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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

DOI: 10.1111/all.14007

Concomitant bilastine and montelukast as additive therapy for seasonal allergic rhinoconjunctivitis and mild-to-moderate asthma. The SKY study

To the Editor,

Histamine and cysteinyl leukotrienes (CysLTs) are potent inflammatory mediators involved in both seasonal allergic rhinoconjunctivitis (SARC) and asthma.^{1,2} A combination therapy against both these agents may provide additive benefit, as demonstrated both in vitro³ and in vivo.⁴⁻⁶

We compared the efficacy and safety of concomitant therapy with bilastine, a second-generation H1 anti-histamine⁷ and montelukast vs each agent alone in patient with SARC and asthma. We hypothesized that bilastine plus montelukast is superior to bilastine monotherapy in reducing SARC symptoms after

4 weeks and in improving asthma quality of life over a longer time period.

Adult patients with SARC and mild-to-moderate asthma partially controlled⁸ by beclomethasone dipropionate or equivalent ≤ 500 $\mu\text{g/d}$ (alone or in combination with long-term β_2 -adrenergic bronchodilators) were enrolled. Patients had a postbronchodilator FEV₁ > 70% of the predicted, a skin prick test positive to at least one seasonal allergen tested at enrolment or previously reported, and a nasal/ocular Total Symptom Score (TSS) ≥ 3 .⁹ Exclusion criteria are reported in the online supplementary. The study (EUDRACT number:2015-004806-40) was conducted in 50 centres across

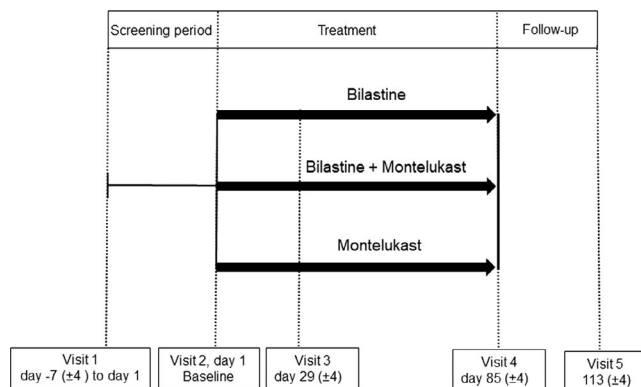


FIGURE 1 Study design and treatment

6 European countries during the relevant regional pollen season for grasses, trees and weeds, with a double-blind, double-dummy, randomized, active-controlled and parallel-group design (Figure 1). It consisted in a 1-week screening period followed by 12 weeks of treatment. During the study, patients quantified SARC symptoms by TSS, Daytime Nasal Symptom Score (DNSS) and Daytime non-Nasal Symptom Score (DNNS); use of rescue medications and occurrence of adverse events were noted. During screening, patients' medical history, vital signs, spirometry results and asthma quality of life questionnaire (AQLQ) scores were obtained. AQLQ was re-assessed after 4 and 12 weeks of treatment; ECG variables, blood and urine samples were re-obtained at the end of treatments for safety purposes.

Enrolled patients were randomly treated once daily with bilastine 20 mg plus montelukast 10 mg, or bilastine 20 mg plus placebo or montelukast 10 mg plus placebo (Figure 1). Naphazoline nasal spray eye drops and salbutamol inhaler were rescue medications for SARC and acute asthma symptoms. Patients' compliance with treatments was calculated. The primary endpoint was changes in baseline TSS values following 4 weeks of treatment.¹⁰ Secondary endpoints were changes in baseline TSS values obtained after 1, 2 and 3 weeks of treatment; changes in baseline DNSS and DNNSS values obtained after 1, 2, 3 and 4 weeks of treatments; changes in baseline AQLQ score obtained after 4 and 12 weeks of treatment. Analyses were performed on the intention-to-treat (ITT) population, ie randomized patients who had received at least one treatment tablet, had a baseline assessment and at least one assessment of primary efficacy variable after the baseline visit. A sensitivity analysis was also performed on the per-protocol (PP) population, ie patients in the ITT population having completed the study without any major protocol violation. The effect of each treatment on primary and secondary endpoints, as well as on use of rescue medications for SARC and asthma was compared by analysis of covariance. A P value $< .05$ was considered as significant. Additional details on the methods are in the online supplementary.

