ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

Long-acting anticholinergic (LAMA) for chronic obstructive pulmonary disease (COPD)

Pharmacoeconomic Unit: Final Report

Doug Coyle, Karen M. Lee, Kelley-Anne Sabarre, Kylie Tingley, Kathryn Coyle, Mirhad Loncar

December 12th, 2014

Note

Some details are censored in this report so as not to preclude publication. Publications (when available) and/or final unpublished reports will be available on the ODPRN website (www.odprn.ca).

Executive Briefing

- In this report we assess both the current evidence for the cost-effectiveness of LAMA alone or in combination with LABA and/or ICS for treatment of chronic obstructive pulmonary disease (COPD); and the economic impact of alternative changes to the funding status of COPD treatments.

- Studies identified in the systematic review of economic evidence have contradictory results. Additionally, the quality and relevance of these studies limit their applicability to this study's questions.

- In 2013, the Ontario Public Drug Program (OPDP) expenditure on COPD pharmacotherapies was $149.1 million.

- Based on current list prices, the de novo economic evaluation did not find LAMA monotherapies cost effective when compared to formoterol (Oxeze) (LABA). When considering only the LAMA monotherapies, aclidinium (Tudorza) was cost effective compared to glycopyrronium (Seebri) and tiotropium (Spiriva), although there is a great deal of uncertainty over this finding.

- Based on current list prices, the de novo economic evaluation did not find LAMA/LABA combination therapies cost effective when compared to budesonide/formoterol (Symbicort) (ICS/LABA). When considering only the LAMA/LABA combination therapies, indacaterol/glycopyrronium (Ultibro) is dominant over umeclidinium/vilanterol (Anoro Ellipta) – i.e. less costly and more effective. Triple therapy with tiotropium/fluticasone/salmeterol (Spiriva plus Advair Diskus) is not cost effective compared to ICS/LABA combination therapies.

- Assuming a general benefit listing for LAMA/LABA combination products would lead to an increase in total expenditure on COPD therapy. A sensitivity analysis whereby the number of units of LAMA/LABA products was based on previous use of LAMA and ICS/LABA products forecasted a smaller budget increase of less than 1%.

- In the base case analysis, negotiating a 25% price reduction with a preferred therapy may lead to a small reduction in OPDP expenditure.

- The reimbursement based economic evaluation found that for LAMA/LABA combinations, it is optimal (cost saving and cost effective) to reimburse indacaterol/glycopyrronium (Ultibro) if decision makers can negotiate a price reduction of at least 29%. Under no price reduction scenario would it be worthwhile to reimburse umeclidinium/vilanterol (Anoro Ellipta). With respect to LAMA products, it is optimal to list only aclidinium (Tudorza).

Table of Contents

List of Tables

List of Figures

List of Abbreviations

CEA	cost-effectiveness analysis
CIHI	Canadian Institute for Health Information
COP	Colombian Peso
COPD	chronic obstructive pulmonary disease
CUA	cost-utility analysis
DC	Doug Coyle
EQ-5D	European Quality of Life-5 Dimensions
FEV_1	Forced Expiratory Volume in 1 Second
GB	general benefit
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICER	incremental cost-effectiveness ratio
ICES	Institute for Clinical Evaluative Sciences
ICS	inhaled corticosteroids
ICS + LABA	inhaled corticosteroids and long-acting beta2-agonist via separate inhalers (dual therapy)
ICS+LABA	inhaled corticosteroids in combination with long-acting beta2-agonist (combination product)
ICUR	incremental cost-utility ratio
KAS	Kelley-Anne Sabarre
KT	Kylie Tingley
LABA	long-acting $beta_2$-agonist
LAMA	long-acting anticholinergic

LAMA + LABA	long-acting anticholinergic and long-acting beta2-agonist via separate inhalers (dual therapy)
LAMA/LABA	long-acting anticholinergic in combination with long-acting beta2-agonist (combination product)
LY	life years
MOHLTC	Ministry of Health and Long-Term Care (Ontario)
N/A	not applicable
NCGC	National Clinical Guideline Centre
NHS	National Health System
NHSEED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
ODPRN	Ontario Drug Research Policy Network
OPDP	Ontario Public Drug Plan
PDE-4	phosphodiesterase type 4 inhibitor
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life year
RCT	randomized controlled trial
RUSIC	Resource Utilization Study in COPD
SGRQ	St. George's Respiratory Questionnaire
SHI	statutory health insurance
USD$	American dollars

Acknowledgments

This review was funded by grants from the Ontario Ministry of Health and Long-Term Care (MOHLTC) Health System Research Fund and Drug Innovation Fund. The work was supported by the Institute for Clinical Evaluative Sciences (ICES), a non-profit research institute sponsored by the Ontario MOHLTC, and by the Canadian Institute for Health Information (CIHI). The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES, CIHI, or the Ontario MOHLTC is intended or should be inferred.

Executive Summary

Research Questions

RQ1. What is the current evidence for the cost-effectiveness of LAMA alone or in combination with LABA and/or ICS compared to single or combination therapies incorporating LABA and ICS?

RQ2. Based on the economic model developed for the ICS/LABA review, what is the cost-effectiveness of LAMA alone or in combination with LABA and/or ICS compared to single or combination therapies incorporating LABA and ICS?

RQ3. What is the economic impact of alternative policies for reimbursing LAMA alone or as a combination product with LABA?

RQ4. Based on the results from the economic model above, what is the cost-effectiveness of reimbursing LAMA/LABA combination therapies?

Review of Economic Literature for LAMA

Most of the relevant studies included in this review were industry sponsored. These studies concluded in favour of the drugs under review, i.e. that the manufacturer's drug was cost-effective or dominant compared to alternatives. This led to inconsistent findings in the literature.

Results from studies that were independent of industry sponsorship had considerable limitations, restricting their usefulness to the research question at hand. Limitations included: no comparison of active treatments, varying results depending on source of effectiveness data, short time frames, and no consideration of distinct COPD populations based on severity.

The review of economic literature from the ICS+LABA project had similar results. Most of the studies were sponsored by industry and have conflicting results. Based on the quality and relevance of the economic evidence, applicability to this study's research questions was limited.

Refer to Appendix A - A Systematic Review of Economic Evidence for a detailed report of the review of economic literature for LAMA.

De novo Economic Evaluation

An economic model developed for the ICS/LABA class review was used to assess the cost effectiveness of alternative reimbursement strategies for LAMA monotherapies and LAMA/LABA combination therapies. A Markov model was developed which modelled disease progression combined with rates of exacerbations and death. Natural history data relating to disease progression was combined with treatment effectiveness and adverse event data from the clinical review conducted as part of this class review. Costs and utilities associated with disease severity, treatment related adverse events and exacerbations were derived from the literature. All analyses are based on current listed prices or wholesale prices for newer agents not presently covered under OPDP. Analysis was conducted from the

perspective of the Ministry of Health with results presented as incremental cost per quality adjusted life years (QALYs) gained. Detailed deterministic and probabilistic sensitivity analysis was performed to determine decision uncertainty.

The analysis found that all LAMA monotherapies were cost effective compared to Pulmicort (ICS), Flovent (ICS) and Serevent (LABA), but not Oxeze (LABA) which was dominant. Tudorza (LAMA) was cost effective compared to other LAMAs – Seebri and Spiriva, although there is a great deal of uncertainty over this finding.

When considering the LAMA/LABA fixed combinations, Anoro Ellipta is not cost effective when compared to any of the therapeutic options; Ultibro is cost effective compared to ICS monotherapies, Advair Diskus (ICS/LABA) and Breo Ellipta (ICS/LABA), but not to LABA or LAMA monotherapies or Symbicort (ICS/LABA). Triple therapy is not cost effective compared to ICS/LABA combination therapies.

Budget Impact Analysis

After discussion with clinical experts, it was determined that the listing of further LAMA products will not have a major budget impact and focus should be on the impact of listing for LAMA/LABA combination products. Assuming general benefit (GB) for LAMA/LABA combination products in patients with COPD, regardless of severity of disease, will lead to an increase in total OPDP expenditure. However, scenarios including a 25% price reduction to both Anoro Ellipta and Ultibro products or to a preferred therapy would lead to a small absolute reduction in OPDP expenditure.

If almost all (99%) patients who concurrently use LAMA and LABA switch to LAMA/LABA combination, this would have a marginal impact in total costs (a rise in total COPD therapy expenditure of 0.029% for only very severe, 0.042% for at least severe and 0.138% for at least moderate).

If a small proportion (20%) of patients using ICS and LABA as combination therapy or dual therapy switch to LAMA/LABA combination, this would lead to a greater rise in total costs ranging from 0.908% to 6.647% (an increase of $1.4 million for only very severe, $3.1 million for at least severe and $9.9 million for at least moderate).

Similarly, if a modest proportion (60%) of patients using ICS, LABA and LAMA either in combination therapies or monotherapies switch to combination therapy (LAMA/LABA) plus ICS, this would lead to a rise in total costs ranging from 1.733% to 5.454% (an increase of $2.6 million for only very severe, $4.1 million for at least severe and $8.1 million for at least moderate).

The combination of all three scenarios above, would yield an increase in OPDP costs ranging from 3.158% to 17.008% (an increase of $4.7 million for only very severe, $9.1 million for at least severe and $25.4 million for at least moderate).

Scenarios where either 25% price reductions for both combination products or for a preferred therapy

are negotiated could lead to cost savings. These scenarios would lead to savings of approximately $2.5 million (for 25% price reductions) based on a modest proportion (60%) of ICS and LABA users with at least moderate COPD switching to LAMA/LABA and a 25% price reduction on both Ultibro and Anoro Ellipta.

In a sensitivity analysis where the use of LAMA/LABA products was assumed to be similar to previous use of LAMA products and was half the use of LABA/ICS products, the increase in budget was minimal. Refer to Appendix C – Budget Impact Analysis for a detailed report of the reimbursement base economic assessment.

Reimbursement Based Economic Evaluation

Assuming that use of LAMA products is not expected to increase and that there is a willingness to continue to reimburse LAMA therapies, an optimal policy, assuming a willingness to pay of $50,000 per QALY, would be to list only Tudorza. If price reductions for the other LAMAs could be negotiated this conclusion may change.

With respect to LAMA/LABA combination therapies, this analysis estimated the number of users of therapies with or without coverage of the LAMA/LABA combination therapies based on expert opinion of the impact of coverage. The estimated costs and QALYs for each therapy from the de novo economic evaluation for males aged 70 were then weighted by the proportion of users with and without the change in coverage. Using this approach, the average costs and QALYs with and without coverage of LAMA/LABA combination therapies were estimated, and the cost effectiveness of different reimbursement strategies was assessed.

Assuming a willingness to pay of $50,000 per QALY, it is not cost effective to fund either LAMA/LABA combination products if there is an inability to negotiate a price reduction. If decision makers can negotiate a price reduction of at least 29%, reimbursement of Ultibro for patients with at least moderate COPD would be optimal. Under no price reduction scenario would it be worthwhile to reimburse Anoro Ellipta.

Appendices

Appendix A - A Systematic Review of Economic Evidence

Research Question

RQ1. What is the current evidence for the cost-effectiveness of LAMA alone or in combination with LABA and/or ICS compared to single or combination therapies incorporating LABA and ICS?

Review of Published Literature

Search Strategy and Search Findings

Search Strategy

A search of the literature from 1946 to present (2014 February 19) in Ovid Medline (indexed, in-process and other non-indexed) and Embase Classic & Embase 1947 to 2014 February 20 was conducted in order to capture all relevant literature. Key words relating to LAMA for the treatment of COPD were combined with a standardized search strategy for identifying economic analyses adopted by National Health Service Economic Evaluation Database (NHSEED). The complete search strategy can be found in Appendix A1: Search Strategy. We also searched the Tufts CEA registry and NHSEED for relevant articles. Grey literature was identified through the Canadian Agency for Drugs and Technologies in Health (CADTH) and National Institute for Health and Care Excellence (NICE) websites. Reference lists from relevant reports were hand searched to identify any additional potentially relevant articles. Finally, we searched evidence submission packages from manufacturers for any relevant reports; a list of these reports can be found in Appendix A2: List of Citations Included by Manufacturer.

Search Findings

A total of 1210 reports were identified: 1206 reports from the original search, two additional citations from manufacturers which were in addition to the original search, and two from grey literature. Results of the search can be found in Appendix A3: Results of Search.
Three reviewers (KAS, KT and DC) independently reviewed the literature to identify potentially relevant articles for the review. Any disagreements were resolved through consensus. Based on titles and abstracts, 131/1210 studies were selected as potentially relevant for the review. 1020 citations were excluded for the following reasons: not an economic analysis, not COPD, or not relevant intervention. An additional 59 citations were excluded because the reports were non-English, not available or not full text.

Full reports for the 131 potential studies were reviewed by three reviewers (KAS, KT and DC). Of these, 14 publications which addressed the objective of the review were selected for inclusion. Those studies that were not included in the review along with the reasons for exclusion are detailed in Appendix A4: List of Excluded Studies. Inclusion/exclusion of manufacturer submissions are detailed in Appendix A2:

List of Citations Included by Manufacturer.

Included Studies

The comprehensive list of included studies can be found in Appendix A5: List of Included Studies.

Summary and Critical Appraisal of Included Studies: LAMA for COPD

Included Studies

Of the fourteen reports selected for inclusion, one involved Canada and the Netherlands,[1] ten were European studies (UK, Netherlands, Germany, Spain, Greece),[2-11] two were American, [12,13] and one study was Colombian.[14] Eleven studies were financed by manufacturers,[1-7,9-11,14] six of which were sponsored by Boehringer Ingelheim. Of the remaining studies, one was financed by NICE,[8] and two did not disclose sponsorship.[12,13]

Seven of the included studies were both cost-effectiveness and cost-utility analyses,[1-4,6,7,14] six were cost-utility analyses,[5,8-11,13] and one was a cost-effectiveness analysis.[12] Ten of fourteen studies compared monotherapies (LABA versus LAMA),[1-3,5-7,9-11,14] two compared monotherapy, dual therapy and triple therapy,[4,8] and two compared monotherapies (LABA, LAMA) to placebo/no therapy.[12,13] Overall, the most common comparator was LABA (salmeterol), followed by LABA (indacaterol).Two studies considered ICS+LABA and ICS+LABA + LAMA as comparators,[4,8] while two studies compared monotherapies to placebo.[12,13] The focus of this report is on results relating to LAMA alone or in combination with LABA and/or ICS compared to single or combination therapies incorporating LABA and ICS.

All relevant reports used Markov models, except one study, which used a trial based analysis that lacked transparency in reporting.[13] Of the Markov model based analyses, cycle lengths ranged from eight days to one year; some studies had varying cycle lengths such as eight days for the first cycle and one month for the subsequent cycles.[1,5-7] All but one study considered a health care system or third party payer perspective; three of which also considered a societal perspective.[2,3,6] The remaining study considered solely a societal perspective.[11] Time horizons considered in the analyses ranged from six months to lifetime, with only four studies considering a lifetime time frame: two in the base case analysis [4,9] and two in the sensitivity analysis.[8,10]

Within the models, all studies used COPD severity based the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, except for one which used the NICE guidelines.[5] Eight studies considered distinct COPD severity populations in their model either as part of the base case analysis or as part of the sensitivity analysis.[2-7,9,12] Half of the reports did not specify the age of the population modelled,[1,2,5-7,11,14] six specified a mean or starting age (range between at least 40 years to 68 years of age)[3,4,8-10,12] and one specified an age limit of at least 40 years old.[13]

Most studies used effectiveness data from more than one RCT;[1,3,5,6,8,11,12] although, some studies did use data from a single RCT.[2,9,10,13,14] One study used effectiveness data from a published mixed treatment comparison.[4] In another report, effectiveness of the treatments was based on three clinical trials using

direct and indirect comparisons.[8] The remaining study used a published economic evaluation as the source for effectiveness data.[7]

Before summarizing the natural history and economic modelling for COPD, there are a number of issues that must be highlighted. Disease severity is often assessed by categorising patients by their FEV_1%, which decreases with time leading to transitions from milder to more severe states. Rates of exacerbations have been shown to increase with disease severity and the proportion of exacerbations requiring hospitalizations similarly increases with severity. Mortality has been shown to be related to hospitalization for exacerbations (which also increases with age) and has been shown to increase with disease severity – this latter increase occurs not just due to the increased rate of hospitalizations due to exacerbations though the forecasted increase in mortality due to disease severity must be parsed into that occurring as a result of exacerbations and that occurring independently from exacerbations. Thus, in modelling the natural history of COPD, inclusion of both mortality due to hospitalizations from exacerbations and unadjusted increases in mortality from disease severity are liable to double counting of the mortality effect from disease progression. The nature of the progression of COPD makes the modelling of treatment effects similarly prone to double counting. Incorporating the effect of treatment on FEV_1%, will lead to delay in transitions across disease severity and thus an indirect effect on both exacerbation rates and mortality. Incorporating the effect of treatment on exacerbations will have an indirect effect on mortality due to reduced hospitalized exacerbations; assuming mortality due to exacerbations is incorporated. Thus, analyses which incorporate any two of the effect of treatment on FEV_1%, exacerbations and mortality will involve double counting of treatment effects and bias in the estimates of cost effectiveness.

All but two studies assessed cost effectiveness using final outcomes in terms of life years (LYs) and/or quality-adjusted life years (QALYs) gained.Of the remaining studies, one used quality-adjusted life months,[1] and another used an intermediate outcome (exacerbations avoided).[12] One of the reports that used a final outcome was subject to double counting of mortality by incorporating both increased mortality with disease severity using standardized morality rates, and mortality due to hospital-treated exacerbations.[4]

Of the thirteen reports which considered utility values, the majority were derived from the EQ-5D;[1-7,9-11,14] however, one report used St. George's Respiratory Questionnaire (SGRQ) scores to map to the EQ-5D,[13] and another used both the EQ-5D and the mapping of SGRQ scores to the EQ-5D.[8] All except for two relevant reports conducted both deterministic and probabilistic sensitivity analyses.[1,2,4-11,13,14] Of the two remaining studies, one considered deterministic and non-parametric bootstrap analyses,[3] while the other only considered deterministic sensitivity analysis.[12]

All of the reports used branded prices; although, one report stated that generic pricing (when available) was considered. It is unclear which treatment costs were generic and is it likely that generic concomitants were considered rather than study medication (LABA, LAMA).[13]

In terms of results, the majority of studies reported meaningful results in terms of incremental cost

effectiveness ratios for relevant treatment options.[1-3,5-11,14] However, two studies only reported incremental cost effectiveness ratios for no treatment compared to alternative treatments,[12,13] and therefore, ratios comparing active treatment were not presented and could not be inferred. Another study only reported results in the form of estimated costs and outcomes which precluded the ability to estimate incremental cost effectiveness ratios.[4]

A table summarizing included studies is provided in Appendix A6: Characteristics of Reviewed Studies.

In summary, the quality of each study was assessed in terms of: the source of effectiveness data; whether cost effectiveness was measured in terms of final outcomes; the appropriateness of modelling disease progression and mortality; the appropriateness of modelling treatment effect; and the adoption of sensitivity analysis. The applicability of each study was assessed in terms of: sponsorship, time horizon, perspective, COPD severity population modelled, and reporting of results.

Common Issues and Considerations

With respect to the COPD patient population that was modelled, eight studies considered distinct severity populations.[2-7,9,12] Additionally, one report only modelled patients with moderate COPD,[12] and another only modelled patients with severe COPD.[4] Analysis by disease severity is of vital importance to reimbursement decisions as cost effectiveness, and hence reimbursement, can vary by severity.
There are few independent studies conducted on the cost-effectiveness of LAMA alone or in combination with LABA and/or ICS compared to single or combination therapies incorporating LABA and ICS. Eleven out of fourteen studies were industry sponsored studies and these may be susceptible to the biases and limitations that have been found in manufacturer sponsored evaluations.[15]

All studies used branded prices for LAMA, LABA, and ICS+LABA as manufacturer sponsored studies tend to be conducted at the point of seeking formulary reimbursement. Although one study stated having used generic pricing when available, it is unclear which therapies were generic (whether concomitant drugs or active treatments were considered).[13] Currently in Canada, LAMA as well as ICS+LABA combinations are not available in generic form. As well, LABA + LAMA combination products will soon available. Therefore, the use of brand name prices in the economic analyses is justified.

The majority of reports considered short time frames. Given that COPD is a chronic disease, modelling costs and outcomes over a lifetime time frame is encouraged.[16] Therefore, failure to model costs and outcomes over a lifetime time horizon limits the applicability of the study to the question at hand.

Canadian Studies

Oostenbrink et al. (2005)

A study by Oostenbrink and colleagues funded by Boehringer Ingelheim GmbH was a cost effectiveness/utility analysis of LAMA (tiotropium), LABA (salmeterol), and PDE-4 (ipratropium) in patients with moderate-very severe COPD based on the GOLD classification. [1] Results relating to

ipratropium were not considered given the scope of this review. This analysis was from a health care perspective, comparing a Dutch and Canadian population.
The study was conducted using a Markov model with a one year time frame. The first cycle length was eight days and all subsequent cycles were one month. The model assumed a marked difference in initial improvement in lung function, and that subsequent changes in lung function remained constant. Efficacy measures were exacerbations. Mortality was not modelled. Effectiveness data were derived from six randomized controlled trials. Utility values were derived from a published observational study and published literature which used the EQ-5D. Costs included within the model were cost of exacerbation (hospitalization and other exacerbation related costs), cost of maintenance therapy, and cost of medication.

Strengths of this analysis include that it is from a Canadian perspective incorporating Canadian costs. The report included both deterministic and probabilistic analyses which considered appropriate distributions for parameter inputs. However, quality adjusted life months rather than quality adjusted life years were considered. Also, it is important to note that this report is not independent, and only considered a comparison of monotherapies (LAMA versus LABA).

Using data from Canada, the incremental cost effectiveness ratios for LAMA versus LABA were €17.65 per exacerbation avoided and €12.00 per quality life adjusted month gained. However, results imply that LAMA dominated LABA when using data from the Netherlands. Deterministic analysis results were reported as ceiling ratios ranging from €0 to ≥ €8,500 per exacerbation avoided and ≥ €1,020 per quality adjusted life months for the Netherlands, while ranging from €0 to ≥ €11,000 per exacerbation avoided and ≥ €2720 per quality adjusted life month gained for Canada. Probabilistic analysis results were reported in the form of a scatterplot; uncertainty regarding the results was greater with data from the Netherlands than from Canada. At a ceiling ratio of greater than €160 for exacerbation avoided and €120 for a gain of one quality adjusted life month, LAMA had the highest probability of being cost-effective in Canada.

This study may be applicable to decisions regarding the cost effectiveness of LAMA and LABA, however, given the study is not independent, is of a limited time horizon (one year), and distinct COPD severity populations were not considered, its applicability is limited.

Non-Canadian Studies

Hoogendoom et al. (2013)

Hoogendoom and colleagues compared the cost effectiveness of LABA (salmeterol) and LAMA (tiotropium) from both a statutory health insurance (SHI) and societal perspective in Germany.[3] This study was sponsored by Boehringer Ingelheim International GmbH.
Using a one year and a five year time horizon, patients with moderate to very severe COPD (based on the GOLD criteria) were modelled. Multiple analyses were conducted using trial based and Markov

models, and one and five year time horizons. In the trial based model, effectiveness data were derived from the POET-COPD trial, while in the Markov model, a meta-analysis of clinical trials was used to obtain effectiveness data. Exacerbation rates were assumed to vary by disease severity, while mortality rates were assumed to vary by disease severity and exacerbation severity. Utility values were derived from the EQ-5D. Costs included within the model were cost of medication, cost of exacerbation, other COPD medication costs, costs paid by the patient (co-payment for hospitalization, ambulance rides, contacts with health care providers and travel costs in the societal perspective), and productivity loss (in the societal perspective).

From a SHI perspective, using a trial based model and a one year time frame, the incremental cost effectiveness ratios for LAMA versus LABA were €1,961 per exacerbation avoided and €118 per exacerbation day avoided. Using a Markov model, the incremental cost effectiveness ratios for LAMA versus LABA were €9,926 per QALY with a one year time frame and €3,488 per QALY with a five year time horizon. From a societal perspective, using a trial based model and a five year time frame, the incremental cost effectiveness ratios for LAMA versus LABA were €2,647 per exacerbation avoided and €159 per exacerbation day avoided. Using a Markov model, the incremental cost utility ratios for LAMA versus LABA were €16,771 per QALY with a one year time frame and €8,141 per QALY with a five year time horizon. Results were similar in deterministic analysis. Using a trial based model and SHI perspective, at a willingness to pay of €5,000 per exacerbation avoided, the probability of LAMA being the most cost-effective was 90%; and 82% using a societal perspective. Using a Markov model and five year time frame, at a willingness to pay of €20,000 per QALY, the probability of LAMA being the most cost-effective was 62.5% using a SHI perspective.

Although mortality and treatment effect were modelled appropriately and distinct COPD severity populations were considered in the sensitivity analysis, the analysis only compared the cost effectiveness of LAMA and LABA, other therapy such as ICS+LABA, LABA + LAMA, or ICS+LABA + LAMA were not considered.

Applicability of this study is limited given that it is not an independent study, is not from the Canadian perspective and is of a limited time horizon (one year and five years).

Price et al. (2013)

A study by Price and associates funded by Novartis Pharmaceuticals, UK Limited was a cost effectiveness analysis of LABA (indacaterol 150 µg, 300 µg), LAMA (tiotropium 18 µg) and LABA (salmeterol 50 µg) from a UK National Health Service perspective.[9] The analysis compared LABA (indacaterol 150 µg, 300 µg) to LAMA (tiotropium 18 µg) and LABA (indacaterol 150 µg) to LABA (salmeterol 50 µg). Results relating to the LABA versus LABA were not considered given the scope of this review.
Using a three year, five year and lifetime time frame, patients with mild to very severe COPD based on GOLD criteria were modelled. Effectiveness data using rates of exacerbation and improvement in lung function according to FEV_1 for indacaterol and tiotropium were derived from a randomized controlled trial. Treatment effect on exacerbation rates was assumed; while mortality rates were assumed to vary

by disease severity. Utility gains were derived from the EQ-5D. Costs included within the model were cost of health care service (physician visits, hospitalization, transportation to emergency, physiotherapy, spirometry, pulmonary rehabilitation, and oxygen therapy), cost of medication, and cost of concomitant medication.

In all time horizons (three year, five year and lifetime), LABA (indacaterol 150 µg and 300 µg) dominated LAMA. In one way deterministic analyses, in general, results were insensitive to changes. The assumptionthat all patients start at moderate COPD and the mortality rates used in the analysis were the main driversof uncertainty with the model results. At a willingness to pay of £20,000 per QALY, LABA (indacaterol) has the highest probability of being cost effective compared to LAMA.

Although the study considered a lifetime time frame and distinct COPD severity populations in the sensitivity analysis, it had many weaknesses. Effectiveness data for indacaterol and tiotropium were derived from a single study, and this is an industry sponsored study; therefore, susceptible to the biases and limitations that have been found in manufacturer sponsored evaluations.[15] Only the cost effectiveness of monotherapies (LABA, LAMA) were considered; treatments such as ICS+LABA, LABA + LAMA, ICS+LABA + LAMA were not considered.

Applicability of this study is limited given that it is not an independent study and that it is not from the Canadian perspective.

