at the time) one of the largest studies of HDM SLIT in mild-to-moderate asthma and the first of its kind for the Chinese investigators, the investigators were particularly concerned about safety (notably respiratory AEs) and requested frequently scheduled study visits (seven) during the one-year treatment phase.

Modern tablet formulations of SLIT with allergens such as grass pollen appeared to be well tolerated in asthma (25); a review of the data from 8 large DBPC RCTs of a single-grass SLIT tablet (including a total of 3,314 adult patients and 881 paediatric patients with AR) found that around a quarter of the participants had a history of (mainly mild) asthma. Treatment-emergent AEs, systemic allergic reactions and severe local allergic swelling were no more common in

patients with well-controlled, mild asthma than in the other patients. There was no evidence to suggest that SLIT was associated with asthma exacerbations. In the large, placebo-controlled study of three dose levels of an HDM SLIT tablet cited above, Mosbech et al. concluded that the HDM SLIT tablet had a benign safety profile in a study population within which 69% of the participants had partly controlled asthma (12). The proportion of patients experiencing SAEs was 3% in both the active treatment and placebo groups (12). Our present findings also agree with a recent report on the administration of an HDM SLIT tablet formulation or placebo in 834 patients with mild to severe asthma (26). The HDM SLIT tablet was well tolerated in (i) patients with at least one FEV₁ measurement below 70% predicted at some point on the study and (ii) patients with uncontrolled asthma (according to the GINA criteria) at randomization. The tablet has recently received marketing authorization in Europe for patients with HDM allergic asthma not well controlled by inhaled corticosteroids and associated with mild to severe HDM allergic rhinitis. Taken as a whole, these observations suggest that SLIT is of value in patients with asthma requiring low-to-moderate doses of inhaled glucocorticoid - even when asthma is not always well controlled.

Our study had some limitations. Firstly, exposure to HDM allergens in each patient's home or workplace was not measured. Secondly, the treatment duration of 12 months was shorter than the minimum of 3 years usually recommended for AIT (2-6). However, with respect to tolerance, the vast majority of AEs occurred in the first four weeks of treatment.

In conclusion, a 300 IR aqueous HDM SLIT formulation was found to be safe, well tolerated and clinically relevant in a large group of patients with mild-to-moderate, persistent asthma. Even though AIT will be avoided in patients with severe uncontrolled asthma, this therapy could be applied to patients with mild-to-moderate asthma who do not want to receive constant or long-term pharmacotherapy or in whom pharmacotherapy induces undesirable side effects (3). Future research should focus on ways of identifying the small numbers of patients at risk of SAEs upon treatment with AIT.

STATEMENT OF INTEREST

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AUTHORS' CONTRIBUTIONS

Philippe Devillier, Riad Fadel and Olivier de Beaumont all made substantial contributions to conception and design of the study and acquisition, analysis and/or interpretation of data. They all contributed to drafting the article or revising it critically for important intellectual content and have given their final approval of the version submitted for consideration for publication.

