FINAL REPORT

Comparative safety and effectiveness of inhaled corticosteroids (ICS) and long-acting beta-agonists (LABAs) for chronic obstructive pulmonary disease (COPD): A rapid review and network meta-analysis

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August 20th, 2014

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Executive Summary

Summary
This rapid review and network meta-analysis was conducted to determine the comparative safety and efficacy of inhaled corticosteroids (ICS) and long-acting beta-agonists (LABA) in patients with COPD. Ranking analysis of the results of an NMA restricted to patients with moderate COPD found that budesonide+formoterol and mometasone+formoterol had the highest probability of reducing the risk of exacerbations. Fluticasone in combination with salmeterol or vilanterol was most likely to increase the risk of pneumonia while mometasone+formoterol was less likely to cause pneumonia. No differences in risk of arrhythmia were found across any of the agents compared in the review.

Implications
Combined ICS+LABA therapies such as budesonide+formoterol and mometasone+formoterol are likely effective in preventing exacerbations in patients with moderate COPD and mometasone+formoterol is less likely to cause pneumonia. These inhalers likely do not increase the risk of cardiac arrhythmia. As this is a rapid review, our results should be interpreted with caution.

What is the current practice in treating COPD with long-acting inhaled agents?
Evidence suggests that therapy with inhaled corticosteroids (ICS) and long-acting beta agonists (LABA) for patients with chronic obstructive pulmonary disease (COPD) is promising.

However, it is not clear which combinations of ICS and LABA are safest and most effective for these patients.

Objective

• To determine the comparative safety and efficacy of long-acting inhaled agents (ICS, LABA) for patients with COPD through a rapid review of the literature

How was the study conducted?

• The protocol (or plan) for the review was developed and revised with input from researchers, clinicians, industry stakeholders, and the Ontario Ministry of Health and Long Term Care

• 3 electronic databases and unpublished literature were searched for randomized controlled trials (RCTs) of long-acting inhaled agents in adults with COPD

• The primary outcome of interest was the proportion of patients with moderate COPD that experienced exacerbations overall and secondary outcomes included pneumonia and arrhythmia

• Screening of literature search results was conducted independently by two reviewers, data abstraction was completed by one reviewer and independently verified by a second, and risk of bias assessment was independently assessed by one reviewer
• Random-effects network meta-analysis (NMA) was conducted based on the availability of evidence.

**What did the study find?**

- 183 published RCTs with 56 companion reports were identified for inclusion in the review.
- Budenoside+formoterol and mometasone+formoterol had the greatest probability of decreasing the risk of exacerbation in patients with moderate COPD (68 RCTs).
- Fluticasone+salmeterol and fluticasone+vilanterol increased risk of pneumonia and were the least safe agents in patients with all COPD severities (33 RCTs).
- There were no significant differences in risk of arrhythmia across all treatment groups (17 RCTs).
Rationale

Evidence from previous systematic reviews and network meta-analyses suggests that therapy with inhaled corticosteroids (ICS), long-acting beta-agonists (LABA), and long-acting muscarinic antagonists (LAMA) for patients with chronic obstructive pulmonary disease (COPD) is promising (1-9). However, to date, it is not clear which combinations of therapies are safest and most effective for these patients. This rapid review and network meta-analysis was completed to address this, and specifically to determine the comparative safety and efficacy of long-acting inhaled agents (ICS, LABA, LAMA) for patients with COPD. This report focuses on the comparative safety and effectiveness of ICS and LABA in any combination.

Methods

Our rapid review protocol was drafted using guidance from the Preferred Reporting Items for Systematic reviews and Meta-analyses for Protocols (PRISMA-P) (10). The protocol was revised based on feedback from various stakeholders, including policy makers from the Ontario Ministry of Health and Long-term care, industry partners, patients, researchers with the ODPRN, and health care professionals. The protocol was registered with the international prospective systematic review register (PROSPERO 2013: CRD42013006725).

Eligibility criteria

We included parallel-group randomised clinical trials (RCTs) examining inhaled LABA, ICS, and combinations of these agents. Studies examining these agents in any combination compared with each other, combinations of each other, LAMA or placebo in adults diagnosed with COPD were included. Concomitant COPD medications were included if both groups received the same interventions (e.g., rescue medication with a short-acting beta-agonist). A full list of included agents can be found in Appendix 1. We excluded studies that did not examine long-acting formulations or inhaler formulations. A full list of the excluded medications can be found in Appendix 2.

The proportion of patients with exacerbations overall (e.g., worsening of COPD symptoms that may require treatment with oral steroids and/or antibiotics) was the primary outcome of interest. Additional outcomes were selected based on feedback from patients with COPD and other stakeholders, including researchers, healthcare providers, and industry partners. We surveyed 19 patients with COPD and asked them to rate the importance of 24 efficacy and safety outcomes that were reported in RCTs of COPD therapies, as outlined in Appendix 3. Further details on the survey methodology are outlined in the qualitative analysis section. Patients identified quality of life, functional status and shortness of breath to be important patient-related efficacy outcomes, as outlined in Appendix 4. The patients also indicated that cardiac events and fractures were important patient-related adverse events associated with therapy. We considered patient’s preferences along with input from other stakeholder groups (such as researchers, healthcare providers, industry partners) and came to a consensus regarding the final outcomes that were chosen.
Studies were included regardless of duration of follow-up, date of dissemination, and publication status. Due to the numerous studies identified, this report focuses on data from published studies. As well, due to feasibility constraints, we limited inclusion to English language articles; this has not been shown to bias meta-analysis estimates in the past (11).

Information sources and literature search
Comprehensive literature searches were conducted by an experienced librarian in consultation with our research team. We searched MEDLINE, EMBASE, and Cochrane Library electronic databases from inception to mid-November 2013. The MEDLINE search is presented in Appendix 5. The main (MEDLINE) search was peer reviewed by another experienced librarian using the Peer Review of Electronic Search Strategies (PRESS) checklist (12). After this exercise, the MEDLINE search was modified and the other databases were searched in a similar manner. Literature saturation was ensured by searching the reference lists of included studies and reference lists of relevant reviews (1-8, 13, 14). The results from the literature search were uploaded to online screening software (Synthesi.SR) (15).

Study selection process
To ensure reliability, a training exercise was conducted prior to commencing screening. Using the inclusion and exclusion criteria, a random sample of 25 titles and abstracts from the literature search was screened by all team members. Inter-rater agreement for study inclusion was calculated using percent agreement and we proceeded to the next stage of study selection when it was >90% across the team. This occurred after 1 round of screening for level 1 (screening of titles and abstract) and 2 rounds of screening for level 2 (screening of full-text articles). Subsequently, two reviewers screened citations for inclusion, independently for level 1 screening and the same process was followed for level 2 screening. Conflicts were resolved by discussion or the involvement of a third reviewer (ACT and SES).

Data items and data abstraction process
We abstracted data on study characteristics (e.g., year of conduct, sample size, setting [e.g., multi-center, single center], country of study conduct, duration of treatment, duration of follow-up, intervention and comparator dosage, monotherapy, combination therapy), participant characteristics (e.g., number of patients, age mean and standard deviation, severity of COPD, diagnosis of COPD), and the definitions of outcomes (e.g., exacerbations [e.g., exacerbation], arrhythmia [e.g., arrhythmia]). We selected three outcomes for analysis for this report based on feedback from our stakeholders; COPD exacerbations for the main efficacy outcome and, pneumonia and arrhythmia for the safety outcomes. We abstracted the outcome results (e.g. number of patients with exacerbations) for the longest duration of follow-up only, as this is the most conservative approach (16). Prior to data abstraction, we completed a calibration exercise of the data abstraction form on a random sample of 5 articles.

Due to the large number of trials included (and the fact that this rapid review was completed in a very short time-frame), we used one reviewer’s answers and a third person verified all of the data.
Risk of bias and methodological quality appraisal process

One reviewer independently assessed each of the included studies using the 7-item Cochrane Risk of Bias Tool (17).

Synthesis of included studies

Study and patient characteristics were summarised descriptively. All outcomes presented here are dichotomous and the odds ratios (OR) were calculated. Clinical, methodological, and statistical heterogeneity were assessed for each pairwise comparison. We assessed statistical heterogeneity using a restricted maximum likelihood (REML) estimator (19) and the $I^2$ statistic, which measures the percentage of variability that cannot be attributed to random error alone. Since the GOLD criteria have changed over time, a clinician (SES) reviewed all of the included studies to establish the average COPD severity of the patients included in each trial using the most recent GOLD guidelines. Meta-analysis was analyzed in the R statistical software using the metafor command (22).

We completed a random effects network meta-analysis to synthesise the available evidence from the network of trials for the three outcomes analyzed. Treatments were grouped into nodes based on input from clinicians, methodologists, and statisticians on the team.

We assessed network heterogeneity using the $I^2$ statistic (23). To assess the consistency assumption in certain parts of the network, we used the loop-specific method (24, 25) and the separating indirect and direct evidence method (26). We evaluated whether the network was consistent as a whole using the design-by-treatment interaction model (27). When important inconsistency and/or heterogeneity were observed, we explored the possible sources using sub-network meta-analysis.

One unique advantage of network meta-analysis is that it allows the ranking of interventions. We estimated the ranking probabilities for all treatments and presented this using rankograms. A treatment hierarchy was also obtained using the surface under the cumulative ranking curve (SUCRA) (28). All network meta-analysis was done in Stata using mvmeta command (29).

As the focus of this report is on the ICS/LABA combinations, we do not report the results of all treatment comparisons considered in the network meta-analysis.

ORs, 95% confidence intervals (CI) and number needed to treat (NNT) or number needed to harm (NNH) for statistically significant results are reported below. NNT and NNH were calculated using the formula:

For OR <1: \[ NNT = \frac{(1-\text{PEER}(1-\text{OR}))}{(\text{PEER}^2(1-\text{OR}))} \]

For OR >1: \[ NNH = \frac{\text{PEER}(\text{OR}-1)+1}{\text{PEER}^2(\text{OR}-1)} \]

where, PEER or Patient Expected Event Rate = SUM (events across all placebo arms) / SUM (sample sizes across all placebo arms) for an outcome.