From April to October 2016, we enrolled 454 patients, 419 of whom (299 females, mean age 35.2 ± 0.2) were randomized to treatment (ITT population). Of these 419 patients, 387 completed the study without protocol violations (PP population, Figure S1). Reasons of patients exclusion are reported in the Figure S1 (data supplement).

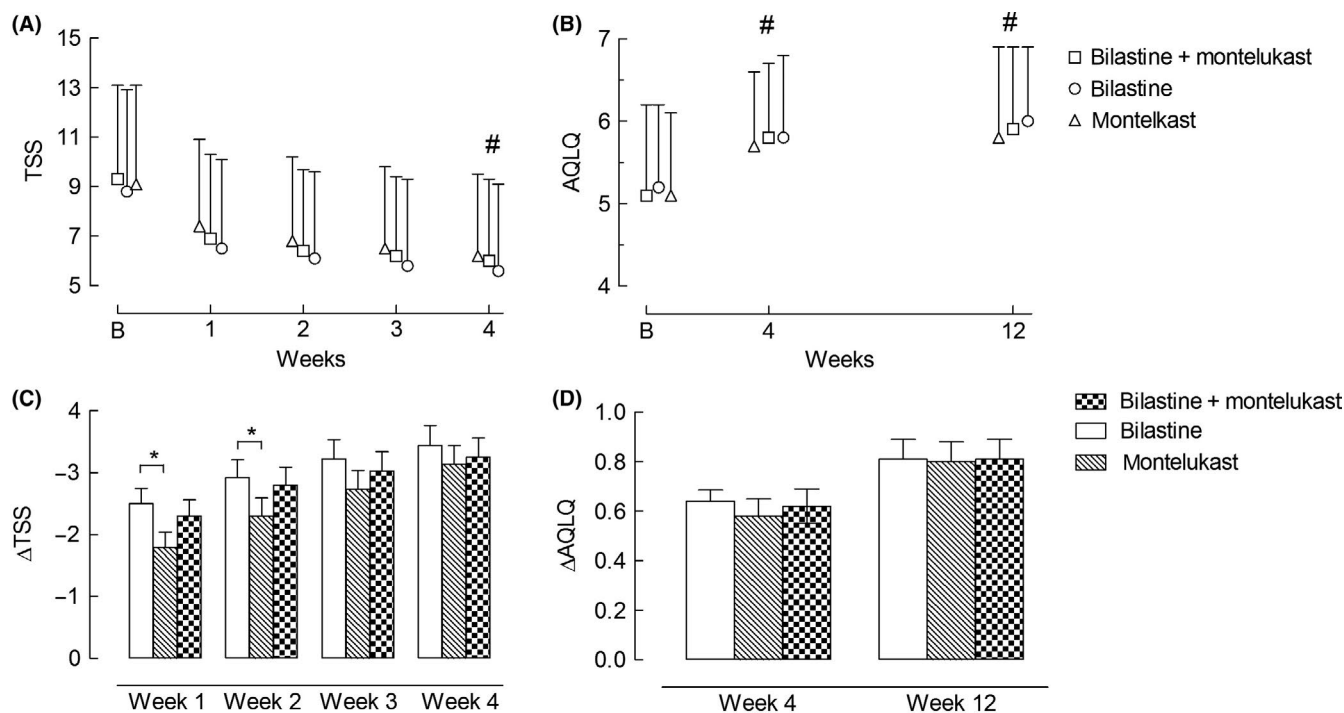


FIGURE 2 Mean (SD) total symptom score (TSS, panel A) and asthma quality of life questionnaire (AQLQ, panel B) values in patients treated with bilastine plus montelukast and in those treated with bilastine or montelukast alone. Estimated (SEM) changes in TSS and AQLQ from the corresponding baseline values observed after each week of treatment with bilastine, montelukast or bilastine plus montelukast are depicted in panel (C) and (D), respectively. B, baseline; *, $P < .05$ comparing TSS values in bilastine vs montelukast after 1 wk of treatment; #, $P < .001$ comparing TSS values observed 4 wk after treatment with bilastine plus montelukast, bilastine or montelukast alone vs corresponding baseline values

