ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

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

Andrea C. Tricco, Lisa Strifler, Fatemeh Yazdi, Paul Khan, Carmen Ng, Jesmin Antony, Kelly Mrklas, Alistair Scott, Jennifer D'Souza, Roberta Cardoso, Sharon E. Straus.

August 20th, 2014

Disclaimer: The information in this report is a summary of available material and is designed to give readers (health systems stakeholders, policy and decision makers) a starting point in considering currently available research evidence. Other relevant scientific findings may have been reported since completion of the review. This report is current to the date of publication and may be superseded by an updated publication on the same topic. This is a preliminary report and will be modified prior to final publication including double data abstraction and assessment of risk of bias as well as inclusion of unpublished data. You should consult other sources in order to confirm the currency, accuracy and completeness of the information contained in this publication and, in the event that medical treatment is required you should take professional expert advice from a legally qualified and appropriately experienced medical practitioner.

Table of Contents

Executive Summary ... 4
Rationale ... 6
Methods ... 6
Eligibility criteria ... 6
Information sources and literature search ... 7
Study selection process ... 7
Data items and data abstraction process ... 7
Risk of bias and methodological quality appraisal process ... 8
Synthesis of included studies ... 8
Results ... 9
Literature search ... 9
Study and patient characteristics ... 9
Risk of bias ... 9
Network meta-analysis results ... 9
Primary efficacy outcome ... 9
Exacerbations for all severities of COPD ... 9
Exacerbations for moderate COPD ... 9
Exacerbations for severe COPD ... 10
Secondary safety outcomes ... 10
Pneumonia ... 10
Arrhythmia ... 11
Meta-analysis results ... 11
Primary efficacy outcome ... 11
Exacerbations for all severities of COPD ... 11
Exacerbations for moderate COPD ... 12
Secondary safety outcomes ... 12
Pneumonia ... 12
Arrhythmia ... 13
Discussion ... 13

Acknowledgements ... 16

References ... 17

Appendices ... 26

Appendix 1: Medications included in the rapid review ... 26

Appendix 2: Medications excluded in the rapid review ... 27

Appendix 3: All efficacy and safety outcomes considered ... 28

Appendix 4: Patient ratings of relevant outcomes ... 29

Appendix 5: Final MEDLINE Search ... 30

Appendix 6: List of included studies ... 37

Appendix 7: Definitions of exacerbations ... 53

Appendix 8: Definitions of pneumonia ... 61

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+formoteroal 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., number of patients with at least 1 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 = (1-[PEER*(1-OR)]) / ([1-PEER]*[PEER]*[1-OR])

For OR >1: NNH = ([PEER*(OR-1)]+1) / [PEER*(OR-1)*(1-PEER)]

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+salmaterol+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 (indaceterol+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), indaceterol (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, indaceterol+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

1. Welsh EJ, Cates CJ, Poole P. Combination inhaled steroid and long-acting beta2-agonist versus tiotropium for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2013;5:CD007891.

2. Karner C, Cates CJ. Combination inhaled steroid and long-acting beta(2)-agonist in addition to tiotropium versus tiotropium or combination alone for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2011(3):CD008532.

3. Nannini LJ, Cates CJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta-agonist in one inhaler versus long-acting beta-agonists for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2007(4):CD006829.

4. Nannini LJ, Poole P, Milan SJ, Kesterton A. Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus inhaled corticosteroids alone for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2013;8:CD006826.

5. Nannini LJ, Poole P, Milan SJ, Holmes R, Normansell R. Combined corticosteroid and long-acting beta-agonist in one inhaler versus placebo for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2013;11:CD003794.

6. Cope S, Donohue JF, Jansen JP, Kraemer M, Capkun-Niggli G, Baldwin M, et al. Comparative efficacy of long-acting bronchodilators for COPD - a network meta-analysis. Respir Res. 2013;14(1):100.

7. Karabis A, Lindner L, Mocarski M, Huisman E, Greening A. Comparative efficacy of aclidinium versus glycopyrronium and tiotropium, as maintenance treatment of moderate to severe COPD patients: a systematic review and network meta-analysis. Int J Chron Obstruct Pulmon Dis. 2013;8:405-23.

8. Puhan MA, Bachmann LM, Kleijnen J, Ter Riet G, Kessels AG. Inhaled drugs to reduce exacerbations in patients with chronic obstructive pulmonary disease: a network meta-analysis. BMC Med. 2009;7:2.

9. Mills EJ, Druyts E, Ghement I, Puhan MA. Pharmacotherapies for chronic obstructive pulmonary disease: a multiple treatment comparison meta-analysis. Clin Epidemiol. 2011;3:107-29.

10. Tricco A, Straus SE. Comparative safety and effectiveness of inhaled long-acting agents (corticosteroids, beta agonists, anticholinergics) for chronic obstructive pulmonary disease: Protocol for a systematic review and network meta-analysis. Drug Class Review on ICS/LABA for COPD [Internet]. January 6 2014. Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42013006725#.UyxBkqhdV70

11. Morrison A, Polisena J, Husereau D, Moulton K, Clark M, Fiander M, et al. The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. Int J Technol Assess Health Care. 2012;28(2):138-44.
12. Sampson M, McGowan J, Cogo E, Grimshaw J, Moher D, Lefebvre C. An evidence-based practice guideline for the peer review of electronic search strategies. J Clin Epidemiol. 2009;62(9):944-52.
13. Mills EJ, Druyts E, Ghement I, Puhan MA. Pharmacotherapies for chronic obstructive pulmonary disease: a multiple treatment comparison meta-analysis. Clin Epidemiol. 2011;3:107-29.
14. Kew KM, Li T. Long-acting inhaled therapy (beta-agonists, anticholinergics and steroids) for COPD: an overview and network meta-analysis. Cochrane Database Syst Rev. 2013(10):CD010178.
15. synthesi.sr. Toronto, Ontario: Knowledge Translation Program, Li Ka Shing Knowledge Institute, St. Michael's Hospital; 2014. Available from: http://knowledgetranslation.ca/sysrev/login.php.
16. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0: The Cochrane Collaboration; 2011 [updated March 2011]. Available from: www.cochrane-handbook.org.
17. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
18. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-34.
19. Raudenbush SW. Analyzing effect sizes: Random effects models. In: H. Cooper LVH, & J. C. Valentine, editor. The handbook of research synthesis and meta-analysis. 2nd ed. New York: Russell Sage Foundation; 2009. p. 295–315.
20. GOLD report. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease 2013. Available from: http://wwwgoldcopdorg/uploads/users/files/GOLD_Report_2013_Feb20pdf.
21. Aaron SD, Fergusson D, Marks GB, Suissa S, Vandemheen KL, Doucette S, et al. Counting, analysing and reporting exacerbations of COPD in randomised controlled trials. Thorax. 2008;63(2):122-8.
22. The R project for statistical computing. Available from: http://www.r-project.org/.
23. Jackson D, Barrett JK, Stephen R, White IR, Higgins JPT. A design-by-treatment interaction model for network meta-analysis with random inconsistency effects. Stat Med. 2013(in press).

24. Veroniki AA, Vasiliadis HS, Higgins JP, Salanti G. Evaluation of inconsistency in networks of interventions. International Journal of Epidemiology. 2013;42(1):332-45.

25. Song F, Altman DG, Glenny AM, Deeks JJ. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. BMJ. 2003;326(7387):472.

26. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. Stat Med. 2010;29(7-8):932-44.

27. Higgins JPT, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. Res Synth Methods. 2012;3(2):98-110.

28. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol. 2011;64(2):163-71.

29. White IR. Multivariate random-effects meta-regression: Updates to mvmeta. Stata Journal. 2011;11(2):255-70.

30. Kew KM, Dias S, Cates CJ. Long-acting inhaled therapy (beta-agonists, anticholinergics and steroids) for COPD: a network meta-analysis. Cochrane Database Syst Rev. 2014(3):CD010844.

31. Kew KM, Seniukovich A. Inhaled steroids and risk of pneumonia for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2014(3):CD010115.