Guillermo Ariza et al. (2012)

Guillermo Ariza and associates compared the cost effectiveness of ICS+LABA (salmeterol/fluticasone), ICS+LABA (formoterol/budesonide), LABA (indacaterol), and LAMA (tiotropium) from a Colombian health care payer perspective.[14] This study was financed by Novartis. Two separate analyses were considered: one comparing ICS+LABA to LABA, and another comparing LABA to LAMA. Results relating to the cost effectiveness of LABA versus ICS+LABA were not considered given the scope of this review; results of that comparison can be found in a previous ODPRN report.
Using the GOLD criteria, patients with mild to very severe COPD were modelled. Treatment effect on exacerbation rates and FEV_1 was assumed. Exacerbation rates did not vary by disease severity, but morality rates did vary by disease severity. Effectiveness data were derived from a randomized controlled trial. Utility values were derived from the EQ-5D. Costs included within the model were cost of medication, cost of maintenance therapy (other medication, physician visits, radiologic and laboratory tests) and cost of exacerbation (dependent on severity, may include ambulatory and emergency visits) which were based on published literature and expert opinion.

The incremental cost effectiveness ratios for LABA versus LAMA were $2,899 per LY gained and $2,584 per QALY. If the price per day of LABA was lowered to $2.14 from $2.17, LABA would dominate LAMA. Results from probabilistic sensitivity analysis suggest that 47.2% of 1000 simulations indicated that LAMA was cost effective.

One strength of this analysis is consideration of final outcomes (QALYs); however, a major limitation of

this analysis is that effectiveness data (improvement in FEV_1 and exacerbation rate) were derived from a single RCT. As well, the analysis is a comparison of monotherapies (LABA, LAMA) and did not consider treatments such as ICS+LABA, LABA + LAMA, ICS+LABA + LAMA.

Applicability of this study is limited given that it is not an independent study, is a of limited time horizon (five years), is not from the Canadian perspective, and does not consider distinct COPD severity populations.

Hertel et al. (2012)

Hertel and colleagues compared the cost effectiveness of monotherapies (LAMA, LABA), dual therapies (ICS+LABA, LABA + LAMA) and triple therapy (LAMA+ ICS+LABA); as well as combinations including roflumilast from a UK NHS perspective.[4] The study was funded by MSD Ltd. Results relating to roflumilast are not considered given the scope of this review.

Using the GOLD criteria, patients with severe COPD were entered into the model.Transition probabilities for progression were based on the rate of FEV_1 decline relative to the natural decline in lung function in general population, while mortality was modelled using standardized mortality ratio for COPD and mortality due to hospital-treated exacerbations. Effectiveness was measured in terms of reduction in exacerbations only and effectiveness data were derived from a published mixed treatment comparison. Utility gains were derived from the EQ-5D. Costs included within the model were cost of medication, cost of maintenance therapy, and cost of exacerbation (community- and hospital treated).

The study included two separate analyses: ICS tolerant patients and ICS intolerant patients. For ICS tolerant patients, the treatments pertinent to this review ranked in terms of their estimated QALYs (from lowest to highest) were LABA, LAMA, ICS+LABA, LABA + LAMA and ICS+LABA + LAMA. The treatments had the same ranking in terms of estimated lifetime costs. For ICS intolerant patients, the treatments pertinent to this review ranked in terms of their estimated QALYs (from lowest to highest) were LABA, LAMA, LABA + LAMA. The treatments had the same ranking in terms of estimated lifetime costs. However, incremental cost effectiveness ratios for the relevant comparisons were not provided and could not be accurately inferred.

Strengths of this study include: the use of effectiveness data derived from a published mixed treatment comparison, the consideration of final outcomes (QALYs and LYs), the variety of comparators considered (monotherapies, dual therapies, and triple therapy), and the extensive sensitivity analysis. Key limitations of this study include: inappropriate modelling of mortality and insufficient description of probabilistic sensitivity analysis limiting its interpretability.

Although this report modelled a distinct COPD severity population, its applicability is limited given it is not an independent study, is not from the Canadian perspective, and results are not reported in a manner which allows estimation of cost effectiveness.

Hoogendoom et al. (2012)

A study by Hoogendoom and colleagues sponsored by Boehringer Ingelheim was a cost effectiveness analysis of LABA (salmeterol) and LAMA (tiotropium) from both a healthcare system and societal perspective in the Netherlands.[2]

Using a one year and five year time horizon, patients with moderate to very severe COPD based on the GOLD criteria were modelled. Effectiveness data were derived from a meta-analysis of the POET-COPD trial and other studies regarding LAMA. The same annual decline in lung function was assumed for the treatments. Treatment effect on exacerbation rates was assumed. Exacerbation rates were assumed to vary by disease severity and treatment group, while mortality rates were assumed to vary by disease severity and exacerbation severity. Probabilities for death were derived from all-cause age and sex-specific mortality rates for COPD patients. Utility gains were derived from the EQ-5D. Costs included in the model were cost of medication, cost of maintenance therapy (which also included travel costs in the societal perspective), and cost of exacerbations (which also included absence paid work in the societal perspective).

From a healthcare system perspective, using a one year time horizon, the incremental cost effectiveness ratios for LAMA versus LABA were €162 per exacerbation avoided and €1015 per QALY gained. Using a five year time horizon, LAMA dominated LABA. From a societal perspective, using a one year and five year time horizon, LAMA dominated LABA. In the deterministic analysis, results were sensitive to exacerbation probabilities and cost for inpatient hospital day and patient characteristics - severity of distribution was a major driver. At a willingness to pay of €20,000 per QALY, LAMA had the highest probability of being cost effective from both a health care and societal perspective in both the one year and five year analyses.

Strengths of this study are that mortality and treatment effect were modelled appropriately and distinct COPD severity populations were considered in sensitivity analysis. However, the analysis only compared the cost effectiveness of LAMA and LABA, dual therapies such as LABA + LAMA and ICS+LABA were not considered.

Applicability of this study is limited given that it is not an independent study, is not from the Canadian perspective, and is of a limited time horizon (one and five years).

Price et al. (2011)

Price and associates compared the cost effectiveness of LABA (indacaterol 150 µg, 300 µg), LAMA (tiotropium 18 µg), and LABA (salmeterol) from a German Health Service perspective.[10] This study was funded by Novartis. Results relating to the cost effectiveness of LABA (salmeterol) compared to LABA (indacaterol) are not considered given the scope of the review.

Using a three year time horizon, patients with mild to very severe COPD based on GOLD criteria were modelled. The model assumed a marked difference in initial improvement in lung function, and that subsequent changes in lung function remained constant. Treatment effect on exacerbation rates was

assumed. Effectiveness data were derived from a randomized controlled trial. Deaths recorded from the clinical trial were assumed to be COPD-related. Utility values were derived from the EQ-5D. Costs included within the model were cost of maintenance, cost of exacerbation, and cost of medication.

LABA (indacaterol 150 µg) dominated LAMA, while the incremental cost effectiveness ratio for LABA (indacaterol 300 µg) compared to LAMA was €28,301 per QALY gained. Results were insensitive to time horizon, mortality rates, utility values, costs, assumption of LABA benefit, lung function, and discontinuation rate; as LABA remained dominant. Results of probabilistic analysis confirmed the findings of the deterministic analysis.

Although this study used preference-based utility measures and appropriate distributions to handle parameter uncertainty, effectiveness data were derived from a single study. The analysis only compared the cost effectiveness of LAMA and LABA, other therapy such as ICS+LABA, LABA + LAMA, or ICS+LABA + LAMA were not considered.

Applicability of this study is limited given that it is not an independent study, is not from the Canadian perspective, and did not consider distinct COPD severity populations.

Gani et al. (2010)

A study by Gani and colleagues financed by Boebringer Ingelheim Ltd and Pfizer Ltd was a cost effectiveness analysis of LABA (salmeterol), LAMA (tiotropium), and PDE-4 (ipratropium) from a UK national healthcare system perspective.[5] Results relating to ipratropium were not considered given the scope of this review.

Using a one year time frame, patients with mild to severe COPD based on the NICE COPD guidelines (equivalent to mild to very severe COPD using the GOLD classification) were modelled. The model assumed a marked difference in initial improvement in lung function, which differed from the following 22 days, and the subsequent months. Treatment effect on exacerbation rates was assumed. Exacerbation rates were assumed to vary by disease severity. Effectiveness data were derived from three randomized controlled trials. Mortality was not considered in the model. Utility values were derived from the EQ-5D. Costs included within the model were cost of exacerbation, cost of maintenance therapy, and cost of medication.

In terms of incremental cost per QALY, LAMA dominated LABA. LAMA remained dominant regardless of distinct COPD severity population in the deterministic analyses. Results of the probabilistic analysis suggest that at a willingness to pay of £20,000 per QALY, LAMA has a 97% probability of being cost effective compared to LABA.

Strengths in the analysis include that distinct COPD severity populations were considered in the deterministic analysis, final outcomes (QALYs) were considered, and distributions for Monte Carlo simulation were appropriate. However, this study did not consider mortality. As well, the analysis only compared the cost effectiveness of LAMA and LABA, other therapy such as ICS+LABA, LABA + LAMA, or

ICS+LABA + LAMA were not considered.

Applicability of this study is limited given that it is not an independent study, is not from the Canadian perspective, and is of a limited time horizon (one year).

Naik et al. (2010)

Naik and colleagues compared the cost effectiveness of LABA (salmeterol), LAMA (tiotropium), and placebo/no therapy from a third party payer US perspective.[12] This study was independent from industry sponsorship.

Using a one year time horizon, patients with moderate COPD based on the GOLD criteria were modelled. Treatment effect on exacerbation rate was assumed. Effectiveness data were derived from four randomized controlled trials. Costs included within the model were cost of health care service (laboratory test, hospitalization, physician visit), cost of medication, and cost of concomitant medication.

The incremental cost effectiveness ratio for LABA versus placebo/no therapy was $2,454.48 per exacerbation avoided and for LAMA versus placebo/no therapy was $1,817.37 per exacerbation avoided. LABA was subject to extended dominance by LAMA and placebo/no therapy. In one-way deterministic analysis, results were sensitive to compliance with medication; in many cases, LAMA dominated LABA. However, ratios comparing active treatment were not presented and could not be inferred.

Even though distinct COPD severity populations were considered and treatment effect was modelled appropriately, final outcomes such as QALYs or LYs gained were not considered and PSA was not considered, limiting the applicability and interpretability of results.

Although this study is not industry sponsored, applicability of this study is limited given that it is not from the Canadian perspective, is of a limited time horizon (one year), and results are not reported in a way to allow assessment comparing active therapies.

NCGC (2010)

A study in 2010 by the National Clinical Guideline Centre (NCGC) was a cost-utility analysis of LAMA (tiotropium), ICS+LABA (budesonide/formoterol, fluticasone/salmeterol) and ICS+LABA + LAMA (tiotropium + budesonide/formoterol, tiotropium + fluticasone/salmeterol) in patients with severe to very severe COPD based on the GOLD criteria.[8] The analysis was from a UK NHS perspective.

The study was conducted using a Markov model with a four year time frame and a one year cycle length. Patients entered the model at age 66. In the base case analysis, it was assumed that treatments had a differential effect on exacerbations only; however, differential treatment effects on mortality and quality of life were considered in the sensitivity analysis. Mortality was modelled using mortality risk by GOLD stage compared to the general population. The effectiveness of the treatments was based on

three clinical trials using direct and indirect comparisons; three separate analyses were conducted using combinations of the three trials. For example, data from Inspire and Optimal studies included direct comparisons of ICS+LABA versus LAMA and ICS+LABA + LAMA versus LAMA, and an indirect comparison of ICS+LABA versus ICS+LABA + LAMA. Utility values were derived from the EQ-5D using published literature as well as SGRQ scores which were then mapped to the EQ-5D. Costs included within the model were cost of medication, cost of exacerbation (non-hospitalized and hospitalized), and cost of maintenance therapy (follow-up visits, additional medications and therapies) which were based on published sources.

In the base case analysis, only exacerbations varied between treatments. Using data from Inspire and Uplift trials, the incremental cost effectiveness ratio for ICS+LABA + LAMA versus ICS+LABA was £187,697 per QALY gained and ICS+LABA was subject to extended dominance by ICS+LABA + LAMA and LAMA. Results were similar using data from Inspire and Optimal trials; the incremental cost effectiveness ratio for ICS+LABA + LAMA versus ICS+LABA was £93,737 per QALY gained and ICS+LABA was subject to extended dominance by ICS+LABA + LAMA and LAMA. However, using data from Uplift and Optimal trials, the incremental cost effectiveness ratio for ICS+LABA + LAMA versus ICS+LABA was still high - £159,353 per QALY gained. However in this instance, LAMA was subject to dominance by ICS+LABA. In sensitivity analyses, results were insensitive to time horizon and cost of non-hospitalized exacerbations, but sensitive to exacerbation rate (depending on source of data). In scenario based analysis, results were sensitive to scenarios including: treatment affects exacerbation and stable quality of life effects, and treatment affects exacerbation and mortality. Results were insensitive, however, to the addition of time horizon changes to the scenarios. At a threshold of £20,000 per QALY, LAMA has the highest probability of being cost effective (using both data from Inspire and Uplift trials and data from Inspire and Optimal trials). However, using the Uplift and Optimal data, at a threshold of £20,000 per QALY, ICS+LABA has the highest probability of being cost effective.

Strengths of this analysis include that it considered final outcomes; mortality and treatment effect were modelled appropriately; and it considered the cost-effectiveness of monotherapy, dual therapy and triple therapy. Furthermore, the study included a variety of sensitivity analyses, with appropriate distributions used to handle parameter uncertainty. Limitations of this analysis include that effectiveness data were derived from both direct and informal indirect comparisons using combinations of the three clinical trials rather than any attempt to synthesize the trial results in a formal manner. As a result, it was not possible to obtain consistent estimates for the cost effectiveness of LAMA versus alternative treatments. Furthermore, results are reported only as incremental cost effectiveness ratios compared to ICS+LABA and not compared to LAMA. Moreover, the analysis did not consider LABA alone as an alternative treatment.

Although this study is independent from industry sponsorship, suggesting that the conclusion from this study may apply to Canada, its applicability is limited given it is not from the Canadian perspective, and distinct COPD severity populations were not considered. Additionally, the inconsistent results due to failure to pool the clinical trial results in a formal manner further limit its usefulness.

Oostenbrink et al. (2008)

Oostenbrink and associates compared the cost effectiveness of LABA (salmeterol), LAMA (tiotropium), and PDE-4 (ipratropium) from a Dutch societal perspective.[11] This study was sponsored by Boehringer Ingelheim International and Pfizer Global Pharmaceuticals. Results relating to ipratropium were not considered given the scope of this review.

Using a five year time frame, patients with moderate to very severe COPD based on the GOLD criteria were modelled. Treatment effect on exacerbation rate was assumed. The model also assumed no differential treatment effect on mortality. Mortality rates were assumed to vary by disease severity. Effectiveness data were derived from three randomized controlled trials. Utility values were derived from the EQ-5D. Costs included within the model were cost of exacerbation, cost of maintenance therapy, and cost of medication.

Base case results suggest that LAMA dominated LABA. Results remain insensitive to changes to utility values.

Strengths in the analysis include that final outcomes (QALYs) were considered and distributions for Monte Carlo simulation were appropriate. However, distinct COPD severity populations were not considered. As well, the analysis only compared the cost effectiveness of LAMA and LABA, other therapy such as ICS+LABA, LABA + LAMA, or ICS+LABA + LAMA were not considered.

Applicability of this study is limited given that it is not an independent study, is not from the Canadian perspective, and is of a limited time horizon (five year).

Oba (2007)

A study in 2007 by Oba was a cost-utility analysis of LAMA (tiotropium), LABA (salmeterol), placebo/no therapy, and PDE-4 (ipratropium) in patients with moderate to severe COPD based on the GOLD criteria.[13] Results relating to ipratropium were not considered given the scope of this review.

The study was a trial based analysis with a six month time frame from a US third party payer perspective. Effectiveness data were derived from a RCT. Utility values were derived from SGRQ which were mapped to the EQ-5D using published literature. Costs included within the model were cost of medication, cost of hospitalization, cost of unscheduled visit, and cost of concomitant medications. Average cost of generic version (if available in generic form) was used; however, it is unknown which treatments were generic and therefore, it is possible that only generic concomitants were considered.

The incremental cost-effectiveness ratio for LAMA versus placebo was $20,000 per QALY gained and for LABA versus placebo was $37,300 per QALY gained. Results from the sensitivity analysis were seldom reported; results and details were not presented for LAMA versus LABA comparison.

Although this analysis considered final outcomes (QALYs), it had key limitations. The study compared the cost effectiveness of monotherapies (LAMA, LABA) to placebo/no therapy; ratios comparing active

treatment were not presented and could not be inferred. As well, there is a lack of transparency in reporting making it difficult to assess the study.

Although this study is independent from industry sponsorship, its applicability may be limited given it is not from the Canadian perspective, is of a limited time horizon (one year), did not consider distinct COPD severity populations, and results are not reported in a way to allow assessment comparing active therapies.

Rutten-van Molken et al. (2007)

Rutten-van Molken and colleagues compared the cost effectiveness of LAMA (tiotropium), LABA (salmeterol), and PDE-4 (ipratropium) in patients with moderate to very severe COPD (based on the GOLD classification) from a Spanish National Health System perspective and societal perspective.[6] This study was funded by Boehringer Ingelheim International and Pfizer Global Pharmaceuticals. Results relating to ipratropium were not considered given the scope of this review.

Using a five year time frame, the model assumed that in the first year, patients were able to transition to worse health states and to better health states, and in subsequent years, patients only transitioned to worse health states. Treatment effect on exacerbation rate was assumed. Effectiveness data were derived from six randomized controlled trials. The model also assumed no differential treatment effect on mortality. Mortality rates were assumed to vary by disease severity. Utility values were derived from a randomized controlled trial which used the EQ-5D.[17] Costs included within the model were the cost of maintenance therapy (physician visits, test and medication), cost of exacerbation (hospitalization, physician visits, concomitant medication) and co-payment and productivity loss costs (in the societal perspective).

Using the Spanish National Health System perspective, the incremental cost effectiveness ratios for LAMA versus LABA were €360 per exacerbation free months and €4,118 per QALY gained. Using a societal perspective, the incremental cost effectiveness ratios for LAMA versus LABA were €308 per exacerbation free months and €3,483 per QALY gained. In scenario based deterministic analysis, results were insensitive to the following scenarios: transition and exacerbation probabilities remained constant over five years; and no difference in disease progression and exacerbation risk between treatment groups after one year. Results were also insensitive to changes to discounting rates. Results of the deterministic analysis also suggest that at a willingness to pay of €7,600 per QALY, LAMA was the preferred treatment for patients with moderate COPD, €8,800 per QALY for patients with severe COPD, and €12,500 per QALY for patients with very severe COPD. Probabilistic analysis results suggest that at a willingness to pay of greater than €1,050 per exacerbation free months and €11,000 per QALY, LAMA has the greatest probability of being cost effective compared to LABA.

The study had key limitations including: industry sponsorship; no description of distributions used to handle parameter uncertainty were, limiting the interpretability of probabilistic analysis results; and no comparison of other therapy such as ICS+LABA, LABA + LAMA, or ICS+LABA + LAMA.

Applicability of this study is limited given it is not from the Canadian perspective, is not an independent analysis, and is of limited time frame (five years).

Maniadakis et al. (2006)

A study by Maniadakis and associates financed by Boehringer Ingelheim Ellas was a cost effectiveness analysis of LABA (salmeterol) and LAMA (tiotropium) from a National Health Service perspective in Greece.[7]

Using a one year time frame, patients with moderate to very severe COPD based on the GOLD criteria were modelled. The model assumed a marked difference in initial improvement in lung function, which differed from the subsequent months. Treatment effect on exacerbation rates was assumed. Exacerbation rates were assumed to vary by disease severity. Effectiveness data were derived from a published economic evaluation. Utility gains were derived from the EQ-5D. Costs included within the model were cost of medication, cost of hospitalization, and cost of health care visits (emergency visit, physician visit and other resources use associated with severe exacerbations).

In terms of incremental cost per exacerbation avoided and incremental cost per QALY gained, LAMA was less costly and more effective than LABA and therefore, dominated LABA. In scenario based deterministic analysis, results were insensitive to transition/exacerbation probabilities, patient characteristics - 100% moderate, 100% severe, 100% very severe, and similar transition probabilities in both groups. At a ceiling ratio of €0, LAMA had a 65% probability of being cost-effective; while at a ceiling ratio of €1000 LAMA had a 77% probability of being cost-effective.

The study had key limitations. This study is not an independent analysis. As well, distributions used to handle parameter uncertainty were not provided, limiting the interpretability and applicability of probabilistic analysis results. Moreover, the analysis only compared the cost effectiveness of LAMA and LABA, other therapy such as ICS+LABA, LABA + LAMA, or ICS+LABA + LAMA were not considered.

Although distinct COPD severity populations were considered in the sensitivity analysis and final outcomes were modelled, applicability of this study is limited given that it is not an independent study, is not from the Canadian perspective, and is of a limited time frame (one year).

Overall Conclusions

Overall, the studies identified in this review are of limited applicability to the current Canadian setting. Most studies were industry sponsored. Studies were mainly an analysis of monotherapies. Time horizons considered in the analyses ranged from six months to lifetime, with only four studies considering a lifetime time frame. Eight of 14 included studies considered distinct COPD severity populations in their model, either in the base case analysis or in the sensitivity analysis. The majority of studies reported meaningful results in terms of incremental cost effectiveness for relevant treatment options.

Only one Canadian study which was a cost effectiveness/utility analysis was identified.[1] Oostenbrink et al.[1] compared LAMA and LABA in patients with moderate to very severe COPD; distinct COPD severity

population and age of population modelled were not specified in the analysis. The results from Oostenbrink et al. [1] suggested that LAMA was more cost effective than LABA in terms of incremental cost per exacerbation avoided and incremental cost per quality life adjusted months. Despite the strengths, this study had limitations primarily relating to study sponsorship.

Of the 13 non-Canadian studies, six included both cost-effectiveness and cost-utility analyses,[1-4,6,7,14] six included only cost-utility analyses,[5,8-11,13] and one only included a cost-effectiveness analysis.[12]

The studies conducted by NCGC, Oba, and Naik et al. were independent of manufacturer sponsorship.[8,12,13] Naik et al. and Oba compared monotherapies (LAMA, LABA) to placebo/no therapy,[12,13] and the NCGC study compared LAMA to ICS+LABA and ICS+LABA + LAMA.[8] The population modelled in the analysis by NCGC was patients with severe to very severe COPD with a mean age of 66 years,[8] while patients with moderate COPD and mean age of 65 years, and patients with moderate to severe COPD at least 40 years of age were modelled in the analysis by Naik et al. and Oba respectively.[12,13]

Results from studies funded by manufacturers of LAMA concluded that LAMA was cost effective compared to LABA or dominated LABA,[1-3,5-7,10,11] while results from studies sponsored by manufacturers of LABA reported the opposite.[9,10,14]

In summary, the results of the NCGC report varied depending on the source of effectiveness data, limiting its usefulness in decision making.[8] Oba and Naik et al. evaluated the cost effectiveness of monotherapies (LAMA, LABA) compared to placebo/no therapy; ratios comparing active treatment were not presented and could not be inferred.[12,13] Results from all manufacturer sponsored economic analyses favoured the manufacturer's treatment.

Overall, the most common comparator was LABA (salmeterol), followed by LABA (indacaterol).Two studies considered ICS+LABA and ICS+LABA + LAMA as comparators,[4,8] and two studies compared monotherapies to placebo.[12,13] Applicability of non-Canadian studies to any decision regarding the cost effectiveness of LAMA alone or in combination is limited given they are not from the Canadian perspective, and all except for three are industry sponsored favouring the manufacturer's therapy.

Relation to ICS+LABA for COPD Report and Overall Summary

In April 2014, ODPRN conducted a pharmacoeconomic study on ICS+LABA for chronic treatment of COPD compared to single or combination therapies incorporating LABA, LAMA and ICS. A systematic review of economic evidence was conducted and of the 1183 articles identified from the original search, nine relevant reports addressed the objective of that review.

All but two studies were financed by manufacturers. Of the reports that were independent from industry sponsorships, one was the NCGC report,[8] and the other was a study by Oba which evaluated the cost effectiveness of ICS+LABA compared to monotherapies (LABA or ICS) and placebo.[18] This study only used effectiveness data derived from a single randomized controlled trial and lacked transparency

in reporting.[18] Results from all manufacturer sponsored economic analyses favoured the manufacturer's treatment.

Given both the contradictory results and the consistent concerns over quality and relevance of the available studies, it was not possible to make any inferences about the cost-effectiveness of ICS+LABA. As a result, ODPRN developed an independent de novo economic model to address the cost effectiveness of ICS and LABA as single and combination therapies.

This review examined current economic evidence for the cost-effectiveness of LAMA alone or in combination with LABA and/or ICS compared to single or combination therapies incorporating LABA and ICS. A total of fourteen analyses were identified; only one included Canadian data. Most were financed by industry. More than half considered distinct COPD severity populations in the main analysis or in the sensitivity analysis. Most studies compared monotherapies. Over half of the studies used effectiveness data from more than one randomized controlled trial. Similar to the ICS+LABA for COPD report, results are contradictory and there are consistent concerns over the quality and relevance of the available studies. Subsequently, it is not possible to make any inferences over the cost effectiveness of LAMA alone or in combination with LABA and/or ICS compared to single or combination therapies incorporating LABA and ICS.

Conclusions

In brief, this review highlights the poor quality of current economic evidence for the cost-effectiveness of LAMA alone or in combination with LABA and/or ICS compared to single or combination therapies incorporating LABA and ICS.

Economic evidence for the cost-effectiveness of LAMA alone or in combination with LABA and/or ICS compared to single or combination therapies incorporating LABA and ICS for the treatment of COPD suggest that there are few independent analyses; most studies are industry financed. Given both contradictory results and the consistent concerns over quality and relevance of the available studies, it is not possible to make any inferences on the cost-effectiveness of LAMA.

Therefore, to assist with the ODPRN review, an independent de novo economic model is required to address the cost effectiveness of ICS, LABA and LAMA as single and combination therapies based on disease severity from the Canadian context. This model can then be used to assess the relative cost effectiveness of alternative reimbursement scenarios relating to LAMA.

Appendix A – Appendices

Appendix A1: Search Strategy

The following is the search strategy used in Medline (Ovid) and Embase.

Embase Classic+Embase (1946 to present (2014 February 20), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations (1947 to 2014 February 19)

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. health economics/

85. exp economic evaluation/

86. exp "health care cost"/

87. exp pharmacoeconomics/

88. 84 or 85 or 86 or 87

89. (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.

90. (expenditure$ not energy).ti,ab.

91. (value adj2 money).ti,ab.

92. budget$.ti,ab.

93. 89 or 90 or 91 or 92

94. 88 or 93

95. Economics/

96. exp "Costs and Cost Analysis"/

97. "Value of Life"/

98. exp Economics, Hospital/

99. Economics, Medical/

100. Economics, Nursing/

101. Economics, Pharmaceutical/

102. 95 or 96 or 97 or 98 or 99 or 100 or 101

103. (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.

104. (expenditure$ not energy).ti,ab.

105. (value adj1 money).ti,ab.

106. budget$.ti,ab.