Most patients had polysensitization to pollens of grasses, trees and weeds. At inclusion, patients' demographics, FEV₁, TSS, AQLQ, DNSS and DNNSS were similar in each treatment arm (Table S1). All treatments significantly ($P < .001$) reduced baseline TSS values over 4 weeks (Figure 2). Overall, the mean $\pm$ SD TSS reduction was -3.2 ± 3.7 , with no significant differences among treatments. Mean TSS value observed 1 and 2 weeks after bilastine was significantly ($P < .05$) lower than after montelukast. (Figure 2). Mean TSS values decreased similarly with all treatments after 3 weeks (Figure 2). However, bilastine reduced baseline TSS more than montelukast after 1 and 2 weeks of treatment (P always $< .05$). Similar findings were observed for DNSS and DNNSS (data not shown). Mean AQLQ increased similarly with all treatments after 4 and 12 weeks. The use of rescue medications for SARC and/or asthma did not differ among treatments, as was patients' compliance with treatments (98.3% overall). Drug-related incidence of adverse events was similar among the treatment groups (4.3% overall). No clinically significant changes in any laboratory tests, ECGs or vital signs were noted.

We compared for the first time the efficacy and safety of concomitant administration of bilastine with montelukast vs respective monotherapies in a large population of patients with SARC and asthma. Contrary to our original hypothesis, concomitant administration of bilastine with montelukast was effective as either agent alone in the treatment of SARC symptoms. The reason(s) for not showing any additive effects of bilastine plus montelukast compared with each agent alone could be likely related to the overall mild intensity of SARC symptoms at baseline that might have reduced the room for improvement thus limiting the probability to detect differences between treatments. The absolute extent of the effect of treatments on symptoms or on the use of rescue medications is impossible to gauge as a placebo arm was not included. Noteworthy, the improvement in TSS values observed in our study is similar to that obtained after 2 weeks of placebo treatment by Bachert et al.⁹ Although the underlying cause is unclear, the large placebo effect observed by Bachert et al.⁹ is not uncommon as observed in other studies with SARC patients.¹¹

Bilastine alone improved SARC symptoms more than montelukast in the first 2 weeks of treatment. This finding is consistent with a more rapid effect of bilastine than montelukast, which may be of relevance for patients who need intermittent treatment to alleviate SARC symptoms. The absolute extent of the effect of these treatments on symptomatology or the use of rescue medication when treating SARC and concomitant asthma are impossible to gauge from this study because a group of patients treated entirely with placebo was not included. Moreover, since changes in lung function were not monitored, it is difficult to gauge how far this improvement reflected possible effects of study treatments on bronchoconstriction and/or lower airways inflammation or how far they reflected a true placebo effect. Previous reports suggest that an improvement in SARC can also improve asthma control.¹² Thus, due to its beneficial effects on SARC symptoms, our results suggest that bilastine, when added to inhaled corticosteroids alone or in combination with long-term β_2 -adrenergic bronchodilators, could improve disease control in mild-to-moderate asthma patients.

In conclusion, treatment with bilastine plus montelukast over 4 weeks does not consistently produce further improvements in SARC symptoms and AQLQ beyond those provided by either agent alone. Thus, there is no benefit of using bilastine plus montelukast to provide relief of SARC symptoms in partially controlled, mild-to-moderate asthma patients.

