

## Author Response 1

Thanks a lot for your comments. We believe our answers to your questions and amendments will bring more clarity and comprehensiveness to the manuscript.

### Major comments

- From a clinician standpoint I don't believe there is clear cut off between exacerbations and pneumonia in COPD patients as if not most but most of the exacerbations happen in the setting of viral/bacterial infection. So, including the cost of both pneumonia and exacerbation means accounting for one adverse event twice, which can affect the cost saving in the different scenarios mentioned in the article. Especially because the cost of treatment in Portugal increased in different scenarios and it was shown to be cost effective in total just because of trade off with the reduction in the adverse events.

We based our analysis on data from published literature. We used studies with specific data on exacerbation and pneumonia. It is impossible to assess potential double counting of pneumonia and exacerbation.

In the discussion we added the following sentence (line 275): "By using different studies to assess the impact of different scenarios on pneumonia and exacerbations, and considering the potential lack of differentiation between both events, it is possible that our analysis double counted events and therefore overestimated the cost benefits of the switch to LAMA/LABA."

- Diabetes related events are not well defined in the study and it is unclear what are the hospitalizations related to DM, either it is directly related to DM like DKA admissions or all the admissions that their risk will be increased in diabetic patients including MI, heart failure and etc.

From a cost perspective, we used the tariffs used for hospitalizations due to diabetes, therefore we are confident costs were properly inputted in the analysis. In the reference used (Price DB et al., 2016) there is no information on the hospitalization. The study shows that the "increase in diabetes-related hospitalization rate" increases by 6% in the ICS arm and 4.5% in the non-ICS arm (table 3), without specifying the cause.

In the discussion after the description of Price DB study, we added (line 281): "In that study, there was no description on the reason for hospitalization so we used the tariff of a diabetes-related hospitalization in our cost analysis. In clinical practice, it is possible that such hospitalizations are coded with a different primary cause for admission, which would lead to a different cost of the disease. In our analysis, changing the cost of diabetes-related hospitalization would not change the direction of the results."

- Patient population defined as "stable" COPD patients in GOLD categories B to D. Unclear what is the definition of stable here and also why stage A is not included. Also, it was mentioned that prior exacerbation history was taken into account in the model while it is unclear how far the history of exacerbation it was meant. If it is in the last 12 months the number of exacerbations is already taken into account in the GOLD staging so unclear if GOLD staging was taken into account and exacerbation history separately or combined.

We removed “stable” to avoid reader’s confusion

GOLD A patients were excluded from the analysis since there is no clinical benefit in treating them with ICS in clinical practice (GOLD guidelines) and GOLD A patients can be prescribed either short- or long-acting bronchodilator. Including GOLD A patients would add uncertainty to the analysis and lowering its quality. In the methodology section, we added “GOLD A patients were excluded from the analysis since there is no recommendations for ICS in this population, treatment can be either short- and long-acting bronchodilator and the choice of treatment depends on the effect of breathlessness.<sup>1</sup>”

Sorry for not being clear for the impact of exacerbation history. We rephrased the methodology section (line 149) “The model took into account differences in patients’ prior exacerbation history and the type of treatment regimen, as both parameters may have a substantial impact on the risk for these inadvertent events” with “the baseline exacerbation risk was altered according to the relative risk of exacerbation associated with prior exacerbation history (relative to no prior exacerbations) and treatment choice (relative to LAMA/LABA).” We hope it is clearer now that the number of exacerbations depended on 2 different variables. We preferred not to talk about GOLD staging as it also takes into consideration symptoms

- In scenario A the percentage of patients on LAMA/LABA/ICS in Portugal increased from baseline (30% from 27%) but still had 1% saving in the total cost. Is there any reason that 30% was chosen for the scenario 1 and not a percentage that for both countries LAMA.LABA/ICS use would decrease?

The selection of the alternative scenarios was arbitrary. The idea of scenario A was to have a moderate switch of ICS-containing regimen, especially from LABA/ICS and scenarios B and C more aggressive switch. We arbitrarily considered a switch from LABA/ICS easier than from LAMA/LABA/ICS in scenario A.

When it comes to Portugal results of scenario A, we had an increase in pharmaceutical costs (slight increase in LAMA/LABA/ICS and significant switch from cheaper LABA/ICS to more expensive LAMA-LABA) and a decrease of exacerbation, pneumonia and diabetes-related event costs.

We do not think we should amend the manuscript for this comment. Please advise otherwise

Minor comments:

- Cost input in in Euros but unclear if adjusted for inflation and if so for what year.

Thanks for highlighting it. We added: “When necessary, costs were inflated to 2019 Euros.” (line 186)

- Minor typos and grammatical errors mostly in discussion section

We edited the document in track changes.

- Legend of the figure in the main file is incomplete in comparison to the excel file.

For some reason, it seems the pdf file doesn’t go through. We re-sized the graph.