Due to the numerous treatment comparisons examined (approximately 600 comparisons), we have appended both statistically significant and not statistically significant results for the meta-analysis results only.
Results

Literature search
The literature search yielded a total of 2,724 titles and abstracts (Figure 1). Of these, 1,255 articles were potentially relevant and their full-text was reviewed. Subsequently, 183 RCTs plus 56 companion reports fulfilled our eligibility criteria and were included. The list of 180 articles reporting the 183 included RCTs can be found in Appendix 6.

Study and patient characteristics
The year of publication ranged from 1989 to 2013. The majority of the RCTs were multi-center, conducted across numerous countries. Only 31 studies were single center trials. The median number of patients per trial was 280, which ranged from 15 to 17,135. The duration of treatment with long-acting inhaled agents ranged from 9 hours to almost 4 years. The mean age of included patients ranged from 47.1 to 65.8 and the percent female ranged from 0 to 58%.

Risk of bias
The most important internal validity criteria for RCTs are adequacy of generating the random sequence (e.g., through the use of a random numbers table) and ensuring that the allocation sequence is adequately concealed (e.g., through the use of sealed, opaque envelopes). Across the included RCTs, the majority were appraised as having unclear random sequence generation and unclear allocation concealment (Figure 2). Furthermore, the majority had a high risk of bias or unclear risk of bias in selective outcome reporting, as the outcomes reported in the registered trial protocols differed from those reported in the final publication. Finally, many of the RCTs had a high or unclear risk of bias due to other bias, mainly due to the potential for funding bias because many studies were funded by a pharmaceutical company and included authors on the trial who were employed by the drug manufacturer.

Network meta-analysis results

Primary efficacy outcome

Exacerbations for all severities of COPD
Ninety-two RCTs reported on exacerbations overall including 64,341 patients with all severities of COPD. This was comprised of 68 trials including patients with moderate COPD, 4 trials including patients with mild to moderate COPD, 5 trials including patients with severe COPD, and 15 trials including patients with mild to severe COPD. A network meta-analysis was done for all severities but inconsistency was present statistically and therefore, we have not reported these results. The results for an analysis of the sub-network of exacerbations for patients with moderate COPD are presented below.

Exacerbations for moderate COPD
Sixty-eight RCTs reported on exacerbations in 53,412 people with moderate COPD and contributed data to 210 treatment comparisons in a network meta-analysis. There was no significant inconsistency in this data statistically. The included RCTs assessed ICS agents (budesonide, fluticasone, mometasone), LABA
agents (formoterol, indacaterol, salmeterol, vilanterol), or ICS/LABA agents (budesonide+formoterol [BFC], fluticasone+vilanterol [FVC], fluticasone+salmeterol [FSC], mometasone+formoterol [MFC]). Comparators included placebo, LAMA agents (aclidinium, glycopyrronium, tiotropium), LABA/LAMA agents (formoterol+tiotropium, salmeterol+tiotropium, indacaterol+tiotropium, indacaterol+glycopyrronium, GSK 961081), or ICS/LABA/LAMA agents (fluticasone+salmeterol+tiotropium).

**ICS+LABA vs. placebo**
Compared with placebo, there was a significant decrease in risk of COPD exacerbation for those patients treated with BFC (NNT 6), FSC (NNT 17), and MFC (NNT 7) (Table 1).

**ICS+LABA vs. ICS+LABA**
Compared with FSC, BFC (NNT 8) and MFC (NNT 10) decreased the risk of exacerbation.

**ICS+LABA vs. ICS alone or LABA alone**
When compared with budesonide therapy, there was a significant decrease in risk of exacerbation when patients were treated with BFC (NNT 6), and MFC (NNT 6) (Table 1).

When compared with indacaterol, treatment with BFC (NNT 7) or MFC (NNT 7) led to decreased risk of exacerbation. Decreased risk of exacerbation was also seen with BFC (NNT 8), or MFC NNT 8) when compared to treatment with salmeterol. When compared with vilanterol, treatment with BFC NNT 7), FVC (NNT 16), or MFC (NNT 8) led to decreased risk of exacerbation.

**Results of our ranking analysis**
Out of all the drugs compared, BFC and MFC had the largest probability of being the most effective for decreasing risk of COPD exacerbation in patients with moderate COPD, with a probability of 86% and 83%, respectively. The probabilities of being the most effective for reducing exacerbations for the other ICS/LABA combinations was 55% for FVC and 40% for FSC.

**Exacerbations for severe COPD**
Five RCTs reported on 2,029 patients with severe COPD. There was insufficient data to complete a network meta-analysis.

**Secondary safety outcomes**

**Pneumonia**
Thirty-seven RCTs reported on pneumonia and 33 RCTs including 47,628 patients contributed data on 153 treatment comparisons in a network meta-analysis. Four studies were excluded because they had zero events in all arms and do not contribute data to the network meta-analysis. The included RCTs assessed ICS agents (budesonide, fluticasone, mometasone), LABA agents (formoterol, indacaterol, salmeterol, vilanterol), or ICS/LABA combined agents (beclomethasone+formoterol, BFC, FSC, FVC, MFC). Comparators included placebo, LAMA agents (glycopyrronium bromide, tiotropium), LABA/LAMA combined agents (indacaterol+glycopyrronium), or ICS/LABA/LAMA combined agents (tiotropium+salmeterol+fluticasone, tiotropium+budesonide+formoterol).
**ICS+LABA vs. placebo**
Statistically significantly more patients receiving FVC (NNH 10) and FSC (NNH 16) experienced pneumonia versus patients who received the placebo (Table 2).

**ICS+LABA vs. ICS+LABA**
Significantly more patients taking FSC experienced pneumonia versus BFC (NNH 19).

**ICS+LABA vs. ICS alone or LABA alone**
Statistically significantly more patients taking FVC experienced pneumonia compared with budesonide (NNH 9), formoterol (NNH 7), and vilanterol (NNH 17). Finally, statistically significantly more patients receiving FSC experienced pneumonia versus those who received budesonide (NNH 13), formoterol (NNH 10), indacaterol (NNH 15), and salmeterol (NNH 19).

**Results of our ranking analysis**
Regarding pneumonia, the probabilities for being the safest ICS/LABA combinations were 62% for MFC, 56% for beclomethasone+formoterol, 48% for BFC, 14% for FSC, and 10% for FVC.

**Arrhythmia**
Forty RCTs reported on arrhythmia and 17 RCTs including 16,761 patients contributed data on 171 treatment comparisons in a network meta-analysis. The other 23 studies were excluded because they had zero events in all arms and do not contribute data to the network meta-analysis. The included RCTs assessed ICS agents (budesonide, fluticasone, mometasone), LABA agents (AZD3199, formoterol, indacaterol, salmeterol, vilanterol), or ICS/LABA combinations (beclomethasone+formoterol, BFC, FSC, FVC, MFC). Comparators included placebo, LAMA agents (glycopyrronium bromide, tiotropium), or combined LABA/LAMA agents (indacaterol+tiotropium, indacaterol+glycopyrronium, umeclidinium+vilanterol).

**ICS+LABA vs. any other comparator**
For arrhythmia, no statistically significant differences were observed across any of the ICS/LABA agents compared with each other, ICS alone, LABA alone, or placebo.

**Results of our ranking analysis**
Given that the results were not statistically significant, we did not rank the agents in terms of their arrhythmia safety.

**Meta-analysis results**

**Primary efficacy outcome**

**Exacerbations for all severities of COPD**
For all severities of COPD, 48 meta-analyses were conducted and 11 of these were statistically significant, of which 6 included ICS/LABA combination therapy.
**ICS+LABA vs. placebo**
The following ICS/LABA combinations led to decreased risk of exacerbation when compared with placebo: FSC (NNT 5) and MFC (NNT 8) (Table 3).

**ICS+LABA vs. ICS+LABA**
No statistically significant differences were observed across any of the comparisons between ICS/LABA combination therapies for all severities of COPD.

**ICS+LABA vs. ICS alone or LABA alone**
Compared with formoterol alone, BFC (NNT 20) and MFC (NNT 12) led to decreased risk of exacerbation. The combination of FSC led to a decreased risk of exacerbation when compared with salmeterol alone (NNT 20). Similarly, FVC led to a decreased risk of exacerbation when compared with vilanterol alone (NNT 16) (Table 3).

**Exacerbations for moderate COPD**
For patients with moderate COPD, 40 meta-analyses were conducted and 8 of these were statistically significant, of which 4 included ICS/LABA combination therapy (Table 4).

**ICS+LABA vs. placebo**
The following agents led to decreased risk of exacerbation when compared with placebo: FSC (NNT 6) and MFC (NNT 9).

**ICS+LABA vs. ICS+LABA**
No statistically significant differences were observed across any of the comparisons between ICS/LABA combination therapies in patients with moderate COPD.

**ICS+LABA vs. ICS alone or LABA alone**
When compared with formoterol alone, MFC (NNT 12) led to decreased risk of exacerbation, whereas BFC was borderline statistically significant (NNT 19). When compared with vilanterol alone, FVC (NNT 18) led to decreased risk of exacerbation (Table 4).

**Results from single studies**
No meta-analysis was conducted for patients with severe COPD, due to a dearth of included studies. Based on data from a single RCT, the only statistically significant result was treatment with FSC, which led to a statistically significant decreased risk of COPD exacerbation when compared to treatment with salmeterol alone.

**Secondary safety outcomes**

**Pneumonia**
A total of 35 meta-analyses were conducted. Five of these were statistically significant, of which 3 included ICS/LABA combination therapy.
**ICS+LABA vs. placebo**
Significantly more patients receiving FSC experienced pneumonia versus those who received placebo (NNH 28).

**ICS+LABA vs. ICS+LABA**
There were no statistically significant differences between ICS/LABA combination therapies in the pair-wise comparisons from head-to-head trials.