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CONFLICTS OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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A safe and efficient 7-week immunotherapy protocol with aluminum hydroxide adsorbed vespid venom

To the Editor,

Systemic anaphylactic reactions to Hymenoptera stings are reported to occur in 3.3% of the general Austrian population. Although field stings could be life-threatening for patients with insect venom allergy and despite the availability of venom immunotherapy (VIT) as an effective causal treatment, poor therapy adherence has been observed in our country.¹

Venom immunotherapy is effective in 77%-84% of patients treated with honeybee venom and in 91%-96% of patients receiving vespid venom.² Adverse events are usually rare and mild, and symptoms occur in only 4.3%-11.4% of patients during the up-dosing.³

A variety of therapy regimes exists for the initial phase, from conventional to rush and ultrarush or clustered modalities.² Although several attempts have been made to shorten protocols for the up-dosing phase of immunotherapy, no prospective clinical trials have been performed recently. Current conventional protocols are still time-consuming for patients and, together with the poor therapy adherence, point to the need for further efforts to enhance the acceptance of this successful treatment. We therefore initiated a prospective clinical trial (EudraCT 2015-002769-44) evaluating an up-dosing protocol with 8 weekly injections in 7 weeks regarding efficacy and safety. The aim of the study was to develop a rapid and safe protocol that meets the requirements of the regulatory authorities to provide an official up-dosing protocol for the Summary of Product Characteristics (SmPC) for the depot *Vespula* venom, Alutard SQ[®], ALK Abelló.

Seventy-six legally competent male and female subjects aged 18 to 70 years with a history of a systemic sting reaction to

vespid stings ($\geq$ grade I according to the classification of Ring and Messmer)⁴ were included. The study was approved by the ethics committee of the Medical University of Graz (approval no. 27-405 ex 14/15). External monitoring was performed during the clinical trial for the purpose of quality assurance. Sensitization was confirmed by IgE determination (ImmunoCAP[®] system, Thermo Fisher Scientific), intradermal tests (0.02 mL of 0.01, 0.1 and 1 μ g/mL) and prick tests (10, 100, 300 μ g/mL solutions). The basophil activation test (Bühlmann Laboratories) helped to distinguish between bee and vespid venom allergy in patients with equivocal history and test results (see Table S1), and only patients with mono-sensitization to vespid venom were included in the study. During the up-dosing phase, patients were treated with oral non-sedative antihistamines (histamine (H1) receptor blockers) one hour before injection. The purified depot preparation Alutard SQ[®] vespid venom (ALK-Abelló) was administered with an initial dose of 1 μ g followed by 5, 10, 20, 40, 60, 80, and 100 μ g corresponding to 1.000, 5.000, 10.000, 20.000, 40.000, 60.000, 80.000, and 100.000 SQ at 1-week intervals by single injections (injection interval: 7 to a maximum of 14 days). The maintenance phase required single injections every 4-6 weeks with 100 μ g. To demonstrate that immunotherapy is effective immediately after up-dosing, sting challenges with live vespids (*Vespula germanica* or *Vespula vulgaris*) were performed, whenever possible, one week after reaching the maintenance dose.

We registered one withdrawal from the study according to the patients' wish, the other 75 completed up-dosing without dose reductions. Only 3 (3.9%, one-sided exact 97.5% confidence interval [CI] 0.0-11.1) patients showed objective symptoms which were mild and limited to the skin, and 5 (6.6%, one-sided exact 97.5% CI 0.0-14.7) patients developed mostly mild and subjective systemic reactions (SR; see Tables 1 and 2). Twenty-two (28.9%)

Christoph Schrautzer and Lisa Arzt-Gradwohl contributed equally.