107. 103 or 104 or 105 or 106

108. 102 or 107

109. 94 or 108

110. 83 and 109

111. remove duplicates from 110

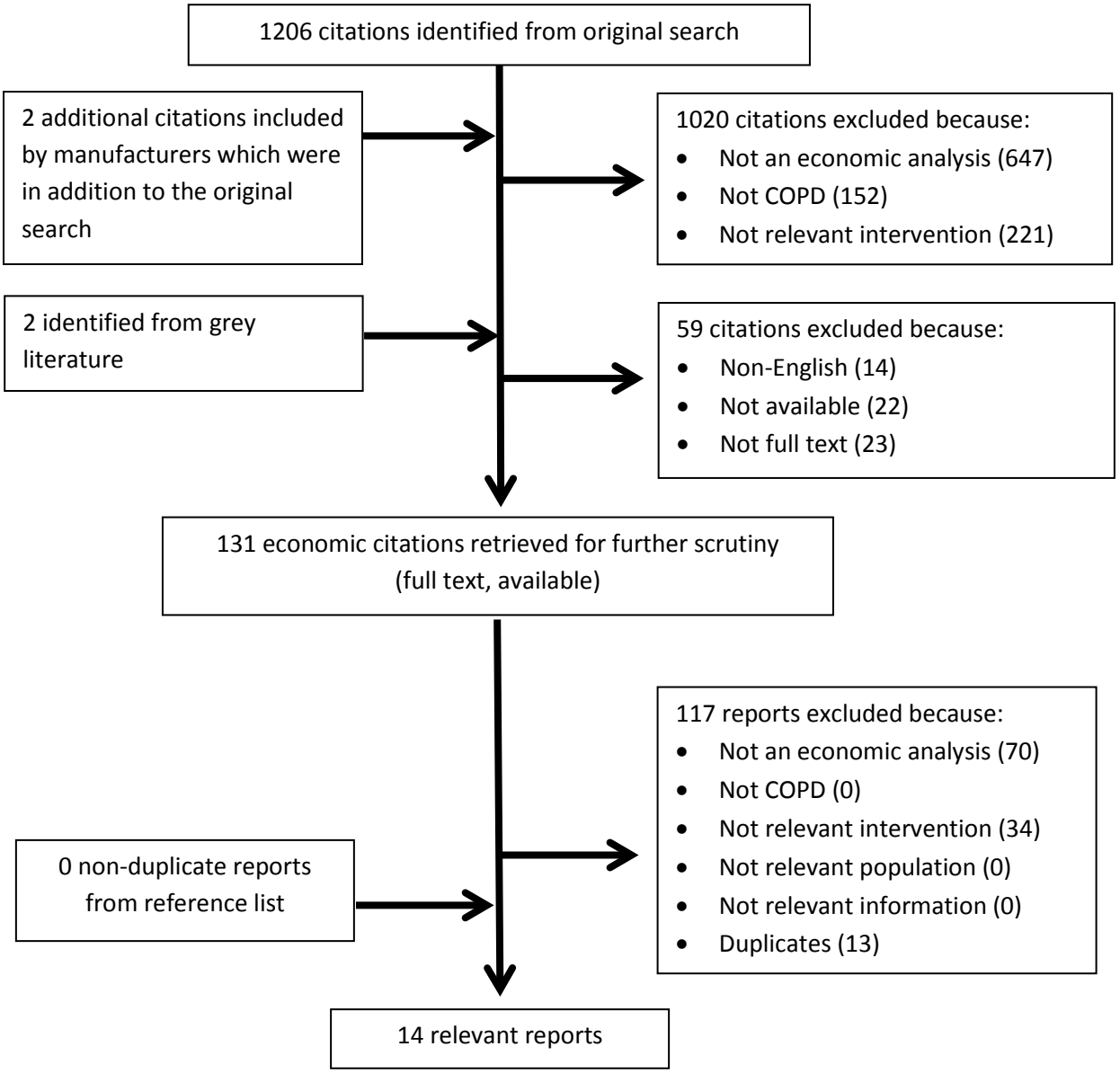
Appendix A2: List of Citations Included by Manufacturer

The following table lists studies which were included by the manufacturer in their evidence submission package.

Study Reference	Additional Citation From Original Search	Relevant Citation	Reason For Inclusion/Exclusion
FitzGerald JM, Haddon JM, Bradley-Kennedy C, et al. Resource use study in COPD (RUSIC): a prospective study to quantify the effects of COPD exacerbations on health care resource use among COPD patients. Can Respir J 2007; 14: 145-152.	Yes	No	This report examines health care resource use. It is therefore not an economic evaluation and as a result, is not considered a relevant study.
Mittmann N, Kuramoto L, Seung SJ, et al. The cost of moderate and severe COPD exacerbations to the Canadian healthcare system. Respir Med 2008; 102: 413-421.	Yes	No	This report reports the cost of exacerbations (reported as intent to treat analysis average cost and clinically evaluable analysis average cost) rather than the incremental cost effectiveness ratios. Therefore, this report is not considered an economic evaluation.
Najafzadeh M, Marra CA, Lynd LD, et al. Future Impact of Various Interventions on the Burden of COPD in Canada: A Dynamic Population Model. PLoS ONE 2012;7:e46746	No	No	This report compares LAMA+placebo, LABA+LAMA, ICS+LABA+LAMA. Relevant reports are those that compare LAMA alone or in combination with LABA and/or ICS to single or combination therapies of LABA and ICS.

Appendix A3: Results of Search

The following illustrates the selected studies for the review.



Appendix A4: List of Excluded Studies

The following table lists the studies excluded from the review in addition to the rationale for their exclusion.

Reference #	Study Reference	Reason for exclusion
19	Dalal AA, Shah MB, D'Souza AO, Lunacsek OE, Nagar SP, Crater GD. Observational study of the outcomes and costs of initiating maintenance therapies in patients with moderate exacerbations of COPD. Respir Res. 2012;13:41. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3490761	Not economic analysis
20	Yu AP, Guerin A, de Leon DP, Ramakrishnan K, Wu EQ, Mocarski M, et al. Clinical and economic outcomes of multiple versus single long-acting inhalers in COPD. Respir Med. 2011 Dec;105(12):1861-71.	Not economic analysis
21	Dalal AA, Roberts MH, Petersen HV, Blanchette CM, Mapel DW. Comparative cost-effectiveness of a fluticasone-propionate/salmeterol combination versus anticholinergics as initial maintenance therapy for chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2011;6:13-22. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3034283	Not economic analysis
22	Dalal AA, Roberts MH, Petersen HV, Blanchette CM, Mapel DW. Comparative cost-effectiveness of a fluticasone-propionate/salmeterol combination versus anticholinergics as initial maintenance therapy for chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2011;6:13-22. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3034283	Not economic analysis
23	Dalal AA, Shah M, D'Souza AO, Mapel DW. COPD-related healthcare utilization and costs after discharge from a hospitalization or emergency department visit on a regimen of fluticasone propionate-salmeterol combination versus other maintenance therapies. Am J Manag Care. 2011 Mar;17(3):e55-e65.	Not economic analysis
24	Hernandez C, Casas A, Escarrabill J, Alonso J, Puig-Junoy J, Farrero E, et al. Home hospitalisation of exacerbated chronic obstructive pulmonary disease patients. Eur Respir J. 2003 Jan;21(1):58-67.	Not economic analysis
25	Chaplin S, Turner A. Glycopyrronium (Seebri Breezhaler): Once-daily LAMA for COPD. Prescriber. 2013;24(21):30-4.	Not economic analysis
26	Dalal AA, Shah MB, D'Souza AO, Lunacsek OE, Nagar SP, Crater GD. Observational study of the outcomes and costs of initiating maintenance therapies in patients with moderate exacerbations of COPD. Respiratory Research. 2012;13:41.	Not economic analysis
27	Guarascio AJ, Ray SM, Finch CK, Self TH. The clinical and economic burden of chronic obstructive pulmonary disease in the USA. ClinicoEconomics and Outcomes Research. 2013;5(1):235-45.	Not economic analysis
28	Cazzola M, Rogliani P, Matera MG. Aclidinium bromide/formoterol fumAarate fixed-dose combination for the treatment of chronic obstructive pulmonary disease. Expert Opinion on Pharmacotherapy. 2013;14(6):775-81.	Not economic analysis
29	Tashkin DP. Tiotropium for the treatment of chronic obstructive pulmonary disease. Clinical Practice. 2013;10(2):141-55.	Not economic analysis

30	van AP. Zone in on: Drug spending: Generic-drug incursion and reduced demand contribute to modest gains. Pharmaceutical Technology. 2012;36(5):26.	Not economic analysis
31	Gross NJ, Hanania NA. The COPD pipeline XII. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2011;8(5):387-91.	Not economic analysis
32	Gross NJ. The COPD pipeline X. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2011;8(3):244-7.	Not economic analysis
33	Dalal AA, Shah MB, D'Souza AO, Lunacsek OE, Nagar SP, Crater GD. Observational study of the outcomes and costs of initiating maintenance therapies in patients with moderate exacerbations of COPD. Respiratory Research. 2012;13:41.	Not economic analysis
34	Park HY, Man SFP, Sin DD. Inhaled corticosteroids for chronic obstructive pulmonary disease. BMJ (Online). 2012;345(7882).	Not economic analysis
35	Gross NJ. The copd pipeline xviii. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2011;9(5):571-3.	Not economic analysis
36	Halpern R, Baker CL, Su J, Woodruff KB, Paulose-Ram R, Porter V, et al. Outcomes associated with initiation of tiotropium or fluticasone/salmeterol in patients with chronic obstructive pulmonary disease. Patient Preference and Adherence. 2011;5:375-88.	Not economic analysis
37	Mapel DW, Roberts MH. New Clinical insights into chronic obstructive pulmonary disease and their implications for pharmacoeconomic analyses. Pharmacoeconomics. 2012;30(10):869-85.	Not economic analysis
38	Dalal AA, Roberts MH, Petersen HV, Blanchette CM, Mapel DW. Comparative cost-effectiveness of a futicasone-propionate/salmeterol combination versus anticholinergics as initial maintenance therapy for chronic obstructive pulmonary disease. International Journal of COPD. 2011;6(1):13-22.	Not economic analysis
39	Kozma CM, Paris AL, Plauschinat CA, Slaton T, Mackowiak JI. Comparison of resource use by COPD patients on inhaled therapies with long-acting bronchodilators: a database study. BMC pulmonary medicine. 2011;11:61.	Not economic analysis
40	Chatterjee A, Shah M, D'Souza AO, Bechtel B, Crater G, Dalal AA. Observational study on the impact of initiating tiotropium alone versus tiotropium with fluticasone propionate/salmeterol combination therapy on outcomes and costs in chronic obstructive pulmonary disease. Respiratory Research. 2012;13:15.	Not economic analysis
41	Roberts MH, Dalal AA. Clinical and economic outcomes in an observational study of COPD maintenance therapies: Multivariable regression versus propensity score matching. International Journal of COPD. 2012;7:221-33.	Not economic analysis

42	Kozma CM, Paris AL, Plauschinat CA, Slaton T, Mackowiak JI. Comparison of resource use by COPD patients on inhaled therapies with long-acting bronchodilators: A database study. BMC pulmonary medicine. 2011;11.	Not economic analysis
43	Dalal AA, Candrilli SD, Davis KL. Outcomes and costs associated with initial maintenance therapy with fluticasone propionate-salmeterol xinafoate 250 microg/50 microg combination versus tiotropium in commercially insured patients with COPD. Managed care (Langhorne, Pa). 2011;20(8):46-55.	Not economic analysis
44	Dalal AA, Shah M, D'Souza AO, Mapel DW. COPD-related healthcare utilization and costs after discharge from a hospitalization or emergency department visit on a regimen of fluticasone propionate-salmeterol combination versus other maintenance therapies. American Journal of Managed Care. 2011;17(3):e55-e65.	Not economic analysis
45	Yu AP, Guerin A, de Leon DP, Ramakrishnan K, Wu EQ, Mocarski M, et al. Clinical and economic outcomes of multiple versus single long-acting inhalers in COPD. Respiratory Medicine. 2011;105(12):1861-71.	Not economic analysis
46	Cao Z, Zou KH, Baker CL, Su J, Paulose-Ram R, Durden E, et al. Respiratory-related medical expenditure and inpatient utilisation among COPD patients receiving long-acting bronchodilator therapy. Journal of Medical Economics. 2011;14(2):147-58.	Not economic analysis
47	Gross NJ. The COPD pipeline VIII. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2011;8(1):52-4.	Not economic analysis
48	Gross N. The COPD pipeline V. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2010;7(4):307-9.	Not economic analysis
49	White P. COPD in primary care: A time of opportunity. British Journal of General Practice. 2010;60(576):477-8.	Not economic analysis
50	Vestbo J. Choice of medications when treating stable COPD. Clinical Respiratory Journal. 2010;4(4):195-6.	Not economic analysis
51	Gross NJ. The COPD pipeline II. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2010;7(1):76-8.	Not economic analysis
52	Alifano M, Cuvelier A, Delage A, Roche N, Lamia B, Molano LC, et al. Treatment of COPD: From pharmacological to instrumental therapies. European Respiratory Review. 2010;19(115):7-23.	Not economic analysis
53	Dalal AA, Petersen H, Simoni-Wastila L, Blanchette CM. Healthcare costs associated with initial maintenance therapy with fluticasone propionate 250 mug/salmeterol 50 mug combination versus anticholinergic bronchodilators in elderly US Medicare-eligible beneficiaries with COPD. Journal of Medical Economics. 2009;12(4):339-47.	Not economic analysis
54	Simoni-Wastila L, Blanchette CM, Qian J, Yang H, Zhao L, Zuckerman IH, et al. Burden of chronic obstructive pulmonary disease in medicare beneficiaries residing in long-term care facilities. American Journal Geriatric Pharmacotherapy. 2009;7(5):262-70.	Not economic analysis

55	Mamary AJ, Criner GJ. Tiotropium bromide for chronic obstructive pulmonary disease. Expert Review of Respiratory Medicine. 2009;3(3):211-20.	Not economic analysis
56	Miravitlles M, Brosa M, Velasco M, Crespo C, Gobartt E, Diaz S, et al. An economic analysis of pharmacological treatment of COPD in Spain. Respiratory Medicine. 2009;103(5):714-21.	Not economic analysis
57	Tashkin DP. The role of tiotropium in the hospital management of exacerbation of chronic obstructive pulmonary disease. Respiratory Care. 2008;53(12):1657-9.	Not economic analysis
58	Chambers S, Schachter M, Price D, Kassianos G, Gaw A, Kirby M, et al. Tiotropium - Advancing the treatment of COPD. Drugs in Context. 2008;4(1):15-28.	Not economic analysis
59	Akazawa M, Hayflinger DC, Stanford RH, Blanchette CM. Economic assessment of initial maintenance therapy for chronic obstructive pulmonary disease. American Journal of Managed Care. 2008;14(7):438-48.	Not economic analysis
60	Reddy CB, Kanner RE. Is combination therapy with inhaled anticholinergics and beta2-adrenoceptor agonists justified for chronic obstructive pulmonary disease? Drugs and Aging. 2007;24(8):615-28.	Not economic analysis
61	Herrick TM, Million RP. Tapping the potential of fixed-dose combinations. Nature Reviews Drug Discovery. 2007;6(7):513-4.	Not economic analysis
62	Patients with severe COPD may benefit from the addition of an inhaled corticosteroid. Formulary. 2007;42(3):178-183.	Not economic analysis
63	Varkey B. Weighing the benefits and risks of inhaled corticosteroids. Current Opinion in Pulmonary Medicine. 2007;13(2):89.	Not economic analysis
64	Saha S, Siva R, Brightling CE, Pavord ID. COPD: An inhaled corticosteroid-resistant, oral corticosteroid-responsive condition. European Respiratory Journal. 2006;27(4):863-5.	Not economic analysis
65	Molken MRV, Lee TA. Economic modeling in chronic obstructive pulmonary disease. Proceedings of the American Thoracic Society. 2006;3(7):630-4.	Not economic analysis
66	Sullivan SD, Briggs A. Improving survival in chronic obstructive pulmonary disease: Assessing the value of life-saving therapy. Proceedings of the American Thoracic Society. 2006;3(7):617-8.	Not economic analysis
67	Shaya FT, El Khoury AC, Samant ND, Scharf SM. Utilization of health care resources in a high-risk medicaid population with chronic obstructive pulmonary disease. P and T. 2006;31(5):261-8.	Not economic analysis
68	Jones D. Long-acting inhaled bronchodilators for COPD--lack of logic continues. The New Zealand medical journal. 2005;118(1222):U1669.	Not economic analysis
69	Kripke C. Tiotropium effective in treatment of COPD. American Family Physician. 2005;72(11).	Not economic analysis
70	Jones D. Long-acting inhaled bronchodilators for COPD - Lack of logic continues. New Zealand Medical Journal. 2005;118(1222).	Not economic analysis

71	Rich A. Corticosteroids and chronic obstructive pulmonary disease in the Nursing Home. Journal of the American Medical Directors Association. 2005;6(3 Suppl):S67-S74.	Not economic analysis
72	Fishman AP. One hundred years of chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine. 2005;171(9):941-8.	Not economic analysis
73	Cooper CB, Tashkin DP. Recent developments in inhaled therapy in stable chronic obstructive pulmonary disease. British Medical Journal. 2005;330(7492):640-4.	Not economic analysis
74	Bryan J. Novel inhaler devices: Balancing innovation against price is important. Pharmaceutical Journal. 2005;274(7338):241-2.	Not economic analysis
75	Izquierdo-Alonso JL, De Miguel-Diez J. Economic impact of pulmonary drugs on direct costs of stable chronic obstructive pulmonary disease. COPD. 2004;1(2):215-23.	Not economic analysis
76	Lee TA, Weiss KB, Sullivan SD, Sin DD, Golmohammadi K, Jacobs P. Cost-effectiveness of inhaled corticosteroids in chronic obstructive pulmonary disease (multiple letters). American Journal of Medicine. 2004;117(8):618-9.	Not economic analysis
77	Mundy C, Kirkpatrick P. Tiotropium bromide. Nature Reviews Drug Discovery. 2004;3(8):643-4.	Not economic analysis
78	ZuWallack AR, ZuWallack RL. Tiotropium bromide, a new, once-daily inhaled anticholinergic bronchodilator for chronic-obstructive pulmonary disease. Expert Opinion on Pharmacotherapy. 2004;5(8):1827-35.	Not economic analysis
79	Friedman M, Menjoge SS, Anton SF, Kesten S. Healthcare costs with tiotropium plus usual care versus usual care alone following 1 year of treatment in patients with Chronic Obstructive Pulmonary Disorder (COPD). Pharmacoeconomics. 2004;22(11):741-9.	Not economic analysis
80	Hutton SF. Tiotropium (Spiriva) for COPD. American Family Physician. 2004;69(12):2901-2.	Not economic analysis
81	Cazzola M, Matera MG. Long-Acting Bronchodilators Are the First-Choice Option for the Treatment of Stable COPD. Chest. 2004;125(1):9-11.	Not economic analysis
82	De BW. Inhaled salmeterol/fluticasone propionate combination in chronic obstructive pulmonary disease. American Journal of Respiratory Medicine. 2002;1(4):283.	Not economic analysis
83	New in the marketplace. Drugs and Therapy Perspectives. 2005;18(11):26.	Not economic analysis
84	Faulkner MA, Hilleman DE. The economic impact of chronic obstructive pulmonary disease. Expert Opinion on Pharmacotherapy. 2002;3(3):219-28.	Not economic analysis
85	Frith P, McKenzie D, Pierce R. Management of chronic obstructive pulmonary disease in the twenty-first century. Internal Medicine Journal. 2001;31(9):508-11.	Not economic analysis
86	Pingleton SK. Pulmonary medicine. Journal of the American Medical	Not economic

	Association. 1996;275(23):1849-50.	analysis
87	Rogol PR, Hahn DL, Kerstjens HAM, Brand PLP, Postma DS. Bronchodilator therapy with or without inhaled corticosteroid therapy for obstructive airways disease. New England Journal of Medicine. 1993;328(14):1044-5.	Not economic analysis
88	Najafzadeh M, Marra CA, Lynd LD, Sadatsafavi M, FitzGerald JM, McManus B, et al. Future impact of various interventions on the burden of COPD in Canada: a dynamic population model. PLoS One. 2012;7(10):e46746. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3469627	Not relevant intervention
89	Hettle R, Wouters H, Ayres J, Gani R, Kelly S, Lion M, et al. Cost-utility analysis of tiotropium versus usual care in patients with COPD in the UK and Belgium. Respir Med. 2012 Dec;106(12):1722-33.	Not relevant intervention
90	Menn P, Leidl R, Holle R. A lifetime Markov model for the economic evaluation of chronic obstructive pulmonary disease. Pharmacoeconomics. 2012 Sep 1;30(9):825-40.	Not relevant intervention
91	Hoogendoorn M, Rutten-van Molken MP, Hoogenveen RT, Al MJ, Feenstra TL. Developing and applying a stochastic dynamic population model for chronic obstructive pulmonary disease. Value Health. 2011 Dec;14(8):1039-47.	Not relevant intervention
92	Zaniolo O, Iannazzo S, Pradelli L, Miravitlles M. Pharmacoeconomic evaluation of tiotropium bromide in the long-term treatment of chronic obstructive pulmonary disease (COPD) in Italy. Eur J Health Econ. 2012 Feb;13(1):71-80.	Not relevant intervention
93	Hoogendoorn M, Rutten-van Molken MP, Hoogenveen RT, van Genugten ML, Buist AS, Wouters EF, et al. A dynamic population model of disease progression in COPD. Eur Respir J. 2005 Aug;26(2):223-33.	Not relevant intervention
94	Spencer M, Briggs AH, Grossman RF, Rance L. Development of an economic model to assess the cost effectiveness of treatment interventions for chronic obstructive pulmonary disease. Pharmacoeconomics. 2005;23(6):619-37.	Not relevant intervention
95	Borg S, Ericsson A, Wedzicha J, Gulsvik A, Lundback B, Donaldson GC, et al. A computer simulation model of the natural history and economic impact of chronic obstructive pulmonary disease. Value Health. 2004 Mar;7(2):153-67.	Not relevant intervention
96	Chandra K, Blackhouse G, McCurdy BR, Bornstein M, Campbell K, Costa V, et al. Cost-effectiveness of interventions for chronic obstructive pulmonary disease (COPD) using an Ontario policy model. Ont Health Technol Assess Ser. 2012;12(12):1-61. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3384363	Not relevant intervention
97	Hettle R, Wouters H, Ayres J, Gani R, Kelly S, Lion M, et al. Cost-utility analysis of tiotropium versus usual care in patients with COPD in the UK and Belgium. Respir Med. 2012 Dec;106(12):1722-33.	Not relevant intervention
98	Najafzadeh M, Marra CA, Lynd LD, Sadatsafavi M, FitzGerald JM,	Not relevant

	McManus B, et al. Future impact of various interventions on the burden of COPD in Canada: a dynamic population model. PLoS One. 2012;7(10):e46746. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3469627	intervention
99	Zaniolo O, Iannazzo S, Pradelli L, Miravitlles M. Pharmacoeconomic evaluation of tiotropium bromide in the long-term treatment of chronic obstructive pulmonary disease (COPD) in Italy. Eur J Health Econ. 2012 Feb;13(1):71-80.	Not relevant intervention
100	Dalal AA, Shah M, D'Souza AO, Crater GD. Rehospitalization risks and outcomes in COPD patients receiving maintenance pharmacotherapy. Respir Med. 2012 Jun;106(6):829-37.	Not relevant intervention
101	Hoogendoorn M, Rutten-van Molken MP, Hoogenveen RT, Al MJ, Feenstra TL. Developing and applying a stochastic dynamic population model for chronic obstructive pulmonary disease. Value Health. 2011 Dec;14(8):1039-47.	Not relevant intervention
102	Mapel DW, Schum M, Lydick E, Marton JP. A new method for examining the cost savings of reducing COPD exacerbations. Pharmacoeconomics. 2010;28(9):733-49.	Not relevant intervention
103	Dal NR, Eandi M, Pradelli L, Iannazzo S. Cost-effectiveness and healthcare budget impact in Italy of inhaled corticosteroids and bronchodilators for severe and very severe COPD patients. Int J Chron Obstruct Pulmon Dis. 2007;2(2):169-76. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2695615	Not relevant intervention
104	Lee KH, Phua J, Lim TK. Evaluating the pharmacoeconomic effect of adding tiotropium bromide to the management of chronic obstructive pulmonary disease patients in Singapore. Respir Med. 2006 Dec;100(12):2190-6.	Not relevant intervention
105	Spencer M, Briggs AH, Grossman RF, Rance L. Development of an economic model to assess the cost effectiveness of treatment interventions for chronic obstructive pulmonary disease. Pharmacoeconomics. 2005;23(6):619-37.	Not relevant intervention
106	Hettle R, Wouters H, Ayres J, Gani R, Kelly S, Lion M, et al. Cost-utility analysis of tiotropium versus usual care in patients with COPD in the UK and Belgium. Respiratory Medicine. 2012;106(12):1722-33.	Not relevant intervention
107	Zaniolo O, Iannazzo S, Pradelli L, Miravitlles M. Pharmacoeconomic evaluation of tiotropium bromide in the long-term treatment of chronic obstructive pulmonary disease (COPD) in Italy. European Journal of Health Economics. 2012;13(1):71-80.	Not relevant intervention
108	Neyt M, Devriese S, Thiry N, Van den BA. Tiotropium's cost-effectiveness for the treatment of COPD: A cost-utility analysis under real-world conditions. BMC pulmonary medicine. 2010;10:47.	Not relevant intervention
109	Lee K-H, Phua J, Lim T-K. Evaluating the pharmacoeconomic effect of adding tiotropium bromide to the management of chronic obstructive pulmonary disease patients in Singapore. Respiratory Medicine. 2006;100(12):2190-6.	Not relevant intervention

110	Spencer M, Briggs AH, Grossman RF, Rance L. Development of an economic model to assess the cost effectiveness of treatment interventions for chronic obstructive pulmonary disease. Pharmacoeconomics. 2005;23(6):619-37.	Not relevant intervention
111	Jones PW, Wilson K, Sondhi S. Cost-effectiveness of salmeterol in patients with chronic obstructive pulmonary disease: An economic evaluation. Respiratory Medicine. 2003;97(1):20-6.	Not relevant intervention
112	Najafzadeh M, Marra CA, Sadatsafavi M, Aaron SD, Sullivan SD, Vandemheen KL, et al. Cost effectiveness of therapy with combinations of long acting bronchodilators and inhaled steroids for treatment of COPD. Thorax. 2008;63(11):962-7.	Not relevant intervention
113	Najafzadeh M, Marra CA, Sadatsafavi M, Aaron SD, Sullivan SD, Vandemheen KL, et al. Cost effectiveness of therapy with combinations of long acting bronchodilators and inhaled steroids for treatment of COPD. Thorax. 2008;63(11):962-7.	Not relevant intervention
114	Nielsen R, Kankaanranta H, Bjermer L, Lange P, Arnetorp S, Hedegaard M, et al. Cost effectiveness of adding budesonide/formoterol to tiotropium in COPD in four Nordic countries. Respiratory Medicine. 2013;107(11):1709-21.	Not relevant intervention
115	Neyt M, Devriese S, Thiry N, Van den BA. Tiotropium's cost-effectiveness for the treatment of COPD: a cost-utility analysis under real-world conditions. BMC Pulm Med. 2010;10:47. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2954895	Not relevant intervention
116	Neyt M, Devriese S, Thiry N, Van den BA. Tiotropium's cost-effectiveness for the treatment of COPD: a cost-utility analysis under real-world conditions. BMC pulmonary medicine. 2010;10:47.	Not relevant intervention
117	Gaebel K, Blackhouse G, Robertson D, Xie F, Assasi N, McIvor A, et al. Triple Therapy for Moderate-to-Severe Chronic Obstructive Pulmonary Disease. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2010 May. [cited 2013 Dec 3]. Available from: http://www.cadth.ca/index.php/en/hta/reports-publications/search/publication/1690	Not relevant intervention
118	Mittmann N, Hernandez P, Mellstrm C, Brannman L, Welte T. Cost effectiveness of budesonide/formoterol added to tiotropium bromide versus placebo added to tiotropium bromide in patients with chronic obstructive pulmonary disease: Australian, Canadian and Swedish healthcare perspectives. Pharmacoeconomics. 2011;29(5):403-14.	Not relevant intervention
119	Najafzadeh M, Marra CA, Sadatsafavi M, Aaron SD, Sullivan SD, Vandemheen KL, et al. Cost effectiveness of therapy with combinations of long acting bronchodilators and inhaled steroids for treatment of COPD. Thorax. 2008;63(11):962-7.	Not relevant intervention
120	Nielsen R, Kankaanranta H, Bjermer L, Lange P, Arnetorp S, Hedegaard M, et al. Cost effectiveness of adding budesonide/formoterol to tiotropium in COPD in four Nordic countries. Respir Med. 2013 Nov;107(11):1709-21.	Not relevant intervention