Figure 1: Study flow

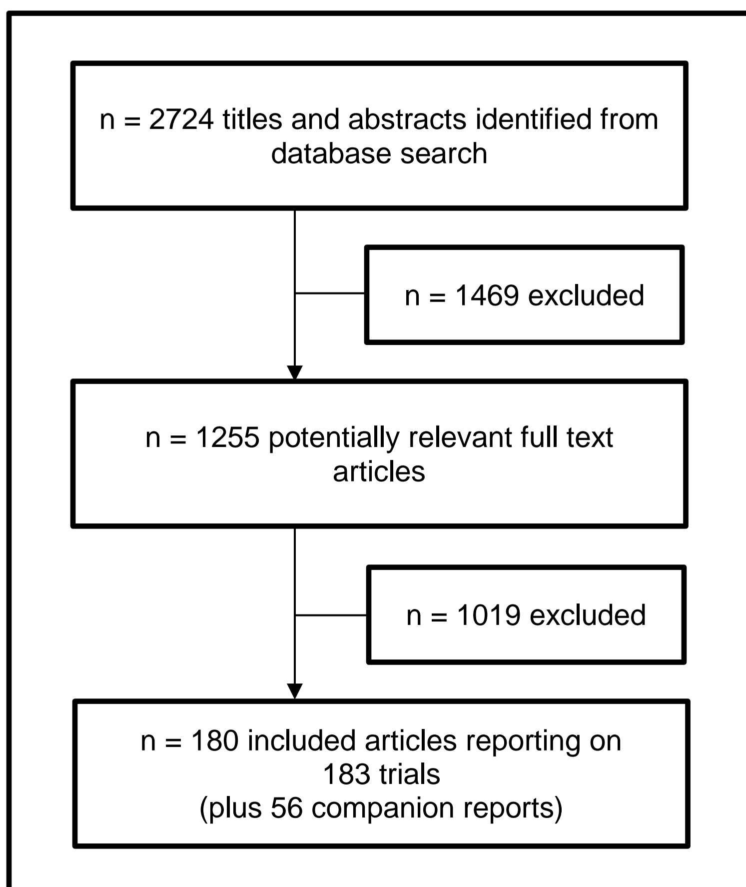

Figure 2: Risk of bias

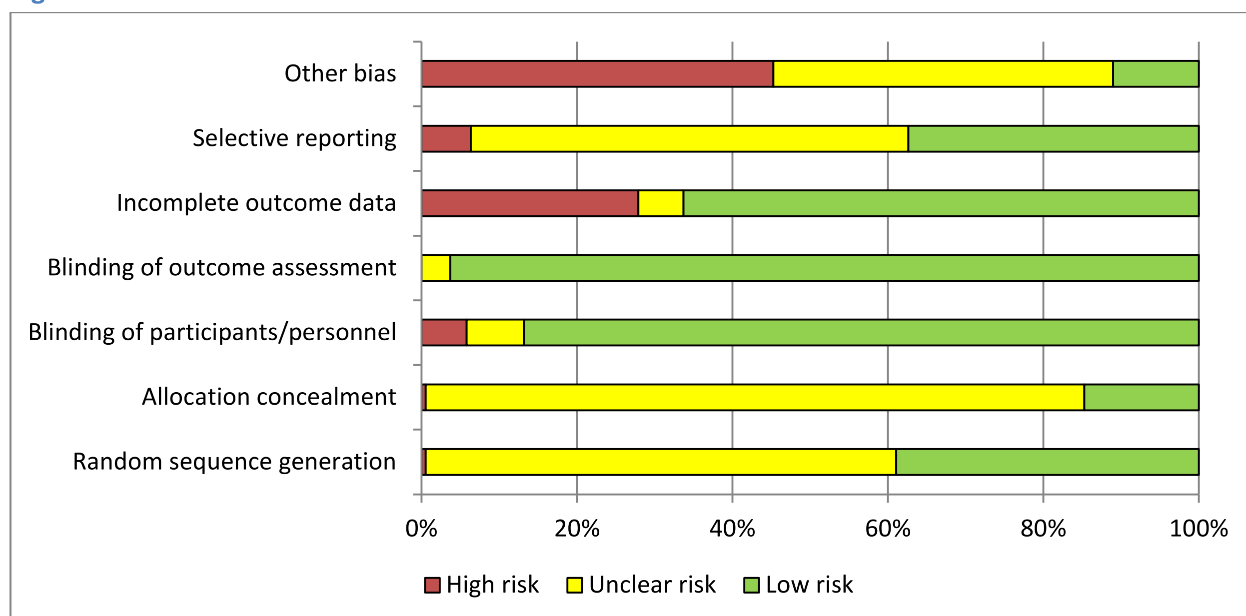

Table 1. Results of Network Meta-analysis for risk of exacerbation with moderate COPD

Intervention	Comparison	NNT
ICS+LABA vs. placebo		
Budesonide + formoterol	Placebo	6
Fluticasone + salmeterol	Placebo	17
Mometasone + formoterol	Placebo	7
ICS+LABA vs. ICS+LABA		
Mometasone+ formoterol	Fluticasone + salmeterol	10
Budesonide + formoterol	Fluticasone + salmeterol	8
ICS+LABA vs. ICS alone or LABA alone		
Budesonide + formoterol	Budesonide	6
Mometasone + formoterol	Budesonide	6
Budesonide + formoterol	Indacaterol	7
Mometasone + formoterol	Indacaterol	7
Budesonide + formoterol	Salmeterol	8
Mometasone + formoterol	Salmeterol	8
Budesonide + formoterol	Vilanterol	7
Fluticasone + vilanterol	Vilanterol	16
Mometasone + formoterol	Vilanterol	8

Table 2. Results of Network Meta-analysis for pneumonia

Intervention	Comparison	NNH
ICS+LABA vs. placebo		
Fluticasone + vilanterol	Placebo	10
Fluticasone + salmeterol	Placebo	16
ICS+LABA vs. ICS+LABA		
Fluticasone + salmeterol	Budesonide + formoterol	19
ICS+LABA vs. ICS alone or LABA alone		
Fluticasone + vilanterol	Budesonide	9
Fluticasone + salmeterol	Budesonide	13
Fluticasone + vilanterol	Formoterol	7
Fluticasone + salmeterol	Formoterol	10
Fluticasone + vilanterol	Vilanterol	17
Fluticasone + salmeterol	Indacaterol	15
Fluticasone + salmeterol	Salmeterol	19

Table 3. Results of Meta-analysis for risk of exacerbation with all severities of COPD

Intervention	Comparison	NNT
ICS+LABA vs. placebo		
Fluticasone + Salmeterol	Placebo	5
Mometasone + Formoterol	Placebo	8
Fluticasone + Vilanterol	Placebo	--
ICS+LABA vs. ICS+LABA		
Budesonide + Formoterol	Beclomethasone + formoterol	--
ICS+LABA vs. ICS alone or LABA alone		
Budesonide + Formoterol	Formoterol	20
Mometasone + Formoterol	Formoterol	12
Beclomethasone + Formoterol	Formoterol	--
Fluticasone + Salmeterol	Salmeterol	20
Fluticasone + Vilanterol	Vilanterol	16
Mometasone + Formoterol	Mometasone	--
Fluticasone + Vilanterol	Fluticasone	--
Fluticasone + Salmeterol	Fluticasone	--

* Statistically significant

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

Intervention	Comparison	NNT
ICS+LABA vs. placebo		
Fluticasone + Salmeterol	Placebo	6
Mometasone + formoterol	Placebo	9
Fluticasone + Vilanterol	Placebo	--
ICS+LABA vs. ICS alone or LABA alone		
Fluticasone + Vilanterol	Fluticasone	--
Fluticasone + Salmeterol	Fluticasone	--
Budesonide + Formoterol	Formoterol	19
Mometasone + formoterol	Formoterol	12
Fluticasone + Vilanterol	Vilanterol	18
Fluticasone + Salmeterol	Salmeterol	--
Mometasone + formoterol	Mometasone	--

* Statistically significant

Appendices

Appendix 1: Medications included in the rapid review

Generic name(s)*	Trade name(s)*
Inhaled long-acting beta$_2$-agonists (LABA)	
formoterol or eformoterol	Foradil, Oxeze, Oxis
Indacaterol	Arcapta
Salmeterol	Serevent, SereventDiskus
olodaterol	Striverdi
vilanterol or GW642444	
Inhaled long-acting muscarinic anticholinergics (LAMA)	
aclidinium bromide	TudorzaGenuair
glycopyrronium bromide	SeebriBreezhaler
tiotropium bromide	Spiriva
umeclidinium bromide or GSK573719	
Inhaled corticosteroids (ICS)	
beclomethasone	QVAR, Clenil
budesonide	Pulmicort
fluticasone or GW685698	Flovent, FloventDiskus, Flixotide
mometasone	
Combo LABA plus ICS in one inhaler**	
formoterol/budesonide	Symbicort
formoterol/mometasone	Zenhale
salmeterol/fluticasone	Advair, AdvairDiskus, Seretide
vilanterol/fluticasone	BreoEllipta
Combo LAMA plus ICS in one inhaler**	
Combo LAMA plus LABA in one inhaler**	
vilanterol/umeclidinium	AnoroEllipta
indacaterol/glycopyrronium	QVA149, Ultibro
Combo LAMA plus LABA in one inhaler (MABA)	
GSK961081 (formerly TD5959)	

*Note: *This is not an exhausitve list. **Combination therapy could also be given in multiple inhalers.*

Appendix 2: Medications excluded in the rapid review

Generic name(s)*	Trade name(s)*
We will exclude the following formulations:	
Long-acting $beta_2$-agonists (LABA) in nebulizer and transdermal form	
formoterol (when in nebulizer form)	
arformoterol	
tulobuterol	
Inhaled corticosteroids (ICS) in nebulizer form	
beclomethasone (when in nebulizer form)	
budesonide (when in nebulizer form)	
We will exclude ALL of the following agents:	
Short-acting beta2-agonists (SABA) (inhaled, nebulizer, oral, injection)	
fenoterol	
levosalbutamol or levalbuterol	Xopenex
salbutamol or albuterol	Ventolin
terbutaline	Bricanyl
Short-acting muscarinic anticholinergics (SAMA) (inhaler, nebulizer)	
ipratropium bromide	Combivent, Atrovent
oxitropium bromide	
Combo SABA plus anticholinergic in one inhaler (inhaler, nebulizer)	
fenoterol/ipratropium	
salbutamol/ipratropium	
Methylxanthines (oral, injection)	
aminophylline	
theophylline	
Systemic corticosteroids (oral)	
prednisone	
methyl-prednisolone	
Phosphodiesterase-4 (PDE4) inhibitors (oral)	
roflumilast	

*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-2I4BC502BT).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.

26 ((longacting or long-acting or ultra-longacting 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.
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 ultralong-acting) and bronchodilator*).tw.
29 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) 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 ultralong-acting).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 Spirocort or Uceris or UNII-Q3OKS62Q6X).tw.
48 51333-22-3.rn.
49 Fluticasone.tw,rn.
50 (Cutivate or Flixonase or Flixotide or Flonase or Flovent or Fluticason* 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.

