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#### REFERENCES

1. Michaelsen KF, Grummer-Strawn L, Begin F. Emerging issues in complementary feeding: Global aspects. *Matern Child Nutr.* 2017;13(Suppl):2.

2. Unicef W. *Global strategy for infant and young child feeding.* Geneva: World Health Organization; 2003.
3. Fewtrell M, Bronsky J, Campoy C, et al. Complementary Feeding: A Position Paper by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) Committee on Nutrition. *J Pediatr Gastroenterol Nutr.* 2017;64:119-132.
4. American Academy of Pediatrics Committee on Nutrition. *Pediatric Nutrition* (7th ed.). Elk Grove Village, IL: American Academy of Pediatrics; 2014.
5. NHMRC. *Infant Feeding Guidelines: Information for Health Workers.* Canberra: National Health and Medical Research Council; 2012.
6. Netting MJ, Allen KJ. Advice about infant feeding for allergy prevention: A confusing picture for Australian consumers? *Journal of Paediatr Child Health.* 2017;53:870-875.
7. Netting MJ, Campbell DE, Koplin JJ, et al. An Australian Consensus on Infant Feeding Guidelines to Prevent Food Allergy: Outcomes From the Australian Infant Feeding Summit. *J Allergy Clin Immunol Pract.* 2017;5:870-875.
8. Victoria CG, Bahle R, Barros A, et al. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. *Lancet.* 2016;387:475-490.
9. Netting MJ, Makrides M. Complementary foods: guidelines and practices. *Nestle Nutr Inst Workshop Ser.* 2017;87:1-12.
10. Fleischer DM, Sicherer S, Greenhawt M, et al. Consensus communication on early peanut introduction and the prevention of peanut allergy in high-risk infants. *J Allergy Clin Immunol.* 2015;136:258-261.

#### SUPPORTING INFORMATION

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

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## 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.<sup>1,2</sup> A combination therapy against both these agents may provide additive benefit, as demonstrated both in vitro<sup>3</sup> and in vivo.<sup>4-6</sup>

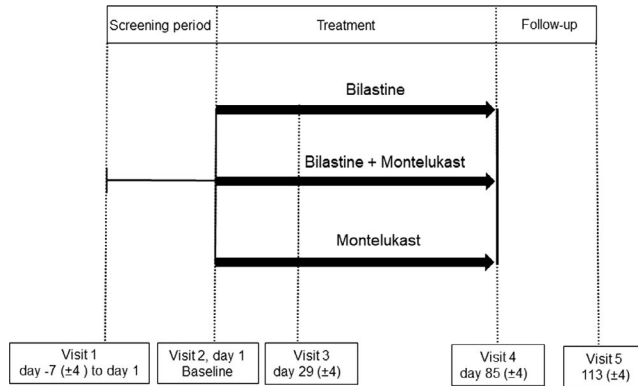
We compared the efficacy and safety of concomitant therapy with bilastine, a second-generation H1 anti-histamine<sup>7</sup> and montelukast vs each agent alone in patient with SARC and asthma. We hypothesized that bilastine plus montelukast is superior to bilastine monotherapy in reducing SARC symptoms 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 controlled<sup>8</sup> by beclomethasone dipropionate or equivalent  $\leq 500 \mu\text{g/d}$  (alone or in combination with long-term  $\beta_2$ -adrenergic bronchodilators) were enrolled. Patients had a postbronchodilator FEV<sub>1</sub> > 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)  $\geq 3$ .<sup>9</sup> Exclusion criteria are reported in the online supplementary. The study (EUDRACT number:2015-004806-40) was conducted in 50 centres across

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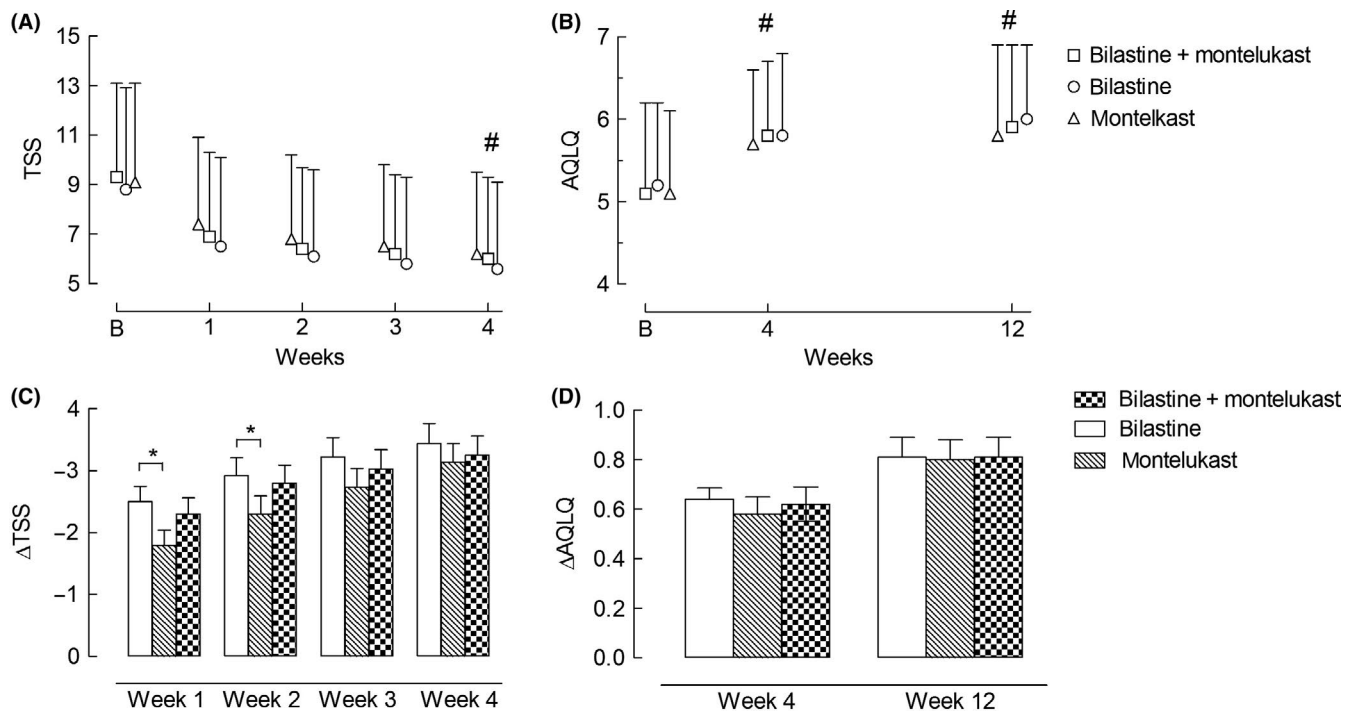