121	Neyt M, Devriese S, Thiry N, Van den BA. Tiotropium's cost-effectiveness for the treatment of COPD: a cost-utility analysis under real-world conditions. BMC Pulm Med. 2010;10:47. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2954895	Not relevant intervention
122	Gani R, Griffin J, Kelly S, Rutten-van MM. Economic analyses comparing tiotropium with ipratropium or salmeterol in UK patients with COPD. Prim Care Respir J. 2010 Mar;19(1):68-74.	Duplicate
123	Hertel N, Kotchie RW, Samyshkin Y, Radford M, Humphreys S, Jameson K. Cost-effectiveness of available treatment options for patients suffering from severe COPD in the UK: a fully incremental analysis. Int J Chron Obstruct Pulmon Dis. 2012;7:183-99. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3325000	Duplicate
124	Hoogendoorn M, Al MJ, Beeh KM, Bowles D, Graf von der Schulenburg JM, Lungershausen J, et al. Cost-effectiveness of tiotropium versus salmeterol: the POET-COPD trial. Eur Respir J. 2013 Mar;41(3):556-64.	Duplicate
125	Hoogendoorn M, Al MJ, Beeh K-M, Bowles D, Von Der Schulenburg JMG, Lungershausen J, et al. Cost-effectiveness of tiotropium versus salmeterol: The POET-COPD trial. European Respiratory Journal. 2013;41(3):556-64.	Duplicate
126	Hertel N, Kotchie RW, Samyshkin Y, Radford M, Humphreys S, Jameson K. Cost-effectiveness of available treatment options for patients suffering from severe COPD in the UK: A fully incremental analysis. International Journal of COPD. 2012;7:183-99.	Duplicate
127	Hoogendoorn M, Kappelhoff BS, Overbeek JA, Wouters EF, Rutten-van Molken MP. Which long-acting bronchodilator is most cost-effective for the treatment of COPD? Neth J Med. 2012 Oct;70(8):357-64.	Duplicate
128	Hoogendoorn M, Kappelhoff BS, Overbeek JA, Wouters EF, Rutten-van Molken MP. Which long-acting bronchodilator is most cost-effective for the treatment of COPD? The Netherlands journal of medicine. 2012;70(8):357-64.	Duplicate
129	Maniadakis N, Tzanakis N, Fragoulakis V, Hatzikou M, Siafakas N. Economic evaluation of tiotropium and salmeterol in the treatment of chronic obstructive pulmonary disease (COPD) in Greece. Current Medical Research and Opinion. 2006;22(8):1599-607.	Duplicate
130	Naik S, Kamal KM, Keys PA, Mattei TJ. Evaluating the cost-effectiveness of tiotropium versus salmeterol in the treatment of chronic obstructive pulmonary disease. ClinicoEconomics and Outcomes Research. 2010;2(1):25-36.	Duplicate
131	Oba Y. Cost-effectiveness of long-acting bronchodilators for chronic obstructive pulmonary disease. Mayo Clinic Proceedings. 2007;82(5):575-82.	Duplicate
132	Oostenbrink JB, Rutten-Van Molken MPMH, Monz BU, FitzGerald JM. Probabilistic Markov model to assess the cost-effectiveness of bronchodilator therapy in COPD patients in different countries.	Duplicate

	Value in Health. 2005;8(1):32-46.	
[133]	Rutten-van Molken MP, Oostenbrink JB, Miravitlles M, Monz BU. Modelling the 5-year cost effectiveness of tiotropium, salmeterol and ipratropium for the treatment of chronic obstructive pulmonary disease in Spain. Eur J Health Econ. 2007 Jun;8(2):123-35. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1913175	Duplicate
[134]	Rutten-Van Molken MPMH, Oostenbrink JB, Miravitlles M, Monz BU. Modelling the 5-year cost effectiveness of tiotropium, salmeterol and ipratropium for the treatment of chronic obstructive pulmonary disease in Spain. European Journal of Health Economics. 2007;8(2):123-35.	Duplicate

Appendix A5: List of Included Studies

The following table lists the studies included within the review.

Reference #	Study Reference
5	Gani R, Griffin J, Kelly S, Rutten-van MM. Economic analyses comparing tiotropium with ipratropium or salmeterol in UK patients with COPD. Prim Care Respir J. 2010 Mar;19(1):68-74.
14	Guillermo AJ, Thuresson P-O, Machnicki G, Mungapen L, Kraemer M, Asukai Y, et al. The Cost-Effectiveness and Budget Impact of Introducing Indacaterol into the Colombian Health System. Value in Health Regional Issues. 2012;1(2):165-71.
4	Hertel N, Kotchie RW, Samyshkin Y, Radford M, Humphreys S, Jameson K. Cost-effectiveness of available treatment options for patients suffering from severe COPD in the UK: a fully incremental analysis. Int J Chron Obstruct Pulmon Dis. 2012;7:183-99. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3325000
3	Hoogendoorn M, Al MJ, Beeh KM, Bowles D, Graf von der Schulenburg JM, Lungershausen J, et al. Cost-effectiveness of tiotropium versus salmeterol: the POET-COPD trial. Eur Respir J. 2013 Mar;41(3):556-64.
2	Hoogendoorn M, Kappelhoff BS, Overbeek JA, Wouters EF, Rutten-van Molken MP. Which long-acting bronchodilator is most cost-effective for the treatment of COPD? Neth J Med. 2012 Oct;70(8):357-64.
7	Maniadakis N, Tzanakis N, Fragoulakis V, Hatzikou M, Siafakas N. Economic evaluation of tiotropium and salmeterol in the treatment of chronic obstructive pulmonary disease (COPD) in Greece. Curr Med Res Opin. 2006 Aug;22(8):1599-607.
12	Naik S, Kamal KM, Keys PA, Mattei TJ. Evaluating the cost-effectiveness of tiotropium versus salmeterol in the treatment of chronic obstructive pulmonary disease. Clinicoecon Outcomes Res. 2010;2:25-36. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3169962
8	National Clinical Guideline Centre. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care. London: National Clinical Guideline Centre; 2010 Jun. [cited 2013 Dec 3]. Available from: http://guidance.nice.org.uk/CG101/Guidance/pdf/English
13	Oba Y. Cost-effectiveness of long-acting bronchodilators for chronic obstructive pulmonary disease. Mayo Clin Proc. 2007 May;82(5):575-82.
11	Oostenbrink JB, Al MJ, Oppe M, Rutten-Van Molken MPMH. Expected value of perfect information: An empirical example of reducing decision uncertainty by conducting additional research. Value in Health. 2008;11(7):1070-80.
1	Oostenbrink JB, Rutten-van Molken MP, Monz BU, FitzGerald JM. Probabilistic Markov model to assess the cost-effectiveness of bronchodilator therapy in COPD patients in different countries. Value Health. 2005 Jan;8(1):32-46.
9	Price D, Asukai Y, Ananthapavan J, Malcolm B, Radwan A, Keyzor I. A UK-based cost-utility analysis of indacaterol, a once-daily maintenance bronchodilator for patients with COPD, using real world evidence on resource use. Applied Health Economics and Health Policy. 2013;11(3):259-74.

Reference #	Study Reference
10	Price D, Gray A, Gale R, Asukai Y, Mungapen L, Lloyd A, et al. Cost-utility analysis of indacaterol in Germany: A once-daily maintenance bronchodilator for patients with COPD. Respiratory Medicine. 2011;105(11):1635-47.
6	Rutten-van Molken MP, Oostenbrink JB, Miravitlles M, Monz BU. Modelling the 5-year cost effectiveness of tiotropium, salmeterol and ipratropium for the treatment of chronic obstructive pulmonary disease in Spain. Eur J Health Econ. 2007 Jun;8(2):123-35. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1913175

Appendix A6: Characteristics of Reviewed Studies

The following tables list characteristics of reviewed studies.

Study	Oostenbrink et al., 2005
Sponsorship	Boehringer Ingelheim GmbH
Country	Netherlands and Canada
Perspective	Health care perspective
Study type	CEA/CUA
Comparators	LAMA (tiotropium) LABA (salmeterol)
Populations	Patients with moderate to very severe COPD based on the GOLD criteria Age not specified
Time horizon	1 year
Type of model	Markov
Cycle length	First cycle, 8 days; subsequent cycles, 1 month
Efficacy inputs	Exacerbation
Adverse events	Not included
Utilities	EQ-5D
Discounting	N/A
Outcomes	Incremental cost per exacerbation avoided Incremental cost per quality-adjusted life months
Results	Netherlands LAMA dominated LABA Canada ICERs for LAMA versus LABA were €17.65 per exacerbation avoided and €12.00 per quality life adjusted months
Types of sensitivity analysis	Deterministic analysis (scenarios) Transition probabilities Exacerbations Utilities Cost of oxygen therapy 100% at baseline in moderate, severe and very severe disease Probabilistic analysis (Monte Carlo Simulation) Transition probabilities (Dirichlet) Resource use (gamma) Utilities (beta) Exacerbation (beta)

Study	Oostenbrink et al., 2005
Sensitivity analysis results	Deterministic analysis (scenarios) For the Netherlands, results were reported as ceiling ratios ranging from €0 to ≥ €8,500 per exacerbation avoided and ≥€1,120 per quality adjusted life months For Canada, results were reported as ceiling ratios ranging from €0 to ≥ €11,000 per exacerbation avoided and ≥ €2,720 per quality adjusted life months for Canada Probabilistic analysis (Monte Carlo Simulation) In Canada, the probability of LAMA being cost-effective or dominant (in the right quadrant) was 95%. In the Netherlands, the probability of LAMA being cost effective at €500 was 60%.
Points to consider	Costs €(2001) Efficacy data from six RCT Adverse events not included Utilities derived from EQ-5D Comparison of monotherapies (LAMA, LABA) Outcome considered quality adjusted life months, not typical QALY Probabilistic sensitivity analysis included relevant distributions for handling uncertainty

Study	Hoogendoorn et al., 2013
Sponsorship	Boehringer Ingelheim International GmbH
Country	Germany
Perspective	German statutory health insurance perspective Societal perspective
Study type	CEA/CUA
Comparators	LAMA (tiotropium) LABA (salmeterol)
Populations	Patients with moderate to very severe COPD based on the GOLD criteria Mean age of 63 years
Time horizon	1 year 5 year
Type of model	Trial based Markov model
Cycle length	1 month
Efficacy inputs	Exacerbation QALY
Adverse events	Not included
Utilities	EQ-5D

Study	Hoogendoorn et al., 2013
Discounting	Costs and outcomes @ 3%
Outcomes	Incremental cost per exacerbation avoided Incremental cost per exacerbation day avoided Incremental cost per QALY
Results	SHI perspective Using a trial based model and a one year time frame, the ICERs for LAMA versus LABA were €1,961 per exacerbations avoided and €118 per exacerbation day avoided Using a Markov model and one year time frame, the ICURs for LAMA versus LABA were €9,926 per QALY and €3,488 per QALY with a five year time horizon Societal perspective Using a trial based model and a five year time frame, the ICERs for LAMA versus LABA were €2,647 per exacerbations avoided and €159 per exacerbation day avoided Using a Markov model and one year time frame, the ICURs for LAMA versus LABA were €16,771per QALY and €8,141 per QALY with a five year time horizon
Types of sensitivity analysis	Deterministic analysis (one-way) Distinct COPD severity population (100% moderate, 100% severe, 100% very severe) Exacerbation probabilities Costs Utilities Discounting Resource use Treatment effect Non parametric Bootstrap Method 1000 iterations
Sensitivity analysis results	Deterministic analysis (one-way) Results insensitive to distinct COPD severity population, exacerbation probabilities, costs, utilities, discounting, resource use, treatment effect Non parametric bootstrap method Using a trial based model and SHI perspective, at a willingness to pay of €5,000 per exacerbation avoided, the probability of LAMA being the most cost-effective is 90%; and 82% using a societal perspective Using a Markov model and five year time frame, at a willingness to pay of €20,000 per QALY, the probability of LAMA being the most cost-effective is 62.5% using a SHI perspective

Study	Hoogendoorn et al., 2013
Points to consider	Costs € (2010) Efficacy data derived from a RCT (trial based) and meta-analysis of POET-COPD trial and four other RCT (Markov) Intermediate and final outcomes considered Adverse events not included Utility values derived from EQ-5D Deterministic analysis considered distinct severity populations Comparison of monotherapies (LAMA, LABA) Two models (trial based and Markov) and two time horizons (1,5 years) were considered

Study	Price et al, 2013
Sponsorship	Novartis Pharmaceuticals, UK Limited
Country	UK
Perspective	UK National Health Service (health care payer) perspective
Study type	CUA
Comparators (Relevant)	LAMA (tiotropium 18 µg) LABA (indacaterol 150 µg, 300 µg)
Populations	Patients with moderate to very severe COPD based on GOLD criteria Mean age 64 years
Time horizon	3 years 5 years Lifetime (20 years)
Type of model	Markov
Cycle length	3 months
Efficacy inputs	Exacerbation Quality of Life
Adverse events	Not included
Utilities	EQ-5D
Discounting	Costs and outcomes @ 3.5%
Outcomes	Incremental cost per QALY
Results	LABA (indacaterol) dominated LAMA

Study	Price et al, 2013
Types of sensitivity analysis	Deterministic analysis (one way) Time horizon Mortality rates Discontinuation rates Utilities Baseline population model Treatment effect Natural history of disease Cost of maintenance Cost of exacerbation Probabilistic analysis (Monte Carlo simulation) Costs and resource use (gamma) Utilities (beta) Rate ratios (log normal)
Sensitivity analysis results	Deterministic analysis (one way) In general results were insensitive to deterministic analysis. All patients started at moderate COPD and the mortality rates used in the analysis were the main drivers for uncertainty Probabilistic sensitivity (Monte Carlo Simulation) At a willingness to pay of £20,000 per QALY, indacaterol has the highest probability of being cost effective compared to tiotropium
Points to consider	Cost £(2011) Efficacy data derived from one randomized trial Adverse events not included Utilities derived from EQ-5D Comparison of monotherapies (LAMA, LABAs)

Study	Guillermo Ariza et al., 2012
Sponsorship	Novartis
Country	Colombia
Perspective	Health care payer perspective
Study type	CEA/CUA
Comparators	LABA [Onbrez Breezhaler (indacaterol)] LAMA [Spiriva (tiotropium)]
Population	Patients with mild to very severe COPD based on the GOLD criteria Age not specified
Time horizon	5 year
Type of model	Markov

Study	Guillermo Ariza et al., 2012
Cycle length	3 months
Efficacy inputs	FEV_1 Exacerbation
Adverse events	Not included
Utilities	EQ-5D
Discounting	Costs and outcomes at 5%
Outcomes	Increment cost per LY gained Increment cost per QALY
Results	ICERs for LABA versus LAMA were $2,899 per LY gained and $2,584 per QALY
Types of sensitivity analysis	Deterministic analysis (one-way) Cost of LABA Probabilistic analysis (Monte Carlo simulation) Transition probability (Dirichlet distribution) Costs (gamma distribution) Utilities (beta distribution) Treatment effect (log normal distribution)
Sensitivity analysis results	Deterministic analysis (one-way) If the price per day of LABA was lowered to $2.14 from $2.17, LABA would dominate LAMA. Probabilistic analysis (Monte Carlo simulation) 47.2% of 1000 simulations indicated that LAMA was cost effective
Points to consider	Costs USD$(2012), conversion 1 USD$ = 1771.13 COP Efficacy data from a single RCT Adverse events not included Utilities derived from the EQ-5D PSA considered Dirichlet (for transition probability), gamma (for costs), beta (for utilities), and log normal (for treatment effect) distributions, results presented in scatterplot Comparison of monotherapies (LABA and LAMA)

Study	Hertel et al., 2012
Sponsorship	MSD Ltd
Country	UK
Perspective	Healthcare system perspective
Study type	CEA/CUA

Study	Hertel et al., 2012
Comparators (relevant)	LABA (salmeterol) LAMA (tiotropium) LABA + LAMA (salmeterol + tiotropium) ICS+LABA (salmeterol/fluticasone) ICS+LABA + LAMA (salmeterol/fluticasone plus tiotropium)
Population	Patients with severe COPD based on the GOLD criteria, associated with chronic bronchitis, with a history of frequent exacerbations and continue to have exacerbation despite existing bronchodilator therapy Assumed to start at age 64
Time horizon	Lifetime [30 years]
Type of model	Markov
Cycle length	1 month
Efficacy inputs	Exacerbations
Adverse events	Not included
Utilities	EQ-5D
Discounting	Costs and outcomes at 3.5%
Outcomes	Mean costs, LYs and QALYs Incremental cost per life years and QALYs gained for relevant comparisons not provided.
Results	For ICS tolerant patients, the ranking of treatments in terms of their estimated QALYs (from lowest to highest) was LABA, LAMA, ICS+LABA, LABA +LAMA then ICS+LABA + LAMA. The treatments had the same ranking in terms of estimated lifetime costs. For ICS intolerant patients, the ranking of treatments in terms of their estimated QALYs (from lowest to highest) was LABA, LAMA, LABA +LAMA. The treatments had the same ranking in terms of estimated lifetime costs.

Study	Hertel et al., 2012
Types of sensitivity analysis	Deterministic analysis (one-way) Treatment effect Adverse events Costs Utilities Natural history of disease Discounting Patient characteristics Deterministic analysis (scenario) Assumptions of exacerbations Assumption of lung function benefit Assumptions of transition cycle Assumption of treatment switching Probabilistic analysis (Monte Carlo simulation) Parameter distributions not provided
Sensitivity analysis results	Results presented only for ICS+LABA + LAMA+ PDE-4 versus ICS+LABA + LAMA
Points to consider	Costs £(2008-11) Efficacy data from published mixed treatment comparison Results reported as mean costs and outcomes, incremental cost effectiveness ratios for relevant comparison not provided Adverse events not included Utilities derived from the EQ-5D Extensive sensitive analyses; however, results are not presented for relevant comparisons Distinct COPD severity population modelled Parameter distributions for PSA not provided Comparison of monotherapies (LAMA, LABA), dual therapies (ICS/LABA, LABA + LAMA) and triple therapy (LAMA+ ICS+LABA)

Study	Hoogendoom et al. 2012
Sponsorship	Boehringer Ingelheim
Country	Netherlands
Perspective	Health care system Societal
Study type	CEA/CUA
Comparators	LAMA (tiotropium) LABA (salmeterol)

Study	Hoogendoom et al. 2012
Populations	Patients with moderate to very severe COPD based on the GOLD criteria Age not specified
Time horizon	1 year 5 years
Type of model	Markov
Cycle length	1 month
Efficacy inputs	Exacerbation Quality of life
Adverse events	Not included
Utilities	EQ-5D
Discounting	Costs @ 4%, outcomes @ 1.5%
Outcomes	Incremental cost per exacerbation avoided Incremental cost per QALY
Results	Health care system perspective Using a one year time horizon, the ICERs for LAMA versus LABA was €162 per exacerbation avoided and €1015 per QALY Using a five year time horizon, LAMA dominated LABA Societal perspective Using a one year and five year time horizon, tiotropium dominated salmeterol
Types of sensitivity analysis	All one-way analysis performed using health care perspective Deterministic analysis (one-way) Patients characteristics - severity of distribution Exacerbation probabilities Discounting No difference in exacerbation risk after one year assumption Different cost for inpatient hospital day assumption 50% lower reduction in utility assumption Probabilistic analysis (Monte Carlo) Distributions not specified
Sensitivity analysis results	Deterministic analysis (one-way) Patients characteristics - severity of distribution was a major driver. Results were sensitive to exacerbation probabilities and cost for inpatient hospital day. Probabilistic analysis (Monte Carlo) At a willingness to pay of €20,000 per QALY, LAMA had the highest probability of being cost effective from both a health care and societal perspective (both in one year & five year analyses)

Study	Hoogendoom et al. 2012
Points to consider	Costs €(2011) Efficacy data from a RCT using a Bayesian fix-effects meta-analysis Adverse events not included Utilities included, did not specify where derived Results were not accurately reported Distributions for handling parameter uncertainty in probabilistic sensitivity analysis were not reported Comparison of monotherapies (LAMA, LABA)

Study	Price et al., 2011
Sponsorship	Novartis
Country	Germany
Perspective	Health Service Perspective
Study type	CUA
Comparators	LAMA (tiotropium 18 µg) LABA (indacaterol 150 µg, 300 µg)
Populations	Patients with moderate to severe COPD based on the GOLD criteria Mean age of 64 years
Time horizon	3 years
Type of model	Markov
Cycle length	3 months
Efficacy inputs	Exacerbation
Adverse events	Not included
Utilities	EQ-5D
Discounting	Costs and outcomes @ 3%
Outcomes	Incremental cost per QALY
Results	LABA (indacaterol 150 µg) dominated LAMA, while the incremental cost effectiveness ratio for LABA (indacaterol 300 µg) compared to LAMA was €28,301 per QALY

Study	Price et al., 2011
Types of sensitivity analysis	Deterministic analysis (one way) Time horizon Mortality rates Utility values Costs Assumption of LABA benefit Lung function Discontinuation rate Probabilistic analysis (Monte Carlo simulation) Costs (gamma) Utilities (beta) Treatment effect (log normal)
Sensitivity analysis results	Deterministic analysis (one way) Results were insensitive to changes Mortality rate by severity (very severe) was a major driver Probabilistic analysis (Monte Carlo simulation) Results are consistent with base case results, all willingness to pay amounts (from 0 and above) indicated a probability of over 70% that LAMA was cost-effective compared to LABA
Points to consider	Costs €2010 Efficacy data derived from one RCT for indacaterol versus tiotropium, and from another RCT for indacaterol versus salmeterol Adverse events not included Utility values derived from the EQ-5D Probabilistic analysis considered appropriate distributions to handle parameter uncertainty Comparison of monotherapies (LABA, LAMA)

Study	Gani et al., 2010
Sponsorship	Boebringer Ingelheim Ltd. And Pfizer Ltd.
Country	UK
Perspective	National Healthcare System perspective
Study type	CUA
Comparators	LAMA (tiotropium) LABA (salmeterol)
Populations	Patients with mild to severe COPD based on the NICE COPD guidelines Age not specified
Time horizon	1 year

Study	Gani et al., 2010
Type of model	Markov
Cycle length	8 days (first cycle), 22 days (second cycle), 1 month (subsequent cycles)
Efficacy inputs	FEV_1 Exacerbation
Adverse events	Not included
Utilities	EQ-5D
Discounting	N/A
Outcomes	Incremental cost per QALY
Results	LAMA dominated LABA
Types of sensitivity analysis	Deterministic analysis (scenario) Distinct COPD severity population (100% mild, 100% moderate, 100% severe) Probabilistic analysis (Monte Carlo simulation) Transition probabilities (Dirichlet) Costs (log normal) Utilities (beta) Treatment effect (beta)
Sensitivity analysis results	Deterministic analysis (scenario) LAMA remained dominant regardless of distinct COPD severity population Probabilistic analysis (Monte Carlo simulation) At a willingness to pay of £20,000 per QALY, LAMA has a 97% probability of being cost effective compared to LABA
Points to consider	Costs £ (2009) Efficacy data derived from four RCTs Mortality not considered in model Adverse events not included Utility values derived from the EQ-5D Appropriate distributions were considered in PSA Deterministic analysis considered distinct COPD severity populations Comparison of monotherapies (LAMA, LABA)

Study	Naik et al., 2010
Sponsorship	None disclosed
Country	USA
Perspective	Third Party Payer Perspective
Study type	CEA
Comparators	LAMA (tiotropium) LABA (salmeterol) placebo/no therapy

Study	Naik et al., 2010
Populations	Patients with moderate COPD based on the GOLD criteria Mean age of 65
Time horizon	1 year
Type of model	Markov
Cycle length	6 months
Efficacy inputs	Exacerbation
Adverse events	Not included
Utilities	N/A
Discounting	N/A
Outcomes	Incremental cost per exacerbation avoided
Results	ICER for LABA versus placebo/no therapy was $2,454.48 per exacerbation avoided ICER for LAMA versus placebo/no therapy was $1,817.37 per exacerbation avoided LABA is subject to extended dominance by LAMA and placebo/no therapy
Types of sensitivity analysis	Deterministic analysis (one-way) Probability of exacerbation Probability of severe exacerbation Probability of hospitalization Compliance with medication
Sensitivity analysis results	Deterministic analysis (one-way) Results were sensitive to compliance with medication; in many cases, LAMA dominated LABA
Points to consider	Cost USD$(2006) Efficacy data derived from four RCTs Intermediate outcome modelled Adverse events not included Utility values not included PSA not conducted Results not meaningful since comparison of placebo/no therapy and monotherapies (LABA, LAMA)

Study	NCGC, 2010
Sponsorship	NICE
Country	UK
Perspective	Healthcare system perspective
Study type	CUA

Study	NCGC, 2010
Comparators	LAMA [Spiriva(tiotropium 18 µg)] ICS+LABA [Symbicort (budesonide 200 µg/ formoterol 6 µg, budesonide 400 µg/ formoterol 12 µg), Seretide (fluticasone 500 µg/salmeterol 50 µg)] Triple therapy (ICS+LABA + LAMA)
Population	Patients with severe to very severe COPD based on the GOLD criteria Assumed to start at age 66 and 46% female
Time horizon	4 years
Type of model	Markov
Cycle length	1 year
Efficacy inputs	Exacerbations Mortality (sensitivity analysis only) Quality of life (sensitivity analysis only)
Adverse events	Not included
Utilities	EQ-5D SGRQ (mapped to the EQ-5D)
Discounting	Costs and outcomes at 3.5%
Outcomes	Incremental cost per QALY
Results	Inspire, Uplift Data ICS+LABA is subject to extended dominance ICUR of triple therapy versus ICS+LABA was £187,697 per QALY Inspire, Optimal Data ICS+LABA is subject to extended dominance ICUR of triple therapy versus ICS+LABA was £93,737 per QALY Uplift, Optimal Data LAMA is subject to dominance ICUR of triple therapy versus ICS+LABA was £159,353 per QALY