57 or/51-56
58 57 and 37
59 or/40-50,58
60 (Fluticasone adj3 salmeterol).tw,rn.
61 (Adoair or Advair or Foxair or "Quikhale SF" or Seretide or Viani).tw.
62 (formoterol adj3 mometasone).tw,rn.
63 (Zenhale or Dulera).tw.
64 (formoterol adj3 budesonide).tw,rn.
65 (Rilast or Symbicord or Symbicort or Vannair).tw.
66 (vilanterol adj3 fluticasone).tw,rn.
67 Breo Ellipta.tw.
68 or/60-67
69 tiotropium.tw,rn.
70 (BA 679 BR or BA 679BR or Spiriva or tiotropium or UNII-0EB439235F or UNII-XX112XZP0J).tw.
71 aclidiniumbromide.tw,rn.
72 (LAS 34273 or LAS W-330 or BretarisGenuair or EkliraGenuair or TudorzaPressair or UNII-UQW7UF9N91).tw.
73 glycoyrroniumbromide.tw,rn.
74 (erythro-glycopyrronium bromide or UNII-9SFK0PX55W).tw.
75 ((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.
76 (LAMA or LAMAs or Ultra-LAMA* or UltraLAMA*).tw.
77 Muscarinic Antagonists/ or Cholinergic Antagonists/
78 77 and 31
79 75 or 76 or 78
80 79 and 37
81 or/69-74,80
82 39 or 59 or 68 or 81
83 7 and 82
84 randomized controlled trial.pt.
85 controlled clinical trial.pt.
86 randomized.ab.
87 placebo.ab.
88 clinical trials as topic/
89 randomly.ab.
90 trial.ti.
91 or/84-90
92 83 and 91
93 exp Animals/ not (exp Animals/ and Humans/)
94 92 not 93

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 flow*)).tw.
103 (COPD or COAD).tw.
104 (chronic adj2 bronchitis).tw.
105 emphysema*.tw.
106 or/100-105
107 formoterol/ or formoterolfumarate/
108 (BD 40A or HSDB 7287 or Oxis or UNII-5ZZ84GCW8B).tw.
109 (eformoterol or Foradil or formoterol).tw.
110 (73573-87-2 or 183814-30-4).rn.
111 indacaterol/
112 (Arcapta or Onbrez or indacaterol or QAB 149 or QAB149 or UNII-8OR09251MQ).tw.
113 312753-06-3.rn.
114 salmeterol/
115 (Aeromax or Astmerole or "GR 33343 X" or "GR 33343X" or HSDB 7315 or Salmeterol or SN408D or UNII-2I4BC502BT).tw.
116 89365-50-4.rn.
117 salmeterolxinafoate/
118 (Arial or Asmerole or Beglan or Betamican or Dilamax or Inaspir or Salmetedur or Salmeterolxinafoate or Serevent or Ultrabeta or UNII-6EW8Q962A5).tw.
119 94749-08-3.rn.
120 ((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.
121 ((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.
122 ((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.
123 ((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.

124 ((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.
125 ((longacting or long-acting or ultra-longacting 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.
126 (LABA or LABAs or Ultra-LABA* or UltraLABA*).tw.
127 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and bronchodilator*).tw.
128 ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (betamimetic* or beta-mimetic*)).tw.
129 exp beta adrenergic receptor stimulating agent/ or brochodilating agent/
130 (longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting).tw.
131 129 and 130
132 or/120-128,131
133 inhalational drug administration/
134 aerosol/
135 (inhal* or aerosol*).tw.
136 or/133-135
137 132 and 136
138 or/107-119,137
139 beclometasone/
140 (Aerobec or AeroBec Forte or Aldecin or Apo-Beclomethasone or Ascocortonyl or AsmabecClickhaler).tw.
141 (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.
142 (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.
143 (BMJ 5800 or EINECS 224-585-9 or UNII-KGZ1SLC28Z).tw.
144 4419-39-0.rn.
145 budesonide/
146 (Budesonide or Micronyl or Preferid or Pulmicort or Respules or Rhinocort or "S 1320" or Spirocort or Uceris or UNII-Q3OKS62Q6X).tw.
147 51333-22-3.rn.
148 fluticasone/ or fluticasone propionate/
149 (Cutivate or Flixonase or Flixotide or Flonase or Flovent or Fluticason* or HSDB 7740 or UNII-CUT2W21N7U).tw.
150 (90566-53-3 or 80474-14-2).rn.
151 glucocorticoid/
152 glucocorticoid*.tw.

153 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

1. Aalbers R, Ayres J, Backer V, Decramer M, Lier PA, Magyar P, et al. Formoterol in patients with chronic obstructive pulmonary disease: a randomized, controlled, 3-month trial. Eur Respir J. 2002;19(5):936-43.

2. Aaron SD, Vandemheen KL, Fergusson D, Maltais F, Bourbeau J, Goldstein R, et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med. 2007;146(8):545-55.

3. Abrahams R, Moroni-Zentgraf P, Ramsdell J, Schmidt H, Joseph E, Karpel J. Safety and efficacy of the once-daily anticholinergic BEA2180 compared with tiotropium in patients with COPD. Respir Med. 2013;107(6):854-62.

4. Ambrosino N, Foglio K, Balzano G, Paggiaro PL, Lessi P, Kesten S, et al. Tiotropium and exercise training in COPD patients: effects on dyspnea and exercise tolerance. Int J Chron Obstruct Pulmon Dis. 2008;3(4):771-80.

5. Anzueto A, Ferguson GT, Feldman G, Chinsky K, Seibert A, Emmett A, et al. Effect of fluticasone propionate/salmeterol (250/50) on COPD exacerbations and impact on patient outcomes. COPD. 2009;6(5):320-9.

6. Auffarth B, Postma DS, de Monchy JG, van der Mark TW, Boorsma M, Koeter GH. Effects of inhaled budesonide on spirometric values, reversibility, airway responsiveness, and cough threshold in smokers with chronic obstructive lung disease. Thorax. 1991;46(5):372-7.

7. Barnes NC, Qiu YS, Pavord ID, Parker D, Davis PA, Zhu J, et al. Antiinflammatory effects of salmeterol/fluticasone propionate in chronic obstructive lung disease. Am J Respir Crit Care Med. 2006;173(7):736-43.

8. Bateman E, Feldman G, Kilbride S, Brooks J, Mehta R, Harris S, et al. Efficacy and safety of the long-acting muscarinic antagonist GSK233705 delivered once daily in patients with COPD. Clin Respir J. 2012;6(4):248-57.

9. Bateman ED, Tashkin D, Siafakas N, Dahl R, Towse L, Massey D, et al. A one-year trial of tiotropium Respimat plus usual therapy in COPD patients. Respir Med. 2010;104(10):1460-72.

10. Bateman ED, van Dyk M, Sagriotis A. Comparable spirometric efficacy of tiotropium compared with salmeterol plus fluticasone in patients with COPD: a pilot study. Pulm Pharmacol Ther. 2008;21(1):20-5.

11. Baumgartner RA, Hanania NA, Calhoun WJ, Sahn SA, Sciarappa K, Hanrahan JP. Nebulized arformoterol in patients with COPD: a 12-week, multicenter, randomized, double-blind, double-dummy, placebo- and active-controlled trial. Clin Ther. 2007;29(2):261-78.

12. Bedard ME, Brouillard C, Pepin V, Provencher S, Milot J, Lacasse Y, et al. Tiotropium improves walking endurance in COPD. Eur Respir J. 2012;39(2):265-71.

13. Beier J, Chanez P, Martinot JB, Schreurs AJ, Tkacova R, Bao W, et al. Safety, tolerability and efficacy of indacaterol, a novel once-daily beta(2)-agonist, in patients with COPD: a 28-day randomised, placebo controlled clinical trial. Pulm Pharmacol Ther. 2007;20(6):740-9.

14. Beier J, Kirsten AM, Mroz R, Segarra R, Chuecos F, Caracta C, et al. Efficacy and safety of aclidinium bromide compared with placebo and tiotropium in patients with moderate-to-severe chronic obstructive pulmonary disease: results from a 6-week, randomized, controlled Phase IIIb study. COPD. 2013;10(4):511-22.

15. Bogdan MA, Aizawa H, Fukuchi Y, Mishima M, Nishimura M, Ichinose M. Efficacy and safety of inhaled formoterol 4.5 and 9 mug twice daily in Japanese and European COPD patients: phase III study results. BMC Pulm Med. 2011;11:51.

16. Bolukbas S, Eberlein M, Eckhoff J, Schirren J. Short-term effects of inhalative tiotropium/formoterol/budenoside versus tiotropium/formoterol in patients with newly diagnosed chronic obstructive pulmonary disease requiring surgery for lung cancer: a prospective randomized trial. Eur J Cardiothorac Surg. 2011;39(6):995-1000.

17. Bourbeau J, Christodoulopoulos P, Maltais F, Yamauchi Y, Olivenstein R, Hamid Q. Effect of salmeterol/fluticasone propionate on airway inflammation in COPD: a randomised controlled trial. Thorax. 2007;62(11):938-43.

18. Bourbeau J, Rouleau MY, Boucher S. Randomised controlled trial of inhaled corticosteroids in patients with chronic obstructive pulmonary disease. Thorax. 1998;53(6):477-82.

19. Boyd G, Morice AH, Pounsford JC, Siebert M, Peslis N, Crawford C. An evaluation of salmeterol in the treatment of chronic obstructive pulmonary disease (COPD). Eur Respir J. 1997;10(4):815-21.

20. Briggs DD, Jr., Covelli H, Lapidus R, Bhattycharya S, Kesten S, Cassino C. Improved daytime spirometric efficacy of tiotropium compared with salmeterol in patients with COPD. Pulm Pharmacol Ther. 2005;18(6):397-404.

21. Buhl R, Dunn LJ, Disdier C, Lassen C, Amos C, Henley M, et al. Blinded 12-week comparison of once-daily indacaterol and tiotropium in COPD. Eur Respir J. 2011;38(4):797-803.

22. Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ. 2000;320(7245):1297-303.

23. Caillaud D, Le Merre C, Martinat Y, Aguilaniu B, Pavia D. A dose-ranging study of tiotropium delivered via Respimat Soft Mist Inhaler or HandiHaler in COPD patients. Int J Chron Obstruct Pulmon Dis. 2007;2(4):559-65.

24. Calverley P, Pauwels R, Vestbo J, Jones P, Pride N, Gulsvik A, et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. Lancet. 2003;361(9356):449-56.

25. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med. 2007;356(8):775-89.

26. Calverley PM, Boonsawat W, Cseke Z, Zhong N, Peterson S, Olsson H. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. Eur Respir J. 2003;22(6):912-9.