**FIGURE 1** Study design and treatment

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.<sup>10</sup> 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  $35.2 \pm 0.2$ ) 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, FEV<sub>1</sub>, 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  $-3.2 \pm 3.7$ , 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.<sup>9</sup> Although the underlying cause is unclear, the large placebo effect observed by Bachert et al.<sup>9</sup> is not uncommon as observed in other studies with SARC patients.<sup>11</sup>

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.<sup>12</sup> 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  $\beta_2$ -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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## REFERENCES

1. Wenzel SE, Larsen GL, Johnston K, et al. Elevated levels of leukotriene C4 in bronchoalveolar lavage fluid from atopic asthmatics after endobronchial allergen challenge. *Am Rev Respir Dis.* 1990;142:112-119.
2. Pavord I, Ward R, Woltmann G, Wardlaw A, Sheller J, Dworski R. Induced sputum eicosanoid concentrations in asthma. *Am J Respir Crit Care Med.* 1999;160:1905-1909.
3. Bjorck T, Dahlen S-E. Leukotrienes and histamine mediate IgE-dependent contractions of human bronchi: pharmacological evidence obtained with tissues from asthmatic and non-asthmatic subjects. *Pulm Pharmacol.* 1993;6:87-96.
4. Davis BE, Illamperuma C, Gauvreau GM, et al. Single-dose desloratadine and montelukast and allergen-induced late airway responses. *Eur Respir J.* 2009;33:1302-1308.
5. Davis BE, Todd DC, Cockcroft DW. Effect of combined montelukast and desloratadine on the early asthmatic response to inhaled allergen. *J Allergy Clin Immunol.* 2005;116(4):768-772.
6. Reicin A, White R, Weinstein SF, et al. Montelukast, a leukotriene receptor antagonist, in combination with loratadine, a histamine receptor antagonist, in the treatment of chronic asthma. *Arch Intern Med.* 2000;160(16):2481-2488.
7. Ridolo E, Montagni M, Bonzano L, Incorvaia C, Canonica GW. Bilastine: new insight into antihistamine treatment. *Clin Mol Allergy.* 2015; 13(1).

8. Global Initiative for Asthma. Global strategy for asthma management and prevention Vancouver (WA): Global Initiative for Asthma; 2012. <http://www.ginasthma.org>
9. Bachert C, Kuna P, Sanquer F, et al. Comparison of the efficacy and safety of bilastine 20 mg vs desloratadine 5 mg in seasonal allergic rhinitis patients. *Allergy*. 2009, 64, 158-165.
10. <https://www.federalregister.gov/documents/2000/06/21/00-15632/draft-guidance-for-industry-on-allergic-rhinitis-clinical-development-programs-for-drug-products>.
11. Van Cauwenberge P, Juniper EF. Comparison of the efficacy, safety and quality of life provided by fexofenadine hydrochloride 120 mg,

- loratadine 10 mg and placebo administered once daily for the treatment of seasonal allergic rhinitis. *Clin Exp Allergy*. 2000;30:891-899.
12. Corren J. Allergic rhinitis and asthma: how important is the link? *J Allergy Clin Immunol*. 1997;99(2):S781-S786.

#### 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.<sup>1</sup>

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

A variety of therapy regimes exists for the initial phase, from conventional to rush and ultrarush or clustered modalities.<sup>2</sup> 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<sup>®</sup>, 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)<sup>4</sup> 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<sup>®</sup> system, Thermo Fisher Scientific), intradermal tests (0.02 mL of 0.01, 0.1 and 1  $\mu$ g/mL) and prick tests (10, 100, 300  $\mu$ 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<sup>®</sup> vespid venom (ALK-Abelló) was administered with an initial dose of 1  $\mu$ g followed by 5, 10, 20, 40, 60, 80, and 100  $\mu$ 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  $\mu$ 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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