To the Editor:

We read with great interest the letter from Doctors Lan and Shi on our SUNSET study manuscript (REF SUNSET). Most of their observations have in principle been already discussed in our paper, but this letter gives us an opportunity to further elaborate on these important topics.

We fully agree that the difference in the potency of bronchodilators used in the two arms of the SUNSET study may have impacted the observed results. A recent network meta-analysis supports superior efficacy of indacaterol (IND) compared to other LABAs, including salmeterol (Donohue JF, Int J Chron Obstruct Pulmon Dis. 2017 Jan 19;12:367-381). Moreover, glycopyrronium (GLY) has been shown to be as effective as tiotropium in terms of lung function and exacerbation prevention (Chapman KR, BMC Pulm Med. 2014 Jan 17;14:4; Kerwin E, et al. Eur Respir J. 2012 Nov;40(5):1106-14), however with a faster onset of action (Marin JM, Int J Chron Obstruct Pulmon Dis. 2016 Jun 28;11:1425-34). In fact we are already stating that "this study cannot be considered as a "pure" inhaled corticosteroids (ICS) withdrawal study, because the LABA and LAMA components differ," (Chapman KR, et al., Am J Respir Crit Care Med. 2018 Aug 1;198(3):329-339) and therefore the results may not be applicable to all LABA/LAMA combinations

The 26 weeks duration of the SUNSET trial represents a limitation for the evaluation of the rates and risk of exacerbations and we agree that ideally this would require a 1-year study. However, certain facts coming from the analysis of our data give us confidence that our observations are accurate. As we mention in the discussion of the paper, patients were recruited across seasons and there were similar numbers of moderate/severe exacerbations in the two study groups in the seasons of winter-fall and summer-spring, minimizing the potential impact of seasonal variations of exacerbations on the study results (Chapman KR, et al., Am J Respir Crit Care Med. 2018 Aug 1;198(3):329-339). Moreover, the difference in exacerbations between the two groups in the patients with increased blood eosinophil counts ≥300 cells/µL was observed the first weeks of the ICS withdrawal (see Figure 4D of the manuscript).

The latter observation also reflects the absence of any long-term "protective" carry-over effect of ICS after the switch to IND/GLY, as the small loss of lung function was evident at Day 29 and stable thereafter (Figure 4B of the original manuscript); moreover, most of the moderate/severe exacerbation events occurred in the first few weeks. A small reduction in lung function was also evident within 3 weeks of complete ICS withdrawal in the WISDOM trial and this difference did not progress further afterwards (Magnussen H, Eur Respir J. 2016 Feb;47(2):651-4). Such observations are also supported by the very short half-life of ICS (Thorsson L, Br J Clin Pharmacol. 2001 Nov; 52(5): 529–538). We also do not consider a carry-over effect of ICS the reason for the small differences in lung function observed between the SUNSET and WISDOM trials. Differences in the potency of long-acting bronchodilators, mainly between indacaterol and salmeterol, may be a more plausible explanation, as mentioned above.

We agree that higher blood eosinophils may represent a predictor of response to inhaled corticosteroids, and this is in fact one of our conclusions, as we clearly state that patients with ≥300 blood eosinophils/µL are the ones who will most likely benefit from continuation of triple therapy. The reason for the exclusion of patients with >600 cells/µL, as well as of those with any history of asthma, was that we wanted to ensure that ICS withdrawal would not happen in patients with a coexisting asthmatic component, as such patients would clearly benefit from the use of inhaled corticosteroids. In fact, only 2 (0.2%) of the screened

patients were excluded due to a blood eosinophil count >600 cells/µL, suggesting no or minimal impact of this parameter to our results.

Finally, we agree that COPD in never smokers is a major health issue in certain parts of the world (Salvi SS & Barnes PJ, Lancet. 2009 Aug 29;374(9691):733-43) that needs to be evaluated in appropriate clinical trials. In SUNSET, as in the vast majority of COPD randomized controlled trials, the evaluation of different treatments was performed in patients with smoking-related COPD and, therefore, we cannot comment on the applicability of the results in never smokers or in those with <10 pack-years

Overall, the SUNSET trial has answered a specific clinically relevant question: “in a population of stable, non-frequently exacerbating COPD patients on long-term triple therapy, what is the impact of a direct switch to the modern dual bronchodilator combination of IND/GLY?” In that specific setting, we have identified the minority of patients within that group (i.e. those with ≥300 blood eosinophils/µL) who will benefit from continuation on triple therapy, with no clinically relevant impacts in the rest of these patients. This is evidence for the personalized management of COPD patients in a dynamic way that aims a minimal exposure to ICS and potential side effects.

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On behalf of the SUNSET investigators