27. Calverley PM, Kuna P, Monso E, Costantini M, Petruzzelli S, Sergio F, et al. Beclomethasone/formoterol in the management of COPD: a randomised controlled trial. Respir Med. 2010;104(12):1858-68.

28. Calverley PM, Lee A, Towse L, van Noord J, Witek TJ, Kelsen S. Effect of tiotropium bromide on circadian variation in airflow limitation in chronic obstructive pulmonary disease. Thorax. 2003;58(10):855-60.

29. Calverley PM, Rennard S, Nelson HS, Karpel JP, Abbate EH, Stryszak P, et al. One-year treatment with mometasone furoate in chronic obstructive pulmonary disease. Respir Res. 2008;9:73.

30. Campbell SC, Criner GJ, Levine BE, Simon SJ, Smith JS, Orevillo CJ, et al. Cardiac safety of formoterol 12 microg twice daily in patients with chronic obstructive pulmonary disease. Pulm Pharmacol Ther. 2007;20(5):571-9.

31. Casaburi R, Kukafka D, Cooper CB, Witek TJ, Jr., Kesten S. Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with COPD. Chest. 2005;127(3):809-17.

32. Casaburi R, Mahler DA, Jones PW, Wanner A, San PG, ZuWallack RL, et al. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. Eur Respir J. 2002;19(2):217-24.

33. Cazzola M, Ando F, Santus P, Ruggeri P, Di Marco F, Sanduzzi A, et al. A pilot study to assess the effects of combining fluticasone propionate/salmeterol and tiotropium on the airflow obstruction of patients with severe-to-very severe COPD. Pulm Pharmacol Ther. 2007;20(5):556-61.

34. Cazzola M, Di Lorenzo G, Di Perna F, Calderaro F, Testi R, Centanni S. Additive effects of salmeterol and fluticasone or theophylline in COPD. Chest. 2000;118(6):1576-81.

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

study using the Breathlessness, Cough and Sputum Scale (BCSS). Respir Med. 2003;97 Suppl A:S35-43.

36. Celli B, ZuWallack R, Wang S, Kesten S. Improvement in resting inspiratory capacity and hyperinflation with tiotropium in COPD patients with increased static lung volumes. Chest. 2003;124(5):1743-8.

37. Chan CK, Maltais F, Sigouin C, Haddon JM, Ford GT, Group SS. A randomized controlled trial to assess the efficacy of tiotropium in Canadian patients with chronic obstructive pulmonary disease. Can Respir J. 2007;14(8):465-72.

38. Chanez P, Burge PS, Dahl R, Creemers J, Chuchalin A, Lamarca R, et al. Aclidinium bromide provides long-acting bronchodilation in patients with COPD. Pulm Pharmacol Ther. 2010;23(1):15-21.

39. Chapman KR, Arvidsson P, Chuchalin AG, Dhillon DP, Faurschou P, Goldstein RS, et al. The addition of salmeterol 50 microg bid to anticholinergic treatment in patients with COPD: a randomized, placebo controlled trial. Chronic obstructive pulmonary disease. Can Respir J. 2002;9(3):178-85.

40. Chapman KR, Rennard SI, Dogra A, Owen R, Lassen C, Kramer B, et al. Long-term safety and efficacy of indacaterol, a long-acting beta(2)-agonist, in subjects with COPD: a randomized, placebo-controlled study. Chest. 2011;140(1):68-75.

41. Choudhury AB, Dawson CM, Kilvington HE, Eldridge S, James WY, Wedzicha JA, et al. Withdrawal of inhaled corticosteroids in people with COPD in primary care: a randomised controlled trial. Respir Res. 2007;8:93.

42. Cooper CB, Celli BR, Jardim JR, Wise RA, Legg D, Guo J, et al. Treadmill endurance during 2-year treatment with tiotropium in patients with COPD: a randomized trial. Chest. 2013;144(2):490-7.

43. Cote C, Pearle JL, Sharafkhaneh A, Spangenthal S. Faster onset of action of formoterol versus salmeterol in patients with chronic obstructive pulmonary disease: a multicenter, randomized study. Pulm Pharmacol Ther. 2009;22(1):44-9.

44. Covelli H, Bhattacharya S, Cassino C, Conoscenti C, Kesten S. Absence of electrocardiographic findings and improved function with once-daily tiotropium in patients with chronic obstructive pulmonary disease. Pharmacotherapy. 2005;25(12):1708-18.

45. Criner GJ, Sharafkhaneh A, Player R, Conoscenti CS, Johnson P, Keyser MT, et al. Efficacy of tiotropium inhalation powder in african-american patients with chronic obstructive pulmonary disease. COPD. 2008;5(1):35-41.

46. Dahl R, Chapman KR, Rudolf M, Mehta R, Kho P, Alagappan VK, et al. Safety and efficacy of dual bronchodilation with QVA149 in COPD patients: the ENLIGHTEN study. Respir Med. 2013;107(10):1558-67.

47. Dahl R, Chung KF, Buhl R, Magnussen H, Nonikov V, Jack D, et al. Efficacy of a new once-daily long-acting inhaled beta2-agonist indacaterol versus twice-daily formoterol in COPD. Thorax. 2010;65(6):473-9.

48. Dahl R, Greefhorst LA, Nowak D, Nonikov V, Byrne AM, Thomson MH, et al. Inhaled formoterol dry powder versus ipratropium bromide in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001;164(5):778-84.

49. Dahl R, Jadayel D, Alagappan VK, Chen H, Banerji D. Efficacy and safety of QVA149 compared to the concurrent administration of its monocomponents indacaterol and glycopyrronium: the BEACON study. Int J Chron Obstruct Pulmon Dis. 2013;8:501-8.

50. Dal Negro RW, Pomari C, Tognella S, Micheletto C. Salmeterol & fluticasone 50 microg/250 microg bid in combination provides a better long-term control than salmeterol 50 microg bid alone and placebo in COPD patients already treated with theophylline. Pulm Pharmacol Ther. 2003;16(4):241-6.

51. Decramer ML, Chapman KR, Dahl R, Frith P, Devouassoux G, Fritscher C, et al. Once-daily indacaterol versus tiotropium for patients with severe chronic obstructive pulmonary disease (INVIGORATE): a randomised, blinded, parallel-group study. Lancet Respir Med. 2013;1(7):524-33.

52. Doherty DE, Tashkin DP, Kerwin E, Knorr BA, Shekar T, Banerjee S, et al. Effects of mometasone furoate/formoterol fumarate fixed-dose combination formulation on chronic obstructive pulmonary disease (COPD): results from a 52-week Phase III trial in subjects with moderate-to-very severe COPD. Int J Chron Obstruct Pulmon Dis. 2012;7:57-71.

53. Donohue JF, Maleki-Yazdi MR, Kilbride S, Mehta R, Kalberg C, Church A. Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD. Respir Med. 2013;107(10):1538-46.

54. Donohue JF, van Noord JA, Bateman ED, Langley SJ, Lee A, Witek TJ, Jr., et al. A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. Chest. 2002;122(1):47-55.

55. Dransfield MT, Bourbeau J, Jones PW, Hanania NA, Mahler DA, Vestbo J, et al. Once-daily inhaled fluticasone furoate and vilanterol versus vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomised controlled trials. Lancet Respir Med. 2013;1(3):210-23.

56. Dransfield MT, Cockcroft JR, Townsend RR, Coxson HO, Sharma SS, Rubin DB, et al. Effect of fluticasone propionate/salmeterol on arterial stiffness in patients with COPD. Respir Med. 2011;105(9):1322-30.

57. D'Urzo A, Ferguson GT, van Noord JA, Hirata K, Martin C, Horton R, et al. Efficacy and safety of once-daily NVA237 in patients with moderate-to-severe COPD: the GLOW1 trial. Respir Res. 2011;12:156.

58. Dusser D, Bravo ML, Iacono P. The effect of tiotropium on exacerbations and airflow in patients with COPD. Eur Respir J. 2006;27(3):547-55.

59. Engel T, Heinig JH, Madsen O, Hansen M, Weeke ER. A trial of inhaled budesonide on airway responsiveness in smokers with chronic bronchitis. Eur Respir J. 1989;2(10):935-9.

60. Feldman G, Siler T, Prasad N, Jack D, Piggott S, Owen R, et al. Efficacy and safety of indacaterol 150 microg once-daily in COPD: a double-blind, randomised, 12-week study. BMC Pulm Med. 2010;10:11.

61. Feldman G, Walker RR, Brooks J, Mehta R, Crater G. 28-Day safety and tolerability of umeclidinium in combination with vilanterol in COPD: a randomized placebo-controlled trial. Pulm Pharmacol Ther. 2012;25(6):465-71.

62. Ferguson GT, Anzueto A, Fei R, Emmett A, Knobil K, Kalberg C. Effect of fluticasone propionate/salmeterol (250/50 microg) or salmeterol (50 microg) on COPD exacerbations. Respir Med. 2008;102(8):1099-108.

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.

64. Fukuchi Y, Samoro R, Fassakhov R, Taniguchi H, Ekelund J, Carlsson LG, et al. Budesonide/formoterol via Turbuhaler(R) versus formoterol via Turbuhaler(R) in patients with moderate to severe chronic obstructive pulmonary disease: phase III multinational study results. Respirology. 2013;18(5):866-73.

65. Gizycki MJ, Hattotuwa KL, Barnes N, Jeffery PK. Effects of fluticasone propionate on inflammatory cells in COPD: an ultrastructural examination of endobronchial biopsy tissue. Thorax. 2002;57(9):799-803.

66. Gupta RK, Chhabra SK. An evaluation of salmeterol in the treatment of chronic obstructive pulmonary diseases. Indian J Chest Dis Allied Sci. 2002;44(3):165-72.

67. Hagedorn C, Kassner F, Banik N, Ntampakas P, Fielder K. Influence of salmeterol/fluticasone via single versus separate inhalers on exacerbations in severe/very severe COPD. Respir Med. 2013;107(4):542-9.