**ICS+LABA vs. ICS alone or LABA alone**
Patients receiving FVC experienced statistically significantly more pneumonia versus patients who received vilanterol alone (NNH 25). Significantly more patients receiving FSC experienced pneumonia versus those who received salmeterol alone (NNH 23).

None of the other meta-analyses displayed a significant difference in pneumonia across all of the pair-wise comparisons from head-to-head trials.

**Arrhythmia**
A total of 20 meta-analyses were conducted. The included RCTs assessed mometasone, formoterol, indacaterol, salmeterol, vilanterol, glycopyrronium bromide, tiotropium, beclomethasone+formoterol, BFC, FSC, MFC, indacaterol+tiotropium, indaceterol+glycopyrronium, or umeclidinium+vilanterol.

**ICS+LABA vs. any other comparator**
There were no statistically significant differences between any of the agents regarding arrhythmia across all of the pair-wise comparisons from head-to-head trials.

**Discussion**
For risk of COPD exacerbation, we could not complete a network meta-analysis for all COPD severities because the data were inconsistent. From the meta-analysis, both FSC (NNT 5) and MFC (NNT 8) were found to be effective at decreasing the risk of exacerbations for all COPD severities when compared with placebo. In addition, MFC (NNT 12) and BFC (NNT 20) were found to decrease risk of exacerbation when compared with formoterol alone, FSC decreased the risk of exacerbation when compared with salmeterol (NNT 20), and, FVC decreased the risk of COPD exacerbation when compared with vilanterol (NNT 16).

When the network meta-analysis was restricted to patients with moderate COPD, BFC, FSC, and MFC were found to be more effective than placebo at decreasing risk of exacerbation (NNT 6 to 17). Compared to FSC, both BFC (NNT 8) and MFC (NNT 10) reduced exacerbations. BFC and MFC decreased the risk of exacerbation when compared with budesonide (NNT 6), indacaterol (NNT 7) and salmeterol (NNT 8). BFC, FVC, and MFC decreased risk of exacerbation compared with vilanterol alone (NNT 7 to 16). According to our ranking analysis, the 2 ICS/LABA combination agents with the highest probability of being the most effective for decreasing risk of COPD exacerbation in patients with moderate COPD were BFC and MFC.
A network meta-analysis could not be done for studies that focused on patients with severe COPD because of insufficient data. Based on data from a single trial (i.e., no pooling was conducted), FSC was found to be more effective than salmeterol alone in decreasing risk of exacerbation.

A previously published network meta-analysis funded by private industry (Merck, Dhome, and Nycomed) concluded that combination therapy is likely superior to single therapy regarding exacerbations (9). The authors included 26 RCTs after searching the literature until 2010. A different network meta-analysis of inhaled drugs for COPD concluded that ICS/LABA combination therapy reduced exacerbations only in patients with low forced expiratory volume (8). The review included 35 RCTs with 26,786 patients.

A recent Cochrane review and network meta-analysis compared four classes of long acting inhalers for COPD (ICS, LABA, ICS/LABA combination, and LAMA) for 2 efficacy outcomes: mean trough forced expiratory volume in one second (FEV1) and mean total score on the St George’s Respiratory Questionnaire (SGRQ) (30). Seventy-one RCTs with 73,062 patients were included. FEV1 data were available for 46 studies (47,409 patients) with 120 treatment nodes across the networks, which provided data after 6 and 12 months of follow-up. Compared with placebo, ICS/LABA combination was the highest ranked class in terms of improved mean FEV1 at 6 and at 12 months. LAMAs and LABAs had a similar effect overall, and ICS ranked fourth. For SGRQ, data were available in 42 studies (54,613 patients) with 118 treatment nodes across the networks, which provided data after 6 and 12 months of follow-up. Similar to lung function, ICS/LABA ranked highest and patients receiving ICS/LABA combination had higher quality of life compared with placebo. LAMAs, LABAs, and ICS ranked second, third, and fourth, respectively, and were all better than placebo in terms of improved quality of life in patients with COPD. As this recent Cochrane review and network meta-analysis did not examine exacerbations, there is no overlap in results with our review.

In our rapid review presented here, the network meta-analysis for pneumonia found that fluticasone combined with salmeterol or vilanterol were most likely to increase risk of pneumonia. MFC was less likely to cause pneumonia. Since treatment effects were different within treatment classes, we chose not to conduct a class analysis.

Our results for pneumonia are consistent with a recent Cochrane review on ICS, LABA and ICS/LABA combination which looked at pneumonia in patients with COPD (31). The study authors found an increased risk of pneumonia for fluticasone versus placebo and for fluticasone/LABA combination versus LABA alone. Budesonide also increased the risk of non-fatal serious pneumonia compared to control, although the effect was less precise and was based on shorter trials.

We found no differences in risks of arrhythmia across any of the compared agents in our rapid review.

The results of our rapid review must be interpreted with caution for several reasons. First, because of the timelines, we could only conduct single data abstraction. However, we verified all data included in the analyses presented here. Second, we were only able to include published literature. As such, the results for treatments with many trials included in the network will likely be more stable than those for treatments with fewer studies, which is usually the case for newer drugs. Third, given the inconsistency
across the data, we could not complete a network meta-analysis for risk of exacerbation for patients with all COPD severities. Fourth, the COPD criteria for severity have changed over time and this has led to heterogeneity across the studies.

Key messages:

- For patients with moderate COPD, BFC or MFC had the greatest probability of decreasing the risk of exacerbation.
- FSC and FVC increased risk of pneumonia and were the least safe agents when considering this outcome in patients with all COPD severities.
- There were no significant differences in risk of arrhythmia across the compared agents.
- The results of our rapid review should be interpreted with caution, as our review was conducted in a very short period of time. For example, we used one reviewer’s answers and another person verified all of the data, we included only published literature, and we were not able to explore possible sources of heterogeneity through meta-regression.
Acknowledgements
ACT is funded by a Canadian Institutes for Health Research Drug Safety and Effectiveness Network New Investigator Award in Knowledge Synthesis and SES is funded by a Tier 1 Canada Research Chair in Knowledge Translation. We thank Becky Skidmore for conducting the literature search and Heather McDonald for peer reviewing the search, Wing Hui for formatting the paper, and Alissa Epworth for obtaining the full-text articles.
References


Figure 1: Study flow

n = 2724 titles and abstracts identified from database search

n = 1469 excluded

n = 1255 potentially relevant full text articles

n = 1019 excluded

n = 180 included articles reporting on 183 trials (plus 56 companion reports)
Figure 2: Risk of bias

- Other bias
- Selective reporting
- Incomplete outcome data
- Blinding of outcome assessment
- Blinding of participants/personnel
- Allocation concealment
- Random sequence generation

High risk, Unclear risk, Low risk
Table 1. Results of Network Meta-analysis for risk of exacerbation with moderate COPD

<table>
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<tr>
<th>Intervention</th>
<th>Comparison</th>
<th>NNT</th>
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<td><strong>ICS+LABA vs. placebo</strong></td>
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<td>Budesonide + formoterol</td>
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<td>Budesonide + formoterol</td>
<td>Fluticasone + salmeterol</td>
<td>8</td>
</tr>
<tr>
<td><strong>ICS+LABA vs. ICS alone or LABA alone</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Budesonide + formoterol</td>
<td>Budesonide</td>
<td>6</td>
</tr>
<tr>
<td>Mometasone + formoterol</td>
<td>Budesonide</td>
<td>6</td>
</tr>
<tr>
<td>Budesonide + formoterol</td>
<td>Indacaterol</td>
<td>7</td>
</tr>
<tr>
<td>Mometasone + formoterol</td>
<td>Indacaterol</td>
<td>7</td>
</tr>
<tr>
<td>Budesonide + formoterol</td>
<td>Salmeterol</td>
<td>8</td>
</tr>
<tr>
<td>Mometasone + formoterol</td>
<td>Salmeterol</td>
<td>8</td>
</tr>
<tr>
<td>Budesonide + formoterol</td>
<td>Vilanterol</td>
<td>7</td>
</tr>
<tr>
<td>Fluticasone + vilanterol</td>
<td>Vilanterol</td>
<td>16</td>
</tr>
<tr>
<td>Mometasone + formoterol</td>
<td>Vilanterol</td>
<td>8</td>
</tr>
</tbody>
</table>
Table 2. Results of Network Meta-analysis for pneumonia

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Comparison</th>
<th>NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ICS+LABA vs. placebo</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluticasone + vilanterol</td>
<td>Placebo</td>
<td>10</td>
</tr>
<tr>
<td>Fluticasone + salmeterol</td>
<td>Placebo</td>
<td>16</td>
</tr>
<tr>
<td><strong>ICS+LABA vs. ICS+LABA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluticasone + salmeterol</td>
<td>Budesonide + formoterol</td>
<td>19</td>
</tr>
<tr>
<td><strong>ICS+LABA vs. ICS alone or LABA alone</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluticasone + vilanterol</td>
<td>Budesonide</td>
<td>9</td>
</tr>
<tr>
<td>Fluticasone + salmeterol</td>
<td>Budesonide</td>
<td>13</td>
</tr>
<tr>
<td>Fluticasone + vilanterol</td>
<td>Formoterol</td>
<td>7</td>
</tr>
<tr>
<td>Fluticasone + salmeterol</td>
<td>Formoterol</td>
<td>10</td>
</tr>
<tr>
<td>Fluticasone + vilanterol</td>
<td>Vilanterol</td>
<td>17</td>
</tr>
<tr>
<td>Fluticasone + salmeterol</td>
<td>Indacaterol</td>
<td>15</td>
</tr>
<tr>
<td>Fluticasone + salmeterol</td>
<td>Salmeterol</td>
<td>19</td>
</tr>
</tbody>
</table>
Table 3. Results of Meta-analysis for risk of exacerbation with all severities of COPD