Study	NCGC, 2010
Types of sensitivity analysis	Deterministic analysis (one-way) Time horizon Costs of non-hospitalized exacerbations Exacerbation rate Deterministic analysis (scenario) Treatment affects exacerbation and stable quality of life effects Treatment affects exacerbation and mortality effects Deterministic analysis (scenario + one-way) Treatment affects exacerbation and stable quality of life effects + time horizon Treatment affects exacerbation and mortality effects + time horizon Probabilistic analysis (Monte Carlo simulation) Treatment effect (log normal) Utilities (normal, gamma, and beta distributions) Costs (gamma distribution)
Sensitivity analysis results	Deterministic analysis (one-way) Results insensitive to time horizon and costs of non-hospitalized exacerbations, but sensitive to exacerbation rate (contingent on the source of data). Deterministic analysis (scenario) Results sensitive to scenarios Deterministic analysis (scenario + one-way) Results insensitive to treatment affects exacerbation and stable quality of life effects scenario + time horizon Results sensitive to treatment affects exacerbation and mortality effects scenario + time horizon Probabilistic analysis (Monte Carlo simulation) Inspire + Uplift Data At a threshold of £20,000 per QALY, LAMA has the highest probability (84%) of being cost effective Inspire + Optimal Data At a threshold of £20,000 per QALY, LAMA has the highest probability (84%) of being cost effective Uplift + Optimal Data At a threshold of £20,000 per QALY, ICS+LABA has the highest probability (92%) of being cost effective

Study	NCGC, 2010
Points to consider	Costs in £ (2007/8) Efficacy data from three randomized controlled trials, using direct and indirect comparison In base case, treatment affects only exacerbation; in scenario deterministic analysis, treatment affects exacerbation and utilities as well as exacerbation and mortality Adverse events not included Utilities derived from the EQ-5D and SGRQ (mapped to the EQ-5D) A variety of sensitivity analyses; appropriate distributions considered in PSA Comparison of monotherapy (LAMA), dual therapy (ICS+LABA) and triple therapy (ICS+LABA + LAMA); LABA alone was not considered

Study	Oostenbrink et al., 2008
Sponsorship	Boehringer Ingelheim International and Pfizer Global Pharmaceuticals
Country	Netherlands
Perspective	Societal
Study type	CUA
Comparators	LAMA (tiotropium) LABA (salmeterol) PDE-4 (ipratropium)
Populations	Patients with moderate to very severe COPD based on the GOLD criteria Age not specified
Time horizon	5 years
Type of model	probabilistic Markov
Cycle length	1 month
Efficacy inputs	Exacerbation
Adverse events	Not included
Utilities	EQ-5D
Discounting	Costs at 4% and outcomes at 1.5%
Outcomes	Incremental cost per QALY
Results	LAMA dominated LABA
Types of sensitivity analysis	Deterministic analysis (additional information) Utilities Probabilistic analysis (Monte Carlo simulation) Transition probabilities (Dirichlet) Costs (gamma) Utilities (beta) Treatment effect (beta)

Study	Oostenbrink et al., 2008
Sensitivity analysis results	Deterministic analysis (additional information) Results insensitive to the additional utility information. Probabilistic analysis (Monte Carlo simulation) Results insensitive; LAMA remained dominant.
Points to consider	Costs €(2001) Efficacy data derived from three RCT Adverse events not included Utility values derived from EQ-5D Analysis of expected value of perfect information Comparison of monotherapies (LAMA, LABA)

Study	Oba 2007
Sponsorship	None disclosed
Country	USA
Perspective	Third Party Payer Perspective
Study type	Cost Utility Analysis
Comparators (Relevant)	LAMA (tiotropium) LABA (salmeterol) Placebo
Populations	Patients with moderate to severe COPD based on the GOLD criteria At least 40 years
Time horizon	6 months
Type of model	trial based analysis
Cycle length	N/A
Efficacy inputs	Quality of life
Adverse events	Not included
Utilities	SGRQ mapped to the EQ-5D
Discounting	N/A
Outcomes	Incremental cost per QALY
Results	ICER for LAMA versus placebo was $20,000 per QALY ICER for LABA versus placebo was $37,300 per QALY

Study	Oba 2007
Types of sensitivity analysis	Deterministic analysis (one-way) Cost hospitalization Unscheduled visits Incremental QALYS Deterministic analysis (scenario) Federal supply cost data Probabilistic analysis (Monte Carlo simulation) Distributions not reported
Sensitivity analysis results	Results presented only for LAMA versus placebo, LABA versus placebo, LAMA versus PDE-4
Points to consider	Cost USD$ (2005) Average cost of generic version (if available in generic form) was used Efficacy data from a single RCT Adverse events not included Utility values derived from SGRQ mapped to EQ-5D Lack transparency of reporting Limited reporting of SA; SA results not presented for relevant comparisons. Comparison of monotherapies (LABA, LAMA)

Study	Rutten-van Molken et al., 2007
Sponsorship	Boehringer Ingelheim International and Pfizer Global Pharmaceuticals
Country	Spain
Perspective	Spanish National Health System Perspective Societal Perspective
Study type	CEA/CUA
Comparators	LAMA (tiotropium) LABA (salmeterol)
Populations	Patients with moderate to very severe COPD based on the GOLD criteria Age not specified
Time horizon	5 years
Type of model	Markov
Cycle length	First cycle, 8 days; subsequent cycles, 1 month
Efficacy inputs	Exacerbation Quality of Life
Adverse events	Not included
Utilities	EQ-5D
Discounting	Costs and outcomes at 6%

Study	Rutten-van Molken et al., 2007
Outcomes	Incremental cost per exacerbation-free months Incremental cost per QALY
Results	Spanish National Health System Perspective ICERs for LAMA versus LABA were €360 per exacerbation free months and €4,118 per QALY Societal Perspective ICERs for LAMA versus LABA were €308 per exacerbation free months and €3,483 per QALY
Types of sensitivity analysis	Deterministic analysis (scenario) Transition and exacerbation probabilities remained constant over 5 years No difference in disease progression and exacerbation risk between treatment groups after one year Patient characteristics (100% moderate, severe, very severe) Deterministic analysis (one-way) Discounting Probabilistic analysis (Monte Carlo simulation) Distributions not specified
Sensitivity analysis results	Deterministic analysis (scenario) Results insensitive to transition and exacerbation probabilities remained constant over five years, as well as, no difference in disease progression and exacerbation risk between treatment groups after one year At a willingness to pay of €7,600 per QALY, LAMA was the preferred treatment for patients with moderate COPD, €8,800 per QALY for patients with severe COPD, and €12,500 per QALY for patients with very severe COPD Deterministic analysis (one-way) Results insensitive to discounting Probabilistic analysis (Monte Carlo simulation) At a willingness to pay of greater than €1,050 per exacerbation free months and €11,000 per QALY, LAMA has the greatest probability of being cost effective compared to LABA
Points to consider	Costs €(2005) Efficacy data from six RCT Adverse events not included Utilities values derived from the EQ-5D Comparison of monotherapies (LAMA, LABA) Distributions to handle parameter uncertainty in probabilistic sensitivity analysis were not reported

Study	Maniadakis et al. 2006
Sponsorship	Boehringer Ingelheim Ellas
Country	Greece
Perspective	National Health Service perspective
Study type	CEA/CUA
Comparators	LAMA (tiotropium) LABA (salmeterol)
Populations	Patients with moderate to very severe COPD based on the GOLD criteria Age not specified
Time horizon	1 year
Type of model	Markov probabilistic model
Cycle length	First cycle, 8 days; subsequent cycles, 1 month
Efficacy inputs	Exacerbation Quality of Life
Adverse events	Not included
Utilities	EQ-5D
Discounting	N/A
Outcomes	Incremental cost Incremental QALY Incremental exacerbation avoided
Results	In terms of incremental cost per QALY and incremental cost per exacerbation avoided , LAMA was less costly and more effective than LABA and therefore, dominated LABA
Types of sensitivity analysis	Deterministic analysis (scenario) Transition/exacerbation probabilities Patient characteristics - 100% moderate, 100% severe, 100% very severe Similar transition probabilities in both groups Probabilistic analysis (Monte Carlo simulation) Distributions not specified
Sensitivity analysis results	Deterministic analysis (scenario) Results were insensitive to transition/exacerbation probabilities, patient characteristics - 100% moderate, 100% severe, 100% very severe, and similar transition probabilities in both groups Probabilistic analysis (Monte Carlo simulation) At a ceiling ratio of €0, LAMA had a 65% probability of being cost-effective; while at a ceiling ratio of €1000 LAMA had a 77% probability of being cost-effective

Study	Maniadakis et al. 2006
Points to consider	Cost €(2005) Efficacy data derived from a published economic analysis Adverse events not included Utility values derived from the EQ-5D from an observational study Results of probabilistic sensitivity analysis are not particularly useful Comparison of monotherapies (LAMA, LABA)

Appendix B – De novo Economic Evaluation

Research Question

RQ2. Based on the economic model developed for the ICS/LABA review, what is the cost-effectiveness of LAMA alone or in combination with LABA and/or ICS compared to single or combination therapies incorporating LABA and ICS?

Study Objectives

Based on the research question, the objectives of the study were to address the following specific questions:

- What is the cost effectiveness of each LAMA monotherapy when compared to ICS and LABA monotherapies and each other?
- What is the cost effectiveness of LAMA/LABA combination therapies compared to ICS, LABA or LAMA monotherapies, ICS+LABA combination therapies and each other?
- What is the cost effectiveness of LAMA +ICS+LABA therapy compared to ICS+LABA combination therapies?

Economic Evaluation

Model Structure

The long term costs and quality adjusted life years (QALYs) of LAMA alone or in combination with LABA and/or ICS compared to single or combination therapies incorporating LABA and ICS was assessed using a Markov model. These estimates can then be used to estimate the relative cost effectiveness of alternative reimbursement strategies for the coverage of LAMA single therapies and LAMA plus LABA combination therapies.

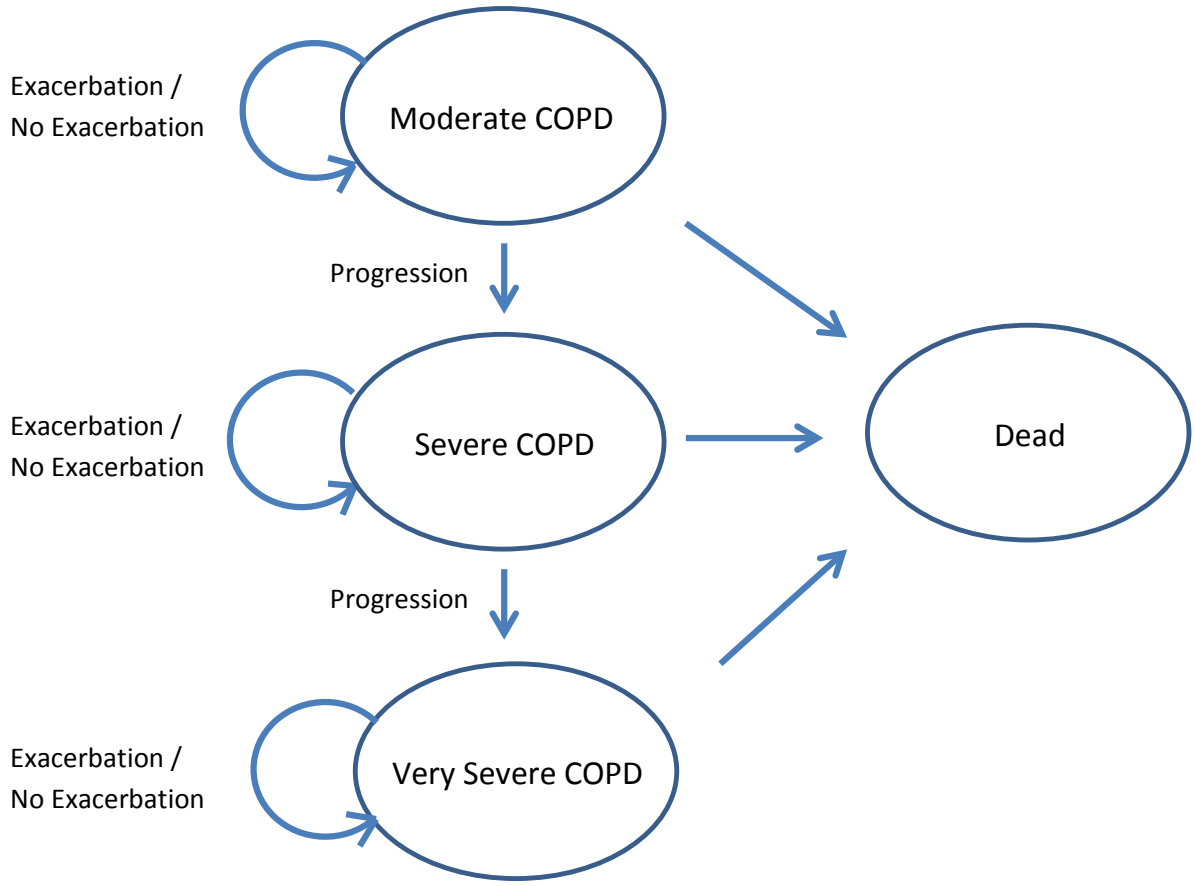
In modelling the disease progression in COPD, previous models have assessed disease severity by categorising patients according to their FEV_1%, which decreases with time leading to transitions from milder to more severe states. Both rates of exacerbations and mortality have been shown to increase with disease severity and the proportion of exacerbations requiring hospitalizations similarly increases with severity. Thus, similar to previous models, the model is comprised of five mutually exclusive states representing COPD disease severity and death. Death is an absorbing state meaning that when individuals enter this state, they remain within the state. The three states of COPD severity are defined according to GOLD guideline criteria for COPD diagnosis which classifies disease severity based on post bronchodilator FEV_1.[135] Moderate disease severity encompasses those patients with an FEV_1 50% and 79% of normal, severe between 30% and 49% of normal and very severe between below 30% of normal (Figure 1).

The cycle length of the model is one month with a lifetime horizon (maximum of 30 years). The model is adaptable, allowing for the estimation of the costs and QALYs associated with COPD treatments in a

cohort of patients at any age from 40 to 80 years and with any severity of COPD.

During each cycle of the model, patients in each of the disease model states may experience an exacerbation of their COPD, progression of their disease or die, either due to COPD or due to other causes. Within the mild, moderate and severe states, patients who experience an exacerbation may either progress to the next more severe state, die due to a hospital treated exacerbation, die due to background mortality or remain within the same COPD severity state. Patients who do not experience an exacerbation may progress to the next more severe state, die due to background mortality or remain within the same COPD severity state. Patients within the very severe state may experience the same outcomes, except they do not progress to a more severe COPD state.

Figure 1 Schematic of Markov Model



Data Inputs

Data Values

Data used within the economic model are provided inAppendix B1: Data Estimates. Details of data

sources are provided below.

Progression of Disease

The progression of COPD depends on the baseline FEV_1 of the cohort entering the model and the rate of decline in FEV_1 over time. The annual rate of decline in lung function in patients with COPD has been estimated to be 52 mL. [136]

Patients were assumed to enter the model with a baseline post bronchodilator FEV_1 equal to the midpoint of each of the COPD category severities, 65% of normal FEV_1 in moderate, 40% of normal FEV_1 in severe and 15% of normal FEV_1 in very severe. The predicted normal FEV_1 for the patient population modelled was estimated using predictive equations from a study which provides estimates for a general population of non-smoking men and women: in males FEV_1 (mean) = (0.0414 X height) – (0.0244 X age) – 2.190, in females FEV_1 (mean) = (0.0342 X height) – (0.0255 X age) – 1.578 (height in cm). [137] The cohort's baseline lung function is then estimated as the product of the baseline FEV_1 percentage, based on COPD severity, and the predicted normal FEV_1.

The time to progression from moderate to severe and severe to very severe disease can then be derived based on the baseline FEV_1 of the cohort with each disease severity and the rate of lung function decline.

Exacerbations

Exacerbations within the model are classified as either moderate, requiring community based care, or severe, requiring hospital based care. The rate of total exacerbations was estimated based on the placebo arm of the TORCH study which compared the efficacy of salmeterol alone, fluticasone alone, and salmeterol plus fluticasone versus placebo. [138] Patients within the placebo arm were not receiving either inhaled long acting beta agonists (LABA) or inhaled or oral corticosteroids and are therefore suitable for providing an estimate of the exacerbation rate in untreated patients. The annual exacerbation frequency per GOLD stage was estimated and was converted within the model to a monthly transition probability.

The proportion of total exacerbations requiring hospitalization was derived from a pooled analysis of the placebo arms of the indacaterol trials. [139] Estimates by COPD severity were possible as the patient's most recent pre-bronchodilator FEV_1 value was recorded before the exacerbation and was used to classify the severity of disease.

Mortality

Patients with COPD are at an increased risk of mortality relative to the general population. In particular, hospital exacerbations of COPD are associated with increased mortality in patients with COPD. As treatments for COPD have been shown to reduce exacerbations, to model the effect of these reductions on mortality it is important to model the background risk of mortality and the hospital exacerbation

associated mortality separately within the model. To do so, the hospital associated mortality must be removed from the background mortality, otherwise double counting of mortality will occur.

This was conducted by first applying the relative increase in all-cause mortality in patients with varying severities of disease to the age specific mortality rates derived from Canadian Life Tables to calculate the all-cause mortality in COPD patients by COPD severity, age and gender. [140,141]

The age specific hospital COPD exacerbation mortality risk was obtained from the 2008 UK National COPD Audit Report. [142] Based on data from 9,716 patients, the age specific hospital mortality due to COPD exacerbation was estimated. To estimate the mortality rate due to hospital exacerbations of COPD by age and COPD severity, these risks were applied to the risk of severe exacerbation by severity of COPD derived from Price 2011 (see Exacerbations). [139]

Utilities

Utilities by disease severity

The literature was reviewed both with respect to utility values associated with the COPD health states as defined within the GOLD guidelines and with respect to the utility decrement associated with both community treated and hospitalized exacerbations.

There were six studies reporting utility values by COPD severity;[143-148] although, only four studies provided estimates of utility values associated with all three categories of COPD severity included within the model. [145-147] Stahl and Borg both used the EQ-5D to elicit quality of life assessments from Swedish COPD patients and yielded similar estimates of utility values by COPD severity; however, the results in moderate and severe patients within the Stahl study were somewhat counterintuitive, producing a slightly higher utility in severe than in moderate patients.

In the base case analysis, the utility values derived by Borg et al. as part of a Swedish cost of illness study were used. In the study, quality of life was assessed through completion of the EQ-5D by 212 individuals with COPD. The EQ-5D was scored using the UK index tariff to allow estimation of the mean utility value for each of the GOLD COPD severity states with estimates of uncertainty. A number of subsequent cost effectiveness analyses have used the utility values from this study.[149,150]

Values from two studies conducted by Rutten-van Molken were used within sensitivity analyses.[145] One study estimated utility values for COPD health states using both a visual analogue scale and time trade off method.[145] The survey was conducted from a societal perspective with 239 Dutch adults drawn from the general public. Values were similar in severe and very severe states to those reported in Borg and Stahl, but higher than other reported values within the mild and moderate states. The second study derived utility values from the UPLIFT trial, a randomized controlled trial of tiotropium versus placebo, however these values apply only to moderate, severe and very severe COPD health states but were more consistent with the estimates of Borg. [144]

A study by Spencer provided estimates of the utilities based on the British Thoracic Society classification of disease severity as derived from the Health Survey for England which does not match the GOLD classification used within the model. [143]The final study derived values from a clinical trial of roflumilast; however, only values for severe and very severe were reported and therefore they would not be applicable within the current model.[148]

Utilities for COPD exacerbations

Sourcing the utility deficit associated with COPD exacerbations is challenging. A large number of studies estimated a percentage utility deficit with exacerbations based on expert clinical opinion due to the lack of evidence in this area.[143,146,150,151] There are, however, some studies which have measured the utility deficit with COPD exacerbations. After assessing the literature, two studies by Goossens and O'Reilly were chosen as the sources of the utility values for COPD exacerbations within this analysis.[152,153] Details of all of the studies are provided below, for comparison purposes, as are the reasons for the selection of the two studies and the exclusion of the remaining analyses from the model.

Rutten van Molken used the time trade off method to estimate the utility deficit associated with a single mild exacerbation within a year time frame and a single severe exacerbation within a one year time frame from a Dutch societal perspective. Many studies have allocated this utility deficit over the time course of a single cycle of a model in order to estimate the utility deficit of an exacerbation.[148] This results in an annual utility deficit of 0.01 QALYs for community treated exacerbations and 0.042 for hospital treated exacerbations. These would equate to a one month utility deficit of 0.504 for hospital exacerbations and 0.12 for community exacerbations. These values were not used within the model, as direct measures of disutility in COPD exacerbations were considered more robust.

In a study by Menn, the quality of life in patients with COPD exacerbations was measured using the EQ-5D, SF12 and SGRQ in German hospitalized patients. [154] Mean utility values as measured using the EQ-5D ranged from 0.60 (stage IV – very severe) to 0.62 (stage III - severe) at admission and from 0.75 (stage IV) to 0.84 (stage III) at discharge. This study did not provide information suitable for the current model as it included only patients with GOLD III and IV.

Paterson also used the EQ-5D to assess the quality of life of patients experiencing an acute exacerbation of chronic bronchitis in a Scottish general practice.[155] Patients completed the EQ-5D at the presenting visit and one week after completion of treatment. The mean change in utility value from baseline to follow up was 0.17 (SD 0.24). Only 53% of patients were considered clinically cured at the follow up assessment and no further assessment was made. The lack of detail within the published report regarding baseline and follow up values precludes the use of this reference within the model.

The two studies which were used to source the utility data for exacerbations within the current model both directly measured the quality of life of patients experiencing an exacerbation. The first, a study by O'Reilly administered the EQ-5D to COPD patients hospitalized for an exacerbation both at the time of admission and the time of discharge. [152] The second by Goossens measured the utility deficit of patients experiencing an exacerbation requiring a clinic visit at four time-points. [153] As these represent the most

direct measures of disutility associated with exacerbations, they were used within the model.

For hospital based exacerbations, a similar approach was taken as in an economic model by Hoogendorn based on the values from the O'Reilly study. [152,156]The average utility value on admission to hospital as measured by O'Reilly in UK patients was -0.077, rising to 0.576 at discharge, after a mean of 11 days in hospital. Based on the assumptions that a patient's utility returns to normal by 4.5 months [149] and that there is a linear increase between hospital admission and discharge and between discharge and 4.5 months, the disutility associated with a hospitalized exacerbation was estimated. This disutility was then allocated to the month in which the exacerbation occurred. The estimated one month loss in utility within the model for a hospitalized exacerbation is 0.3933.

In the study by Goossens, the EQ-5D was administered to 59 patients experiencing a community based exacerbation of COPD as defined by a worsening of symptoms lasting 3 or more days and requiring a change in treatment. Quality of life was assessed at baseline, day 7, day 14 and at day 42. Participants lost an average of 0.00896 QALYs (SD 0.0086) during the exacerbation. This disutility was allocated to the month in which the community acquired exacerbation occurred. The one month loss in utility within the model for a community exacerbation is 0.1075.

Resource Use and Costs

The costs of COPD can be subdivided into the costs associated with maintenance treatment, those associated with exacerbations, both community based and hospital based, and the costs associated with drug therapies. All costs were inflated to 2013 dollars using the Bank of Canada Inflation calculator.[157]

COPD Maintenance Costs

Maintenance costs are those associated with the day to day management of COPD during the time when patients are not experiencing an exacerbation. These include drug acquisition, oxygen therapy, laboratory and diagnostic tests and clinic visits. Canadian specific maintenance costs for the treatment of COPD by disease severity were estimated by Spencer et al.[143] The costs were reported for patients with mild to moderate COPD, severe COPD and very severe COPD.

Costs of Exacerbations

The cost of treating a community based exacerbation in Canada was estimated at $222.65 and the cost of a hospital based exacerbation was estimated at $10,765.00.[158] These estimates were based on resource use data sourced from the Canadian study entitled, Resource Utilization Study in COPD (RUSIC), which collected data on the health care resources associated with moderate and severe exacerbations in COPD over a 52 week period for 609 patients. Information was collected with respect to emergency room visits, outpatient visits and hospitalizations and included physician visits, laboratory and diagnostic testing, medications, length of stay and mode of transportation. The costs included within the model were limited to those reimbursed through the healthcare system. Costs were obtained from Ontario provincial sources, hospital databases and published literature.

Costs of Medications

Costs for medications were based on the most commonly prescribed dose for each product within the OPDP. Daily required dosages were based on clinical guidelines. Annual costs were derived from the Ontario Drug Formulary where available or from wholesale providers for those not covered under OPDP and also included an 8% pharmacy mark-up and four $8.83 dispensing fees annually.

External Validation

The mortality rate forecasted by the model was validated externally against three year survival data derived from the Copenhagen City Heart Study and the Copenhagen General Population Study. [159]

Treatment Effectiveness

The nature of the progression of COPD makes the modelling of treatment effects prone to double counting. Incorporating the effect of treatment on FEV_1 can lead to both an improvement in COPD severity and a delay in transitions across disease severity and thus, an indirect effect on both exacerbation rates and mortality. Incorporating the effect of treatment on exacerbations will have an indirect effect on mortality due to reduced hospitalized exacerbations; assuming mortality due to exacerbations is incorporated. Thus, analyses which incorporate any two of the effect of treatment on FEV_1, on exacerbations or on mortality will involve double counting of treatment effects and bias in the estimates of cost effectiveness.

In the analysis, effectiveness was modelled in terms of the effects on exacerbation rates which will have an indirect effect on mortality. Thus, modelling did not involve any change in disease severity or change in disease progression, rather analysis assumed that treatment affected the rate of exacerbations within each state of disease severity with a resulting indirect effect on mortality. Data from the companion systematic review on the relative risk of exacerbation across all disease severities were used within this analysis.

Treatment Adverse Effects

Inhaled corticosteroids have been associated with an increased incidence of pneumonia in COPD patients and therefore the comparative effects of treatments on rates of pneumonia was incorporated within the model using data from the network meta-analysis contained within the companion systematic review. The utility decrements associated with both community treated and hospitalized pneumonia were sourced from a previously published economic analysis which reported a loss of 0.006 QALYs and 0.008 QALYs respectively.[160] The costs of treatment were derived from Canadian sources. Based on an analysis of Alberta administrative databases, the 2013 cost of treating a hospital case of pneumonia was estimated at $6,148 and the cost of treating a community based case was $183 including physician and medication costs.[161] The same analysis found that 23.7% of pneumonia cases required hospitalization with a 12.93% mortality rate for hospitalized cases. The excess mortality due to hospitalized pneumonia in those receiving COPD treatments was incorporated within the model.

Cost Effectiveness

A cost utility analysis was conducted whereby, lifetime costs and effects as measured by life years and quality adjusted life years (QALYs) gained associated with COPD treatments are estimated via the model. Costs and QALYs are both discounted at a standard rate of 5% per annum.[162] The cost effectiveness of each of the treatments is then estimated as the cost per QALY gained relative to the comparator treatment.

For the base case analysis, results were presented for the three degrees of disease severity for male COPD patients aged 70 years. Subgroup analysis was conducted by varying the patient age (60, 70 and 80) and gender (male and female).

Treatment Comparators

For the first question, each LAMA therapy (Tudorza, Seebri and Spiriva) is compared to each ICS (Pulmicort and Flovent) and LABA (Oxeze and Salmeterol) monotherapy as well as to each other. Foradil was not used as a treatment comparator based on available prescribing data.