68. Hanania NA, Crater GD, Morris AN, Emmett AH, O'Dell DM, Niewoehner DE. Benefits of adding fluticasone propionate/salmeterol to tiotropium in moderate to severe COPD. Respir Med. 2012;106(1):91-101.

69. Hanania NA, Darken P, Horstman D, Reisner C, Lee B, Davis S, et al. The efficacy and safety of fluticasone propionate (250 microg)/salmeterol (50 microg) combined in the Diskus inhaler for the treatment of COPD. Chest. 2003;124(3):834-43.

70. Hanania NA, Feldman G, Zachgo W, Shim JJ, Crim C, Sanford L, et al. The efficacy and safety of the novel long-acting beta2 agonist vilanterol in patients with COPD: a randomized placebo-controlled trial. Chest. 2012;142(1):119-27.

71. Hasani A, Toms N, Agnew JE, Sarno M, Harrison AJ, Dilworth P. The effect of inhaled tiotropium bromide on lung mucociliary clearance in patients with COPD. Chest. 2004;125(5):1726-34.

72. Hattotuwa KL, Gizycki MJ, Ansari TW, Jeffery PK, Barnes NC. The effects of inhaled fluticasone on airway inflammation in chronic obstructive pulmonary disease: a double-blind, placebo-controlled biopsy study. Am J Respir Crit Care Med. 2002;165(12):1592-6.

73. Hoshino M, Ohtawa J. Effects of adding salmeterol/fluticasone propionate to tiotropium on airway dimensions in patients with chronic obstructive pulmonary disease. Respirology. 2011;16(1):95-101.

74. Hoshino M, Ohtawa J. Effects of tiotropium and salmeterol/fluticasone propionate on airway wall thickness in chronic obstructive pulmonary disease. Respiration. 2013;86(4):280-7.

75. Johansson G, Lindberg A, Romberg K, Nordstrom L, Gerken F, Roquet A. Bronchodilator efficacy of tiotropium in patients with mild to moderate COPD. Prim Care Respir J. 2008;17(3):169-75.

76. Jones PW, Bosh TK. Quality of life changes in COPD patients treated with salmeterol. Am J Respir Crit Care Med. 1997;155(4):1283-9.

77. Jones PW, Singh D, Bateman ED, Agusti A, Lamarca R, de Miquel G, et al. Efficacy and safety of twice-daily aclidinium bromide in COPD patients: the ATTAIN study. Eur Respir J. 2012;40(4):830-6.

78. Jung KS, Park HY, Park SY, Kim SK, Kim YK, Shim JJ, et al. Comparison of tiotropium plus fluticasone propionate/salmeterol with tiotropium in COPD: a randomized controlled study. Respir Med. 2012;106(3):382-9.

79. Kardos P, Wencker M, Glaab T, Vogelmeier C. Impact of salmeterol/fluticasone propionate versus salmeterol on exacerbations in severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2007;175(2):144-9.

80. Kaushik ML, Kashyap S, Bansal SK, Sharma A. Effectiveness of salmeterol in stable COPD. Indian J Chest Dis Allied Sci. 1999;41(4):207-12.

81. Kerwin E, Hebert J, Gallagher N, Martin C, Overend T, Alagappan VK, et al. Efficacy and safety of NVA237 versus placebo and tiotropium in patients with COPD: the GLOW2 study. Eur Respir J. 2012;40(5):1106-14.

82. Kerwin EM, D'Urzo AD, Gelb AF, Lakkis H, Garcia Gil E, Caracta CF, et al. Efficacy and safety of a 12-week treatment with twice-daily aclidinium bromide in COPD patients (ACCORD COPD I). COPD. 2012;9(2):90-101.

83. Kerwin EM, Gotfried MH, Lawrence D, Lassen C, Kramer B. Efficacy and tolerability of indacaterol 75 mug once daily in patients aged >/=40 years with chronic obstructive pulmonary disease: results from 2 double-blind, placebo-controlled 12-week studies. Clin Ther. 2011;33(12):1974-84.

84. Kerwin EM, Scott-Wilson C, Sanford L, Rennard S, Agusti A, Barnes N, et al. A randomised trial of fluticasone furoate/vilanterol (50/25 mug; 100/25 mug) on lung function in COPD. Respir Med. 2013;107(4):560-9.

85. Kinoshita M, Lee SH, Hang LW, Ichinose M, Hosoe M, Okino N, et al. Efficacy and safety of indacaterol 150 and 300 microg in chronic obstructive pulmonary disease patients from six Asian areas including Japan: a 12-week, placebo-controlled study. Respirology. 2012;17(2):379-89.

86. Korn S, Kerwin E, Atis S, Amos C, Owen R, Lassen C, et al. Indacaterol once-daily provides superior efficacy to salmeterol twice-daily in COPD: a 12-week study. Respir Med. 2011;105(5):719-26.

87. Kornmann O, Dahl R, Centanni S, Dogra A, Owen R, Lassen C, et al. Once-daily indacaterol versus twice-daily salmeterol for COPD: a placebo-controlled comparison. Eur Respir J. 2011;37(2):273-9.

88. Koser A, Westerman J, Sharma S, Emmett A, Crater GD. Safety and efficacy of fluticasone propionate/salmeterol hydrofluoroalkane 134a metered-dose-inhaler compared with fluticasone propionate/salmeterol diskus in patients with chronic obstructive pulmonary disease. Open Respir Med J. 2010;4:86-91.

89. Kuna P, Ivanov Y, Trofimov VI, Saito T, Beckman O, Bengtsson T, et al. Efficacy and safety of AZD3199 vs formoterol in COPD: a randomized, double-blind study. Respir Res. 2013;14:64.

90. Lapperre TS, Snoeck-Stroband JB, Gosman MM, Jansen DF, van Schadewijk A, Thiadens HA, et al. Effect of fluticasone with and without salmeterol on pulmonary outcomes in chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med. 2009;151(8):517-27.

91. Littner MR, Ilowite JS, Tashkin DP, Friedman M, Serby CW, Menjoge SS, et al. Long-acting bronchodilation with once-daily dosing of tiotropium (Spiriva) in stable chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2000;161(4 Pt 1):1136-42.

92. Llewellyn-Jones CG, Harris TA, Stockley RA. Effect of fluticasone propionate on sputum of patients with chronic bronchitis and emphysema. Am J Respir Crit Care Med. 1996;153(2):616-21.

93. Lomas DA, Lipson DA, Miller BE, Willits L, Keene O, Barnacle H, et al. An oral inhibitor of p38 MAP kinase reduces plasma fibrinogen in patients with chronic obstructive pulmonary disease. J Clin Pharmacol. 2012;52(3):416-24.

94. Lotvall J, Bakke PS, Bjermer L, Steinshamn S, Scott-Wilson C, Crim C, et al. Efficacy and safety of 4 weeks' treatment with combined fluticasone furoate/vilanterol in a single inhaler given once daily in COPD: a placebo-controlled randomised trial. BMJ Open. 2012;2(1):e000370.

95. Lung Health Study Research G. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. N Engl J Med. 2000;343(26):1902-9.

96. Magnussen H, Bugnas B, van Noord J, Schmidt P, Gerken F, Kesten S. Improvements with tiotropium in COPD patients with concomitant asthma. Respir Med. 2008;102(1):50-6.

97. Mahler DA, Donohue JF, Barbee RA, Goldman MD, Gross NJ, Wisniewski ME, et al. Efficacy of salmeterol xinafoate in the treatment of COPD. Chest. 1999;115(4):957-65.

98. Mahler DA, D'Urzo A, Bateman ED, Ozkan SA, White T, Peckitt C, et al. Concurrent use of indacaterol plus tiotropium in patients with COPD provides superior bronchodilation compared with tiotropium alone: a randomised, double-blind comparison. Thorax. 2012;67(9):781-8.

99. Mahler DA, Wire P, Horstman D, Chang CN, Yates J, Fischer T, et al. Effectiveness of fluticasone propionate and salmeterol combination delivered via the Diskus device in the treatment of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2002;166(8):1084-91.

100. Maltais F, Celli B, Casaburi R, Porszasz J, Jarreta D, Seoane B, et al. Aclidinium bromide improves exercise endurance and lung hyperinflation in patients with moderate to severe COPD. Respir Med. 2011;105(4):580-7.

101. Maltais F, Hamilton A, Marciniuk D, Hernandez P, Sciurba FC, Richter K, et al. Improvements in symptom-limited exercise performance over 8 h with once-daily tiotropium in patients with COPD. Chest. 2005;128(3):1168-78.

102. Mansori F, Nemat Khorasani A, Boskabady MH, Boskabady M. The effect of inhaled salmeterol, alone and in combination with fluticasone propionate, on management of COPD patients. Clin Respir J. 2010;4(4):241-7.

103. Martinez FJ, Boscia J, Feldman G, Scott-Wilson C, Kilbride S, Fabbri L, et al. Fluticasone furoate/vilanterol (100/25; 200/25 mug) improves lung function in COPD: a randomised trial. Respir Med. 2013;107(4):550-9.

104. McNicholas WT, Calverley PM, Lee A, Edwards JC, Tiotropium Sleep Study in CI. Long-acting inhaled anticholinergic therapy improves sleeping oxygen saturation in COPD. Eur Respir J. 2004;23(6):825-31.

105. Mirici A, Bektas Y, Ozbakis G, Erman Z. Effect of Inhaled Corticosteroids on Respiratory Function Tests and Airway Inflammation in Stable Chronic Obstructive Pulmonary Disease. Clinical Drug Investigation. 2001;21(12):835-42.

106. Moita J, Barbara C, Cardoso J, Costa R, Sousa M, Ruiz J, et al. Tiotropium improves FEV1 in patients with COPD irrespective of smoking status. Pulm Pharmacol Ther. 2008;21(1):146-51.

107. Mroz RM, Minarowski L, Chyczewska E. Indacaterol add-on therapy improves lung function, exercise capacity and life quality of COPD patients. Adv Exp Med Biol. 2013;756:23-8.