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Comparison</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>ICS+LABA vs. placebo</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluticasone + Salmeterol</td>
<td>Placebo</td>
<td>5</td>
</tr>
<tr>
<td>Mometasone + Formoterol</td>
<td>Placebo</td>
<td>8</td>
</tr>
<tr>
<td>Fluticasone + Vilanterol</td>
<td>Placebo</td>
<td>--</td>
</tr>
<tr>
<td><em>ICS+LABA vs. ICS+LABA</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Budesonide + Formoterol</td>
<td>Beclomethasone + formoterol</td>
<td>--</td>
</tr>
<tr>
<td><em>ICS+LABA vs. ICS alone or LABA alone</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Budesonide + Formoterol</td>
<td>Formoterol</td>
<td>20</td>
</tr>
<tr>
<td>Mometasone + Formoterol</td>
<td>Formoterol</td>
<td>12</td>
</tr>
<tr>
<td>Beclomethasone + Formoterol</td>
<td>Formoterol</td>
<td>--</td>
</tr>
<tr>
<td>Fluticasone + Salmeterol</td>
<td>Salmeterol</td>
<td>20</td>
</tr>
<tr>
<td>Fluticasone + Vilanterol</td>
<td>Vilanterol</td>
<td>16</td>
</tr>
<tr>
<td>Mometasone + Formoterol</td>
<td>Mometasone</td>
<td>--</td>
</tr>
<tr>
<td>Fluticasone + Vilanterol</td>
<td>Fluticasone</td>
<td>--</td>
</tr>
<tr>
<td>Fluticasone + Salmeterol</td>
<td>Fluticasone</td>
<td>--</td>
</tr>
</tbody>
</table>

* Statistically significant
Table 4. Results of Meta-analysis for risk of exacerbation with moderate COPD

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Comparison</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ICS+LABA vs. placebo</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluticasone + Salmeterol</td>
<td>Placebo</td>
<td>6</td>
</tr>
<tr>
<td>Mometasone + formoterol</td>
<td>Placebo</td>
<td>9</td>
</tr>
<tr>
<td>Fluticasone + Vilanterol</td>
<td>Placebo</td>
<td>--</td>
</tr>
<tr>
<td><strong>ICS+LABA vs. ICS alone or LABA alone</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluticasone + Vilanterol</td>
<td>Fluticasone</td>
<td>--</td>
</tr>
<tr>
<td>Fluticasone + Salmeterol</td>
<td>Fluticasone</td>
<td>--</td>
</tr>
<tr>
<td>Budesonide + Formoterol</td>
<td>Formoterol</td>
<td>19</td>
</tr>
<tr>
<td>Mometasone + formoterol</td>
<td>Formoterol</td>
<td>12</td>
</tr>
<tr>
<td>Fluticasone + Vilanterol</td>
<td>Vilanterol</td>
<td>18</td>
</tr>
<tr>
<td>Fluticasone + Salmeterol</td>
<td>Salmeterol</td>
<td>--</td>
</tr>
<tr>
<td>Mometasone + formoterol</td>
<td>Mometasone</td>
<td>--</td>
</tr>
</tbody>
</table>

* Statistically significant
# Appendices

## Appendix 1: Medications included in the rapid review

<table>
<thead>
<tr>
<th>Generic name(s)*</th>
<th>Trade name(s)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaled long-acting beta₂-agonists (LABA)</td>
<td></td>
</tr>
<tr>
<td>formoterol or eformoterol</td>
<td>Foradil, Oxeze, Oxis</td>
</tr>
<tr>
<td>Indacaterol</td>
<td>Arcapta</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>Serevent, SereventDiskus</td>
</tr>
<tr>
<td>olodaterol</td>
<td>Striverdi</td>
</tr>
<tr>
<td>vilanterol or GW642444</td>
<td></td>
</tr>
<tr>
<td>Inhaled long-acting muscarinic anticholinergics (LAMA)</td>
<td></td>
</tr>
<tr>
<td>aclidinium bromide</td>
<td>TudorzaGenuair</td>
</tr>
<tr>
<td>glycopyrronium bromide</td>
<td>SeebriBreezhaler</td>
</tr>
<tr>
<td>tiotropium bromide</td>
<td>Spiriva</td>
</tr>
<tr>
<td>umeclidinium bromide or GSK573719</td>
<td></td>
</tr>
<tr>
<td>Inhaled corticosteroids (ICS)</td>
<td></td>
</tr>
<tr>
<td>beclomethasone</td>
<td>QVAR, Clenil</td>
</tr>
<tr>
<td>budesonide</td>
<td>Pulmicort</td>
</tr>
<tr>
<td>fluticasone or GW685698</td>
<td>Flovent, FloventDiskus, Flixotide</td>
</tr>
<tr>
<td>mometasone</td>
<td></td>
</tr>
<tr>
<td>Combo LABA plus ICS in one inhaler**</td>
<td></td>
</tr>
<tr>
<td>formoterol/budesonide</td>
<td>Symbicort</td>
</tr>
<tr>
<td>formoterol/mometasone</td>
<td>Zenhale</td>
</tr>
<tr>
<td>salmeterol/fluticasone</td>
<td>Advair, AdvairDiskus, Seretide</td>
</tr>
<tr>
<td>vilanterol/fluticasone</td>
<td>BreoEllipta</td>
</tr>
<tr>
<td>Combo LAMA plus ICS in one inhaler**</td>
<td></td>
</tr>
<tr>
<td>Combo LAMA plus LABA in one inhaler**</td>
<td></td>
</tr>
<tr>
<td>vilanterol/umeclidinium</td>
<td>AnoroEllipta</td>
</tr>
<tr>
<td>indacaterol/glycopyrronium</td>
<td>QVA149, Ultibro</td>
</tr>
<tr>
<td>Combo LAMA plus LABA in one inhaler (MABA)</td>
<td></td>
</tr>
<tr>
<td>GSK961081 (formerly TD5959)</td>
<td></td>
</tr>
</tbody>
</table>

*Note: *This is not an exhaustive list. **Combination therapy could also be given in multiple inhalers.*
Appendix 2: Medications excluded in the rapid review

<table>
<thead>
<tr>
<th>Generic name(s)*</th>
<th>Trade name(s)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-acting beta(_2)-agonists (LABA) in nebulizer and transdermal form</td>
<td></td>
</tr>
<tr>
<td>formoterol (when in nebulizer form)</td>
<td></td>
</tr>
<tr>
<td>arformoterol</td>
<td></td>
</tr>
<tr>
<td>tulobuterol</td>
<td></td>
</tr>
<tr>
<td>Inhaled corticosteroids (ICS) in nebulizer form</td>
<td></td>
</tr>
<tr>
<td>beclomethasone (when in nebulizer form)</td>
<td></td>
</tr>
<tr>
<td>budesonide (when in nebulizer form)</td>
<td></td>
</tr>
<tr>
<td>We will exclude ALL of the following agents:</td>
<td></td>
</tr>
<tr>
<td>Short-acting beta2-agonists (SABA) (inhaled, nebulizer, oral, injection)</td>
<td></td>
</tr>
<tr>
<td>fenoterol</td>
<td></td>
</tr>
<tr>
<td>levosalbutamol or levalbuterol Xopenex</td>
<td></td>
</tr>
<tr>
<td>salbutamol or albuterol Ventolin</td>
<td></td>
</tr>
<tr>
<td>terbutaline Bricanyl</td>
<td></td>
</tr>
<tr>
<td>Short-acting muscarinic anticholinergics (SAMA) (inhaler, nebulizer)</td>
<td></td>
</tr>
<tr>
<td>ipratropium bromide Combivent, Atrovent</td>
<td></td>
</tr>
<tr>
<td>oxitropium bromide</td>
<td></td>
</tr>
<tr>
<td>Combo SABA plus anticholinergic in one inhaler (inhaler, nebulizer)</td>
<td></td>
</tr>
<tr>
<td>fenoterol/ipratropium</td>
<td></td>
</tr>
<tr>
<td>salbutamol/ipratropium</td>
<td></td>
</tr>
<tr>
<td>Methylxanthines (oral, injection)</td>
<td></td>
</tr>
<tr>
<td>aminophylline</td>
<td></td>
</tr>
<tr>
<td>theophylline</td>
<td></td>
</tr>
<tr>
<td>Systemic corticosteroids (oral)</td>
<td></td>
</tr>
<tr>
<td>prednisone</td>
<td></td>
</tr>
<tr>
<td>methyl-prednisolone</td>
<td></td>
</tr>
<tr>
<td>Phosphodiesterase-4 (PDE4) inhibitors (oral)</td>
<td></td>
</tr>
<tr>
<td>roflumilast</td>
<td></td>
</tr>
</tbody>
</table>

*Note: *This is not an exhaustive list.*
Appendix 3: All efficacy and safety outcomes considered

Efficacy outcomes:

1. Proportion of patients with exacerbations (primary outcome of interest)
2. Number of hospitalizations (overall and due to exacerbations)
3. Number of emergency room visits (overall and due to exacerbations)
4. Function (e.g., 6 minute walk test, paced shuttle walk test)
5. Forced expiratory volume (FEV)
6. Quality of life
7. Number of patients with ischemic heart disease
8. Dyspnea
9. Mortality (including cardiovascular-related mortality)

Safety outcomes:

1. All harms
2. Serious harms
3. Withdrawals due to lack of efficacy
4. Treatment-related withdrawals
5. Fractures
6. Bone mineral density
7. Heart failure
8. Arrhythmia
9. Pneumonia
10. Cataracts
11. Oral thrush
12. Palpitations
13. Headache
14. Constipation
15. Dry mouth
Appendix 4: Patient ratings of relevant outcomes

TOP 3 - MOST important efficacy outcomes:
1. Quality of Life (10/19 rated this outcome in their top 4)
2. Shortness of Breath (9/19 rated this in their top 4)
3. Functional Abilities (8/19 rated this in their top 4)

TOP 3 - LEAST important efficacy outcomes:
1. Mortality (7/19 rated this in their bottom 4)
2. Emergency Room Visits (6/19 rated in bottom 4)
3. Hospitalizations/Exacerbations/FEV (5/19 people rated this in their bottom 4)

