A Response to: Letter to the Editor Regarding “Clinical Remission in Severe Asthma: A Pooled Post Hoc Analysis of the Patient Journey with Benralizumab”

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Dear Editor,

We were happy to read the letter from Calzetta and Rogliani regarding our recently published manuscript, “Clinical Remission in Severe Asthma: A Pooled Post Hoc Analysis of the Patient Journey with Benralizumab”, which applied a composite definition of clinical remission in severe asthma, adapted from two Delphi studies [1, 2], to a pooled population of patients from the SIROCCO [3], CALIMA [4], and ZONDA [5] trials [6].

We appreciate that including the “no oral corticosteroid (OCS)” use criterion for the SIROCCO and CALIMA trials in our analysis could cause confusion. The protocols for the SIROCCO and CALIMA clinical trials did not allow for reductions in maintenance OCS use during treatment and, as such, patients could not have achieved zero OCS use over the course of those two trials [3, 4]. Although our post hoc analysis did exclude SIROCCO and CALIMA patients who were using OCS at the baseline visit, we did not exclude patients who used OCS, allowed at the investigators discretion, during the trial; indeed, there were a small number of patients who used OCS during those trials and that is why “no OCS” was included as one of the four.

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criteria to achieve clinical remission in the SIROCCO/CALIMA pooled analysis. In short, if the "no OCS" criterion were not included for patients from SIROCCO/CALIMA (i.e. if only three of the four remission criteria were applied to the analyses of SIROCCO and CALIMA patients), we believe the analysis could have overestimated the true percentages of those patients who achieved clinical remission.

Regarding the FEV1 criterion, there is a difference between measuring a super-response (> 500 mL) and measuring clinical remission, where we have used a surrogate of 100 mL improvement for "best possible lung function", because for many patients with airway remodelling it will be impossible to return the lung function to normal. We agree with the authors that post hoc analyses are often characterized by intrinsic weaknesses such as type 1 errors. In fact, as a result of the potential for these errors in post hoc analyses, we reported our results in a descriptive manner with no statistical analyses, specifically to avoid overstating the impact of our findings. Nevertheless, we agree with the authors that Fisher’s exact test and relative risk analysis are a useful approach to evaluate the statistical significance of our study; indeed, the authors’ finding that, compared to the placebo group, benralizumab 30 mg every 8 weeks (Q8W, first three doses 4 weeks apart) led to statistically significant improvements in the percentage of patients achieving clinical remission is certainly consistent with the results of our pooled analysis.

We agree with the authors that Delphi methods carry inherent limitations due to their subjective nature. Furthermore, while the prior Delphi definitions do comprise opinions from a broad range of experts in the field, the definitions have yet to be broadly applied in the clinical setting and thus could be difficult to apply in practice [1, 2]. We would also note that the SIROCCO [3], CALIMA [4], and ZONDA [5] trials were designed and completed before definitions for severe asthma remission were available. As such, these trials were not optimally designed for subsequent remission analyses.

Ultimately, it is critical for experts in the field to develop a widely accepted and rigorously validated consensus definition of clinical remission in severe asthma in the near future. Nevertheless, in the absence of such a validated consensus definition, we believe that post hoc analyses of prior clinical trials in severe asthma will help to advance the notion of clinical remission by stimulating conversations about remission among experts in the field. Moreover, by applying additional alternative remission criteria (e.g. lung function measures, symptom control assessments, or time spans) than those in the two previous Delphi studies, such post hoc analyses could help inform criteria for use in future data-driven definitions of severe asthma remission.

We contend that the concept of remission in severe asthma could be clinically relevant over time spans shorter than 1 year and therefore our analysis included results from both 6 months and 12 months of treatment. While further studies are necessary to understand the impact of including a predefined time criterion in the definition of severe asthma remission, it is noteworthy that for some conditions (e.g. Crohn’s disease, rheumatoid arthritis, ulcerative colitis) disease remission is more a state of being or point in time (absence of certain signs or symptoms) than something achieved after a specific period of time [2]. In conclusion, we thank Calzetta and Rogliani for their thoughtful letter and independent analysis of our study. We look forward to future conversations and articles around the concept of clinical remission in severe asthma and we are optimistic about the implications for improvements in long-term patient outcomes.

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Compliance With Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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