108. Nicolini A. Short term effects of tiotropium on copd patients treated with long acting bronchodilators. Tanaffos. 2012;11(1):26-31.

109. Niewoehner DE, Rice K, Cote C, Paulson D, Cooper JA, Jr., Korducki L, et al. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial. Ann Intern Med. 2005;143(5):317-26.

110. O'Donnell DE, Fluge T, Gerken F, Hamilton A, Webb K, Aguilaniu B, et al. Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. Eur Respir J. 2004;23(6):832-40.

111. O'Donnell DE, Sciurba F, Celli B, Mahler DA, Webb KA, Kalberg CJ, et al. Effect of fluticasone propionate/salmeterol on lung hyperinflation and exercise endurance in COPD. Chest. 2006;130(3):647-56.

112. Ozol D, Aysan T, Solak ZA, Mogulkoc N, Veral A, Sebik F. The effect of inhaled corticosteroids on bronchoalveolar lavage cells and IL-8 levels in stable COPD patients. Respir Med. 2005;99(12):1494-500.

113. Paggiaro PL, Dahle R, Bakran I, Frith L, Hollingworth K, Efthimiou J. Multicentre randomised placebo-controlled trial of inhaled fluticasone propionate in patients with chronic obstructive pulmonary disease. International COPD Study Group. Lancet. 1998;351(9105):773-80.

114. Pasqua F, Biscione G, Crigna G, Auciello L, Cazzola M. Combining triple therapy and pulmonary rehabilitation in patients with advanced COPD: a pilot study. Respir Med. 2010;104(3):412-7.

115. Pauwels RA, Lofdahl CG, Laitinen LA, Schouten JP, Postma DS, Pride NB, et al. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. N Engl J Med. 1999;340(25):1948-53.

116. Perng DW, Tao CW, Su KC, Tsai CC, Liu LY, Lee YC. Anti-inflammatory effects of salmeterol/fluticasone, tiotropium/fluticasone or tiotropium in COPD. Eur Respir J. 2009;33(4):778-84.

117. Powrie DJ, Wilkinson TM, Donaldson GC, Jones P, Scrine K, Viel K, et al. Effect of tiotropium on sputum and serum inflammatory markers and exacerbations in COPD. Eur Respir J. 2007;30(3):472-8.

118. Pukhta MA, Ashai ZA, Shah MA, Abbas Z, Farhat S, Mir SA, et al. A preliminary randomized open labeled comparative analysis of efficacy & safety of inhaled tiotropium and tiotropium plus formoterol in COPD. JK Science. 2010;12(1):27-30.

119. Rabe KF, Timmer W, Sagkriotis A, Viel K. Comparison of a combination of tiotropium plus formoterol to salmeterol plus fluticasone in moderate COPD. Chest. 2008;134(2):255-62.

120. Reid DW, Wen Y, Johns DP, Williams TJ, Ward C, Walters EH. Bronchodilator reversibility, airway eosinophilia and anti-inflammatory effects of inhaled fluticasone in COPD are not related. Respirology. 2008;13(6):799-809.

121. Renkema TE, Schouten JP, Koeter GH, Postma DS. Effects of long-term treatment with corticosteroids in COPD. Chest. 1996;109(5):1156-62.

122. Rennard S, Bantje T, Centanni S, Chanez P, Chuchalin A, D'Urzo A, et al. A dose-ranging study of indacaterol in obstructive airways disease, with a tiotropium comparison. Respir Med. 2008;102(7):1033-44.

123. Rennard SI, Anderson W, ZuWallack R, Broughton J, Bailey W, Friedman M, et al. Use of a long-acting inhaled beta2-adrenergic agonist, salmeterol xinafoate, in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001;163(5):1087-92.

124. Rennard SI, Tashkin DP, McElhattan J, Goldman M, Ramachandran S, Martin UJ, et al. Efficacy and tolerability of budesonide/formoterol in one hydrofluoroalkane pressurized metered-dose inhaler in patients with chronic obstructive pulmonary disease: results from a 1-year randomized controlled clinical trial. Drugs. 2009;69(5):549-65.

125. Rossi A, Kristufek P, Levine BE, Thomson MH, Till D, Kottakis J, et al. Comparison of the efficacy, tolerability, and safety of formoterol dry powder and oral, slow-release theophylline in the treatment of COPD. Chest. 2002;121(4):1058-69.

126. Rubin AS, Souza FJ, Hetzel JL, Moreira Jda S. [Immediate bronchodilator response to formoterol in poorly reversible chronic obstructive pulmonary disease]. J Bras Pneumol. 2008;34(6):373-9.

127. Rutgers SR, Koeter GH, van der Mark TW, Postma DS. Short-term treatment with budesonide does not improve hyperresponsiveness to adenosine 5'-monophosphate in COPD. Am J Respir Crit Care Med. 1998;157(3 Pt 1):880-6.

128. Rutten-van Molken M, Roos B, Van Noord JA. An empirical comparison of the St George's Respiratory Questionnaire (SGRQ) and the Chronic Respiratory Disease Questionnaire (CRQ) in a clinical trial setting. Thorax. 1999;54(11):995-1003.

129. Santus P, Buccellati C, Centanni S, Fumagalli F, Busatto P, Blasi F, et al. Bronchodilators modulate inflammation in chronic obstructive pulmonary disease subjects. Pharmacol Res. 2012;66(4):343-8.

130. Schermer T, Chavannes N, Dekhuijzen R, Wouters E, Muris J, Akkermans R, et al. Fluticasone and N-acetylcysteine in primary care patients with COPD or chronic bronchitis. Respir Med. 2009;103(4):542-51.

131. Schermer TR, Albers JM, Verblackt HW, Costongs RJ, Westers P. Lower inhaled steroid requirement with a fluticasone/salmeterol combination in family practice patients with asthma or COPD. Fam Pract. 2007;24(2):181-8.

132. Scherr A, Schafroth Torok S, Jochmann A, Miedinger D, Maier S, Taegtmeyer AB, et al. Response to add-on inhaled corticosteroids in COPD based on airway hyperresponsiveness to mannitol. Chest. 2012;142(4):919-26.

133. Sechaud R, Renard D, Zhang-Auberson L, Motte Sde L, Drollmann A, Kaiser G. Pharmacokinetics of multiple inhaled NVA237 doses in patients with chronic obstructive pulmonary disease (COPD). Int J Clin Pharmacol Ther. 2012;50(2):118-28.

134. Senderovitz T, Vestbo J, Frandsen J, Maltbaek N, Norgaard M, Nielsen C, et al. Steroid reversibility test followed by inhaled budesonide or placebo in outpatients with stable chronic obstructive pulmonary disease. The Danish Society of Respiratory Medicine. Respir Med. 1999;93(10):715-8.

135. Shaker SB, Dirksen A, Ulrik CS, Hestad M, Stavngaard T, Laursen LC, et al. The effect of inhaled corticosteroids on the development of emphysema in smokers assessed by annual computed tomography. COPD. 2009;6(2):104-11.

136. Sharafkhaneh A, Southard JG, Goldman M, Uryniak T, Martin UJ. Effect of budesonide/formoterol pMDI on COPD exacerbations: a double-blind, randomized study. Respir Med. 2012;106(2):257-68.

137. Sin DD, Man SF, Marciniuk DD, Ford G, FitzGerald M, Wong E, et al. The effects of fluticasone with or without salmeterol on systemic biomarkers of inflammation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2008;177(11):1207-14.

138. Sposato B, Franco C. Short term effect of a single dose of formoterol or tiotropium on the isolated nocturnal hypoxemia in stable COPD patients: a double blind randomized study. Eur Rev Med Pharmacol Sci. 2008;12(3):203-11.

139. Sridevi K, MohanaRao V, Vijaya N, Someswar GM. Safety and efficacy of tiotropium bromide in bronchial asthma and copd patients, cross over studies by placebo. Int J LifeSc Bt & Pharm Res. 2012;1(4):250-62.

140. Stockley RA, Chopra N, Rice L. Addition of salmeterol to existing treatment in patients with COPD: a 12 month study. Thorax. 2006;61(2):122-8.

141. Struijs A, Mulder H. The effects of inhaled glucocorticoids on bone mass and biochemical markers of bone homeostasis: a 1-year study of beclomethasone versus budesonide. Neth J Med. 1997;50(6):233-7.

142. Sugiura H, Ichinose M, Yamagata S, Koarai A, Shirato K, Hattori T. Correlation between change in pulmonary function and suppression of reactive nitrogen species production following steroid treatment in COPD. Thorax. 2003;58(4):299-305.

143. Suzuki H, Sekine Y, Yoshida S, Suzuki M, Shibuya K, Takiguchi Y, et al. Efficacy of perioperative administration of long-acting bronchodilator on postoperative pulmonary function and quality of

life in lung cancer patients with chronic obstructive pulmonary disease. Preliminary results of a randomized control study. Surg Today. 2010;40(10):923-30.

144. Szafranski W, Cukier A, Ramirez A, Menga G, Sansores R, Nahabedian S, et al. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. Eur Respir J. 2003;21(1):74-81.

145. Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med. 2008;359(15):1543-54.

146. Tashkin DP, Doherty DE, Kerwin E, Matiz-Bueno CE, Knorr B, Shekar T, et al. Efficacy and safety of a fixed-dose combination of mometasone furoate and formoterol fumarate in subjects with moderate to very severe COPD: results from a 52-week Phase III trial. Int J Chron Obstruct Pulmon Dis. 2012;7:43-55.

147. Tashkin DP, Pearle J, Iezzoni D, Varghese ST. Formoterol and tiotropium compared with tiotropium alone for treatment of COPD. COPD. 2009;6(1):17-25.

148. Tashkin DP, Rennard SI, Martin P, Ramachandran S, Martin UJ, Silkoff PE, et al. Efficacy and safety of budesonide and formoterol in one pressurized metered-dose inhaler in patients with moderate to very severe chronic obstructive pulmonary disease: results of a 6-month randomized clinical trial. Drugs. 2008;68(14):1975-2000.

