Author’s response to reviews

Title: Post hoc analysis of initial treatments and control status in the INITIAL study: An observational study of newly diagnosed patients with asthma

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Author’s response to reviews:

Dear Dr Alejandro Comellas,

On behalf of my fellow authors, I wish to thank you for considering our manuscript "Post hoc analysis of initial treatments and control status in the INITIAL study: An observational study of newly diagnosed patients with asthma" (PULM-D-19-00125R1) for publication in BMC Pulmonary Medicine.

We have updated the manuscript and have provided a point-by-point response to the reviewer’s comments below. All revisions have been highlighted in red and deletions by strikethrough.

Reviewer 1

Language of text is not very clear.
We thank the reviewer for the comment. We have made extensive modifications to the text to make it clear and easy to understand.

The Results content has been modified. The revised text has been highlighted in red. See text on lines 147–157 on pages 7, lines 158–159, lines 161–164, lines 169–174, and lines 178–180 on page 8, and lines 181–182 on page 9.

Reviewer 2

In general, this is an interesting research. The authors aim to assess asthma severity among newly diagnosed patients as well as their prescribed medications and response to treatment and to further investigate the medications and medication combinations prescribed at baseline during the INITIAL study and to determine the impact of the change in asthma control criteria between the Global Initiative for Asthma (GINA) 2012 and 2018 guidelines. However, there are some major points should be improved.

We thank the reviewer for the positive comments. The manuscript has been amended according to the reviewer’s comments. Please see changes below.

Major comment

In the Statistical Analysis section was not provided in the materials and methods section. The specific statistical analysis that compared level of asthma control between GINA 2012 and GINA2018 should be provided.

Information regarding statistical analysis has been added in the Methods section. Only descriptive statistics were used, and no inferential statistics were performed. We also added the objectives of this post hoc study in the Methods.

Text added, see lines 136–141 on page 7.

1. Introduction

   - In overall, the background is too short. The more rational of this study should be added.

   We have expanded the Introduction section, with background and rationale added.

   See lines 69–90 on page 4 and lines 91–94 and lines 98–103 on page 5.

2. Methods

   - In the Statistical Analysis section was not provided in the materials and methods section.
- The specific statistical analysis that compared level of asthma control between GINA 2012 and GINA 2018 should be provided.

- The specific statistical analysis that compared level of asthma control between GINA 2012, GINA 2018, and ACQ-5 should be provided.

Please refer to the response to point 2 above. In this post hoc analysis, only descriptive statistics were used, and no inferential statistics were performed.

Text added, see lines 139–141 on page 7.

3. Results

- In the table 3, Figure 1 and 2, the p-value that derived from statistical analysis should be specified.

We thank the reviewer for the comment. In this post hoc analysis, only descriptive statistics were used, and no inferential statistics were performed because of inadequate power due to the limited sample size. Thus, we are unable to provide p-values for these results.

No changes were made regarding this comment.

4. Conclusion

- I think that the first paragraph of the conclusion was not relevant to the objective of the study. It should be removed from the conclusion section.

We thank the reviewer for the suggestion. The first paragraph of the conclusion has been removed.

See lines 264–267 on page 12. Deletion was highlighted by strikethrough.

5. Minor

- In the reference section. Reference no. 2, 3, 4, and 10 should include the URL website and the date of assessed which accordance to the format of the journal.

For these references, we have added URL and assessed date in accord with the journal format.

See reference 1, 2, 3, 15, and 23.

Reviewer 3

The diagnosis of asthma (Even in INITIAL study) was not clearly stated. Does a diagnosis of asthma require spirometry with reversibility in China. Majority of patients were between 30-60
years and about nearly 30% were either ever or current smokers. There may be some patients with undiagnosed COPD.

We thank the reviewer for these comments. The detailed information about asthma diagnosis has been provided in the Methods, and the key exclusion criteria, including COPD, have been added.

Spirometry and other lung function tests were used to as the gold-standard tool for making a diagnosis of asthma. Symptoms of patients were also taken into consideration for diagnosis.

What’s more, specially attention was paid to patients with COPD during screening, who were excluded from the study. Therefore, there was a low possibility, if any, that patients with undiagnosed COPD were included.

The revised text has been highlighted in red. See lines 114–125 on page 6.

The conclusion that addition of LTRA does not add to better control of asthma - Discussion should include the benefits seen in asthma patients with LTRA are those with a history of concurrent allergic rhinitis.

The potential benefits of LTRA for patients with asthma and allergic rhinitis have been added in the Discussion.

Patients with asthma and allergic rhinitis only represented 22.1% of patients included in our study. While they might derive benefits from LTRA, the majority of patients in our study still required a more effective treatment, such as ICS/LABA, to reduce symptoms and risk of exacerbations.

See lines 208–225 on page 10.

The ICS/LABA in this study was predominantly budesonide/formoterol in all groups. Was there a reason for this? Different devices.

Budesonide/formoterol in a single inhaler (e.g. Symbicort) is a convenient therapy for patients with asthma. The efficacy of this combination has been supported by evidence, and it has been recommended by GINA 2019 as the preferred controller formulation of ICS-formoterol at step 1 and 2 and as a reliever therapy.

Statements pertaining to this point have been added in the Discussion.


Other changes

1. Funding
We previously enquired about a change in the funding statement, due to the Human Genetic Resources policy in China.

In compliance with journal requirement, we still disclose the funder for this study. The statement is “This study was funded by AstraZeneca, China.”

See line 302 on page 14.

2. Acknowledgements

We previously enquired about a change in the Acknowledgements.

In compliance with journal requirement and Good Publication Practice, we still acknowledge the medical writing support from a professional medical writer: “The authors would like to thank Dr Tom Priddle of Nucleus Global for medical writing support, which was provided in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).”

See line 308–310 on page 14.