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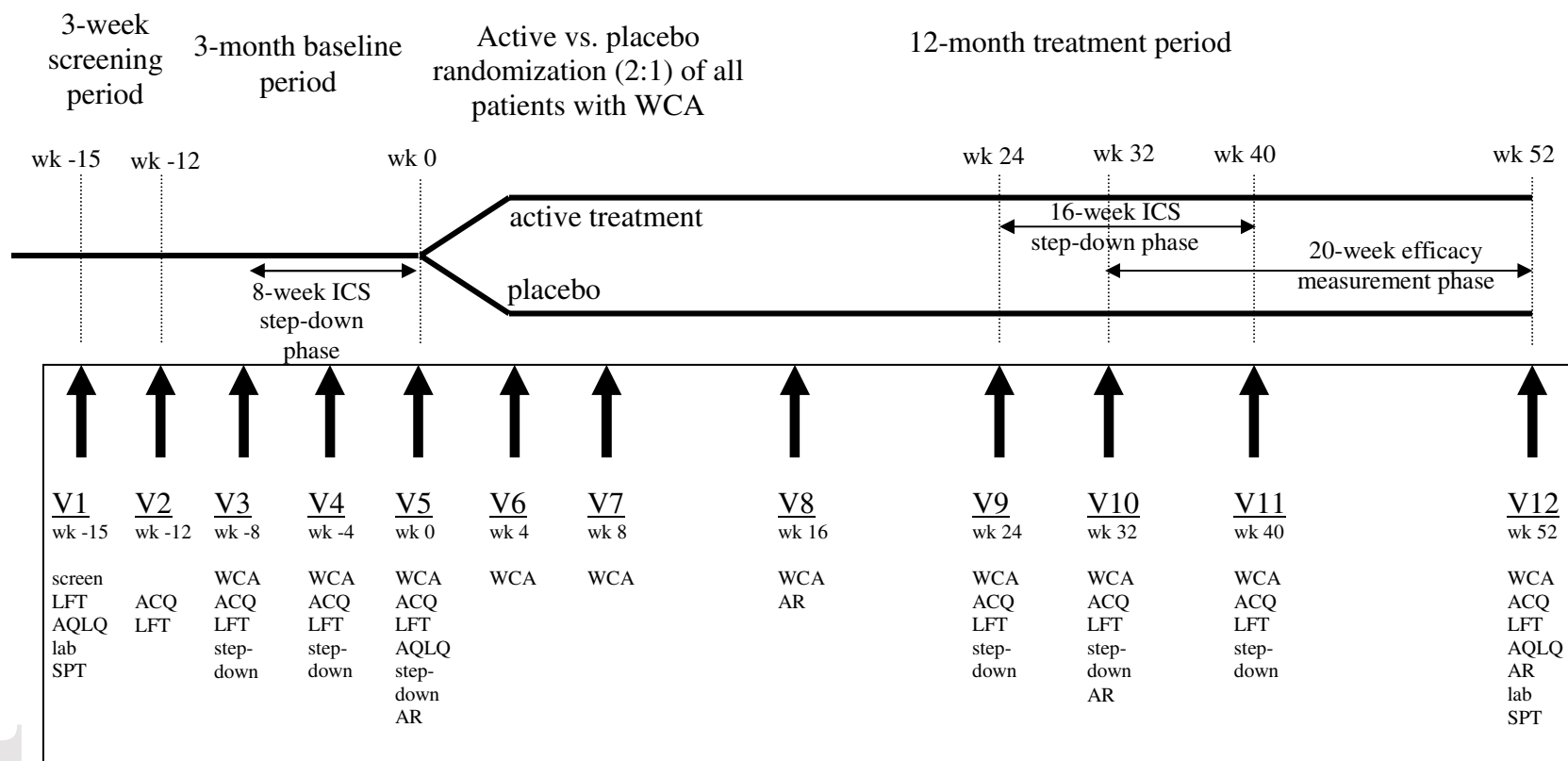
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Figure 1. Study design.



WCA: well-controlled asthma; wk: week; ICS: inhaled corticosteroid; LFT: lung function test; AQLQ: Asthma Quality of Life

Questionnaire; lab: laboratory tests for safety assessment; SPT: skin prick test; ACQ: Asthma Control Questionnaire; WCA: well-controlled asthma assessment; AR: overall allergic rhinitis assessment.