149. Tonnel AB, Perez T, Grosbois JM, Verkindre C, Bravo ML, Brun M, et al. Effect of tiotropium on health-related quality of life as a primary efficacy endpoint in COPD. Int J Chron Obstruct Pulmon Dis. 2008;3(2):301-10.

150. Tzani P, Crisafulli E, Nicolini G, Aiello M, Chetta A, Clini EM, et al. Effects of beclomethasone/formoterol fixed combination on lung hyperinflation and dyspnea in COPD patients. Int J Chron Obstruct Pulmon Dis. 2011;6:503-9.

151. Ulubay G, Oner FE, Bozbas SS, A S. Three regimens of inhaled bronchodilators for chronic obstructive pulmonary disease: Comparison of pulmonary function and cardiopulmonary exercise test parameters. Turkish Respiratory Journal. 2005;6(2):89-94.

152. Um SW, Yoo CG, Kim YW, Han SK, Shim YS. The combination of tiotropium and budesonide in the treatment of chronic obstructive pulmonary disease. J Korean Med Sci. 2007;22(5):839-45.

153. Van de Maele B, Fabbri LM, Martin C, Horton R, Dolker M, Overend T. Cardiovascular safety of QVA149, a combination of Indacaterol and NVA237, in COPD patients. COPD. 2010;7(6):418-27.

154. van den Boom G, Rutten-van Molken MP, Molema J, Tirimanna PR, van Weel C, van Schayck CP. The cost effectiveness of early treatment with fluticasone propionate 250 microg twice a day in subjects with obstructive airway disease. Results of the DIMCA program. Am J Respir Crit Care Med. 2001;164(11):2057-66.

155. van den Broek KM, Wielders PL, Creemers JP, Smeenk FW. Efficacy of formoterol Turbuhaler in the emergency treatment of patients with obstructive airway diseases. Respir Med. 2008;102(4):579-85.

156. van der Valk P, Monninkhof E, van der Palen J, Zielhuis G, van Herwaarden C. Effect of discontinuation of inhaled corticosteroids in patients with chronic obstructive pulmonary disease: the COPE study. Am J Respir Crit Care Med. 2002;166(10):1358-63.

157. van Noord JA, de Munck DR, Bantje TA, Hop WC, Akveld ML, Bommer AM. Long-term treatment of chronic obstructive pulmonary disease with salmeterol and the additive effect of ipratropium. Eur Respir J. 2000;15(5):878-85.

158. Verhoeven GT, Hegmans JP, Mulder PG, Bogaard JM, Hoogsteden HC, Prins JB. Effects of fluticasone propionate in COPD patients with bronchial hyperresponsiveness. Thorax. 2002;57(8):694-700.

159. Verhoeven GT, Wijkhuijs AJ, Hooijkaas H, Hoogsteden HC, Sluiter W. Effect of an inhaled glucocorticoid on reactive oxygen species production by bronchoalveolar lavage cells from smoking COPD patients. Mediators Inflamm. 2000;9(2):109-13.

160. Verkindre C, Bart F, Aguilaniu B, Fortin F, Guerin JC, Le Merre C, et al. The effect of tiotropium on hyperinflation and exercise capacity in chronic obstructive pulmonary disease. Respiration. 2006;73(4):420-7.

161. Vestbo J, Sorensen T, Lange P, Brix A, Torre P, Viskum K. Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. Lancet. 1999;353(9167):1819-23.

162. Vogelmeier C, Hederer B, Glaab T, Schmidt H, Rutten-van Molken MP, Beeh KM, et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. N Engl J Med. 2011;364(12):1093-103.

163. Vogelmeier C, Kardos P, Harari S, Gans SJ, Stenglein S, Thirlwell J. Formoterol mono- and combination therapy with tiotropium in patients with COPD: a 6-month study. Respir Med. 2008;102(11):1511-20.

164. Vogelmeier C, Verkindre C, Cheung D, Galdiz JB, Guclu SZ, Spangenthal S, et al. Safety and tolerability of NVA237, a once-daily long-acting muscarinic antagonist, in COPD patients. Pulm Pharmacol Ther. 2010;23(5):438-44.

165. Vogelmeier CF, Bateman ED, Pallante J, Alagappan VK, D'Andrea P, Chen H, et al. Efficacy and safety of once-daily QVA149 compared with twice-daily salmeterol-fluticasone in patients with chronic obstructive pulmonary disease (ILLUMINATE): a randomised, double-blind, parallel group study. Lancet Respir Med. 2013;1(1):51-60.

166. Wadbo M, Lofdahl CG, Larsson K, Skoogh BE, Tornling G, Arwestrom E, et al. Effects of formoterol and ipratropium bromide in COPD: a 3-month placebo-controlled study. Eur Respir J. 2002;20(5):1138-46.

167. Watkins ML, Wilcox TK, Tabberer M, Brooks JM, Donohue JF, Anzueto A, et al. Shortness of Breath with Daily Activities questionnaire: validation and responder thresholds in patients with chronic obstructive pulmonary disease. BMJ Open. 2013;3(10):e003048.

168. Wedzicha JA, Calverley PM, Seemungal TA, Hagan G, Ansari Z, Stockley RA, et al. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. Am J Respir Crit Care Med. 2008;177(1):19-26.

169. Weir DC, Bale GA, Bright P, Sherwood Burge P. A double-blind placebo-controlled study of the effect of inhaled beclomethasone dipropionate for 2 years in patients with nonasthmatic chronic obstructive pulmonary disease. Clin Exp Allergy. 1999;29 Suppl 2:125-8.

170. Welte T, Metzenauer P, Hartmann U. Once versus twice daily formoterol via Novolizer for patients with moderate to severe COPD--a double-blind, randomised, controlled trial. Pulm Pharmacol Ther. 2008;21(1):4-13.

171. Welte T, Miravitlles M, Hernandez P, Eriksson G, Peterson S, Polanowski T, et al. Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2009;180(8):741-50.

172. Wesseling GJ, Quaedvlieg M, Wouters EF. Inhaled budesonide in chronic bronchitis. Effects on respiratory impedance. Eur Respir J. 1991;4(9):1101-5.

173. Wielders PL, Ludwig-Sengpiel A, Locantore N, Baggen S, Chan R, Riley JH. A new class of bronchodilator improves lung function in COPD: a trial with GSK961081. Eur Respir J. 2013;42(4):972-81.

174. Wise RA, Anzueto A, Cotton D, Dahl R, Devins T, Disse B, et al. Tiotropium Respimat inhaler and the risk of death in COPD. N Engl J Med. 2013;369(16):1491-501.

175. Woolhouse IS, Hill SL, Stockley RA. Symptom resolution assessed using a patient directed diary card during treatment of acute exacerbations of chronic bronchitis. Thorax. 2001;56(12):947-53.

176. Wouters EF, Postma DS, Fokkens B, Hop WC, Prins J, Kuipers AF, et al. Withdrawal of fluticasone propionate from combined salmeterol/fluticasone treatment in patients with COPD causes immediate and sustained disease deterioration: a randomised controlled trial. Thorax. 2005;60(6):480-7.

177. Yildiz F, Basyigit I, Yildirim E, Boyaci H, Ilgazli A. Does addition of inhaled steroid to combined bronchodilator therapy affect health status in patients with COPD? Respirology. 2004;9(3):352-5.

178. Zheng JP, Yang L, Wu YM, Chen P, Wen ZG, Huang WJ, et al. The efficacy and safety of combination salmeterol (50 microg)/fluticasone propionate (500 microg) inhalation twice daily via accuhaler in Chinese patients with COPD. Chest. 2007;132(6):1756-63.

179. Zhong N, Zheng J, Wen F, Yang L, Chen P, Xiu Q, et al. Efficacy and safety of budesonide/formoterol via a dry powder inhaler in Chinese patients with chronic obstructive pulmonary disease. Curr Med Res Opin. 2012;28(2):257-65.

180. Mathioudakis AG, Amanetopoulou SG, Gialmanidis IP, Chatzimavridou-Grigoriadou V, Siasos G, Evangelopoulou E, et al. Impact of long-term treatment with low-dose inhaled corticosteroids on the bone mineral density of chronic obstructive pulmonary disease patients: aggravating or beneficial? Respirology. 2013;18(1):147-53.

Appendix 7: Definitions of exacerbations

Study	Definition of Exacerbation	COPD Severity
Aalbers, 2002	Worsening symptoms of COPD requiring the use of any additional treatment other than rescue albuterol/salbutamol	Mild to very severe
Aaron, 2007	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	Moderate to very severe
Abrahams, 2013	Exacerbations not defined	Moderate
Ambrosino, 2008	Exacerbations not defined	Moderate to severe
Anzueto, 2009	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.	Moderate to severe
Barnes, 2006	Exacerbations not defined	Moderate to severe
Bateman, 2010	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	Moderate to severe
Baumgartner, 2007	On-treatment exacerbation, including moderate (acute worsening of COPD requiring systemic corticosteroids and/or antibiotics) or severe (requiring hospitalisation)	Moderate
Beier, 2007	Exacerbation which was treated with mucolytics	Mild to moderate
Bogdan, 2011	Exacerbations not defined	Moderate to very severe
Bourbeau, 1998	Exacerbations not defined	Moderate to severe
Boyd, 1997	Chronic obstructive airways disease exacerbated	Moderate to severe
Briggs, 2005	Worsening of symptoms required a change in medication	Moderate to very severe
Buhl, 2011	Number of patients with at least one exacerbation, defined as requiring a change in medication and/or hospitalization	Moderate to very severe
Burge, 2000	Exacerbations of COPD, determined on clinical grounds by the local physician	Moderate
Caillaud, 2007	Worsening of COPD symptoms that required any change in normal treatment	Moderate to severe
Calverley, 2010	Need for treatment with oral corticosteroids and/or antibiotics and/or the need to visit or be admitted to a hospital	Severe
Calverley, 2003	Exacerbations not defined	Mild to severe
Calverley, 2008	Exacerbations not defined	Moderate to severe
Campbell, 2007	Exacerbations not defined	Mild to severe
Casaburi, 2002	Acute exacerbations, defined according to the TSANZ COPDX guidelines (worsening symptoms requiring	Mild to moderate