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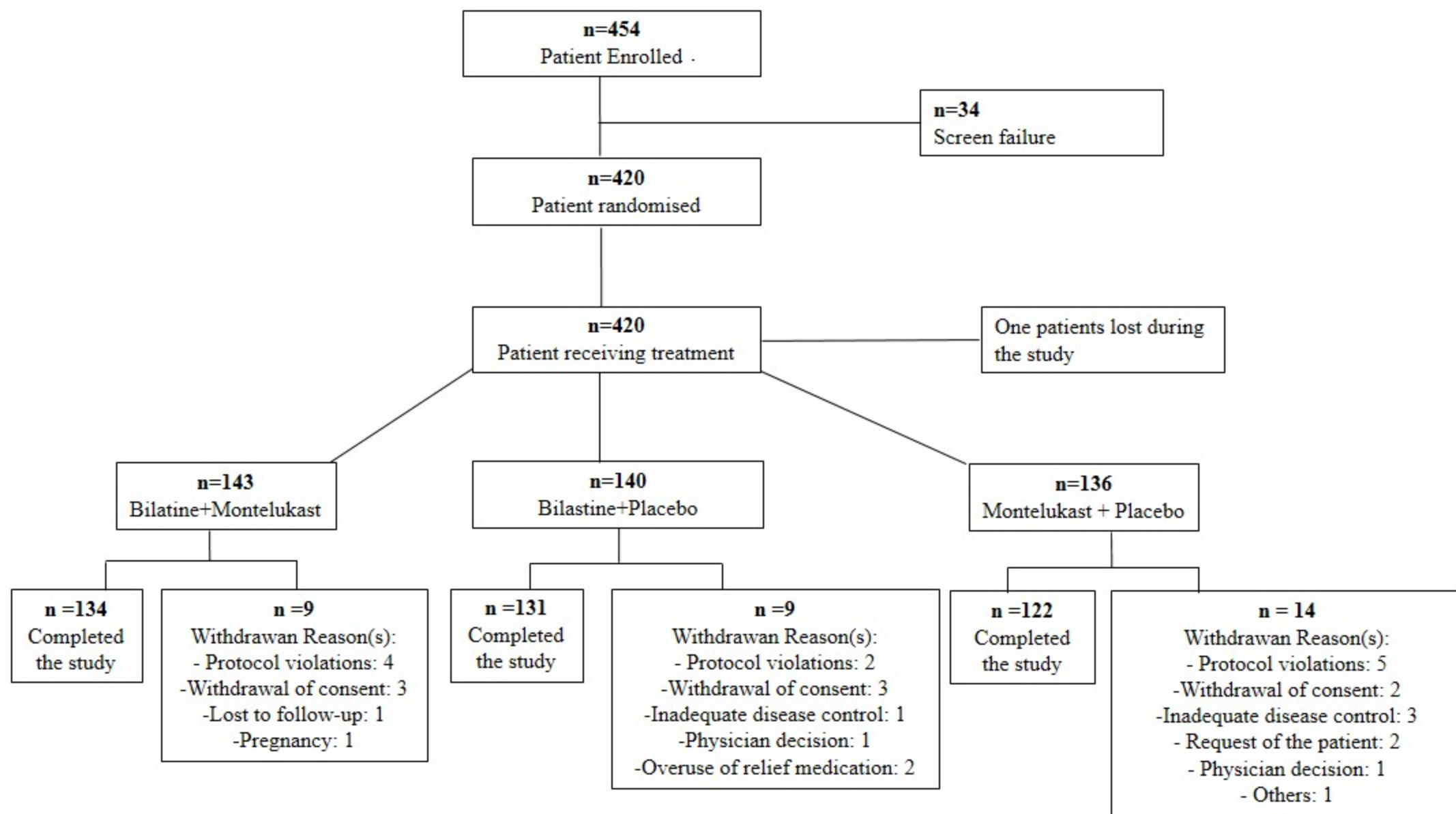


Table 1. Patients' baseline characteristics of each treatment arm (ITT population).

Bilastine + Montelukast (n=143)					Bilastine (n=140)					Montelukast (n=136)				
Sex	Age (yr)	FEV ₁ (% pred.)	TSS	AQLQ	Sex	Age (yr)	FEV ₁ (% pred.)	TSS	AQLQ	Sex	Age (yr)	FEV ₁ (% pred.)	TSS	AQLQ
69 F	34.9	93.5	9.3	5.1	83 F	35.5	94.3	8.8	5.2	73 F	35.4	94.3	9.1	5.1
74 M	(11.1)	(11.6)	(3.8)	(1.1)	57 M	(11.0)	(12.7)	(4.1)	(1.0)	63 M	(10.7)	(12.7)	(4.0)	(1.0)

Values are means ($\pm$ SD); ITT, intent to treat; TTS, total symptoms score; AQLQ, asthma quality of life questionnaire; FEV₁, forced expiratory volume at 1 sec; pred, predicted value.