Figure 2 Patient disposition

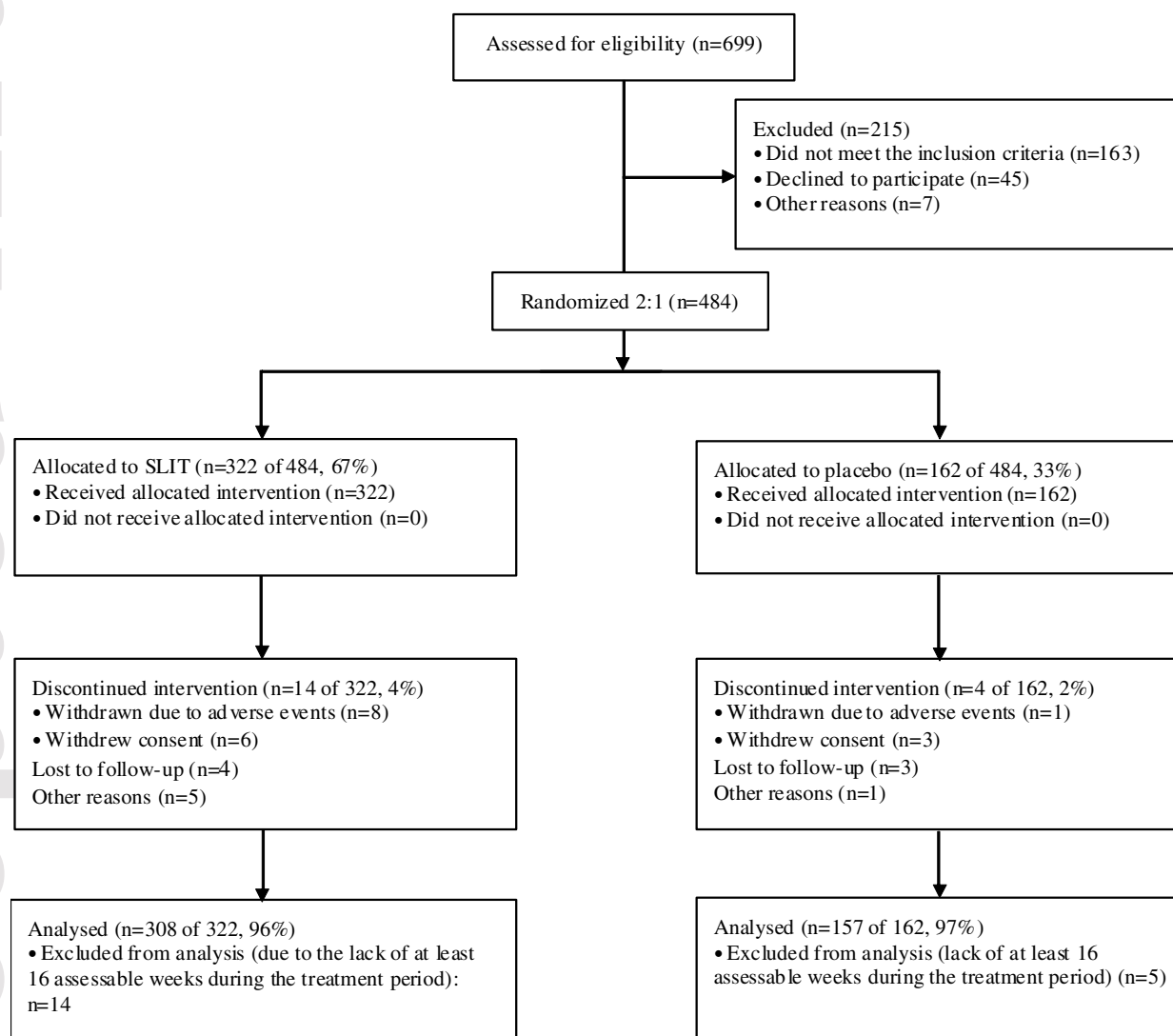


Table 1 **Characteristics of the safety analysis set (SAS).**

	Active treatment group					Placebo group				
	Entire group	<200 µg ^[a]	200-400 µg ^[a]	401-800 µg ^[a]	>800 µg ^[a]	Entire group	<200 µg ^[a]	200-400 µg ^[a]	401-800 µg ^[a]	>800 µg ^[a]
n	322	32	164	121	5	162	14	80	62	6
Age (years, mean (SD)) range	31.1 (8.9) 14–50	30.2 (9.9) 16–48	29.6 (8.3) 16–49	33.1 (9.1) 14–50	37.4 (8.2) 30–50	31.2 (8.2) 16–49	30.4 (8.2) 17–44	29.2 (7.8) 16–45	33.5 (8.1) 17–49	35.0 (9.7) 22–45
Gender (n females, (%))	173 (53.73)	19 (59.38)	91 (55.49)	61 (50.41)	2 (40)	94 (58.02)	9 (64.29)	42 (52.50)	41 (66.13)	2 (33.33)
BMI (kg/m ²) (mean (SD))	22.68 (3.46)	23.25 (3.07)	22.02 (2.82)	23.36 (4.19)	24.08 (1.71)	22.95 (3.44)	23.48 (3.12)	22.56 (3.03)	23.11 (3.98)	25.42 (2.62)
Asthma duration, in years (mean (SD))	12.66 (9.79)	12.84 (9.95)	12.15 (9.84)	13.23 (9.38)	14.80 (17.71)	13.60 (9.90)	12.36 (9.16)	12.27 (9.44)	15.16 (10.55)	17.83 (9.30)
Asthma exacerbations requiring oral	16.46	6.25	15.24	20.66	20.00	20.37	14.29	12.50	29.03	50.00