TOP 3 - MOST important safety/side effects:
1. & 2. Heart Attack & Heart Failure (12/19 rated this in top 5)
3. Bone Fractures (8/19 rated this in top 5)

TOP 3 - LEAST important safety/side effects:
1. Dry Mouth (13/19 rated this in bottom 5)
2. Headache (9/19 rated this in bottom 5)
3. Constipation & Cataracts (7/19 rated this in bottom 5)
Appendix 5: Final MEDLINE Search
1  exp Pulmonary Disease, Chronic Obstructive/
2  exp Emphysema/ or exp Pulmonary Emphysema/
3  ((chronic adj2 obstructi*) and (pulmonary or airway* or air way* or lung$1 or airflow* or air flow*)).tw.
4  (COPD or COAD).tw.
5  (chronic adj2 bronchitis).tw.
6  emphysema*.tw.
7  or/1-6
8  Formoterol*.tw,rn.
9  (BD 40A or HSDB 7287 or Oxis or UNII-5ZZ84GCW8B).tw.
10 (eformoterol or Foradil).tw.
11  73573-87-2.rn.)
12  Indacaterol.tw,rn.
13  (Arcapta or Onbrez or QAB 149 or QAB149 or UNII-8OR09251MQ).tw.
14  312753-06-3.rn.
15  Salmeterol*.tw,rn.
16  (Aeromax or Astmerole or "GR 33343 X" or "GR 33343X" or HSDB 7315 or SN408D or UNII-214BC502BT).tw.
17  89365-50-4.rn.
18  Salmeterolxinafoate.tw,rn.
19  (Arial or Asmerole or Beglan or Betamican or Dilamax or Inaspir or Salmetedur or Serevent or Ultrabeta or UNII-6EW8Q962A5).tw.
20  94749-08-3.rn.
21  ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (beta-agonist* or betaagonist* or beta-adrenergic* or adrenergic beta-receptor* or beta-receptor agonist* or beta-adrenoceptor agonist*)).tw.
22  ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (beta-2-agonist* or beta-2agonist* or beta-2-adrenergic* or adrenergic beta-2-receptor* or beta-2-receptor agonist* or beta-2-adrenoceptor agonist*)).tw.
23  ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (beta2-agonist* or beta2agonist* or beta2-adrenergic* or adrenergic beta2-receptor* or beta2-receptor agonist* or beta2- adrenoceptor agonist*)).tw.
24  ((longacting or long-acting) and ("beta(2)-agonist*" or "beta(2)agonist*" or "beta(2)-adrenergic*" or "adrenergic beta(2)-receptor*" or "beta(2)-receptor agonist*" or "beta(2)-adrenoceptor agonist*"))_.tw.
25  ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (B2-agonist* or B2-adrenergic* or adrenergic B2-receptor* or B2-receptor agonist* or B2-adrenoceptor agonist*)).tw.
Ontario Drug Policy Research Network

26  ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralongacting) and (B-2-agonist* or B-2-adrenergic* or adrenergic B-2-receptor* or B-2-receptor agonist* or B-2-adrenoceptor agonist*)).tw.
27  (LABA or LABAs or Ultra-LABA* or UltraLABA*).tw.
28  ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralongacting) and bronchodilator*).tw.
29  ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralongacting) and (betamimetic* or beta-mimetic*)).tw.
30  exp Adrenergic beta-Agonists/ or Bronchodilator Agents/
31  (longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralongacting).tw.
32  30 and 31
33  or/21-29,32
34  Administration, Inhalation/
35  exp Aerosols/
36  (inhal* or aerosol*).tw.
37  or/34-36
38  33 and 37
39  or/8-20,38 )
40  Beclomethasone/
41  (Aerobec or AeroBec Forte or Aldecin or Apo-Beclomethasone or Ascocortonyl or AsmabecClickhaler).tw.
42  (Beclamet or Beclazone or BecloAsma or Beclo AZU or Beclocort or Becloforte or Beclomet or Beclometason* or Beclomethasone or Beclorhinol or Becloturmant or Beclovent or Becodisk* or Beconase or Becotide or BemedrexEasyhaler or Bronchocort).tw.
43  (Ecobec or Filair or Junik or Nasobec Aqueous or Prolair or Propaderm or Qvar or Respocort or Sanasthmax or Sanasthmyl or Vancenase or Vanceril or Ventolair or Viarin).tw.
44  (BMJ 5800 or EINECS 224-585-9 or UNII-KGZ1SLC28Z).tw.
45  4419-39-0.rn.
46  Budesonide/
47  (Budesonide or Micronyl or Preferid or Pulmicort or Respules or Rhinocort or "S 1320" or Spirocut or Uceris or UNII-Q3OKS62Q6X).tw.
48  51333-22-3.rn.
49  Fluticasone.tw,rn.
50  (Cutivate or Flixonase or Flixtotide or Flonase or Flovent or Fluticas* or HSDB 7740 or UNII-CUT2W21N7U).tw.
51  Glucocorticoids/
52  glucocorticoid*.tw.
53  Adrenal Cortex Hormones/
54  (corticoid* or corticosteroid* or cortico-steroid*).tw.
55  ((adrenal cortex or adrenal cortical) adj3 hormon*).tw.
56  ((adrenal cortex or adrenal cortical) adj3 steroid*).tw.
(Fluticasone adj3 salmeterol).tw,rn.

(Adoair or Advair or Foxair or "Quikhale SF" or Seretide or Viani).tw.

(formoterol adj3 mometasone).tw,rn.

(Zenhale or Dulera).tw.

(formoterol adj3 budesonide).tw,rn.

(Rilast or Symbicord or Symbicort or Vannair).tw.

(vilanterol adj3 fluticasone).tw,rn.

Breo Ellipta.tw.

tiotropium.tw,rn.

(BA 679 BR or BA 679BR or Spiriva or tiotropium or UNII-0EB439235F or UNII-XX112XZP0J).tw.

acldiniumbromide.tw,rn.

(LAS 34273 or LAS W-330 or BretarisGenuair or EkliraGenuair or TudorzaPressair or UNII-UQW7UF9N91).tw.

glycoyrroniumbromide.tw,rn.

(erythro-glycopyrronium bromide or UNII-9SFK0PX55W).tw.

((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (anticholinergic* or anti-cholinergic* or cholinolytic* or cholinergic-blocking or antimuscarinic* or anti-muscarinic* or ((cholinergic or acetylcholine or muscarinic) adj3 antagonist*)\)).tw.

(LAMA or LAMAs or Ultra-LAMA* or UltraLAMA*).tw.

Muscarinic Antagonists/ or Cholinergic Antagonists/

77 and 31

79 or 76 or 78

79 and 37

or/69-74,80

39 or 59 or 68 or 81

7 and 82

randomized controlled trial.pt.

controlled clinical trial.pt.

randomized.ab.

placebo.ab.

clinical trials as topic/

randomly.ab.

trial.ti.

or/84-90

83 and 91

exp Animals/ not (exp Animals/ and Humans/)
95  (interview or news).pt.
96  94 not 95
97  96 use mesz
98  96 use prem
99  97 or 98
100 chronic obstructive lung disease/
101 lung emphysema/ or emphysema/
102 ((chronic adj2 obstructi*) and (pulmonary or airway* or air way* or lung$1 or airflow* or air
103 flow*)).tw.
104 (COPD or COAD).tw.
105 (chronic adj2 bronchitis).tw.
106 emphysema*.tw.
107 or/100-105
108 formoterol/ or formoterolfumarate/
109 (BD 40A or HSDB 7287 or Oxis or UNII-5ZZ84GCW8B).tw.
110 (eformoterol or Foradil or formoterol).tw.
111 (73573-87-2 or 183814-30-4).rn.
112 indacaterol/
113 (Arcapta or Onbrez or indacaterol or QAB 149 or QAB149 or UNII-8OR09251MQ).tw.
114 312753-06-3.rn.
115 salmeterol/
116 (Aeromax or Astmerole or "GR 33343 X" or "GR 33343X" or HSDB 7315 or Salmeterol or SN408D
117 or UNII-2I4BC502BT).tw.
118 89365-50-4.rn.
119 salmeterolxinafoate/
120 (Arial or Asmerole or Beglan or Betamican or Dilamax or Inaspir or Salmetedur or
121 Salmeterolxinafoate or Serevent or Ultrabeta or UNII-6EW8Q962A5).tw.
122 94749-08-3.rn.
123 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-
124 acting) and (beta-agonist* or betaagonist* or beta-adrenergic* or adrenergic beta-receptor* or beta-
125 receptor agonist* or beta-adrenoceptor agonist*)).tw.
126 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-
127 acting) and (beta-2-agonist* or beta2agonist* or beta-2-adrenergic* or adrenergic beta-2-receptor* or
128 beta-2-receptor agonist* or beta-2-adrenoceptor agonist*)).tw.
129 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-
130 acting) and (beta2-agonist* or beta2agonist* or beta2-adrenergic* or adrenergic beta2-receptor* or
131 beta2-receptor agonist* or beta2- adrenoceptor agonist*)).tw.
132 ((longacting or long-acting) and ("beta(2)-agonist*" or "beta(2)-agonist*" or "beta(2)-adrenergic*"
133 or "adrenergic beta(2)-receptor*" or "beta(2)-receptor agonist*" or "beta(2)-adrenoceptor
134 agonist*"))).tw.
(longacting or long-acting or ultra-long-acting or ultra-long-acting or ultralongacting or ultralong-acting) and (B2-agonist* or B2-adrenergic* or adrenergic B2-receptor* or B2-receptor agonist* or B2-adrenoceptor agonist*).tw.

(longacting or long-acting or ultra-long-acting or ultra-long-acting or ultralongacting or ultralong-acting) and (B-2-agonist* or B-2-adrenergic* or adrenergic B-2-receptor* or B-2-receptor agonist* or B-2-adrenoceptor agonist*).tw.

(LABA or LABAs or Ultra-LABA* or UltraLABA*).tw.

(longacting or long-acting or ultra-long-acting or ultra-long-acting or ultralongacting or ultralong-acting) and bronchodilator*.tw.

