Author Response 1

Response document for **Manuscript number: TAR-19-140**, titled *'Functional respiratory imaging assessment of glycopyrrolate and formoterol fumarate metered dose inhalers formulated using co-suspension delivery technology in patients with COPD'*

Reviewer 1 comments	**Response**	**Page no.**
General comments		
In this manuscript the authors aim to characterize the effects of glycopyrrolate (a LAMA) and formoterol fumarate (a LABA) both administered via a metered dose inhaler on airway volume and resistance measured using Functional respiratory imaging (FRI) in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD). They report that both therapies significantly improved airway volume and airway resistance at Day 15 versus baseline and that these improvements were grater with Formoterol compared to glycopyrrolate although some individuals displayed greater responses with each of the two treatments. They conclude that FRI endpoints demonstrated increased sensitivity and that intrapatient differences in treatment response between the LAMA and the LABA provide further support for the benefit of dual bronchodilator therapies. The manuscript is very well written and provides information on the action of two bronchodilators, belonging in different drug classes, on the bronchial tree in COPD patients. The results provide information on airway function beyond spirometry. My comments are the following:		
Specific comments		
1. The authors provide information on alterations on airway resistance and airway volume. It is the fact that these alterations are not very well represented by spirometric data, with the exception of IC, which leads to the conclusion that both therapies are effective in ameliorating air trapping. However, it is a fact that all patients included in the study were	We agree with the reviewer that it would be interesting to assess whether FRI measurements correspond with symptomatic improvement. However, due to the short time frame of each study treatment period (2 weeks) and the small number of patients (~20), a noticeable improvement in symptoms in this study would not be expected, and would likely not be statistically detectable. Therefore, while we collected CAT and mMRC scores at baseline to characterize the patient population, we did	NA

symptomatic and it would be interesting to see whether these differences are related with symptomatic improvement in their group of patients (mainly dyspnea but also CAT score)	not collect data on symptomatic improvement throughout the study.	
2. The authors state that there were intrapatient differences in treatment response between the LAMA and the LABA. This fact in combination with the observation that Formoterol seems to be more potent in the small airways raises some questions. Is it possible to provide data on the differences between patients which are more responsive to LAMA and those more responsive to LABA? Is this difference in response related to disease severity, air trapping or the presence of emphysema? If the authors have data they should provide them.	We agree with the reviewer that it would be of interest to determine potential patient characteristics that predict response to either a LAMA or a LABA. Due to the small sample size of this study, which was powered to detect differences in FRI outcomes, we are not able to provide comprehensive findings regarding this topic. Any conclusions drawn would be speculative, based on a small number of individual patients, and as such we feel that such analyses would not necessarily be valuable to the reader.	NA
3. Table 1 is very poor since it shows only baseline characteristics. I believe that it should be expanded showing results at the end of treatment with formoterol and at the end of treatment with glycopyrrolate.	The intention of Table 1 is to provide baseline demographics and clinical characteristics to describe the patient population at study entry. The results for the pre-specified study outcomes are provided in Tables 2 and 3.	NA
4. Figure 4 is very confusing. The authors should find another way of reporting the differences of the two types of drugs in the different airway generations.	Thank you for the suggestion. We have re-plotted this figure as a dot plot with generation on the X-axis, rather than percentile. We believe this format now more clearly displays the concept of the between-treatment differences increasing at later airway generations.	Fig 4
5. What is the clinical impact of these findings? The authors report the necessity for dual bronchodilation	As described in the manuscript Discussion, a similar study has been conducted on the fixed-dose combination of glycopyrrolate and formoterol (GFF MDI), and the improvements were	NA

but do not provide data on patients receiving both drugs so it is unclear if there will be a benefit in such an occasion regarding the primary and secondary outcomes of the current study.	considerably larger than those observed with the monocomponents in the current study. Taken together, the findings of both studies demonstrate the benefits of dual bronchodilation on airway volume and resistance relative to monocomponents. Pooled analyses of the results from both studies are ongoing and will be presented in a future review manuscript. In addition, the differences in treatment response by airway generation in the current study and the fact that some patients responded better to either a LAMA or LABA are of interest to clinicians and may help explain why some patients display an inadequate response to monotherapy.	
Reviewer 2 comments	**Response**	**Page no.**
General comment		
This is a methodologically well-done paper with an aim to compare two long-term bronchodilators glycopyrrolate (GP MDI) and formoterol fumarate (FF MDI) by the use of new interesting method –functional respiratory imaging (FRI). Both bronchodilators improved the most important parameters of FRI – specific image based airway volume (siVaw) and resistance (siRaw) and the improvements were larger for FF MDI.		
Major comment		
Both bronchodilators improved IC and siVaw, but there were almost no changes in FRC! How authors can explain this discrepancy?	The changes in FRC were a 2.2% reduction with GP MDI (geometric mean ratio 0.98) and a 6.2% reduction with FF MDI (geometric mean ratio 0.94). These data were presented as ratios due to the skewed distribution of the plethysmography endpoints, so while these changes seem small as a percentage of total FRC (~5 L at baseline), in absolute terms the improvements are ~100mL with GP and ~300mL with FF. As discussed in the manuscript (on page 13), the plethysmography endpoints were not well powered in this study compared to the FRI endpoints, which are more precise, so these changes did not reach statistical significance.	NA
Minor comment		

No information was presented about smoking history of patients (only % of current smokers) and also about history of exacerbations and previous treatment.	We have added the median and range for pack-years smoked and the percentage of patients with a moderate/severe exacerbation in the previous year to Table 1. The most frequently reported prior COPD medications (either alone or as part of combination therapy) were salbutamol (39.1%), fluticasone (30.4%), and tiotropium (30.4%). We did not analyze prior COPD medications by class due to the small sample size of this study.	Table 1