corticoids in the previous year (% participants)										
FEV ₁ (% predicted) at randomisation (V5) (mean (SD))	85.26 (11.28)	93.94 (14.28)	86.60 (10.07)	81.67 (10.34)	73.00 (5.05)	84.60 (11.22)	92.86 (7.73)	87.15 (11.41)	80.06 (9.62)	78.17 (10.83)
ACQ at V5 (mean (SD)) [ACQ < 0.75 (% participants)]	0.68 (0.53) [67.08]	0.54 (0.44) [81.25]	0.62 (0.51) [69.51]	0.81 (0.56) [60.33]	0.77 (0.36) [60.00]	0.75 (0.58) [62.35]	0.45 (0.35) [85.71]	0.66 (0.49) [65.00]	0.94 (0.68) [53.23]	0.71 (0.43) [66.67]

Results describing continuous variables are expressed as the mean (SD). Results describing categorical variables are expressed as n (number of participants) and as a percentage of the population. BMI: body mass index. FEV₁: forced expiratory volume in 1 second; ACQ: Asthma Control Questionnaire; V: visit. [a]: mean µg budesonide per day over the four weeks prior to randomization.

Table 2. Overview of AEs by treatment group in the SAS

	Active (n=322)		Placebo (n=162)		Comparison
<i>Patients with at least one:</i>	n	%	n	%	p value
AE	280	87.0	123	75.9	0.0029
ADR	254	78.9	78	48.1	<0.0001
SAE	4	1.2	1	0.6	n.s.
Serious ADR	0	0	0	0	-
AE leading to premature study termination	7	2.2	1	0.6	n.s.
ADR leading to premature study termination	0	0	0	0	-
AE leading to death	0	0	0	0	-

AE: adverse event; ADR: adverse drug reaction; SAE: serious adverse event; n.s. not significant; p value: in Fisher's exact test.

Table 3 Summary of AEs and ADRs by severity and treatment group in the SAS

	Active (n=322)		Placebo (n=162)		Comparison
Severity:	n	%	n	%	p value
AEs:					
mild	259	80.4	101	62.3	<0.0001
moderate	149	46.3	63	38.9	n.s.
severe	17	5.3	10	6.2	n.s.
life-threatening or disabling	0	0	0	0	-
death	0	0	0	0	-
ADRs:					
mild	228	70.8	70	43.2	<0.0001
moderate	96	29.8	24	14.8	0.0003
severe	10	3.1	3	1.9	n.s.
life-threatening or disabling	0	0	0	0	-
death	0	0	0	0	-

AE: adverse event; ADR: adverse drug reaction; n.s.: not significant; p value: in Fisher's exact test.

Table 4 Summary of SAEs by treatment group in the SAS.

	Active (n=322)		Placebo (n=162)	
	n	%	n	%
At least one SAE	4	1.2	1	0.6
Hepatobiliary disorders	1	0.3	0	0
Arnold-Chiari syndrome *	1	0.3	0	0
Infections and infestations	1	0.3	0	0
Pneumonia	1	0.3	0	0
Injury, poisoning and procedural complications	1	0.3	1	0.6
Lower limb fracture	1	0.3	0	0
Traumatic brain injury	0	0	1	0.6
Reproductive system and breast disorders	1	0.3	0	0
Ovarian cyst ruptured	1	0.3	0	0
Skin and subcutaneous tissue disorders	1	0.3	0	0
Dermatitis contact	1	0.3	0	0

SAE: serious adverse event

Table 5 Summary of treatment-emergent ADRs (affecting >5% of patients in the corresponding treatment group) by system-organ class and preferred term in the SAS.