(longacting or long-acting or ultra-long-acting or ultra-long-acting or ultralongacting or ultralong-acting) and bronchodilator*.tw.

exp beta adrenergic receptor stimulating agent/ or brochodilating agent/

(longacting or long-acting or ultra-long-acting or ultra-long-acting or ultralongacting or ultralong-acting).tw.

or/120-128,131

inhalational drug administration/

aerosol/

(inhal* or aerosol*).tw.

or/133-135

132 and 136

or/107-119,137

beclometasone/

(Aerobec or AeroBec Forte or Aldecin or Apo-Beclomethasone or Ascocortonyl or AsmabecClickhaler).tw.

(Beclamet or Beclazine or BecloAsma or Beclo AZU or Beclocort or Becloforte or Beclomet or Beclometason* or Beclomethasone or Beclorhinol or Becloturmant or Bectolvent or Becodisk* or Beconase or Becotide or BemedrexEasyhaler or Bronchocort).tw.

(Ecobec or Filair or Junik or Nasobec Aqueous or Prolair or Propaderm or Qvar or Respocort or Sanasthmax or Sanasthmyl or Vancenase or Vanceril or Violanil).tw.

(BMJ 5800 or EINECS 224-585-9 or UNII-KGZ1SLC28Z).tw.

4419-39-0.rn.

budesonide/

(Budesonide or Micronyl or Preferid or Pulmicort or Respules or Rhinocort or "S 1320" or Spirocort or Uceris or UNII-Q3OKS62Q6X).tw.

51333-22-3.rn.

fluticasone/ or fluticasone propionate/

(Cutivate or Flixonase or Flixotide or Flonase or Flovent or Fluticason* or HSDB 7740 or UNII-CUT2W21N7U).tw.

(90566-53-3 or 80474-14-2).rn.

glucocorticoid/

glucocorticoid*.tw.
35 corticosteroid/
154 (corticoid* or corticosteroid* or cortico-steroid*).tw.
155 (adrenal cortex or adrenal cortical) adj3 (hormon* or steroid*).tw.
156 or/151-155
157 156 and 136
158 or/139-150,157
159 fluticasone propionate plus salmeterol/
160 (Adoair or Advair or Foxair or "Quikhale SF" or Seretide or Viani).tw.
161 (fluticasone adj3 salmeterol).tw.
162 136112-01-1.rn.
163 formoterolfumarate plus mometasonefuroate/
164 (formoterol adj3 mometasone).tw.
165 (Zenhale or Dulera).tw.
166 budesonide plus formoterol/
167 (formoterol adj3 budesonide).tw.
168 (Rilast or Symbicord or Symbicort or Vannair).tw.
169 150693-37-1.rn.
170 fluticasone furoate plus vilanterol/
171 (vilanterol adj3 fluticasone).tw.
172 Breo Ellipta.tw.
173 or/159-172
174 tiotropium bromide/
175 (BA 679 BR or BA 679BR or Spiriva or tiotropium or UNII-0EB439235F or UNII-XX112XZP0J).tw.
176 (186691-13-4 or 136310-93-5).rn.
177 aclidinium bromide/
178 (LAS 34273 or LAS W-330 or BretarisGenuair or EkliraGenuair or TudorzaPressair or UNII-UQW7UF9N91).tw.
179 320345-99-1.rn.
180 glycoyrronium bromide.tw.
181 (erythro-glycopyrronium bromide or UNII-9SFK0PX55W).tw.
182 (longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (anticholinergic* or anti-cholinergic* or cholinolytic* or cholinergic-blocking or antimuscarinic* or anti-muscarinic* or (cholinergic or acetylcholine or muscarinic) adj3 antagonist*)).tw.
183 (LAMA or LAMAs or Ultra-LAMA* or UltraLAMA*).tw.
184 muscarinic receptor blocking agent/
185 cholinergic receptor blocking agent/
186 (184 or 185) and 130
187 182 or 183 or 186
188 187 and 136
189 or/174-181,188
190 138 or 158 or 173 or 189
191 106 and 190
192 randomized controlled trial/
193 controlled clinical trial/
194 randomized.ab.
195 placebo.ab.
196 "clinical trial (topic)"
197 randomly.ab.
198 trial.ti.
199 or/192-198
200 191 and 199
201 exp animals/ or exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/
202 exp humans/ or exp human experimentation/ or exp human experiment/
203 201 not 202
204 200 not 203
205 204 use emcz
206 99 or 205
207 remove duplicates from 206
Appendix 6: List of included studies


35. Celli B, Halpin D, Hepburn R, Byrne N, Keating ET, Goldman M. Symptoms are an important outcome in chronic obstructive pulmonary disease clinical trials: results of a 3-month comparative


63. Freeman D, Lee A, Price D. Efficacy and safety of tiotropium in COPD patients in primary care—the SPIRiva Usual Care (SPRUCE) study. Respir Res. 2007;8:45.