Concomitant Bilastine and Montelukast as treatment for seasonal allergic rhinoconjunctivitis and asthma. The SKY Study

Federico Lavorini, Andrea Matucci, Oliviero Rossi and Massimo Pistolesi
on behalf of the SKY study investigators.

Supplement data

The study (EUDRA-CT number: 2015-004806-40) was conducted in accordance with the Declaration of Helsinki and approved by Independent Ethics Committees of each participating; an informed consent was signed by each patient, and all patient-related information disseminated prior to recruitment of the patients

We excluded patients with non-allergic rhinitis, nasal polyps or any clinically important nasal abnormalities, acute (i.e. within 30 days before enrolment) or chronic sinusitis, eye or intranasal surgery within 3 months, or upper respiratory infections including colds and systemic infections. Patients with any clinically significant cardiovascular, neurological, hepatic, renal or malignant diseases were also not enrolled in the study, as were pregnant or breast-feeding women and patients with history of hypersensitivity to any component of the study medications. Other exclusion criteria were immunotherapy, treatment with ICS, alone or in combination with short and/or long term β_2 -adrenergic bronchodilators, at dosage ≥ 500 mcg beclomethasone dipropionate or equivalent, daily treatment with antihistaminic drugs or Montelukast within 7 days prior the enrolment, systemic or intranasal corticosteroids (4 weeks), Ketotifen (2 weeks), macrolides and imidazolic antifungals (7 days), anticholinergic drugs (7 days), drugs with antihistamine properties (e. g. phenothiazine) (7 days), intranasal and systemic decongestants (3 days), Lodoxamide (7 days).

Study design and treatments

This was a double-blind, double-dummy, randomised, active-controlled, parallel group (n= 3) study design conducted during the relevant pollen season in 50 centres across 6 European countries.

27 The study involved a 1-week screening period followed by a 12-week treatment period. During the
 28 screening visit (visit 1) patients' medical history, vital signs, 12-lead ECG variables were recorded;
 29 blood and urine samples, including urinary pregnancy strip tests in women of childbearing potential,
 30 were collected for standard safety laboratory assessment. The same variables were re-assessed at the
 31 end of treatments for safety purposes. Patients were requested to record throughout the study, in a
 32 web-based diary, nasal and ocular symptoms assessed by using the Total Symptom Score (TSS), the
 33 Daytime Nasal Symptom Score (DNSS), and the Daytime non-Nasal Symptom Score (DNNS); use
 34 of concomitant medications and any adverse events occurring during the study were also noted. At
 35 the end of the screening period (visit 2) patients were re-assessed for eligibility based on the medical
 36 history, nasal symptoms severity and medications used. At visit 2, the degree of asthma quality of
 37 life, assessed by the asthma quality of life questionnaire (AQLQ), and spirometry results were also
 38 obtained. Enrolled patients were then randomised to receive in fasting condition an oral daily dose of
 39 Bilastine 20 mg + Montelukast 10 mg tablets, or Bilastine 20 mg tablets + Placebo tablets or
 40 Montelukast 10 mg + Placebo tablets for a treatment period of 12 weeks. Patients were provided
 41 Naphazoline nasal spray and eye drops as relief medications for SARC, as well as salbutamol pMDI
 42 100 µg per actuation as reliever medication for acute asthma symptoms. Assessment of SARC
 43 symptoms and asthma quality of life were re-evaluated after 4 and 12 weeks of treatment as
 44 described above. Patients' compliance with treatment was assessed by drug accountability and
 45 calculated as follows:

$$\begin{aligned}
 & \% \text{ compliance} = (\text{number of tablets actually taken} / \text{expected number of tablets which should have} \\
 & \hspace{15em} \text{been taken}) \times 100.
 \end{aligned}$$

48 A subject that has taken at least 60% and no more than 120% of the required intake since the last visit
 49 was considered compliant.