For the second question, each LAMA/LABA combination therapy (Ultibro and Anoro Ellipta) is compared to each LAMA, ICS and LABA monotherapy and ICS+LABA combination therapies (Symbicort, Advair Diskus and Breo Ellipta) as well as to each other.

For the third question, a combination of LAMA plus ICS+LABA combination therapy (Spiriva plus Advair Diskus) is compared to each ICS+LABA combination therapy.

Deterministic Sensitivity Analyses

A deterministic sensitivity analysis was conducted to determine impact of the following parameter inputs on the results: time horizon (1, 5, 10 years), discounting (0% and 3%), and assuming treatment had no impact on the rate of pneumonia.

Probabilistic Sensitivity Analyses

A probabilistic sensitivity analysis (PSA) was conducted in order to estimate the impact of parameter uncertainty on the cost effectiveness. The PSA involved a Monte Carlo simulation with 5000 estimates of outcomes obtained by sampling from the probability distributions for each parameter. The parameters included within the PSA and their corresponding distributions are reported in Appendix B1: Data Estimates. A gamma distribution was used for costs and the probability of an exacerbation. A beta distribution was used for the probability that an exacerbation resulted in hospitalization and for utilities by COPD severity. A log normal distribution was used for the relative risks associated with treatment effect. A normal distribution was used for the disutilities associated with community and hospital exacerbations. To model the impact of hospital exacerbations on utility, a Cholesky decomposition matrix was employed to account for the correlation between the admission and discharge utility value for hospital exacerbations.

The results of the PSA are presented by cost effectiveness acceptability curves depicting the probability, with respect to each research question, that each comparator is the most cost effective given different

threshold values for a QALY.

Findings

Base Case

The base case sought to answer the three specific objectives of the economic analysis. The base case analysis is focused on males, 70 years of age beginning treatment with moderate COPD, severe COPD and very severe COPD. Analysis for additional subgroups is discussed below.

Before presenting the results pertaining to the three specific objectives of the analysis, it is necessary to consider the cost effectiveness of all the considered therapies compared to no therapy. Assuming a decision maker's maximum willingness to pay for a QALY is $50,000, only one therapy is cost effective compared to no therapy for each disease severity – Oxeze (Appendix B2: Base Case Results).

The first objective was to assess the cost effectiveness of each LAMA monotherapy compared to ICS and LABA monotherapies and the other LAMA monotherapies.

Table 1 Base Case – Cost Effectiveness of LAMA Monotherapies

	INCREMENTAL COST PER QALY GAINED LAMA VERSUS:					
	ICS		LABA		LAMA	
	Pulmicort (budesonide)	Flovent (fluticasone)	Oxeze (formoterol)	Serevent (salmeterol)	Seebri (glyco-pyrronium)	Spiriva (tiotropium)
Tudorza (aclidinium)						
Moderate	Tudorza dominates	Tudorza dominates	Oxeze dominates	Tudorza dominates	Tudorza dominates	Tudorza dominates
Severe	Tudorza dominates	Tudorza dominates	Oxeze dominates	Tudorza dominates	Tudorza dominates	Tudorza dominates
Very Severe	Tudorza dominates	Tudorza dominates	Oxeze dominates	Tudorza dominates	Tudorza dominates	Tudorza dominates
Spiriva (tiotropium)						
Moderate	$1,190	Spiriva dominates	Oxeze dominates	$9,254	$567,326	
Severe	Spiriva dominates	Spiriva dominates	Oxeze dominates	Spiriva Dominates	$168,577	
Very Severe	Spiriva dominates	Spiriva dominates	Oxeze dominates	Spiriva Dominates	$113,518	
Seebri (glycopyrronium)						
Moderate	Seebri dominates	Seebri dominates	Oxeze dominates	Seebri dominates		
Severe	Seebri dominates	Seebri dominates	Oxeze dominates	Seebri dominates		
Very Severe	Seebri dominates	Seebri dominates	Oxeze dominates	Seebri dominates		

Summary of Findings for Table 1

1. In all severities of COPD, all LAMA monotherapies (Tudorza, Seebri and Spiriva) dominated Flovent in that they were less costly and more effective in terms of QALYs gained. For all disease severities, Tudorza and Seebri dominated Pulmicort. For severe and very severe disease, Spiriva dominated Pulmicort, but for moderate disease it was more effective and more costly with an ICUR of $1,190 (Table 1, Appendix B2: Base Case Results)
2. In all severities of COPD, all LAMA monotherapies (Tudorza, Seebri and Spiriva) were dominated by Oxeze in that they were more costly and less effective. In all severities of COPD, Seebri and Tudorza dominated Serevent. Spiriva dominated Serevent in severe and very severe disease but in moderate disease, Spiriva was more effective and more costly than Serevent with an ICUR of $9,254.
3. In comparing the three LAMA monotherapies, for all severities the estimated QALYs were similar with a range no greater than 0.006. Tudorza dominated both Seebri and Spiriva in that it was associated with the highest QALYs and lowest costs. However, the difference in lifetime costs between Tudorza and Seebri was less than $500 in all disease severities. Spiriva was more effective and more costly than Seebri, with the ICUR for Spiriva versus Seebri ranging from $113,518 to $567,326.

Table 2 Base Case – Cost Effectiveness of LAMA/LABA Combination Therapies versus Monotherapies

	INCREMENTAL COST PER QALY GAINED LAMA/LABA VERSUS:						
	ICS		LABA		LAMA		
	Pulmicort (budesonide)	Flovent (fluticasone)	Oxeze (formoterol)	Serevent (salmeterol)	Seebri (glyco-pyrronium)	Spiriva (tiotropium)	Tudorza (aclidinium)
Ultibro (indacaterol/glycopyrronium)							
Moderate	$45,207	Ultibro dominates	Oxeze dominates	$1.2 million	Seebri dominates	Spiriva dominates	Tudorza dominates
Severe	$10,351	Ultibro dominates	Oxeze dominates	$280,601	Seebri dominates	Spiriva dominates	Tudorza dominates
Very Severe	Ultibro dominates	Ultibro dominates	Oxeze dominates	$190,526	Seebri dominates	Spiriva dominates	Tudorza dominates
Anoro Ellipta (umeclidinium/vilanterol)							
Moderate	Pulmicort Dominates	Flovent dominates	Oxeze dominates	Serevent dominates	Seebri dominates	Spiriva dominates	Tudorza dominates
Severe	Pulmicort Dominates	Flovent dominates	Oxeze dominates	Serevent dominates	Seebri dominates	Spiriva dominates	Tudorza dominates
Very Severe	Pulmicort Dominates	Flovent dominates	Oxeze dominates	Serevent dominates	Seebri dominates	Spiriva dominates	Tudorza dominates

Summary of Findings for Table 2

1. The second question was with respect to the cost effectiveness of LAMA/LABA combination therapies as compared with ICS, LABA or LAMA monotherapies and ICS+LABA combination therapies.
2. With respect to the comparison with monotherapies, Anoro Ellipta was dominated by all monotherapies in that its estimated costs were higher and its estimated QALYs were lower.
3. Ultibro dominated Flovent in all disease severities and dominated Pulmicort in severe and very severe disease and was more costly and more effective in moderate and severe disease with ICURs of $45,207 and $10,351 respectively.
4. Ultibro was dominated by Oxeze, Seebri, Spiriva and Tudorza for all disease severities. Ultibro was more costly and more effective in all disease severities compared with Serevent with ICURs ranging from $190,526 to $1.2 million (Table 2, Appendix B2: Base Case Results).
5. In all disease severities Ultibro dominated Anoro Ellipta.

Table 3 Base Case – Cost Effectiveness of LAMA/LABA Combination Therapies versus ICS/LABA Combination Therapies

	INCREMENTAL COST PER QALY GAINED LAMA/LABA VERSUS ICS/LABA:		
	Symbicort (budesonide/formoterol)	**Advair Diskus (fluticasone/salmeterol)**	**Breo Ellipta (fluticasone/vilanterol)**
Ultibro (indacaterol/glycopyrronium)			
Moderate	Symbicort dominates	Ultibro dominates	Ultibro dominates
Severe	Symbicort dominates	$135,836*	Ultibro dominates
Very Severe	Symbicort dominates	$66,734*	$1.8 million^
Anoro Ellipta (umeclidinium/vilanterol)			
Moderate	Symbicort dominates	Advair Diskus dominates	Breo Ellipta dominates
Severe	Symbicort dominates	Advair Diskus dominates	Breo Ellipta dominates
Very Severe	Symbicort dominates	Advair Diskus dominates	Breo Ellipta dominates

*ICUR for Advair Diskus compared to Ultibro

^ICUR for Breo Ellipta compared to Ulti

Summary of Findings for Table 3

1. With respect to the comparison with ICS+LABA combination therapies, Anoro Ellipta was dominated by all combination therapies for all disease severities.

2. Ultibro dominated Advair Diskus in moderate disease and Breo Ellipta for moderate and severe disease. Advair Diskus was more effective than Ultibro in severe and very severe disease with ICURs of $135,836 and $66,734 respectively. Breo Ellipta was more effective than Ultibro in very severe disease with an ICUR of $1.8 million. Symbicort dominated Ultibro for all disease severities. (Table 3, Appendix B2: Base Case Results).

Table 4 Base Case – Cost Effectiveness of LAMA+ICS/LABA Triple Therapy versus ICS/LABA Combination Therapies

	INCREMENTAL COST PER QALY GAINED LAMA+ICS/LABA VERSUS ICS/LABA:		
	Symbicort (budesonide/formoterol)	**Advair (fluticasone/salmeterol)**	**Breo Ellipta (fluticasone/vilanterol)**
Spiriva+Advair (tiotropium/fluticasone/salmeterol)			
Moderate	Symbicort dominates	$86,055	$213,414
Severe	Symbicort dominates	$78,112	$177,578
Very Severe	Symbicort dominates	$71,110	$158,259

For the final question, triple therapy (Spiriva plus Advair Diskus) was dominated by Symbicort for all disease severities. Triple therapy was more effective than Advair Diskus alone with ICURs ranging from $71,110 to $86,055. Triple therapy was more effective than Breo Ellipta alone with ICURs ranging from $158,259 to $213,414 (Table 4, Appendix B2: Base Case Results).

Analysis by Patient Sub Populations

Analysis was conducted for cohorts of males starting therapy at age 60 and age 80 for each severity of COPD and for females starting therapy at age 60, 70 and 80 for each severity of COPD.

The results vary mainly in terms of the magnitude of the ICURs. However, for all study questions the conclusions to be drawn from the results of the subgroup analysis are the same as those drawn from the base case analysis (Appendix B3: Analysis by Patient Sub Populations).

Deterministic Sensitivity Analysis

One-way sensitivity analyses found the results to be robust to the incorporation of alternative utility values, to changes in time horizon including 1 year, 5 year and 10 years and discount rates of 0% and

3%.

Table 5 Deterministic Sensitivity Analysis – Cost Effectiveness of Ultibro versus Advair Diskus and Breo Ellipta

	INCREMENTAL COST PER QALY GAINED ULTIBRO VERSUS:	
	Advair Diskus (fluticasone/salmeterol)	**Breo Ellipta (fluticasone/vilanterol)**
Base Case		
Moderate	Ultibro dominates	Ultibro dominates
Severe	$135,836*	Ultibro dominates
Very Severe	$66,734*	$1.8 million^
Sensitivity analysis assuming no treatment effect on pneumonia		
Moderate	$88,105	$320,408
Severe	$48,917	$227,405
Very Severe	$33,403	$189,749

*ICUR for Advair Diskus compared to Ultibro

^ICUR for Breo Ellipta compared to Ultibro

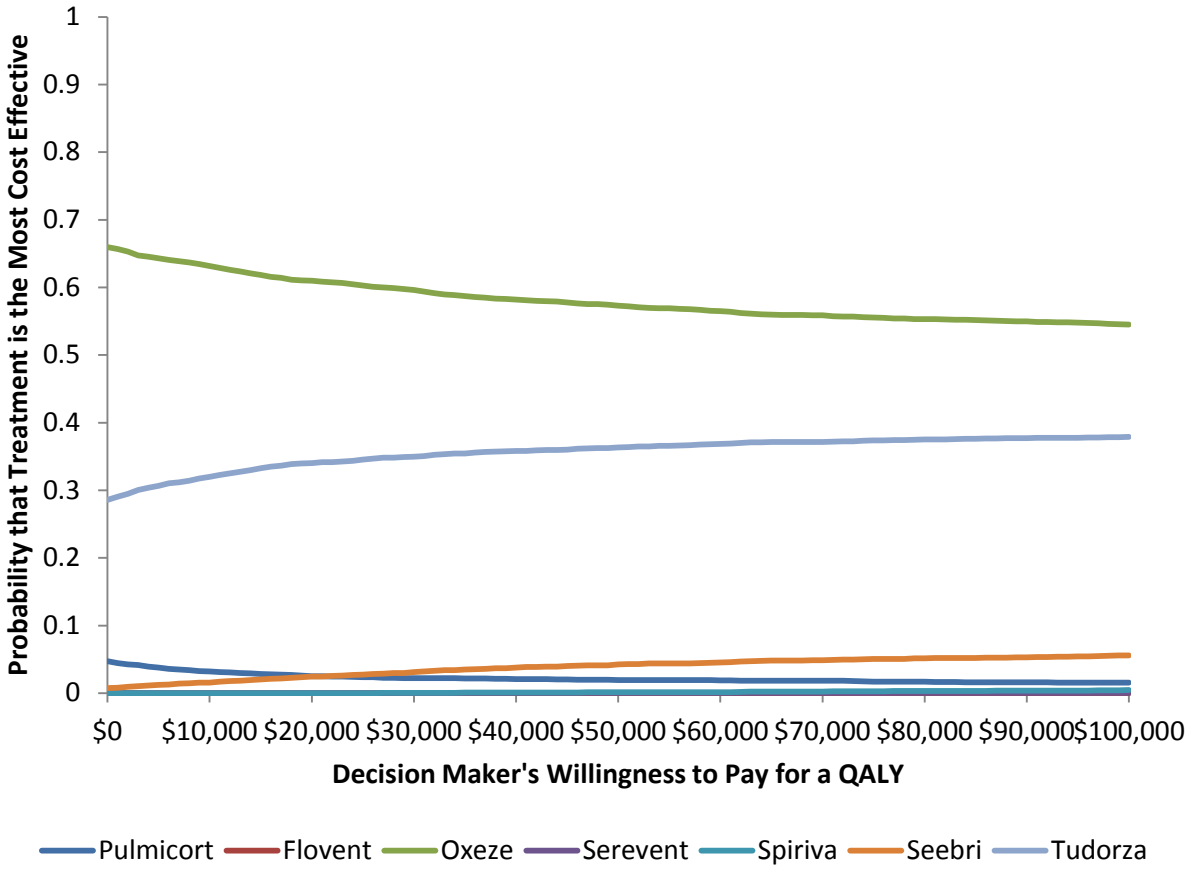
Summary of Findings for Table 5

The results with respect to the comparisons of Ultibro versus Advair Diskus and Breo Ellipta changed when it was assumed that treatment has no impact on the rate of pneumonia although the interpretation of the result would only change with respect to the comparison with Advair Diskus in severe and very severe disease (Table 5). All other results were robust to this change in assumption.

Probabilistic Sensitivity Analysis

The results of the Monte Carlo Simulation as they pertain to each of the objectives of the analysis are presented below. Results are presented for a Male aged 70 with moderate disease. The estimated incremental costs and QALYs versus no therapy for each of the therapies and the associated 95% credible intervals along with cost effectiveness ellipses are presented in Appendix B4: Probabilistic Sensitivity Analysis. It should be noted that the degree of uncertainty around the estimates for each therapy are large particularly for Tudorza, Breo Ellipta, Ultibro and Anoro Ellipta.

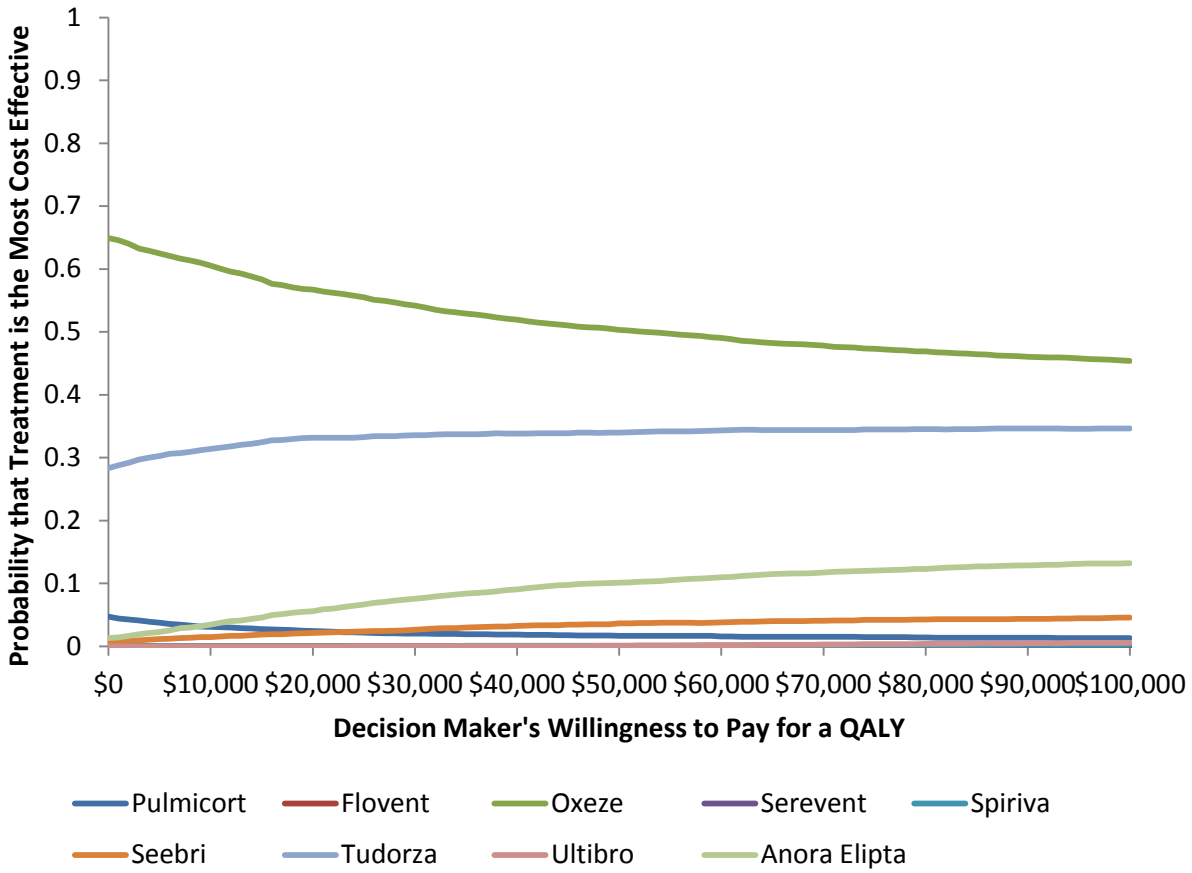
Figure 2 Cost Effectiveness Acceptability Curve for Monotherapies



Summary of Findings for Figure 2

With respect to the comparative cost effectiveness of monotherapies (LABA, ICS and LAMA), at a willingness to pay of $50,000 per QALY, the treatment with the highest probability of being cost effective was Oxeze at 57.5% (Figure 2). At a threshold of $50,000 per QALY, the probabilities that Tudorza, Seebri and Spiriva were most cost effective were 36.3%, 4.1% and 0.1%, respectively. However, when considering only the LAMA monotherapies, the probabilities that Tudorza was more cost effective compared to Seebri and to Spiriva were 57.2% and 52.3%, respectively.

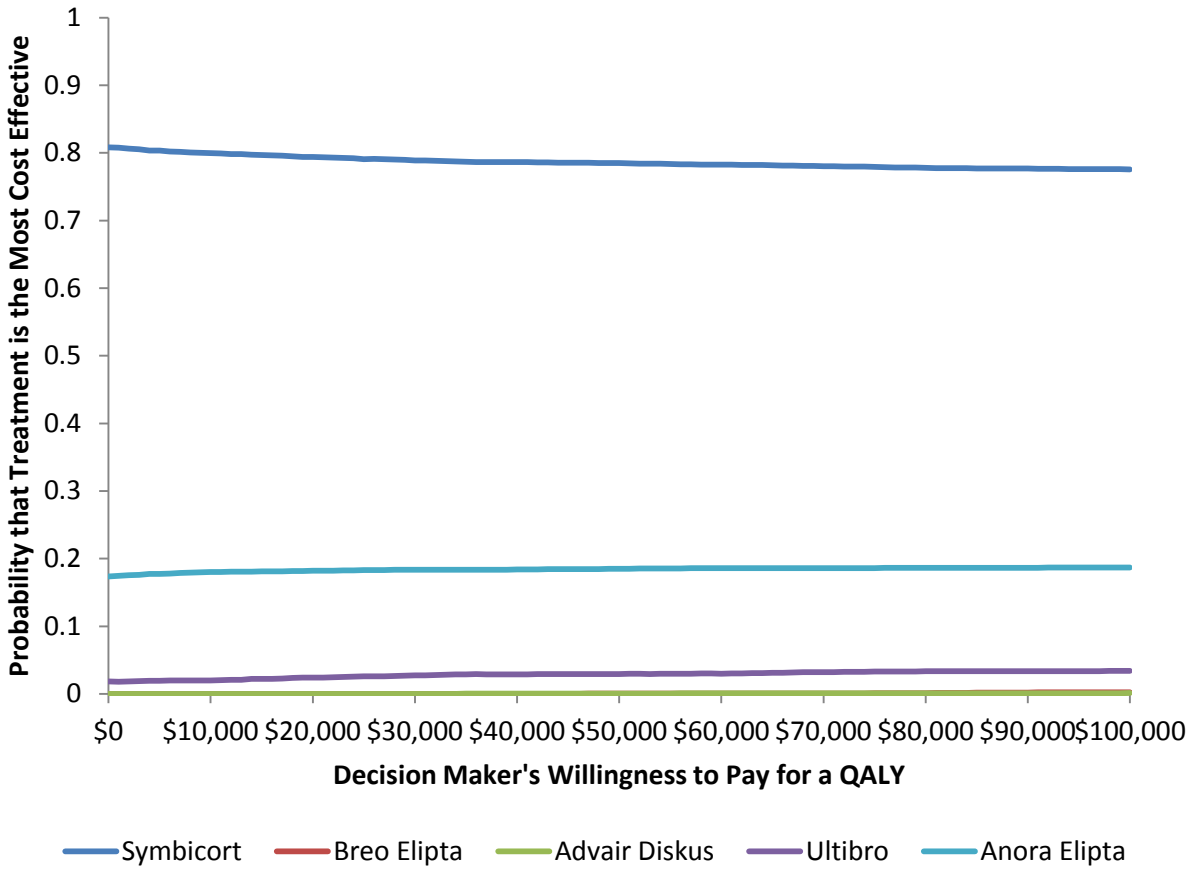
Figure 3 Cost Effectiveness Acceptability Curve for LAMA/LABA Combination Therapies and ICS, LAMA and LABA Monotherapies



Summary of Findings for Figure 3

With respect to the comparative cost effectiveness of LAMA/LABA combination therapy and ICS, LAMA and LABA monotherapies, at a willingness to pay of $50,000 per QALY, the treatment with the highest probability of being cost effective was Oxeze at 50.3% (Figure 3). The probabilities that Ultibro and Anoro Ellipta were the most cost effective were 0.1% and 10.1%, respectively. However, the probability that Ultibro was more cost effective than Anoro Ellipta was 69.3%. This may appear counter intuitive but arises due to the high degree of uncertainty around the estimated cost and outcomes associated with Anoro Ellipta.

Figure 4 Cost Effectiveness Acceptability Curve for LAMA/LABA and ICS+LABA Combination Therapies

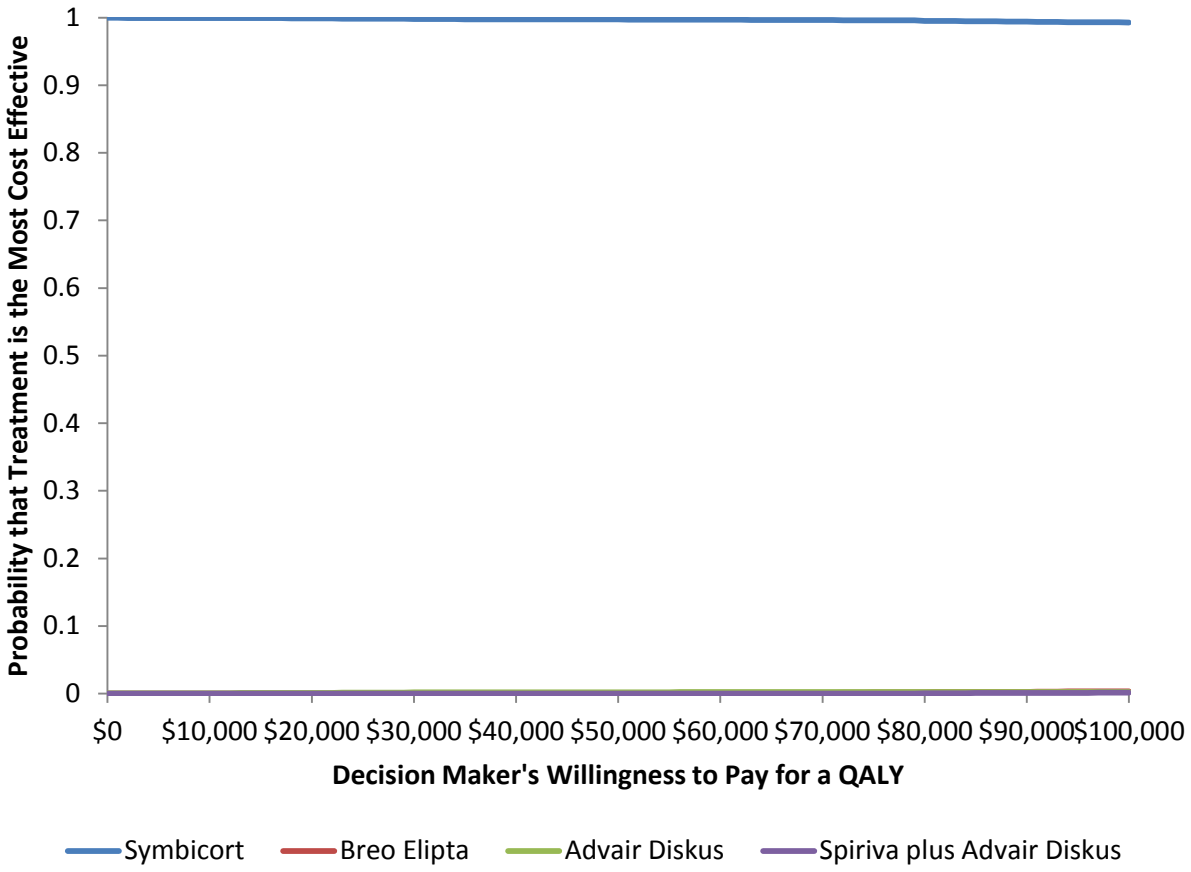


Summary of Findings for Figure 4

With respect to the comparative cost effectiveness of LAMA/LABA and ICS+LABA combination therapies, at a willingness to pay of $50,000 per QALY, the treatment with the highest probability of being cost effective was Symbicort at 78.5% (Figure 4). The probabilities that Ultibro and AnoroEllipta were the most cost effective were 2.9% and 18.5%, respectively, although as reported above, the probability that Ultibro was more cost effective than Anoro Ellipta was 69.3%. This again may appear counter intuitive, but arises due to the high degree of uncertainty around the estimated cost and outcomes associated with Anoro Ellipta.