	Active (n=322)		Placebo (n=162)		Comparison
<i>Patients with at least one:</i>	n	%	n	%	p value
ADR (all SOCs)	254	78.9	78	48.1	<0.0001
Gastrointestinal disorders	239	74.2	58	35.8	<0.0001
Swollen tongue	85	26.4	2	1.2	<0.0001
Abdominal pain	81	25.2	17	10.5	<0.0001
Oral pruritus	75	23.3	23	14.2	0.0224
Glossitis	64	19.9	17	10.5	0.0096
Cheilitis	36	11.2	8	4.9	0.0285
Edema mouth	26	8.1	0	0	<0.0001
Infections and infestations	67	20.8	30	18.5	n.s.
Rhinitis	67	20.8	28	17.3	n.s.

ADR: adverse drug reaction; SOC: system-organ class. n.s.: not significant; p value: in Fisher's exact test.

Supplementary Table 1. Improvement and non-improvement in AQLQ scores and subscores during the treatment period, by treatment group in the FAS.

		Active (n=322)		Placebo (n=162)	
		n	%	n	%
Overall AQLQ score	Improvement	64	24.0	35	25.0
	No improvement	203	76.0	105	75.0
	<i>Missing data</i>	36		15	
Activity limitation	Improvement	80	28.4	29	19.7
	No improvement	202	71.6	118	80.3
	<i>Missing data</i>	21		8	
Symptom score	Improvement	68	23.5	40	26.7
	No improvement	221	76.5	110	73.3
	<i>Missing data</i>	14		5	
Emotional function	Improvement	94	31.4	47	30.5
	No improvement	205	68.6	107	69.5
	<i>Missing data</i>	4		1	
Exposure to environmental stimuli	Improvement	111	37.8	57	38.0
	No improvement	183	62.2	93	62.0
	<i>Missing data</i>	9		5	

AQLQ: Asthma Quality of Life Questionnaire

Supplementary Table 2. Details of SAEs (all unrelated to the study treatment) in the SAS.

<u>Description of SAE</u>	<u>Study group</u>	<u>Relationship to study treatment</u>	<u>Date of first administration of study treatment</u>	<u>Start date</u>	<u>End date</u>	<u>Context and management of the adverse event</u>
Arnold-Chiari malformation	Active	Not related	21 Mar 2008	22 Apr 2008	8 July 2008	Surgery for neck malformation, odontoidectomy process excision. Treatment with antibiotics after surgery.
Lower limb fracture	Active	Not related	26 Feb 2008	24 Feb 2009	20 Apr 2009	The patient fell down the stairs and was hospitalized for right knee bone fracture. The leg was put in plaster and the fracture healed.
Traumatic brain injury	Placebo	Not related	27 Mar 2008	6 Feb 2009	18 Mar 2009	The patient was hospitalized for craniocerebral trauma following a road accident which occurred at night in a context of drunk driving. A craniotomy was performed for extradural hematoma.
Ovarian cyst ruptured and pneumonia	Active	Not related Not related	12 Mar 2008	8 Aug 2008 30 Aug 2008	15 Aug 2008 5 Sept 2008	The patient experienced uterine bleeding and was hospitalised. Ovariorrhesis was diagnosed and ovarian surgery was performed. Corrective treatment included intravenous cefotaxime oral ethinylestradiol and oral vitamin C. The patient was hospitalised for community-acquired pneumonia. Corrective treatment included intravenous ofloxacin and intravenous cefoperazone.
Dermatitis contact	Active	Not related	23 Jan 2008	12 July 2008	16 July 2008	Due to the patient's wife's gynaecological disease, unspecified

						topical antibiotic was prescribed to both husband and wife. The patient developed red spots on his genitals and was hospitalized for contact dermatitis. The patient received unspecified anti-allergic corrective treatment.
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