design and modification. The authors were involved in the study design and collection, analysis, and interpretation of data. All authors had full access to all the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

CONFLICT OF INTEREST
Laura Haya is an employee of Red Maple Trials, Inc. Rym Mehri and Shawn Somers-Neal received grant contributions from Mitacs and Red Maple Trials, Inc. Stefan Van de Mosselaer and Ashley Spence are employees of Red Maple Trials, Inc, and Red Maple Trials received wage subsidies for their positions through the Biotalent Student Work Placement Program. Suzanne Kelly is a stockholder and employee of Red Maple Trials, Inc. Edgar Matida was the academic supervisor for Rym Mehri and Shawn Somers-Neal. William H. Yang is a stockholder and employee of Red Maple Trials, Inc. He has received consultant and speaker fees from CSL Behring, Shire/Takeda, Novartis, Sanofi, Merck. Also, he has received research grants from CSL Behring, Shire/Takeda, BioCryst, Pharvaris, Sanofi, Regeneron, GSK, AstraZeneca, Amgen, Genentec/Roche, Pfizer, ALK, Stallergenes, Providence, Galderma, Glenmark, Dermira/Eli Lilly, AnaptysBio, Celgene, Johnson & Johnon, and Pharming.

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SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher’s website.

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Prospective studies are needed to elucidate the clinical impact of predominant Api m 10 sensitization

To the Editor,
In 2016, it was published that a predominant sensitization to Api m 10 may be a risk factor for therapy failure in patients treated with bee venom immunotherapy (bee VIT).1 The authors also reported that some bee venom preparations, two non-purified and one purified preparation, contain little to no Api m 10. Although these data were interesting, the scientific discussion went in a strange direction.

Moreover, some companies claimed (partly with no available data on safety and effectiveness) that their venom preparations were superior because of the higher Api m 10 content compared to commonly used products. Within a few years, this unproven narrative left the impression that patients with predominant sensitization to Api m 10 should be treated with non-purified venoms. However, this was not supported by any published data or endorsed by the EAACI guidelines.2

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Given the higher frequency of adverse events during treatment with non-purified venom preparations, a recommendation to generally use such products in a subset of patients is at least questionable. Therefore, we would like to point out obvious limitations of the study by Frick et al. and present our own preliminary but quite different data. They retrospectively compared the IgE sensitization profile of currently available recombinant single bee venom allergens between 79 responders and 36 non-responders treated with bee VIT in six different centers. First, the patient number was low and not calculated to ensure a sufficient level of statistical power. Second, the definition of “predominant sensitization” can be questioned. They chose 50% of sIgE to bee venom, but the calculation was only based on the odds ratios for nonresponding to VIT and not related to the amount of sIgE to other bee venom allergens. Third, and most importantly, it was implied that two separate findings were correlated: the risk for treatment failure and the lack of Api m 10 in bee venom preparations. In the publication, different venom preparations were analyzed regarding the Api m 10 content. However, although the venom preparations used for 109 patients were known, there was no correlation analysis done to show that particular venom preparations were associated with therapy failure. Therefore, these data may indicate a possible risk for treatment failure in patients predominantly sensitized to Api m 10 but are not adequate to show a correlation between treatment failure and Api m 10 content of venom preparations. Finally, looking at the literature, there is no evidence for the superiority of non-purified venom preparations.
preparations containing Api m 10 compared to purified (with possibly low or no Api m 10) preparations: 83%–91% tolerated the sting challenge after non-purified bee VIT2-6 and 86% after purified bee VIT7 (p = .933, Figure 1). The latter can be confirmed by our preliminary data: effectiveness was 88% (42/48) in patients treated with a purified depot bee venom preparation. Predominant sensitization to one of the single bee venom allergens evaluated (defined as 65% of the bee venom sIgE to ensure predominance to one allergen only) was detected in 20 patients who tolerated sting challenges and in four of six patients who relapsed (Figure 2).

Our preliminary data suggest that other predominant sensitizations, such as Api m 2 and 5, may also play an important role in patients with therapy failure. Furthermore, one may speculate that the Api m 10 content is maybe not relevant for tolerance induction. This may be explained by the fact that Api m 10 is a minor part of bee venom with less than 1% of the dry weight.8 Moreover, it has been presented orally but not yet published that the IgG4 production against Api m 10 was very low in tolerant beekeepers, which puts the low IgG4 levels in non-responders into perspective.1

In summary, the study by Frick et al. is an important basis for further research, but the results should by no means be over-interpreted in sense of recommending certain preparations for bee VIT. Until further data are available, the selection of a venom preparation should be based on studies demonstrating safety and clinical effectiveness not on the measured amount of a single venom allergen. Whether predominant sensitization to a single bee venom allergen may be considered a risk factor for treatment, failure needs to be addressed in a prospective multicenter study including sting challenges to monitor effectiveness.

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