## Appendix 7: Definitions of exacerbations

<table>
<thead>
<tr>
<th>Study</th>
<th>Definition of Exacerbation</th>
<th>COPD Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aalbers, 2002</td>
<td>Worsening symptoms of COPD requiring the use of any additional treatment other than rescue albuterol/salbutamol</td>
<td>Mild to very severe</td>
</tr>
<tr>
<td>Aaron, 2007</td>
<td>An increase in or the new onset of more than one respiratory symptom (cough, sputum, sputum purulence, wheezing, or dyspnea) lasting 3 days or more and requiring treatment with an antibiotic or a systemic corticosteroid</td>
<td>Moderate to very severe</td>
</tr>
<tr>
<td>Abrahams, 2013</td>
<td>Exacerbations not defined</td>
<td>Moderate</td>
</tr>
<tr>
<td>Ambrosino, 2008</td>
<td>Exacerbations not defined</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Anzueto, 2009</td>
<td>A complex of respiratory events (i.e. cough, wheezing, dyspnoea or sputum production) lasting greater than 3 days. These were generally treated with antibiotics and/or oral steroids.</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Barnes, 2006</td>
<td>Exacerbations not defined</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Bateman, 2010</td>
<td>A complex of respiratory events or symptoms that lasted greater than or equal to 3 days and required treatment with antibiotics and/or systemic corticosteroids, or prompted the investigator to change the patient’s regular respiratory medication</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Baumgartner, 2007</td>
<td>On-treatment exacerbation, including moderate (acute worsening of COPD requiring systemic corticosteroids and/or antibiotics) or severe (requiring hospitalisation)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Beier, 2007</td>
<td>Exacerbation which was treated with mucolytics</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td>Bogdan, 2011</td>
<td>Exacerbations not defined</td>
<td>Moderate to very severe</td>
</tr>
<tr>
<td>Bourbeau, 1998</td>
<td>Exacerbations not defined</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Boyd, 1997</td>
<td>Chronic obstructive airways disease exacerbated</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Briggs, 2005</td>
<td>Worsening of symptoms required a change in medication</td>
<td>Moderate to very severe</td>
</tr>
<tr>
<td>Buhl, 2011</td>
<td>Number of patients with at least one exacerbation, defined as requiring a change in medication and/or hospitalization</td>
<td>Moderate to very severe</td>
</tr>
<tr>
<td>Burge, 2000</td>
<td>Exacerbations of COPD, determined on clinical grounds by the local physician</td>
<td>Moderate</td>
</tr>
<tr>
<td>Caillaud, 2007</td>
<td>Worsening of COPD symptoms that required any change in normal treatment</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Calverley, 2010</td>
<td>Need for treatment with oral corticosteroids and/or antibiotics and/or the need to visit or be admitted to a hospital</td>
<td>Severe</td>
</tr>
<tr>
<td>Calverley, 2003</td>
<td>Exacerbations not defined</td>
<td>Mild to severe</td>
</tr>
<tr>
<td>Calverley, 2008</td>
<td>Exacerbations not defined</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Campbell, 2007</td>
<td>Exacerbations not defined</td>
<td>Mild to severe</td>
</tr>
<tr>
<td>Casaburi, 2002</td>
<td>Acute exacerbations, defined according to the TSANZ COPDX guidelines (worsening symptoms requiring</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td>Study</td>
<td>Definition of Exacerbation</td>
<td>COPD Severity</td>
</tr>
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</tr>
<tr>
<td>Celli, 2003</td>
<td>Worsening in symptoms requiring treatment with a course of systemic steroid or hospitalization</td>
<td>Moderate to very severe</td>
</tr>
<tr>
<td>Chanez, 2010</td>
<td>Exacerbations not defined</td>
<td>Moderate to very severe</td>
</tr>
<tr>
<td>Chapman, 2002</td>
<td>Exacerbations not defined</td>
<td>Mild to severe</td>
</tr>
<tr>
<td>Covelli, 2005</td>
<td>Exacerbations not defined</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td>Criner, 2008</td>
<td>Exacerbations not defined</td>
<td>Moderate to very severe</td>
</tr>
<tr>
<td>D’Urzo, 2011</td>
<td>Symptomatic deterioration requiring the short term use of oral/intravenous steroids, antibiotics, or both, by the physician's discretion</td>
<td>Moderate to very severe</td>
</tr>
<tr>
<td>Dahl, 2010</td>
<td>Worsening of COPD that required treatment with a course of oral corticosteroids, hospitalization, or both.</td>
<td>Moderate to very severe</td>
</tr>
<tr>
<td>Dahl, 2013</td>
<td>Worsening of respiratory symptoms that required treatment with a short course of oral corticosteroids or antibiotics as judged by the study physician</td>
<td>Moderate to very severe</td>
</tr>
<tr>
<td>Decramer, 2013</td>
<td>Acute infective exacerbations</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Doherty, 2012</td>
<td>Subjects with ≥1 moderate/severe exacerbation: worsening symptoms requiring treatment with antibiotics, oral corticosteroids, and/or hospitalization</td>
<td>Moderate to very severe</td>
</tr>
<tr>
<td>Donohue, 2002</td>
<td>Exacerbations not defined</td>
<td>Moderate to very severe</td>
</tr>
<tr>
<td>Dransfield, 2013a</td>
<td>Exacerbations of COPD were diagnosed by the physician and reported as adverse events</td>
<td>Severe</td>
</tr>
<tr>
<td>Dransfield, 2013b</td>
<td>Presence, for greater than or equal to 2 days consecutively, of an increase in any two major symptoms (dyspnoea, sputum purulence and sputum volume) or in one major and one minor symptom (wheeze, sore throat, cough and symptoms of a common cold)</td>
<td>Mild to severe</td>
</tr>
<tr>
<td>Dusser, 2006</td>
<td>Mild: clinically judged deterioration of COPD symptoms (managed with increased short-acting bronchodilator use; ≥12 inhalations/day of SABA/short acting anticholinergic, or ≥2 nebulized treatments/day of 2.5mg SABA/short-acting anticholinergic) on any 2 consecutive days. Moderate: clinically judged deterioration of COPD with an acute change in symptoms that required antibiotic and/or oral steroid treatment for lower airway disease. Severe: deterioration of COPD that resulted in emergency treatment or hospitalization due to COPD.</td>
<td>Mild to very severe</td>
</tr>
<tr>
<td>Engel, 1989</td>
<td>Exacerbations not defined</td>
<td>Moderate to very severe</td>
</tr>
<tr>
<td>Feldman, 2010</td>
<td>COPD exacerbation met criteria for a severe AE (eg, was life-threatening, required hospitalization or prolonged hospitalization) it was recorded as an AE (AE events ≥2% incidence)</td>
<td>Moderate to very severe</td>
</tr>
<tr>
<td>Feldman, 2012</td>
<td>COPD exacerbations, defined as use of systemic</td>
<td>Mild to severe</td>
</tr>
<tr>
<td>Study</td>
<td>Definition of Exacerbation</td>
<td>COPD Severity</td>
</tr>
<tr>
<td>-------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Freeman, 2007</td>
<td>Exacerbations not defined</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Fukuchi, 2013</td>
<td>A new onset or worsening of more than one respiratory symptom (i.e., dyspnoea, cough, sputum purulence or volume, or wheeze) present for more than 3 consecutive days plus either a documented change or increase in COPD-related treatment due to worsening symptoms (e.g., steroids/antibiotics/oxygen), or documented COPD-related hospitalizations or emergency room visits.</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Hanania, 2013</td>
<td>Exacerbations not defined</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Hattotuwa, 2002</td>
<td>Exacerbations were defined in terms of increased dyspnea, sputum production, and sputum purulence.</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Johansson, 2008</td>
<td>Worsening of two or more major symptoms (dyspnoea, sputum volume or sputum purulence) for at least 2 consecutive days or worsening of any one major symptom together with any minor symptom (colds, fever without other cause, increased cough, increased wheeze or sore throat) for at least 2 consecutive days.</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Jung, 2012</td>
<td>An exacerbation was defined as symptomatic deterioration requiring the shortterm use of oral/intravenous steroids, antibiotics, or both, by the physician’s discretion.</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Kardos, 2007</td>
<td>As a complex of respiratory events/symptoms with duration of 3 or more days (from patient's diary card) requiring a change in treatment (including patient initiated increases). A complex of respiratory events/symptoms meant ≥2 of the following (increase of symptoms or new onset): shortness of breath, sputum production (volume) cough, wheezing and chest tightness. The change in (or requirement of) treatment included prescription of antibiotics and/or systemic steroids and/or significant change (including increase) of the prescribed respiratory medication (bronchodilators including theophylline).</td>
<td>Mild to very severe</td>
</tr>
<tr>
<td>Kerwin, 2012</td>
<td>Severe exacerbation (defined as worsening of COPD leading to treatment with systemic corticosteroids [oral or parenteral] and/or hospitalization/emergency room visits)</td>
<td>Mild to very severe</td>
</tr>
<tr>
<td>Kerwin, 2013</td>
<td>Onset or worsening of more than one respiratory symptom (dyspnoea, cough, sputum purulence or volume or wheeze) for &gt;3 consecutive days (based on diary cards or patients’ reports of their health since the previous visit) plus documented proof of</td>
<td>Moderate to very severe</td>
</tr>
<tr>
<td>Study</td>
<td>Definition of Exacerbation</td>
<td>COPD Severity</td>
</tr>
<tr>
<td>------------------------</td>
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</tr>
<tr>
<td>Kerwin, 2011a</td>
<td>Exacerbations not defined</td>
<td>Mild to severe</td>
</tr>
<tr>
<td>Kerwin, 2011b</td>
<td>Exacerbations of COPD were reported as adverse events. The investigator decided whether worsening of symptoms was severe enough to be considered an exacerbation of COPD as there was no a priori definition.</td>
<td>Moderate to very severe</td>
</tr>
<tr>
<td>Kinoshita, 2011</td>
<td>An episode with one or more unscheduled contacts with either a GP or a chest physician due to worsening of respiratory symptoms. Values abstracted for # patients and # events came from adding up the numbers in figure 3.</td>
<td>Mild to severe</td>
</tr>
<tr>
<td>Korn, 2011</td>
<td>Exacerbations, defined as moderate (acute worsening of COPD requiring systemic corticosteroids and/or antibiotics) or severe (requiring hospitalisation), reported as safety outcome.</td>
<td>Moderate to very severe</td>
</tr>
<tr>
<td>Kornmann, 2011</td>
<td>Exacerbations requiring treatment with antibiotics alone or a course of antibiotics and systemic steroids</td>
<td>Severe to very severe</td>
</tr>
<tr>
<td>Kuna, 2013</td>
<td>Deterioration of COPD</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Littner, 2000</td>
<td>COPD exacerbations requiring additional therapy</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Llewellyn-Jones, 1996</td>
<td>Reported as the observed number of all moderate plus severe exacerbations [Moderate exacerbations: worsening of chronic obstructive pulmonary disease (COPD) symptoms that required both a change of respiratory medication (increased dose of prescribed drug or addition of new drugs, i.e., antibiotics, mucolytics, systemic steroids, theophylline) and medical assistance. Severe exacerbations: deterioration in COPD resulting in hospitalization or emergency room treatment.]</td>
<td>Severe to very severe</td>
</tr>
<tr>
<td>Lomas, 2012</td>
<td>COPD exacerbations were defined as at least two new or increased respiratory symptoms (cough, wheeze, dyspnea, chest congestion, shortness of breath, chest tightness, or sputum production) occurring for at least 3 days and reported as an adverse event.</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Mahler, 1999</td>
<td>Exacerbations not defined</td>
<td>Moderate to very severe</td>
</tr>
<tr>
<td>Mahler, 2012a</td>
<td>Exacerbations not defined</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Mahler, 2012b</td>
<td>Bronchitis (COPD exacerbation) reported as AE</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Maltais, 2005</td>
<td>An exacerbation was defined as an increase in symptoms requiring either a course of oral corticosteroids or antibiotics or a hospital admission. This change in medication was at the investigator's discretion</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td>Study</td>
<td>Definition of Exacerbation</td>
<td>COPD Severity</td>
</tr>
<tr>
<td>--------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Maltais, 2011</td>
<td>Worsening of COPD symptoms requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids, and other bronchodilator therapy. [Severity: mild, were self managed by the patient at home; moderate exacerbations required treatment by a family physician or as a hospital outpatient; severe exacerbations resulted in hospital admission.]</td>
<td>Mild to severe</td>
</tr>
<tr>
<td>Martinez, 2013</td>
<td>COPD exacerbation reported as AE and defined in the protocol as an increase in symptoms leading to any change in baseline medication or additional medical attention (eg, hospitalization, emergency department visit).</td>
<td>Moderate to very severe</td>
</tr>
<tr>
<td>Moita, 2008</td>
<td>Worsening for at least two consecutive days of two or more of the major symptoms (dyspnoea, sputum volume, or sputum purulence) or worsening of any one major symptom together with any one minor symptom (sore throat, colds [nasal discharge or nasal congestion], fever without other cause, increased cough, or increased wheeze)</td>
<td>Severe</td>
</tr>
<tr>
<td>Niewoehner, 2005</td>
<td>Exacerbations not defined</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>O'Donnell, 2004</td>
<td>A clinically significant worsening of COPD symptoms requiring treatment with antibiotics and/or systemic steroids</td>
<td>Mild to very severe</td>
</tr>
<tr>
<td>O'Donnell, 2006</td>
<td>COPD exacerbation: a complex of respiratory symptoms (increase or new-onset) of more than 1 of the following: cough, sputum, wheezing, dyspnea, or chest tightness with a duration of at least 3 days requiring treatment with antibiotics or systemic steroids, hospitalization, or both.</td>
<td>Moderate to very severe</td>
</tr>
<tr>
<td>Paggiaro, 1998</td>
<td>Data from AEs; use of oral steroids for exacerbations of COPD</td>
<td>Moderate to very severe</td>
</tr>
<tr>
<td>Powrie, 2007</td>
<td>At least 1 exacerbation, defined as chest problems requiring treatment with antibiotics and/or oral corticosteroids, self-reported by patients; [from primary publication: median yearly exacerbation rate (worsening of respiratory symptoms that required treatment with oral corticosteroids or antibiotics, or both, as judged by the general practitioner; specific symptom criteria were not used)]</td>
<td>Mild to very severe</td>
</tr>
<tr>
<td>Rabe, 2008</td>
<td>Exacerbations not defined</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Reid, 2008</td>
<td>Defined as a complex of lower, respiratory events/symptoms (increased or new onset), related to the underlying COPD, with a duration of 3 days or, more, requiring a change in treatment where a complex of, lower respiratory events/symptoms</td>
<td>Moderate to very severe</td>
</tr>
<tr>
<td>Study</td>
<td>Definition of Exacerbation</td>
<td>COPD Severity</td>
</tr>
<tr>
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</tr>
<tr>
<td>Rennard, 2001</td>
<td>COPD exacerbations were identified by the investigator and reported as AEs. An exacerbation was defined as symptoms that did not resolve with the use of trial medications (and any established medication) and therefore required additional medical therapy</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Rossi, 2002</td>
<td>Exacerbations not defined</td>
<td>Moderate</td>
</tr>
<tr>
<td>Schermer, 2009</td>
<td>As worsening symptoms of COPD requiring drug therapy in addition to study drug, rescue medication and doses of concomitant COPD medication. Both adverse events that had been flagged by the investigator as an exacerbation and adverse that were described as an exacerbation were included in the analysis</td>
<td>Moderate to very severe</td>
</tr>
<tr>
<td>Shaker, 2009</td>
<td>As a worsening of respiratory disease requiring a change in medication and/or hospital care, emergency room care or an unscheduled outpatient visit. Data for number of patients is as an AE.</td>
<td>Mild to very severe</td>
</tr>
<tr>
<td>Sharafkhaneh, 2012</td>
<td>Exacerbations were episodes that required medical attention. During an exacerbation, at least two of the following three criteria had to be present: (1) episode with increased (productive) coughing and/or dyspnea and/or wheezing, (2) change in sputum color, or (3) increased use of bronchodilatory drugs</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Sin, 2008</td>
<td>Exacerbations were defined as a combination of at least 2 of 3 criteria (increased dyspnea - measurement method not reported, increased sputum production and change in sputum colour)</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Stockley, 2005</td>
<td>An exacerbation was defined as the onset of at least one, clinical descriptor (worsening of dyspnoea, cough or sputum, production; appearance of purulent sputum; fever; appearance of new chest radiograph abnormality) lasting, at least 2 days and requiring a new prescription or an increase in, the dose of b2-agonists, antibiotics, corticosteroids or bronchodilators</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Tashkin, 2008</td>
<td>Worsening of COPD symptoms leading to hospitalization, a visit to the emergency room, or use of an antimicrobial agent and/or systemic corticosteroids as an outpatient</td>
<td>Moderate to very severe</td>
</tr>
<tr>
<td>Tashkin, 2009</td>
<td>An exacerbation was defined by criteria used by Anthonisen and coworkers [ref 41: Anthonisen NR,</td>
<td>Mild to very severe</td>
</tr>
<tr>
<td>Study</td>
<td>Definition of Exacerbation</td>
<td>COPD Severity</td>
</tr>
<tr>
<td>--------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Tashkin, 2012</td>
<td>Those that required treatment with oral corticosteroids and/or antibiotics or required hospitalization</td>
<td>Moderate to very severe</td>
</tr>
<tr>
<td>Van de Maele, 2010</td>
<td>Episodes (new onset or worsening of at least 2 respiratory symptoms) with a duration of 3 days or more requiring systemic steroids or antibiotics.</td>
<td>Moderate to very severe</td>
</tr>
<tr>
<td>van Den Boom, 2001</td>
<td>Exacerbations not defined</td>
<td>Moderate to very severe</td>
</tr>
<tr>
<td>van der Valk, 2002</td>
<td>A sustained worsening of the patient’s respiratory condition, from the stable state and beyond normal day-to-day variations, necessitating a change in regular medication in a patient with underlying COPD. For the purposes of the trial, we considered that a patient had experienced a new COPD exacerbation if he or she had not been receiving oral steroids and antibiotics for at least 14 days after the previous exacerbation.</td>
<td>Moderate to very severe</td>
</tr>
<tr>
<td>van Noord, 2000</td>
<td>An increase in or new onset of more than one symptom of COPD (cough, sputum, wheezing, dyspnea, or chest tightness), with at least one symptom lasting 3 days or more and leading the patient’s attending physician to initiate treatment with systemic glucocorticoids, antibiotics, or both (criterion for moderate exacerbation) or to hospitalize the patient (criterion for severe exacerbation).</td>
<td>Moderate to very severe</td>
</tr>
<tr>
<td>Vogelmeier, 2010</td>
<td>As a worsening symptoms of COPD requiring a change in drug therapy</td>
<td>Moderate to very severe</td>
</tr>
<tr>
<td>Vogelmeier, 2011</td>
<td>If a patient on two or more consecutive days used three or more extra inhalations of salbutamol per 24 hours above their reference rescue value (RRV; mean daily salbutamol use in the run-in period), this was counted as one mild exacerbation. If the patient’s condition worsened and a course of oral corticosteroids was indicated based on a clinician’s judgment standardised course of prednisolone tablets 30 mg/day for 10 days at the discretion of the physician accompanied by a 10 day course of antibiotics), the exacerbation was defined as moderate. If hospitalisation was required at the discretion of the clinician, the exacerbation was considered severe.</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Vogelmeier, 2013</td>
<td>Exacerbations not defined</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Study</td>
<td>Definition of Exacerbation</td>
<td>COPD Severity</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------------------------------------------------------------------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Vogelmeier, 2008</td>
<td>Exacerbations not defined</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Wedzicha, 2008</td>
<td>Exacerbations not defined</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Welte, 2009</td>
<td>Exacerbations not defined</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Wielders, 2013</td>
<td>Moderate exacerbations were defined as worsening symptoms of COPD (≥2 consecutive days) necessitating treatment with oral corticosteroids or antibiotics, or both; severe exacerbations were similar events that necessitated hospital admission</td>
<td>Moderate to very severe</td>
</tr>
<tr>
<td>Wouters, 2005</td>
<td>Moderate exacerbations were defined as worsening symptoms of COPD (≥2 consecutive days) necessitating treatment with oral corticosteroids or antibiotics, or both; severe exacerbations were similar events that necessitated hospital admission</td>
<td>Moderate to very severe</td>
</tr>
</tbody>
</table>
### Appendix 8: Definitions of pneumonia

