

Peer Review File

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Reviewer A

Thank you for asking me to review this manuscript. The article is very wordy and has lots of repetitions. It is difficult to read and is written like a mini-thesis. The tables given are very lengthy and difficult to follow. Here are some suggestions for the authors which may improve this article:

Comment 1: The running head may be shortened to: LAMA/LABA FDCs for COPD in China.

Reply 1: We have exchanged the running head to *LAMA/LABA FDCs for COPD in China* (see Page 1, line 21).

Comment 2: The brand names of LAMA/LABA inhalers currently available in China and the names of their accompanying patented devices should be omitted.

Reply 2: We have removed the brand names and names of their accompanying patented devices in text and tables (see Page 18, line 364; and Page 24).

Comment 3: The list of already published trials in Table 2 has previously been described and analysed in a meta-analysis. Hence this Table can be removed.

Reply 3: We have exchanged the contents of Table 2. We have only made a summary of current clinical trials for LAMA/LABA, which were mentioned in the original Table 2 and 3 (see Page 25).

Comment 4: Tables 3 & 5 can be made less wordy by using abbreviations such as MC, DB, RCT, etc., and these could be defined at the bottom of the tables (MC = multi-centre, DB = double-blind, RCT = randomized controlled trial).

Reply 4: We have exchanged phrases into abbreviations in Table 4 (which is the original table 5, since the original Table 3 was merged with Table 2). We have only made a summary of current clinical trials (which was mentioned in the original Table 2 and 3) for LAMA/LABA (see Page 25).

Comment 5: The key recommendations of guidelines in Tables 4 & 6 are also described in the text, which simply is duplication. A better way would be to briefly highlight any important differences between these guidelines (including the Chinese guidelines) in the text.

Reply 5: We have tried to emphasize the change of guidelines on the important differences by the update time. However, consider we have listed several guidelines which recommended LAMA/LABA for the first time in their latest version, it is hard to make a description only on important differences (see Page 10, line 193 ~ 207; Page 11, line 213 ~ 216 and line 219 ~ 222; Page 15, line 300 ~ 306 and line 312 ~ 322).

Comment 6: There are a number of abbreviations used in the text such as FEV1, cAMP, DAG, and PKC. These should be written in words with the abbreviations given in parentheses, at their first mention in the text.

Reply 6: We have checked the manuscript overall to ensure all abbreviations are written in correct form when first used in the text (for instance, see Page 7, line 130, 138; Page 8, line 139 and line 142).

Comment 7: The molecular basis of why the LAMA/LABA FDCs work better than their single component or even their use as separate single drug inhalers is useful but this section of the text should be shortened with just the key points highlighted. Best is to concentrate on why LAMAs and LABAs are synergistic, and why FDCs show better efficacy than single drug inhalers taken separately. There is also a clear cost benefit favouring LAMA/LABA FDCs versus two separate single drug inhalers. This also needs to be emphasized.

Reply7: We have removed the detail description on mechanism of LAMA and LABA (see Page 7, line 119 ~ 123). We have also added a brief comparison of LAMA/LABA FDCs and free combination (see Page 18, line 381 ~ 384).

Comment 8: There is not much in the discussion to support the conclusion that LAMA/LABA FDCs are better than separate single drug LAMA and LABA inhalers, LABA/ICS inhalers, or even the triple therapy LAMA/LABA/ICS inhalers. LAMA/LABA FDCs have found their rightful place in COPD maintenance therapy algorithms. However, combinations containing ICS have a clear role in frequent exacerbators, COPD/asthma overlap patients, and those with elevated blood eosinophil counts. These points are worth discussing as well.

Reply 8: We have also added a discussion on comparison of LAMA/LABA FDCs with other inhale medicine (see Page 19, line 404 ~ 414).

Reviewer B

This manuscript reviewing the currents in LAMA/LABA FDC in China presents remarkable works to suggest future perspective in COPD management in China. I have some minor remarks that can be addressed by the authors.

Comment 1: Line 80-83

In search strategies, authors mentioned Google Scholar and Wanfang Data. Is there any reason not to use Pubmed, or EMbase to review the published studies?
It would be also necessary to describe more about the Wanfang Data.

Reply 1: We have exchanged the search tool mentioned in the text (from Google Scholar to Pubmed) (see Page 6, line 108). There is no obvious difference between the search results of Google Scholar and Pubmed. Besides, we also added a brief description of Wanfang Database (see Page 6, line 109 ~ 111).

Comment 2: Line 35-36

Poor clinical outcomes should be discussed in detail.

Reply 2: We have added some examples to explain the “poor clinical outcomes” mentioned in the text (see Page 4, line 59 ~ 60).

Comment 3: Subtitles in this manuscript is confused. For example, is it correct that 'LAMA/LABA combination Therapy in China' contains lung function, health status, dyspnea, exacerbation and safety? Subtitle which is followed by them was 'Chinese Guidelines and Consensus' but, this should be located next to the subtitle 'Research in China'.

I recommend numbering of subtitle should be present to improve readability.

Reply 3: We have changed subsection titles “lung function”, “health status”, “dyspnea”, “exacerbation and safety” to subsubsection titles, and numbered them (see Page 12, line 241 and 250; Page 13, line 258 and 264; Page 14, line 278).

Comment 4: Please check the abbreviation in the manuscript (Study or drug names).

Reply 4: We have checked all abbreviation in manuscript and exchanged some incorrect ones (for instance, see Page 8, line 156).

Comment 5: In table 2, use the phrase (not a sentence) to summarize key objective of studies.

i.e) SPARK: Superiority of QVQ149 over glycopyrronium based on the rate of moderate or severe COPD exacerbations during the treatment period.

Reply 5: We have exchanged the contents of Table 2. We have only made a summary of current clinical trials for LAMA/LABA, which were mentioned in the original Table 2 and 3 (see Page 25).