50 The primary efficacy measure was the change in TSS from visit 2 (baseline value, defined as the
 51 mean of the 6 last assessments of the patients' diary before randomisation) to visit 3, i.e. following 4
 52 weeks of treatment. TSS was computed as the sum of 7 single symptoms (nasal congestion,

rhinorrhoea, nasal itching, sneezing, ocular redness, ocular itching and tearing) recorded by patients twice daily (morning and evening) in the patient's diary according to a reflective assessment ("*How have you felt over the last 12 hours?*"). Each TSS item was scored from 0 (symptom absent) to 3 (severe, barely tolerable symptom interfering with daily activities or sleep). Thus, the TSS ranged between 0 and the maximum attainable score of 21.

Secondary efficacy endpoints were changes in baseline TSS values obtained after 1, 2 and 3 weeks of treatment; changes in baseline Daytime Nasal Symptom Score (DNSS) and Daytime Non Nasal Symptom Score (DNNSS) values obtained after 1, 2 3 and 4 weeks of treatments; changes in baseline AQLQ score obtained at 4 and 12 weeks of treatments. The DNSS was the mean of the individual scores of nasal congestion, rhinorrhoea, nasal itching and sneezing, whereas the DNNSS was the mean of the individual scores of ocular redness, ocular itching and tearing. Each item of DNSS and DNNSS was scored from 0 (symptom absent) to 3 (symptom severe) with a maximum score of 12 and 9 for DNSS and DNNSS, respectively. The AQLQ comprises four categories: symptoms (11 items), activity limitation (12 items, 5 of which are individualised), emotional function (5 items), and environmental exposure (4 items). Each of the 32 questionnaire items was scored on a 7-point scale (where 7 means "*not impaired at all*" and 1 means "*severely impaired*"). The overall AQLQ score was the mean of all 32 responses with lower scores indicate more severe impairment due to asthma. Other secondary efficacy endpoints were the use of relief medications for SARC or asthma over the 4 or 12 weeks, respectively.

Safety and tolerability were evaluated according to routine laboratory tests (haematology and biochemistry), 12-lead ECGs, clinical examinations and the incidence, severity and types of adverse events reported by patients over the course of treatments.

Based on previous findings [E1-E4], we estimated that at least 363 patients (121 per treatment arm) would be required to detect a mean treatment difference in TSS of -1.18 with a standard deviation for both groups of 3.05, using an independent samples t-test with a significance level of 95% (two-sided, α set to 0.05) and a power of 85% ($\beta = 0.15$). Considering approximately a 15% of

79 screening failures and 5% of withdrawal, the sample size of inclusions was calculated to be of 454
80 patients (~151 per treatment arm).

81 Analyses of all efficacy measures and treatment compliance were performed on the Intention-To-
82 Treat (ITT) population, which consisted of all randomised patients who had received at least one
83 treatment tablet and had had a baseline assessment and at least one assessment of primary efficacy
84 variable after the baseline visit. Similarly, analyses of the safety measures were conducted in all
85 patients who had received at least one treatment tablet (“safety population”). A sensitivity analysis
86 was also performed on the Per-Protocol (PP) population, i.e. all patients in the ITT population having
87 completed the study without any major protocol violation. Qualitative variables were summarised as
88 the frequency and quantitative variables as mean $\pm$ SD as otherwise stated. Comparisons of mean
89 changes in baseline TSS observed after 4 weeks of Bilastine and Montelukast concomitant therapy
90 *versus* Bilastine monotherapy was performed by analysis of covariance with the TSS change from
91 baseline as the dependent variable, treatment as fixed effect, centre as random effect and baseline
92 TSS as covariate. The same statistical procedure was used to compare the effect of each treatment
93 arm on secondary efficacy endpoints. Furthermore, analysis of variance was employed to compare
94 the effect of treatment on the number of days with 0, 1, and ≥ 2 daily doses of relief medications for
95 SARC and asthma. In all instances, the minimum level of statistical significance was $P < 0.05$.

96 Patients’ baseline characteristics of each treatment arm (ITT population) are reported in Table 1.

97 Patients disposition is illustrated in Figure 1

98

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113

114

115 Figure legend

116 Figure 1. Patients disposition.

117

Fig 1.