<table>
<thead>
<tr>
<th>Study</th>
<th>Definition of Pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anzueto, 2009</td>
<td>Pneumonia not defined</td>
</tr>
<tr>
<td>Bateman, 2010</td>
<td>Pneumonia not defined</td>
</tr>
<tr>
<td>Bogdan, 2011</td>
<td>Pneumonia not defined</td>
</tr>
<tr>
<td>Calverley, 2010</td>
<td>Pneumonia not defined</td>
</tr>
<tr>
<td>Calverley, 2007</td>
<td>Pneumonia not defined</td>
</tr>
<tr>
<td>Chapman, 2011</td>
<td>Pneumonia not defined</td>
</tr>
<tr>
<td>D’Urzo, 2011</td>
<td>Pneumonia-like AE (includes pneumonia, bacterial pneumonia, and bronchopneumonia)</td>
</tr>
<tr>
<td>Dahl, 2013</td>
<td>Pneumonia not defined</td>
</tr>
<tr>
<td>Decramer, 2013</td>
<td>Pneumonia AE (includes bacterial pneumonia, pneumonia, lobar pneumonia, bronchopneumonia, staphylococcal pneumonia, pneumonitis)</td>
</tr>
<tr>
<td>Doherty, 2012</td>
<td>Pneumonias - AE in ≥5% confirmed by chest x-ray</td>
</tr>
<tr>
<td>Dransfield, 2013a</td>
<td>Pneumonia - AEs occurring in &gt;3%</td>
</tr>
<tr>
<td>Dransfield, 2013b</td>
<td>Pneumonia - AE (confirmed by chest X-ray)</td>
</tr>
<tr>
<td>Ferguson, 2008</td>
<td>Pneumonia - AE (includes pneumonia, pneumonia viral, pneumonia aspiration, and lobar pneumonia)</td>
</tr>
<tr>
<td>Fukuchi, 2013</td>
<td>Pneumonia not defined</td>
</tr>
<tr>
<td>Hanania, 2013</td>
<td>Pneumonia-related (total) AE (includes pneumonia, bronchopneumonia, pneumococcal pneumonia)</td>
</tr>
<tr>
<td>Johansson, 2008</td>
<td>Pneumonia not defined</td>
</tr>
<tr>
<td>Jung, 2012</td>
<td>Pneumonia - AE with an incidence &gt; 1</td>
</tr>
<tr>
<td>Kardos, 2007</td>
<td>Pneumonia not defined</td>
</tr>
<tr>
<td>Kerwin, 2013</td>
<td>Pneumonia not defined</td>
</tr>
<tr>
<td>Kerwin, 2012</td>
<td>Pneumonia not defined</td>
</tr>
<tr>
<td>Kinoshita, 2011</td>
<td>Pneumonia not defined</td>
</tr>
<tr>
<td>Martinez, 2013</td>
<td>Pneumonia-related (total) [Pneumonia, Bronchopneumonia, Lobar pneumonia, Pneumonia staphylococcal]</td>
</tr>
<tr>
<td>Powrie, 2007</td>
<td>Pneumonia - AE (confirmed by chest X-ray)</td>
</tr>
<tr>
<td>Rennard, 2009</td>
<td>Pneumonia not defined</td>
</tr>
<tr>
<td>Sharafkhaneh, 2012</td>
<td>Pneumonia not defined</td>
</tr>
<tr>
<td>Tashkin, 2012</td>
<td>Pneumonia not defined</td>
</tr>
<tr>
<td>Tashkin, 2008a</td>
<td>Pneumonia not defined</td>
</tr>
<tr>
<td>Tashkin, 2008b</td>
<td>Pneumonia not defined</td>
</tr>
<tr>
<td>Vestbo, 1999</td>
<td>Pneumonia - AE (The diagnosis of pneumonia was based on clinical judgment, with radiologic confirmation not necessarily obtained even in episodes reported as lobar or bronchopneumonia)</td>
</tr>
<tr>
<td>Vogelmeier, 2013</td>
<td>Pneumonia (radiologically confirmed)</td>
</tr>
<tr>
<td>Vogelmeier, 2011</td>
<td>Pneumonia (events reported as adverse events and those confirmed radiographically)</td>
</tr>
<tr>
<td>Wedzicha, 2008</td>
<td>Pneumonia (events reported as adverse events and those confirmed radiographically)</td>
</tr>
<tr>
<td>Welte, 2009</td>
<td>Pneumonia not defined</td>
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</tbody>
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