rescue medication use is generally favored as the primary outcome by both regulatory agencies and professional societies.[4]

The authors suggested that a single-point change in the Rhinoconjunctivitis Total Symptom Score (RTSS) is not clinically relevant, whereas Devillier et al[5] recently concluded that "the MID in the RTSS was consistently estimated as 1.1-1.3."

The authors make some unusual comments concerning safety. When comparing the safety of SLIT with that of SCIT, Di Bona et al[1] write that "in contrast, the total number of adverse events is higher in SLIT than in SCIT." First, this statement is debatable, especially if the incidence of local reactions to SCIT is taken into account. They did not take account of the incidence, severity, duration, recurrence, and systemic versus local nature of the adverse events (AEs).

The authors do not consider the persistent efficacy conveyed by allergen immunotherapy (AIT)'s disease-modifying effect through induction of immune tolerance that can translate into long-term symptomatic improvement years beyond discontinuation.

This long-term benefit should be included in the patient/physician-shared decision-making discussion.

In conclusion, Di Bona et al[1] performed a rigorous meta-analysis but overinterpreted the results while losing sight of other important parameters.

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Reply

To the Editor:

A point-by-point reply to the specific criticisms by Cox et al[1] of our meta-analysis[2] is available in this article's Online Repository at www.jacionline.org. Here we will focus on the most critical methodological defect of the sublingual immunotherapy (SLIT) randomized controlled trials (RCTs), which is the metric they used to assess the clinical benefit. This metric is mathematically incorrect because, as clearly explained in our work,[2] it calculates the percentage difference between SLIT and placebo, not taking into account the symptom score (SS) scale range and leading to a huge magnification of the difference between groups. By using this metric, a 1-point difference will be the same percentage difference in an 18-point scale (the most common SS scale used), a 100-point scale, or any other scale, and this is mathematically unacceptable (a detailed explanation has been reported in Fig 1 and our original article[2]).

The correct metric, which takes into account the scale range, was indicated by the World Allergy Organization (WAO)[3] and is based on the comparison between the pretreatment and post-treatment SSs of the active and placebo groups. Using this metric in our work, we showed a small difference between SLIT and placebo, which is less than the US Food and Drug Administration (FDA; 15%) and WAO (20%) thresholds of efficacy.[2] The baseline in the case of SLIT RCTs is the retrospective (prior year) total symptom score (RTSS), which is used by the investigators of the original RCTs as inclusion criteria. In other words the RTSS is assumed by the investigators as the SS that the patients would have in the absence of any treatment (corresponding to the inclusion criteria). We acknowledge that the RTSS might be imprecise, but it should be similar to the SS of the treatment season, especially if the pollen count of the 2 consecutive seasons is similar, and we have shown for the Cox study (see the Methods section in this article's Online Repository) that this possible imprecision does not affect the results.

In our work[2] we also reported the difference between SLIT and placebo not only in terms of the standardized mean difference (SMD) but also in terms of the mean difference (MD), which is the difference in SS points between SLIT and placebo. We showed that this difference is −0.83 SS points (95% CI, −1.03 to −0.63). In a recent work Devillier himself[4] estimated the minimally important difference, which is defined as the smallest improvement considered worthwhile by a patient, as 1.1 to 1.3 SS points in patients with grass

A

18-point scale.

Example study	SLIT	Placebo	Difference	Percentage improvement
RTSS (baseline)	15	15		
Mean SS during treatment	3	4	-1	(3 - 4)/4 = **-25%** **(not including the scale)**
Difference	-12	-11	-1	
Percentage improvement	80%	74%		80%-74% = **- 6%** **(11 - 12)/15 = - 6% (including the scale)**

B

Hypothetical 100-point scale, with a hypothetical RTSS (baseline score) = 95, congruent with a 100-point scale.

Example study	SLIT	Placebo	Difference	Percentage improvement
RTSS (baseline)	95	95		
Mean SS during treatment	3	4	-1	(3 - 4)/4 = **- 25%** **(not including the scale)**
Difference	-92	-91	-1	
Percentage improvement	96.85%	95.80%		95.80%-96.85% = **- 1.05%** **(91 - 92)/95 = -1.05% (including the scale)**

FIG 1. **A** and **B**, With the calculation shown in RCTs *(horizontal arrow)*, only the mean SS during treatment is considered, ignoring the scale range. The scale range, the same that we propose *(vertical arrow)*, is included in the WAO-indicated calculation. The inclusion of the scale in the calculation changes the percentage of improvement, even if the difference between the 2 groups remains the same. Alternatively, the difference between the groups can be calculated as follows: SSt SLIT (t = during treatment) − SSt Placebo (t = during treatment)/SSu (u = untreated, baseline SS of SLIT or placebo, which are equal because of randomization). This calculation allows us to incorporate the scale range in the evaluation of the clinical improvement in contrast to the usual method (SLIT SSt − Placebo SSt/Placebo SSt [t = during treatment]), which does not take into account the scale range used and thus overstates the treatment effect. The baseline RTSS is shown.

pollen–related rhinoconjunctivitis. Therefore the difference of −0.83 SS points reported in our meta-analysis is less than the minimally important difference estimated by Devillier et al (see the Methods section in this article's Online Repository for details).

In conclusion, the analyses based on the Devillier minimally important difference as the threshold of efficacy (1.1 SS points) confirms the conclusions of our work, estimating a small treatment benefit (less than the FDA's 15% or WAO's 20% difference thresholds) and that the incorrect metric used in the SLIT RCTs highly overstated the treatment benefit.

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