Study	Definition of Exacerbation	COPD Severity
	additional treatment with antibiotics or systemic corticosteroids, or both)	
Celli, 2003	Worsening in symptoms requiring treatment with a course of systemic steroid or hospitalization	Moderate to very severe
Chanez, 2010	Exacerbations not defined	Moderate to very severe
Chapman, 2002	Exacerbations not defined	Mild to severe
Covelli, 2005	Exacerbations not defined	Mild to moderate
Criner, 2008	Exacerbations not defined	Moderate to very severe
D'Urzo, 2011	Symptomatic deterioration requiring the short term use of oral/intravenous steroids, antibiotics, or both, by the physician's discretion	Moderate to very severe
Dahl, 2010	Worsening of COPD that required treatment with a course of oral corticosteroids, hospitalization, or both.	Moderate to very severe
Dahl, 2013	Worsening of respiratory symptoms that required treatment with a short course of oral corticosteroids or antibiotics as judged by the study physician	Moderate to very severe
Decramer, 2013	Acute infective exacerbations	Moderate to severe
Doherty, 2012	Subjects with ≥1 moderate/severe exacerbation: worsening symptoms requiring treatment with antibiotics, oral corticosteroids, and/or hospitalization	Moderate to very severe
Donohue, 2002	Exacerbations not defined	Moderate to very severe
Dransfield, 2013a	Exacerbations of COPD were diagnosed by the physician and reported as adverse events	Severe
Dransfield, 2013b	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)	Mild to severe
Dusser, 2006	Mild: clinically judged deterioration of COPD symptoms (managed with increased short-acting bronchodilator use; ≥12 inhalations/day of SABA/short acting anticholinergic, or ≥2 neubulized 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.	Mild to very severe
Engel, 1989	Exacerbations not defined	Moderate to very severe
Feldman, 2010	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)	Moderate to very severe
Feldman, 2012	COPD exacerbations, defined as use of systemic	Mild to severe

Study	Definition of Exacerbation	COPD Severity
	antibiotics and/or systemic glucocorticosteroids and/or hospitalization related to COPD	
Freeman, 2007	Exacerbations not defined	Moderate to severe
Fukuchi, 2013	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.	Moderate to severe
Hanania, 2013	Exacerbations not defined	Moderate to severe
Hattotuwa, 2002	Exacerbations were defined in terms of increased dyspnea, sputum production, and sputum purulence.	Moderate to severe
Johansson, 2008	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	Moderate to severe
Jung, 2012	An exacerbation was defined as symptomatic deterioration requiring the shortterm use of oral/intravenous steroids, antibiotics, or both, by the physician's discretion.	Moderate to severe
Kardos, 2007	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 inititated 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).	Mild to very severe
Kerwin, 2012	Severe exacerbation (defined as worsening of COPD leading to treatment with systemic corticosteroids [oral or parenteral] and/or hospitalization/emergency room visits)	Mild to very severe
Kerwin, 2013	Onset or worsening of more than one respiratory symptom (dyspnoea, cough, sputum purulence or volume or wheeze) for >3 consecutive days (based on diary cards or patients' reports of their health since the previous visit) plus documented proof of	Moderate to very severe

Study	Definition of Exacerbation	COPD Severity
	intensified treatment (eg, systemic steroids, antibiotics or oxygen) and/or hospitalisation or emergency room visit	
Kerwin, 2011a	Exacerbations not defined	Mild to severe
Kerwin, 2011b	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.	Moderate to very severe
Kinoshita, 2011	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.	Mild to severe
Korn, 2011	Exacerbations, defined as moderate (acute worsening of COPD requiring systemic corticosteroids and/or antibiotics) or severe (requiring hospitalisation), reported as safety outcome	Moderate to very severe
Kornmann, 2011	Exacerbations requiring treatment with antibiotics alone or a course of antibiotics and systemic steroids	Severe to very severe
Kuna, 2013	Deterioration of COPD	Moderate to severe
Littner, 2000	COPD exacerbations requiring additional therapy	Moderate to severe
Llewellyn-Jones, 1996	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.]	Severe to very severe
Lomas, 2012	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.	Moderate to severe
Mahler, 1999	Exacerbations not defined	Moderate to very severe
Mahler, 2012a	Exacerbations not defined	Moderate to severe
Mahler, 2012b	Bronchitis (COPD exacerbation) reported as AE	Moderate to severe
Maltais, 2005	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	Mild to moderate

Study	Definition of Exacerbation	COPD Severity
Maltais, 2011	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.]	Mild to severe
Martinez, 2013	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).	Moderate to very severe
Moita, 2008	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)	Severe
Niewoehner, 2005	Exacerbations not defined	Moderate to severe
O'Donnell, 2004	A clinically significant worsening of COPD symptoms requiring treatment with antibiotics and/or systemic steroids	Mild to very severe
O'Donnell, 2006	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.	Moderate to very severe
Paggiaro, 1998	Data from AEs; use of oral steroids for exacerbations of COPD	Moderate to very severe
Powrie, 2007	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)]	Mild to very severe
Rabe, 2008	Exacerbations not defined	Moderate to severe
Reid, 2008	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	Moderate to very severe

Study	Definition of Exacerbation	COPD Severity
	meant at least two of, the following: Shortness of breath; sputum production, (volume); occurrence of purulent sputum; cough;, wheezing; chest tightness. Captured as AEs.	
Rennard, 2001	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	Moderate to severe
Rossi, 2002	Exacerbations not defined	Moderate
Schermer, 2009	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	Moderate to very severe
Shaker, 2009	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.	Mild to very severe
Sharafkhaneh, 2012	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	Moderate to severe
Sin, 2008	Exacerbations were defined as a combination of at least 2 of 3 criteria (increased dyspnea - measurement method not reported, increased sputum prodution and change in sputum colour)	Moderate to severe
Stockley, 2005	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	Moderate to severe
Tashkin, 2008	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	Moderate to very severe
Tashkin, 2009	An exacerbation was defined by criteria used by Anthonisen and coworkers [ref 41: Anthonisen NR,	Mild to very severe

Study	Definition of Exacerbation	COPD Severity
	Manfreda J, Warren CPW, Hershfield ES, Harding GKM, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 1987;106:196–204.]	
Tashkin, 2012	Those that required treatment with oral corticosteroids and/or antibiotics or required hospitalization	Moderate to very severe
Van de Maele, 2010	Episodes (new onset or worsening of at least 2 respiratory symptoms) with a duration of 3 days or more requiring systemic steroids or antibiotics.	Moderate to very severe
van Den Boom, 2001	Exacerbations not defined	Moderate to very severe
van der Valk, 2002	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.	Moderate to very severe
van Noord, 2000	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).	Moderate to very severe
Vogelmeier, 2010	As a worsening symptoms of COPD requiring a change in drug therapy	Moderate to very severe
Vogelmeier, 2011	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.	Moderate to severe
Vogelmeier, 2013	Exacerbations not defined	Moderate to severe

Study	Definition of Exacerbation	COPD Severity
Vogelmeier, 2008	Exacerbations not defined	Moderate to severe
Wedzicha, 2008	Exacerbations not defined	Moderate to severe
Welte, 2009	Exacerbations not defined	Moderate to severe
Wielders, 2013	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	Moderate to very severe
Wouters, 2005	Moderate exacerbations were defi ned 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	Moderate to very severe

Appendix 8: Definitions of pneumonia

Study	Definition of Pneumonia
Anzueto, 2009	Pneumonia not defined
Bateman, 2010	Pneumonia not defined
Bogdan, 2011	Pneumonia not defined
Calverley, 2010	Pneumonia not defined
Calverley, 2007	Pneumonia not defined
Chapman, 2011	Pneumonia not defined
D'Urzo, 2011	Pneumonia-like AE (includes pneumonia, bacterial pneumonia, and bronchopneumonia)
Dahl, 2013	Pneumonia not defined
Decramer, 2013	Pneumonia AE (includes bacterial pneumonia, pneumonia, lobar pneumonia, bronchopneumonia, staphylococcal pneumonia, pneumonitis)
Doherty, 2012	Pneumonias - AE in ≥5% confirmed by chest x-ray
Dransfield, 2013a	Pneumonia - AEs occurring in >3%
Dransfield, 2013b	Pneumonia - AE (confirmed by chest X-ray)
Ferguson, 2008	Pneumonia - AE (includes pneumonia, pneumonia viral, pneumonia aspiration, and lobar pneumonia)
Fukuchi, 2013	Pneumonia not defined
Hanania, 2013	Pneumonia-related (total) AE (includes pneumonia, bronchopneumonia, pneumococcal pneumonia)
Johansson, 2008	Pneumonia not defined
Jung, 2012	pneumonia - AE with an incidence > 1
Kardos, 2007	Pneumonia not defined
Kerwin, 2013	Pneumonia not defined
Kerwin, 2012	Pneumonia not defined
Kinoshita, 2011	Pneumonia not defined
Martinez, 2013	Pneumonia-related (total) [Pneumonia, Bronchopneumonia, Lobar pneumonia, Pneumonia staphylococcal]
Powrie, 2007	Pneumonia - AE (confirmed by chest X-ray)
Rennard, 2009	Pneumonia not defined
Sharafkhaneh, 2012	Pneumonia not defined
Tashkin, 2012	Pneumonia not defined
Tashkin, 2008a	Pneumonia not defined
Tashkin, 2008b	Pneumonia not defined
Vestbo, 1999	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)
Vogelmeier, 2013	Pneumonia (radiologically confirmed)
Vogelmeier, 2011	Pneumonia (events reported as adverse events and those confirmed radiographically)
Wedzicha, 2008	Pneumonia (events reported as adverse events and those confirmed radiographically)
Welte, 2009	Pneumonia not defined