Figure 5 Cost Effectiveness Acceptability Curve for Triple Therapy and ICS+LABA Combination

Therapies



Summary of Findings for Figure 5

In the comparison of triple therapy with ICS+LABA combination therapies, the probability Symbicort was the most cost effective was greater than 99% for all values of a QALY from $0 to $100,000 (Figure 5).

Conclusions of Primary Analysis

The following conclusions can be drawn from the above analysis assuming a decision maker was willing to pay $50,000 per QALY gained:

- All of the LAMA monotherapies were found to be cost effective compared to Pulmicort, Flovent and Serevent, but not Oxeze which was dominant.
- Tudorza was cost effective compared to Seebri and Spiriva, although there is a great deal of uncertainty around this finding.
- Anoro Ellipta is not cost effective compared to LABA, ICS and LAMA monotherapies, ICS/LABA combination therapies and Ultibro.

- Ultibro is cost effective compared to ICS monotherapies, AdvairDiskus and Breo Ellipta. Ultibro is not cost effective compared to LABA or LAMA monotherapies and Symbicort.
- Triple therapy is not cost effective compared to ICS/LABA combination therapies.

Overall Summary

In comparing the cost effectiveness of LAMA, LABA and ICS monotherapies, Oxeze was the most cost effective therapy dominating all other monotherapies. Of the LAMA monotherapies, Tudorza is the most cost effective, although this finding is highly uncertain.

Neither Anora Elllipta nor Ultibro are cost effective compared to LABA or LAMA monotherapies. Anora Elllipta is dominated by all monotherapies and combination products. Ultibro is cost effective compared to Advair Diskus and Breo Elllipta but not Symbicort.

Triple therapy with Spiriva and Advair Diskus is not cost effective compared to ICS/LABA combination therapies.

There are a number of limitations to this analysis primarily driven by the lack of available data. The nature of COPD makes it impossible to model the direct effect of treatment on more than one outcome. Based on clinical expert opinion, the base case model modelled the effect of treatments through a direct effect on exacerbations which leads to an indirect effect on mortality.

A further limitation with the analysis is that the definition of exacerbations may be inconsistent between studies. If the definitions were more subjective in nature and blinding was not consistently maintained, this may lead to bias in the indirect comparisons of treatments.

Analysis considered comparisons of therapeutic options and not a direct consideration of supportive care. It should be noted that only one therapy was cost effective compared to no therapy for each disease severity – Ozeze.

Conclusions

This analysis did not find LAMA monotherapies cost effective when compared to Oxeze. Of the LAMA monotherapies, Tudorza appears to be the most cost effective, although this is highly uncertain.

This analysis did not find LAMA/LABA combination therapies cost effective when compared to Symbicort. Of the LAMA/LABA combination therapies, Ultibro appears to be the most cost effective.

Triple therapy is not cost effective compared to ICS/LABA combination therapies.

Appendix B – Appendices

Appendix B1: Data Estimates

Table 6 Data Esimates

INPUT	DATA	VALUE (SE/95% CI)	DISTRIBUTION	SOURCE
Progression				
Mean FEV_1 at start of model	Moderate Severe	65% 40%		Mid-point of range in GOLD guidelines[135]
Annual decline in FEV_1		0.052 (0.029)	Normal	[136]
Monthly probability of progression	Moderate to severe Severe to very severe	0.0088 0.0132	Derived Derived	
Exacerbations per year	Moderate Severe Very severe	0.82 (0.03) 1.24 (0.03) 1.79 (0.07)	Gamma Gamma Gamma	[138]
Proportion of exacerbations requiring hospitalization	Moderate Severe Very severe	0.06 (0.02) 0.08 (0.02) 0.09 (0.04)	Beta Beta Beta	[139]
Mortality RR vs gen pop	Moderate Severe Very severe	1.50 (0.64) 3.10 (0.68) 5.02 (0.83)		[140]
Mortality with hospital exacerbation	40-49 years 50-59 years 60-69 years 70-79 years 80-89 years 90+ years	0.015 (0.009) 0.031 (0.006) 0.052 (0.005) 0.070 (0.004) 0.117 (0.006) 0.201 (0.024)	Beta Beta Beta Beta Beta Beta	[142]
Utilities				
COPD utility	Moderate Severe Very severe	0.7551 (0.0309) 0.7481 (0.0352) 0.5493 (0.0591)	Beta Beta Beta	[146,163]
QALY loss due to exacerbation	Community exacerbation Hospital exacerbation	0.1075 (0.0134) 0.3933 (0.072)	Normal Normal	[152,153]
Costs				

INPUT	DATA	VALUE (SE/95% CI)	DISTRIBUTION	SOURCE
Drug costs (annual)	Pulmicort (budesonide) Flovent (fluticasone) Oxeze (formoterol) Serevent (salmeterol) Spiriva (tiotropium) Seebri (glycopyrronium) Tudorza (aclidinium) Symbicort (budesonide/formoterol) Advair Diskus (fluticasone/salmeterol) Breo Ellipta (fluticasone/vilanterol) Ultibro (glycopyrronium/indacaterol) Anoro Ellipta (umeclinidium/vilanterol)	$538.79 $1119.90 $623.99 $772.47 $889.43 $733.05 $733.05 $1124.63 $1315.55 $1612.12 $1158.26 $1149.99	Fixed	[164]
Exacerbation costs	Community exacerbation Hospital exacerbation	$223 (56) $10757 (2689)	Gamma Gamma	[143,158,165]
Maintenance (costs/year) excluding exacerbations	Moderate COPD Severe COPD Very severe COPD	$174 (43.5) $709 (177.2) $844 (210.9)	Gamma Gamma Gamma	
Relative Treatment Effects				
Relative risk of exacerbations	Budesonide Fluticasone Formoterol Salmeterol Tiotropium Glycopyrronium Aclidinium Budesonide/formoterol Fluticasone/salmeterol Fluticasone/vilanterol Glycopyrronium/indacaterol Umeclidinium/vilanterol Tiotropium/fluticasone/salmeterol	Censored for publication	Log Normal Log Normal Log Normal Log Normal Log Normal Log Normal Log Normal Log Normal Log Normal Log Normal Log Normal Log Normal Log Normal	Network meta-analysis
Adverse Events – Pneumonia				
Treatment Costs	Community Hospital	$183.85 $6147.93		[161]
Disutility	Community Hospital	0.006 QALYs 0.008 QALYs		[160]

INPUT	DATA	VALUE (SE/95% CI)	DISTRIBUTION	SOURCE
Probability of hospitalization		23.7%		[161]
Mortality rate for hospitalized pneumonia		12.93%		[161]
Relative risk of exacerbations	Budesonide Fluticasone Formoterol Salmeterol Tiotropium Glycopyrronium Aclidinium Budesonide/formoterol Fluticasone/salmeterol Fluticasone/vilanterol Glycopyrronium/indacaterol Umeclidinium/vilanterol Tiotropium/fluticasone/salmeterol	Censored for publication	Log Normal Log Normal Log Normal Log Normal Log Normal Log Normal Log Normal Log Normal Log Normal Log Normal Log Normal Log Normal	Network meta-analysis

Figures in parenthesis are standard errors for data characterized by gamma, beta and normal distributions and 95% CI for data characterized by log-normal distributions.

Appendix B2: Base Case Results

Table 7 Results of Base Case: Moderate Disease

Therapy	Costs	QALYs	Life Years	Incremental Cost per QALY gained versus No Therapy
No therapy	**$10,060**	**5.40**	**7.40**	
Pulmicort	$14,717	5.39	7.39	Dominated by No Therapy
Flovent	$17,332	5.42	7.41	$324,425
Oxeze	$12,121	5.49	7.48	$24,692
Serevent	$14,583	5.44	7.43	$124,805
Spiriva	$14,809	5.46	7.46	$78,325
Seebri	$13,738	5.46	7.46	$62,608
Tudorza	$13,542	5.46	7.46	$57,021
Symbicort	$15,158	5.50	7.49	$50,586
Breo Ellipta	$20,544	5.43	7.40	$457,206
Advair Diskus	$18,194	5.44	7.42	$220,524
Ultibro	$17,212	5.44	7.43	$185,965
Anoro Ellipta	$22,651	5.27	7.28	Dominated by No Therapy
Spiriva plus Advair Diskus	$24,144	5.47	7.45	$217,463

Table 8 Results of Base Case: Severe Disease

Therapy	Costs	QALYs	Life Years	Incremental Cost per QALY gained versus No Therapy
No therapy	**$13,807**	**3.70**	**5.64**	
Pulmicort	$17,750	3.68	5.62	Dominated by No Therapy
Flovent	$18,705	3.73	5.66	$159,126
Oxeze	$14,035	3.78	5.72	$2,744
Serevent	$16,597	3.73	5.67	$72,956
Spiriva	$16,417	3.76	5.70	$42,495
Seebri	$15,706	3.75	5.69	$33,196
Tudorza	$15,413	3.76	5.70	$25,629
Symbicort	$15,924	3.80	5.74	$20,174
Breo Ellipta	$20,809	3.74	5.66	$167,820
Advair Diskus	$19,007	3.75	5.67	$106,035
Ultibro	$18,425	3.74	5.68	$103,182
Anoro Ellipta	$25,548	3.56	5.50	Dominated by No Therapy
Spiriva plus Advair Diskus	$23,244	3.77	5.70	$129,454

Table 9 Results of Base Case: Very Severe Disease

Therapy	Costs	QALYs	Life Years	Incremental Cost per QALY gained versus No Therapy
No therapy	**$14,702**	**2.60**	**4.90**	
Pulmicort	$18,362	2.58	4.88	Dominated by No Therapy
Flovent	$18,584	2.63	4.93	$117,752
Oxeze	$14,105	2.68	4.99	Dominates No Therapy
Serevent	$16,740	2.64	4.94	$53,321
Spiriva	$16,376	2.66	4.96	$27,598
Seebri	$15,819	2.65	4.96	$20,032
Tudorza	$15,480	2.66	4.96	$12,516
Symbicort	$15,497	2.70	5.01	$7,600
Breo Ellipta	$20,211	2.65	4.94	$116,889
Advair Diskus	$18,636	2.65	4.95	$75,430
Ultibro	$18,227	2.64	4.94	$76,587
Anoro Ellipta	$26,175	2.47	4.76	Dominated by No Therapy
Spiriva plus Advair Diskus	$22,145	2.67	4.97	$100,138

Appendix B3: Analysis by Patient Sub Populations

Males 60

Table 10 Males 60– Cost Effectiveness of LAMA Monotherapies

	INCREMENTAL COST PER QALY GAINED LAMA VERSUS:					
	ICS		LABA		LAMA	
	Pulmicort (budesonide)	Flovent (fluticasone)	Oxeze (formoterol)	Serevent (salmeterol)	Seebri (glyco-pyrronium)	Spiriva (tiotropium)
Tudorza (aclidinium)						
Moderate	Tudorza dominates	Tudorza dominates	Oxeze dominates	Tudorza dominates	Tudorza dominates	Tudorza dominates
Severe	Tudorza dominates	Tudorza dominates	Oxeze dominates	Tudorza dominates	Tudorza dominates	Tudorza dominates
Very Severe	Tudorza dominates	Tudorza dominates	Oxeze dominates	Tudorza dominates	Tudorza dominates	Tudorza dominates
Spiriva (tiotropium)						
Moderate	Spiriva dominates	Spiriva dominates	Oxeze dominates	$6,247	$1,153,262	
Severe	Spiriva dominates	Spiriva dominates	Oxeze dominates	Spiriva dominates	$178,734	
Very Severe	Spiriva dominates	Spiriva dominates	Oxeze dominates	Spiriva dominates	$117,819	
Seebri (glycopyrronium)						
Moderate	Seebri dominates	Seebri dominates	Oxeze dominates	Seebri dominates		
Severe	Seebri dominates	Seebri dominates	Oxeze dominates	Seebri dominates		
Very Severe	Seebri dominates	Seebri dominates	Oxeze dominates	Seebri dominates		

Table 11 Males 60– Cost Effectiveness of LAMA/LABA Combination Therapies versus Monotherapies

	INCREMENTAL COST PER QALY GAINED LAMA/LABA VERSUS:						
	ICS		LABA		LAMA		
	Pulmicort (budesonide)	Flovent (fluticasone)	Oxeze (formoterol)	Serevent (salmeterol)	Seebri (glyco-pyrronium)	Spiriva (tiotropium)	Tudorza (aclidinium)
Ultibro (indacaterol/glycopyrronium)							
Moderate	$40,298	Ultibro dominates	Oxeze dominates	$7,402,076	Seebri dominates	Spiriva dominates	Tudorza dominates
Severe	Ultibro dominates	Ultibro dominates	Oxeze dominates	$309,735	Seebri dominates	Spiriva dominates	Tudorza dominates
Very Severe	Ultibro dominates	Ultibro dominates	Oxeze dominates	$202,081	Seebri dominates	Spiriva dominates	Tudorza dominates
Anoro Ellipta (umeclidinium/vilanterol)							
Moderate	Pulmicort dominates	Flovent dominates	Oxeze dominates	Serevent dominates	Seebri dominates	Spiriva dominates	Tudorza dominates
Severe	Pulmicort dominates	Flovent dominates	Oxeze dominates	Serevent dominates	Seebri dominates	Spiriva dominates	Tudorza dominates
Very Severe	Pulmicort dominates	Flovent dominates	Oxeze dominates	Serevent dominates	Seebri dominates	Spiriva dominates	Tudorza dominates

Table 12 Males 60– Cost Effectiveness of LAMA/LABA Combination Therapies versus ICS/LABA Combination Therapies

	INCREMENTAL COST PER QALY GAINED LAMA/LABA VERSUS ICS/LABA:		
	Symbicort (budesonide/formoterol)	Advair Diskus (fluticasone/salmeterol)	Breo Ellipta (fluticasone/vilanterol)
Ultibro (indacaterol/glycopyrronium)			
Moderate	Symbicort dominates	Ultibro dominates	Ultibro dominates
Severe	Symbicort dominates	$199,49^8	Ultibro dominates
Very Severe	Symbicort dominates	$80,961^	Ultibro dominates
Anoro Ellipta (umeclidinium/vilanterol)			
Moderate	Symbicort dominates	Advair Diskus dominates	Breo Ellipta dominates
Severe	Symbicort dominates	Advair Diskus dominates	Breo Ellipta dominates
Very Severe	Symbicort dominates	Advair Diskus dominates	Breo Ellipta dominates

^ ICUR for Advair diskus versus Ultibro

Table 13 Males 60– Cost Effectiveness of LAMA+ICS/LABA Triple Therapy versus ICS/LABA Combination Therapies

	INCREMENTAL COST PER QALY GAINED LAMA+ICS/LABA VERSUS ICS/LABA:		
	Symbicort (budesonide/formoterol)	Advair Diskus (fluticasone/salmeterol)	Breo Ellipta (fluticasone/vilanterol)
Spiriva+Advair (tiotropium/fluticasone/salmeterol)			
Moderate	Symbicort dominates	$179,105	$69,358
Severe	Symbicort dominates	$149,468	$63,055
Very Severe	Symbicort dominates	$134,131	$57,881

Males 80

Table 14 Males 80– Cost Effectiveness of LAMA Monotherapies

	INCREMENTAL COST PER QALY GAINED LAMA VERSUS:					
	ICS		LABA		LAMA	
	Pulmicort (budesonide)	Flovent (fluticasone)	Oxeze (formoterol)	Serevent (salmeterol)	Seebri (glyco-pyrronium)	Spiriva (tiotropium)
Tudorza (aclidinium)						
Moderate	Tudorza dominates	Tudorza dominates	Oxeze dominates	Tudorza dominates	Tudorza dominates	Tudorza dominates
Severe	Tudorza dominates	Tudorza dominates	Oxeze dominates	Tudorza dominates	Tudorza dominates	Tudorza dominates
Very Severe	Tudorza dominates	Tudorza dominates	Oxeze dominates	Tudorza dominates	Tudorza dominates	Tudorza dominates
Spiriva (tiotropium)						
Moderate	Spiriva dominates	Spiriva dominates	Oxeze dominates	$4,648	$346,208	
Severe	Spiriva dominates	Spiriva dominates	Oxeze dominates	Spiriva dominates	$151,650	
Very Severe	Spiriva dominates	Spiriva dominates	Oxeze dominates	Spiriva dominates	$107,393	
Seebri (glycopyrronium)						
Moderate	Seebri dominates	Seebri dominates	Oxeze dominates	Seebri dominates		
Severe	Seebri dominates	Seebri dominates	Oxeze dominates	Seebri dominates		
Very Severe	Seebri dominates	Seebri dominates	Oxeze dominates	Seebri dominates		

Table 15 Males 80– Cost Effectiveness of LAMA/LABA Combination Therapies versus Monotherapies

	INCREMENTAL COST PER QALY GAINED LAMA/LABA VERSUS:						
	ICS		LABA		LAMA		
	Pulmicort (budesonide)	Flovent (fluticasone)	Oxeze (formoterol)	Serevent (salmeterol)	Seebri (glyco-pyrronium)	Spiriva (tiotropium)	Tudorza (aclidinium)
Ultibro (indacaterol/glycopyrronium)							
Moderate	$47,170	Ultibro dominates	Oxeze dominates	$584,148	Seebri dominates	Spiriva dominates	Tudorza dominates
Severe	$13,507	Ultibro dominates	Oxeze dominates	$243,212	Seebri dominates	Spiriva dominates	Tudorza dominates
Very Severe	Ultibro dominates	Ultibro dominates	Oxeze dominates	$176,709	Seebri dominates	Spiriva dominates	Tudorza dominates
Anoro Ellipta (umeclidinium/vilanterol)							
Moderate	Pulmicort dominates	Flovent dominates	Oxeze dominates	Serevent dominates	Seebri dominates	Spiriva dominates	Tudorza dominates
Severe	Pulmicort dominates	Flovent dominates	Oxeze dominates	Serevent dominates	Seebri dominates	Spiriva dominates	Tudorza dominates
Very Severe	Pulmicort dominates	Flovent dominates	Oxeze dominates	Serevent dominates	Seebri dominates	Spiriva dominates	Tudorza dominates

Table 16 Males 80– Cost Effectiveness of LAMA/LABA Combination Therapies versus ICS/LABA Combination Therapies

	INCREMENTAL COST PER QALY GAINED LAMA/LABA VERSUS ICS/LABA:		
	Symbicort (budesonide/formoterol)	Advair Diskus (fluticasone/salmeterol)	Breo Ellipta (fluticasone/vilanterol)
Ultibro (indacaterol/glycopyrronium)			
Moderate	Symbicort dominates	$543,745^	Ultibro dominates
Severe	Symbicort dominates	$101,627^	$1,553,583*
Very Severe	Symbicort dominates	$57,613^	$434,169*
Anoro Ellipta (umeclidinium/vilanterol)			
Moderate	Symbicort dominates	Advair Diskus dominates	Breo Ellipta dominates
Severe	Symbicort dominates	Advair Diskus dominates	Breo Ellipta dominates
Very Severe	Symbicort dominates	Advair Diskus dominates	Breo Ellipta dominates

^ICUR for Advair Diskus compared to Ultibro

*ICUR for Breo Ellipta compared to Ultibro

Table 17 Males 80– Cost Effectiveness of LAMA+ICS/LABA Triple Therapy versus ICS/LABA Combination Therapies

	INCREMENTAL COST PER QALY GAINED LAMA+ICS/LABA VERSUS ICS/LABA:		
	Symbicort (budesonide/formoterol)	**Advair Diskus (fluticasone/salmeterol)**	**Breo Ellipta (fluticasone/vilanterol)**
Spiriva+Advair (tiotropium/fluticasone/salmeterol)			
Moderate	Symbicort dominates	$250,027	$108,695
Severe	Symbicort dominates	$202,807	$95,702
Very Severe	Symbicort dominates	$180,585	$86,277

Females 60

Table 18 Females 60– Cost Effectiveness of LAMA Monotherapies

	INCREMENTAL COST PER QALY GAINED LAMA VERSUS:					
	ICS		LABA		LAMA	
	Pulmicort (budesonide)	Flovent (fluticasone)	Oxeze (formoterol)	Serevent (salmeterol)	Seebri (glyco-pyrronium)	Spiriva (tiotropium)
Tudorza (aclidinium)						
Moderate	Tudorza dominates	Tudorza dominates	Oxeze dominates	Tudorza dominates	Tudorza dominates	Tudorza dominates
Severe	Tudorza dominates	Tudorza dominates	Oxeze dominates	Tudorza dominates	Tudorza dominates	Tudorza dominates
Very Severe	Tudorza dominates	Tudorza dominates	Oxeze dominates	Tudorza dominates	Tudorza dominates	Tudorza dominates
Spiriva (tiotropium)						
Moderate	Spiriva dominates	Spiriva dominates	Oxeze dominates	$1,783	$461,580	
Severe	Spiriva dominates	Spiriva dominates	Oxeze dominates	Spiriva dominates	$144,736	
Very Severe	Spiriva dominates	Spiriva dominates	Oxeze dominates	Spiriva dominates	$108,328	
Seebri (glycopyrronium)						
Moderate	Seebri dominates	Seebri dominates	Oxeze dominates	Seebri dominates		
Severe	Seebri dominates	Seebri dominates	Oxeze dominates	Seebri dominates		
Very Severe	Seebri dominates	Seebri dominates	Oxeze dominates	Seebri dominates		

Table 19 Females 60– Cost Effectiveness of LAMA/LABA Combination Therapies versus Monotherapies

	INCREMENTAL COST PER QALY GAINED LAMA/LABA VERSUS:						
	ICS		LABA		LAMA		
	Pulmicort (budesonide)	Flovent (fluticasone)	Oxeze (formoterol)	Serevent (salmeterol)	Seebri (glyco-pyrronium)	Spiriva (tiotropium)	Tudorza (aclidinium)
Ultibro (indacaterol/glycopyrronium)							
Moderate	$25,931	Ultibro dominates	Oxeze dominates	$1,017,593	Seebri dominates	Spiriva dominates	Tudorza dominates
Severe	Ultibro dominates	Ultibro dominates	Oxeze dominates	$249,564	Seebri dominates	Spiriva dominates	Tudorza dominates
Very Severe	Ultibro dominates	Ultibro dominates	Oxeze dominates	$186,003	Seebri dominates	Spiriva dominates	Tudorza dominates
Anoro Ellipta (umeclidinium/vilanterol)							
Moderate	Pulmicort dominates	Flovent dominates	Oxeze dominates	Serevent dominates	Seebri dominates	Spiriva dominates	Tudorza dominates
Severe	Pulmicort dominates	Flovent dominates	Oxeze dominates	Serevent dominates	Seebri dominates	Spiriva dominates	Tudorza dominates
Very Severe	Pulmicort dominates	Flovent dominates	Oxeze dominates	Serevent dominates	Seebri dominates	Spiriva dominates	Tudorza dominates

Table 20 Females 60– Cost Effectiveness of LAMA/LABA Combination Therapies versus ICS/LABA Combination Therapies

	INCREMENTAL COST PER QALY GAINED LAMA/LABA VERSUS ICS/LABA:		
	Symbicort (budesonide/formoterol)	Advair Diskus (fluticasone/salmeterol)	Breo Ellipta (fluticasone/vilanterol)
Ultibro (indacaterol/glycopyrronium)			
Moderate	Symbicort dominates	Ultibro dominates	Ultibro dominates
Severe	Symbicort dominates	$139,444^	Ultibro dominates
Very Severe	Symbicort dominates	$77,510^	Ultibro dominates
Anoro Ellipta (umeclidinium/vilanterol)			
Moderate	Symbicort dominates	Advair Diskus dominates	Breo Ellipta dominates
Severe	Symbicort dominates	Advair Diskus dominates	Breo Ellipta dominates
Very Severe	Symbicort dominates	Advair Diskus dominates	Breo Ellipta dominates

^ICUR for Advair Diskus compared to Ultibro

Table 21 Females s 60– Cost Effectiveness of LAMA+ICS/LABA Triple Therapy versus ICS/LABA Combination Therapies

	INCREMENTAL COST PER QALY GAINED LAMA+ICS/LABA VERSUS ICS/LABA:		
	Symbicort (budesonide/formoterol)	Advair Diskus (fluticasone/salmeterol)	Breo Ellipta (fluticasone/vilanterol)
Spiriva+Advair (tiotropium/fluticasone/salmeterol)			
Moderate	Symbicort dominates	$157,324	$62,827
Severe	Symbicort dominates	$130,303	$55,633
Very Severe	Symbicort dominates	$118,335	$51,208

Females 70

Table 22 Females 70– Cost Effectiveness of LAMA Monotherapies

	INCREMENTAL COST PER QALY GAINED LAMA VERSUS:					
	ICS		LABA		LAMA	
	Pulmicort (budesonide)	Flovent (fluticasone)	Oxeze (formoterol)	Serevent (salmeterol)	Seebri (glyco-pyrronium)	Spiriva (tiotropium)
Tudorza (aclidinium)						
Moderate	Tudorza dominates	Tudorza dominates	Oxeze dominates	Tudorza dominates	Tudorza dominates	Tudorza dominates
Severe	Tudorza dominates	Tudorza dominates	Oxeze dominates	Tudorza dominates	Tudorza dominates	Tudorza dominates
Very Severe	Tudorza dominates	Tudorza dominates	Oxeze dominates	Tudorza dominates	Tudorza dominates	Tudorza dominates
Spiriva (tiotropium)						
Moderate	Spiriva dominates	Spiriva dominates	Oxeze dominates	$3,293	$344,761	
Severe	Spiriva dominates	Spiriva dominates	Oxeze dominates	Spiriva dominates	$137,261	
Very Severe	Spiriva dominates	Spiriva dominates	Oxeze dominates	Spiriva dominates	$102,566	
Seebri (glycopyrronium)						
Moderate	Seebri dominates	Seebri dominates	Oxeze dominates	Seebri dominates		
Severe	Seebri dominates	Seebri dominates	Oxeze dominates	Seebri dominates		
Very Severe	Seebri dominates	Seebri dominates	Oxeze dominates	Seebri dominates		

Table 23 Females 70– Cost Effectiveness of LAMA/LABA Combination Therapies versus Monotherapies

	INCREMENTAL COST PER QALY GAINED LAMA/LABA VERSUS:						
	ICS		LABA		LAMA		
	Pulmicort (budesonide)	Flovent (fluticasone)	Oxeze (formoterol)	Serevent (salmeterol)	Seebri (glyco-pyrronium)	Spiriva (tiotropium)	Tudorza (aclidinium)
Ultibro (indacaterol/glycopyrronium)							
Moderate	$30,480	Ultibro dominates	Oxeze dominates	$631,067	Seebri dominates	Spiriva dominates	Tudorza dominates
Severe	Ultibro dominates	Ultibro dominates	Oxeze dominates	$228,634	Seebri dominates	Spiriva dominates	Tudorza dominates
Very Severe	Ultibro dominates	Ultibro dominates	Oxeze dominates	$172,131	Seebri dominates	Spiriva dominates	Tudorza dominates
Anoro Ellipta (umeclidinium/vilanterol)							
Moderate	Pulmicort dominates	Flovent dominates	Oxeze dominates	Serevent dominates	Seebri dominates	Spiriva dominates	Tudorza dominates
Severe	Pulmicort dominates	Flovent dominates	Oxeze dominates	Serevent dominates	Seebri dominates	Spiriva dominates	Tudorza dominates
Very Severe	Pulmicort dominates	Flovent dominates	Oxeze dominates	Serevent dominates	Seebri dominates	Spiriva dominates	Tudorza dominates

Table 24 Females 70– Cost Effectiveness of LAMA/LABA Combination Therapies versus ICS/LABA Combination Therapies

	INCREMENTAL COST PER QALY GAINED LAMA/LABA VERSUS ICS/LABA:		
	Symbicort (budesonide/formoterol)	Advair Diskus (fluticasone/salmeterol)	Breo Ellipta (fluticasone/vilanterol)
Ultibro (indacaterol/glycopyrronium)			
Moderate	Symbicort dominates	$7,330,348^	Ultibro dominates
Severe	Symbicort dominates	$101,924^	Ultibro dominates
Very Severe	Symbicort dominates	$61,982^	$5,461,084*
Anoro Ellipta (umeclidinium/vilanterol)			
Moderate	Symbicort dominates	Advair Diskus dominates	Breo Ellipta dominates
Severe	Symbicort dominates	Advair Diskus dominates	Breo Ellipta dominates
Very Severe	Symbicort dominates	Advair Diskus dominates	Breo Ellipta dominates

^ICUR for Advair Diskus compared to Ultibro

*ICUR for Breo Ellipta compared to Ultibro

Table 25 Females 70– Cost Effectiveness of LAMA+ICS/LABA Triple Therapy versus ICS/LABA Combination Therapies

	INCREMENTAL COST PER QALY GAINED LAMA+ICS/LABA VERSUS ICS/LABA:		
	Symbicort (budesonide/formoterol)	Advair Diskus (fluticasone/salmeterol)	Breo Ellipta (fluticasone/vilanterol)
Spiriva+Advair (tiotropium/fluticasone/salmeterol)			
Moderate	Symbicort dominates	$186,076	$77,026
Severe	Symbicort dominates	$153,165	$67,885
Very Severe	Symbicort dominates	$136,949	$61,422

Females 80

Table 26 Females 80– Cost Effectiveness of LAMA Monotherapies

	INCREMENTAL COST PER QALY GAINED LAMA VERSUS:					
	ICS		LABA		LAMA	
	Pulmicort (budesonide)	Flovent (fluticasone)	Oxeze (formoterol)	Serevent (salmeterol)	Seebri (glyco-pyrronium)	Spiriva (tiotropium)
Tudorza (aclidinium)						
Moderate	Tudorza dominates	Tudorza dominates	Oxeze dominates	Tudorza dominates	Tudorza dominates	Tudorza dominates
Severe	Tudorza dominates	Tudorza dominates	Oxeze dominates	Tudorza dominates	Tudorza dominates	Tudorza dominates
Very Severe	Tudorza dominates	Tudorza dominates	Oxeze dominates	Tudorza dominates	Tudorza dominates	Tudorza dominates
Spiriva (tiotropium)						
Moderate	Spiriva dominates	Spiriva dominates	Oxeze dominates	$7,441	$264,638	
Severe	Spiriva dominates	Spiriva dominates	Oxeze dominates	Spiriva dominates	$128,303	
Very Severe	Spiriva dominates	Spiriva dominates	Oxeze dominates	Spiriva dominates	$96.018	
Seebri (glycopyrronium)						
Moderate	Seebri dominates	Seebri dominates	Oxeze dominates	Seebri dominates		
Severe	Seebri dominates	Seebri dominates	Oxeze dominates	Seebri dominates		
Very Severe	Seebri dominates	Seebri dominates	Oxeze dominates	Seebri dominates		

Table 27 Females 80– Cost Effectiveness of LAMA/LABA Combination Therapies versus Monotherapies

	INCREMENTAL COST PER QALY GAINED LAMA/LABA VERSUS:						
	ICS		LABA		LAMA		
	Pulmicort (budesonide)	Flovent (fluticasone)	Oxeze (formoterol)	Serevent (salmeterol)	Seebri (glyco-pyrronium)	Spiriva (tiotropium)	Tudorza (aclidinium)
Ultibro (indacaterol/glycopyrronium)							
Moderate	$35,059	Ultibro dominates	Oxeze dominates	$436,281	Seebri dominates	Spiriva dominates	Tudorza dominates
Severe	$8,902	Ultibro dominates	Oxeze dominates	$206,737	Seebri dominates	Spiriva dominates	Tudorza dominates
Very Severe	Ultibro dominates	Ultibro dominates	Oxeze dominates	$157,844	Seebri dominates	Spiriva dominates	Tudorza dominates
Anoro Ellipta (umeclidinium/vilanterol)							
Moderate	Pulmicort dominates	Flovent dominates	Oxeze dominates	Serevent dominates	Seebri dominates	Spiriva dominates	Tudorza dominates
Severe	Pulmicort dominates	Flovent dominates	Oxeze dominates	Serevent dominates	Seebri dominates	Spiriva dominates	Tudorza dominates
Very Severe	Pulmicort dominates	Flovent dominates	Oxeze dominates	Serevent dominates	Seebri dominates	Spiriva dominates	Tudorza dominates

Table 28 Females 80– Cost Effectiveness of LAMA/LABA Combination Therapies versus ICS/LABA Combination Therapies

	INCREMENTAL COST PER QALY GAINED LAMA/LABA VERSUS ICS/LABA:		
	Symbicort (budesonide/formoterol)	Advair Diskus (fluticasone/salmeterol)	Breo Ellipta (fluticasone/vilanterol)
Ultibro (indacaterol/glycopyrronium)			
Moderate	Symbicort dominates	$305,737^	Ultibro dominates
Severe	Symbicort dominates	$82,241^	$1,080,039*
Very Severe	Symbicort dominates	$52,280^	$433,887*
Anoro Ellipta (umeclidinium/vilanterol)			
Moderate	Symbicort dominates	Advair Diskus dominates	Breo Ellipta dominates
Severe	Symbicort dominates	Advair Diskus dominates	Breo Ellipta dominates
Very Severe	Symbicort dominates	Advair Diskus dominates	Breo Ellipta dominates

^ICUR for Advair Diskus compared to Ultibro
*ICUR for Breo Ellipta compared to Ultibro

Table 29 Females 80– Cost Effectiveness of LAMA+ICS/LABA Triple Therapy versus ICS/LABA Combination Therapies

	INCREMENTAL COST PER QALY GAINED LAMA+ICS/LABA VERSUS ICS/LABA:		
	Symbicort (budesonide/formoterol)	Advair Diskus (fluticasone/salmeterol)	Breo Ellipta (fluticasone/vilanterol)
Spiriva+Advair (tiotropium/fluticasone/salmeterol)			
Moderate	Symbicort dominates	$220,320	$97,393
Severe	Symbicort dominates	$177,496	$83,814
Very Severe	Symbicort dominates	$156,068	$74,142

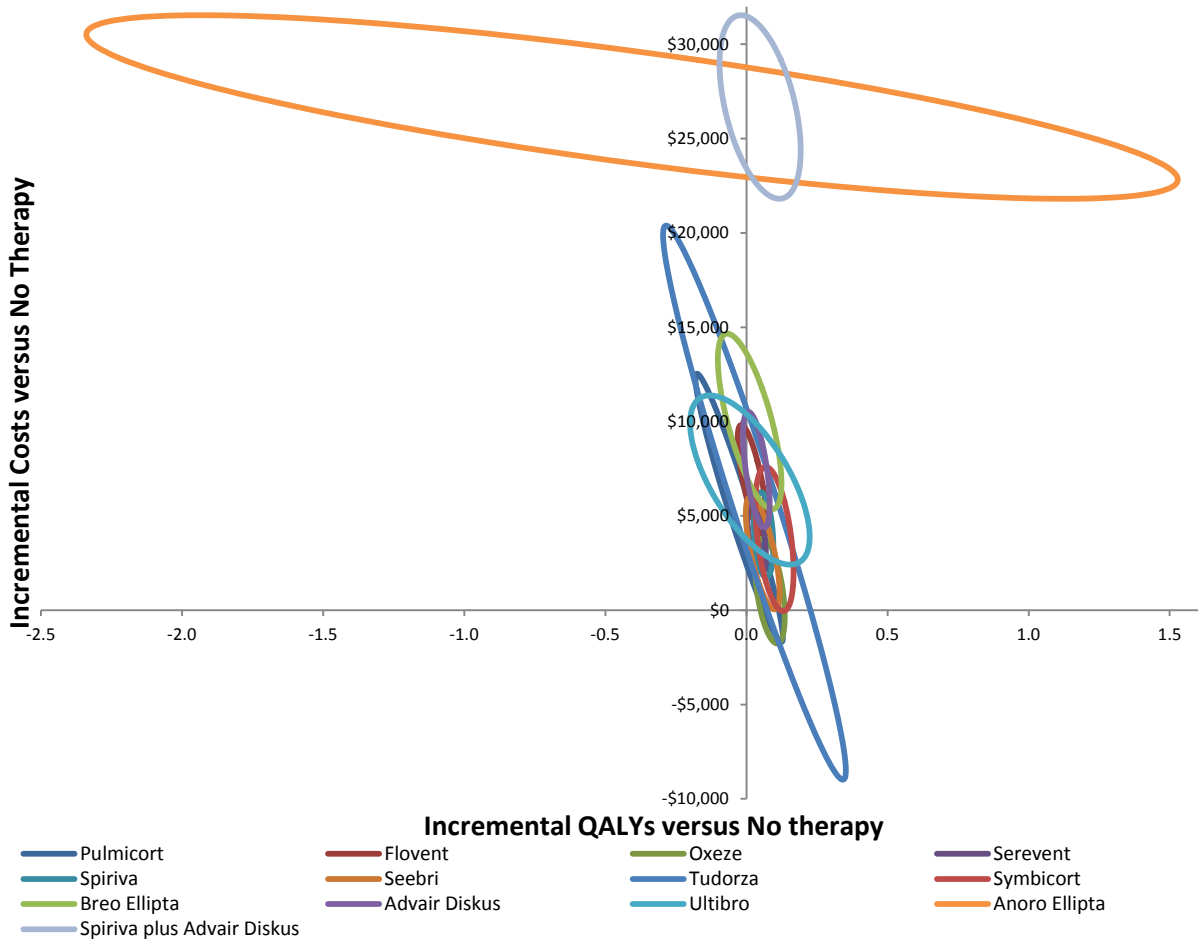
Appendix B4: Probabilistic Sensitivity Analysis

Table 30 Results of Probabilistic Sensitivity Analysis

	Incremental Costs versus No Therapy	Incremental QALYs versus No Therapy	Incremental Cost per QALY gained versus No Therapy	Incremental Net Benefit versus No Therapy (λ=$50,000)
Pulmicort	$4,993 (1662, 9877)	-0.03 (-0.17, 0.07)	Dominated by no therapy	-$6,337, (-18465, 1994)
Flovent	$7,429 (5521, 9605)	0.02 (-0.02, 0.06)	$357,352	-$6,389, (-10339, -2800)
Oxeze	$2,167 (110, 3950)	0.08 (0.05, 0.13)	$26,002	$2,000, (-1103, 5613)
Serevent	$4,629 (3249, 6127)	0.04 (0.01, 0.06)	$129,308	-$2,839, (-5144, -416)
Spiriva	$4,865 (3205, 6606)	0.06 (0.04, 0.09)	$79,823	-$1,818, (-4042, 683)
Seebri	$3,817 (1810, 5698)	0.06 (0.01, 0.11)	$66,916	-$965, (-4856, 2996)
Tudorza	$4,554 (-1146, 14822)	0.03 (-0.31, 0.19)	$152,967	-$3,066, (-29264, 10089)
Symbicort	$5,295 (2494, 7933)	0.1 (0.05, 0.16)	$53,323	-$330, (-4690, 4309)
Breo Ellipta	$10,793 (7949, 14035)	0.01 (-0.09, 0.09)	$796,231	-$10,115, (-17524, -4044)
Advair Diskus	$8,308 (6186, 10743)	0.04 (0, 0.07)	$234,860	-$6,540, (-10218, -3030)
Ultibro	$7,633 (4827, 10991)	0.01 (-0.18, 0.11)	$752,466	-$7,126, (-20599, -68)
Anoro Ellipta	$20,890 (1682, 88429)	-0.41 (-2.78, 0.2)	Dominated by no therapy	-$41,763, (-225732, 7486)
Spiriva plus Advair Diskus	$14,514 (11312, 18474)	0.05 (-0.09, 0.13)	$302,499	-$12,115, (-21755, -6058)

Figures in parenthesis are 95% certainty intervals

Figure 6 Cost Effectiveness Ellipses for Comparison with No Therapy



Appendix C – Budget Impact Analysis

Research Question

RQ3. What is the economic impact of alternative policies for reimbursing LAMA alone or as a combination product with LABA?

Reimbursement Based Economic Assessment

An applied, policy-oriented economic model focusing on financial impact was created to facilitate consideration of alternative reimbursement scenarios for COPD therapy. The analysis used OPDP data on usage of ICS, LABA and LAMA, both as single and combination therapies, from April 1, 2012 to March 31, 2013. COPD patients who were dispensed at least one prescription for a COPD therapy (LABA, LAMA, ICS, ICS+LABA) in Ontario were included in the analysis. The model was developed using Microsoft Excel.

First, COPD therapies were defined, as follows:

Table 31 COPD Therapy Details

COPD Therapy	Details
Multiple Prescriptions	Multiple prescriptions dispensed during period of continuous use
Triple therapy (combo)	If overlap between ICS+LABA combo product and LAMA for minimum 30 days
Triple therapy (dual)	If overlap between all three of ICS + LAMA + LABA for minimum 30 days
Combination therapy	If use of ICS+LABA combination product
Dual therapy	(a) If overlap between ICS + LABA for minimum 30 days (b) If overlap between ICS + LAMA for minimum 30 days (c) If overlap between LAMA + LABA for minimum 30 days
Single therapy	(a) If use of ICS (b) If use of LABA (c) If use of LAMA
Single Prescription	Period of continuous use consists of only a single prescription
Single prescription – single therapy	If duration of period of continuous use is 0 days (i.e. patient only received a single prescription) (a) If prescription was for ICS (b) If prescription was for LABA (c) If prescription was for LAMA (d) If prescription was for ICS+LABA combination product
Single prescription – multiple therapy	If multiple prescriptions are dispensed on the same day, where duration of period of continuous use for each prescription is 0 days (a) If prescription for ICS+LABA combo + LAMA (b) If prescription for ICS + LAMA + LABA (c) If prescription for ICS + LABA (d) If prescription for ICS + LAMA (e) If prescription for LAMA + LABA

Second, the context and assumptions for the analysis were specified. The context and general

assumptions for the budget impact analysis were defined, as follows:

Table 32 Budget Impact Analysis Context and General Assumptions

Context
Based on expert opinion, there would be no increase in use of LAMA only products with the listing of further LAMA products
LAMA/LABA combo products Anoro Ellipta and Ultibro have received NOC and will be considered for coverage shortly
Assume impact of LABA+LAMA (combination product)listing as general benefit
Assumptions
A proportion of COPD patients who are currently on treatment will switch to combination therapy (LAMA/LABA)
The number of units are split equally (50-50) between Anoro Ellipta and Ultibro

Additional details regarding the budget impact analysis and specific assumptions for each scenario can be found in Appendix C1: Model Details.

Third, consultations with clinical experts were conducted to identify approaches to reimbursement for COPD therapies. After discussion with clinical experts, it was determined that listing of further LAMA products will not have a major budget impact and focus should be on the impact of listing for LAMA/LABA combination products. Subsequently, alternative approaches to reimbursement of COPD therapy were identified. The reimbursement scenarios included in this analysis were: LABA only and LAMA only users switching to LAMA/LABA (Scenarios GB1-GB3); LAMA and LABA users switching to LAMA/LABA (Scenarios GB4-GB6); ICS and LABA users switching to LAMA/LABA (Scenarios GB7-GB9); ICS and LABA users switching to LAMA/LABA plus ICS (Scenarios GB10-GB12); ICS and LABA and LAMA users switching to LAMA/LABA plus ICS (Scenarios GB13-GB15); and finally, combining all scenarios into one (Scenarios GB16-GB18). For each of these approaches, three COPD patient populations were considered – Only Very Severe, At Least Severe, and At Least Moderate.

Table 33 Reimbursement Scenarios

REIMBURSEMENT SCENARIOS		ASSUMED IMPACT
If a modest proportion (50%) of LABA only and LAMA only users switch to LAMA/LABA		
GB1	Only Very Severe	Current users with very severe COPD on single therapy (LAMA or LABA) or single prescription, single therapy (LAMA or LABA) may switch to combination therapy (LAMA/LABA).
GB2	At Least Severe	Current users with very severe and severe COPD on single therapy (LAMA or LABA) or single prescription, single therapy (LAMA or LABA) may switch to combination therapy (LAMA/LABA).

REIMBURSEMENT SCENARIOS		ASSUMED IMPACT
GB3	At Least Moderate	Current users with very severe, severe, and moderate COPD on single therapy (LAMA or LABA) or single prescription, single therapy (LAMA or LABA) may switch to combination therapy (LAMA/LABA).
If almost all (99%) of LAMA and LABA (dual therapy) users switch to LAMA/LABA		
GB4	Only Very Severe	Current users with very severe COPD on LAMA and LABA (dual therapy) or single prescription, multiple therapy (LAMA and LABA) may switch to combination therapy (LAMA/LABA).
GB5	At Least Severe	Current users with very severe and severe COPD on LAMA and LABA (dual therapy) or single prescription, multiple therapy (LAMA and LABA) may switch to combination therapy (LAMA/LABA).
GB6	At Least Moderate	Current users with very severe, severe, and moderate COPD on LAMA and LABA (dual therapy) or single prescription, multiple therapy (LAMA and LABA) may switch to combination therapy (LAMA/LABA).
If a modest proportion (60%) of ICS and LABA users switch to LAMA/LABA		
GB7	Only Very Severe	Current users with very severe COPD on combination therapy (ICS+LABA), dual therapy (ICS + LABA), single prescription ICS+LABA combo, or single prescription, multiple therapy - ICS + LABA may switch to combination therapy (LAMA/LABA).
GB8	At Least Severe	Current users with very severe and severe COPD on combination therapy (ICS+LABA), dual therapy (ICS + LABA), single prescription ICS+LABA combo, or single prescription, multiple therapy - ICS + LABA may switch to combination therapy (LAMA/LABA).
GB9	At Least Moderate	Current users with very severe, severe, and moderate COPD on combination therapy (ICS+LABA), dual therapy (ICS + LABA), single prescription ICS+LABA combo, or single prescription, multiple therapy - ICS + LABA may switch to combination therapy (LAMA/LABA).
If a small proportion (20%) of ICS and LABA users switch to LAMA/LABA plus ICS		
GB10	Only Very Severe	Current users with very severe COPD on combination therapy (ICS+LABA), dual therapy (ICS + LABA), single prescription ICS+LABA combo, or single prescription, multiple therapy - ICS + LABA may switch to combination therapy (LAMA/LABA) plus ICS.
GB11	At Least Severe	Current users with very severe and severe COPD on combination therapy (ICS+LABA), dual therapy (ICS + LABA), single prescription ICS+LABA combo, or single prescription, multiple therapy - ICS + LABA may switch to combination therapy (LAMA/LABA) plus ICS.
GB12	At Least Moderate	Current users with very severe, severe, and moderate COPD on combination therapy (ICS+LABA), dual therapy (ICS + LABA), single prescription ICS+LABA combo, or single prescription, multiple therapy - ICS + LABA may switch to combination therapy (LAMA/LABA) plus ICS.
If a modest proportion (50%) of ICS and LABA and LAMA users switch to LAMA/LABA plus ICS		

REIMBURSEMENT SCENARIOS		ASSUMED IMPACT
GB13	Only Very Severe	Current users with very severe COPD on triple therapy combo (ICS+LABA plus LAMA), triple therapy - dual therapy (ICS + LABA + LAMA), single prescription ICS+LABA combo + LAMA, or single prescription, multiple therapy - ICS + LABA + LAMA may switch to combination therapy (LAMA/LABA) plus ICS.
GB14	At Least Severe	Current users with very severe and severe COPD on triple therapy combo (ICS+LABA plus LAMA), triple therapy - dual therapy (ICS + LABA + LAMA), single prescription ICS+LABA combo + LAMA, or single prescription, multiple therapy - ICS + LABA + LAMA may switch to combination therapy (LAMA/LABA) plus ICS.
GB15	At Least Moderate	Current users with very severe, severe, and moderate COPD on triple therapy combo (ICS+LABA plus LAMA), triple therapy - dual therapy (ICS + LABA + LAMA), single prescription ICS+LABA combo + LAMA, or single prescription, multiple therapy - ICS + LABA + LAMA may switch to combination therapy (LAMA/LABA) plus ICS.
All of the above		
GB16	Only Very Severe	Current users with very severe COPD on single therapy (LAMA or LABA) or single prescription, single therapy (LAMA or LABA), LAMA and LABA (dual therapy) or single prescription, multiple therapy (LAMA and LABA) may switch to combination therapy (LAMA/LABA). As well, current users with very severe COPD on combination therapy (ICS+LABA), dual therapy (ICS + LABA), single prescription ICS+LABA combo, or single prescription, multiple therapy - ICS + LABA may switch to combination therapy (LAMA/LABA) or combination therapy (LAMA/LABA) plus ICS. Also, current users with very severe COPD on single therapy triple therapy combo (ICS+LABA plus LAMA), triple therapy - dual therapy (ICS + LABA + LAMA), single prescription ICS+LABA combo + LAMA, or single prescription, multiple therapy - ICS + LABA + LAMA may switch to combination therapy (LAMA/LABA) plus ICS.
GB17	At Least Severe	Current users with very severe and severe COPD on single therapy (LAMA or LABA) or single prescription, single therapy (LAMA or LABA), LAMA and LABA (dual therapy) or single prescription, multiple therapy (LAMA and LABA) may switch to combination therapy (LAMA/LABA). As well, current users with very severe and severe COPD on combination therapy (ICS+LABA), dual therapy (ICS + LABA), single prescription ICS+LABA combo, or single prescription, multiple therapy - ICS + LABA may switch to combination therapy (LAMA/LABA) or combination therapy (LAMA/LABA) plus ICS. Also, current users with very severe and severe COPD on triple therapy combo (ICS+LABA plus LAMA), triple therapy - dual therapy (ICS + LABA + LAMA), single prescription ICS+LABA combo + LAMA, or single prescription, multiple therapy - ICS + LABA + LAMA may switch to combination therapy (LAMA/LABA) plus ICS.

REIMBURSEMENT SCENARIOS		ASSUMED IMPACT
GB18	At Least Moderate	Current users with very severe, severe, and moderate COPD on single therapy (LAMA or LABA) or single prescription, single therapy (LAMA or LABA), LAMA and LABA (dual therapy) or single prescription, multiple therapy (LAMA and LABA) may switch to combination therapy (LAMA/LABA). As well, current users with very severe, severe, and moderate COPD on combination therapy (ICS+LABA), dual therapy (ICS + LABA), single prescription ICS+LABA combo, or single prescription, multiple therapy - ICS + LABA may switch to combination therapy (LAMA/LABA) or combination therapy (LAMA/LABA) plus ICS. Also, current users with very severe, severe, and moderate COPD on triple therapy combo (ICS+LABA plus LAMA), triple therapy - dual therapy (ICS + LABA + LAMA), single prescription ICS+LABA combo + LAMA, or single prescription, multiple therapy - ICS + LABA + LAMA may switch to combination therapy (LAMA/LABA) plus ICS.

For **GB1** – If a modest proportion (50%) of LABA only and LAMA only users with Only Very Severe COPD switch to LAMA/LABA. Costs were estimated by assuming 50% of current users with very severe COPD on single therapy (LAMA or LABA) or single prescription, single therapy (LAMA or LABA) switch to combination therapy (LAMA/LABA).

For **GB2** – If a modest proportion (50%) of LABA only and LAMA only users with At Least Severe COPD switch to LAMA/LABA. The same approach as **GB1** was adopted with the addition of users with severe COPD.

For **GB3** – If a modest proportion (50%) of LABA only and LAMA only users with At Least Moderate COPD switch to LAMA/LABA. The same approach as **GB1** was adopted with the addition of users with severe and moderate COPD.

For **GB4** – If almost all (99%) of LAMA and LABA users with Only Very Severe COPD switch to LAMA/LABA. Costs were estimated by assuming 99% of current users with very severe COPD on LAMA and LABA (dual therapy) or single prescription, multiple therapy (LAMA and LABA) switch to combination therapy (LAMA/LABA).

For **GB5** – If almost all (99%) of LAMA and LABA users with At Least Severe COPD switch to LAMA/LABA. The same approach as **GB4** was adopted with the addition of users with severe COPD.

For **GB6** – If almost all (99%) of LAMA and LABA users with At Lease Moderate COPD switch to LAMA/LABA. The same approach as **GB4** was adopted with the addition of users with severe and moderate COPD.

For **GB7** – If a modest proportion (60%) of ICS and LABA users with Only Very Severe COPD switch to LAMA/LABA. Costs were estimated by assuming 60% of current users with very severe COPD on combination therapy (ICS+LABA), dual therapy (ICS + LABA), single prescription ICS+LABA combo, or single prescription, multiple therapy - ICS + LABA switch to combination therapy (LAMA/LABA).

For **GB8** – If a modest proportion (60%) of ICS and LABA users with At Least Severe COPD switch to LAMA/LABA. The same approach as **GB7** was adopted with the addition of users with severe COPD.

For **GB9** – If a modest proportion (60%) of ICS and LABA users with At Least Moderate COPD switch to LAMA/LABA. The same approach as **GB7** was adopted with the addition of users with severe and moderate COPD.

For **GB10** – If a small proportion (20%) of ICS and LABA users with Only Very Severe COPD switch to LAMA/LABA plus ICS. Costs were estimated by assuming 20% of current users with very severe COPD on combination therapy (ICS+LABA), dual therapy (ICS + LABA), single prescription ICS+LABA combo, or single prescription, multiple therapy - ICS + LABA switch to combination therapy (LAMA/LABA) plus ICS.

For **GB11** – If a small proportion (20%) of ICS and LABA users with At Least Severe COPD switch to LAMA/LABA plus ICS. The same approach as **GB10** was adopted with the addition of users with severe COPD.

For **GB12** – If a small proportion (20%) of ICS and LABA users with At Least Moderate COPD switch to LAMA/LABA plus ICS. The same approach as **GB10** was adopted with the addition of users with severe and moderate COPD.

For **GB13** – If a modest proportion (50%) of ICS and LABA and LAMA users with Only Very Severe COPD switch to LAMA/LABA plus ICS. Costs were estimated by assuming 50% of current users with very severe COPD on triple therapy combo (ICS+LABA plus LAMA), triple therapy - dual therapy (ICS + LABA + LAMA), single prescription ICS+LABA combo + LAMA, or single prescription, multiple therapy - ICS + LABA + LAMA switch to combination therapy (LAMA/LABA) plus ICS.

For **GB14** – If a modest proportion (50%) of ICS and LABA and LAMA users with At Least Severe COPD switch to LAMA/LABA plus ICS. The same approach as **GB13** was adopted with the addition of users with severe COPD.

For **GB15** – If a modest proportion (50%) of ICS and LABA and LAMA users with At Least Moderate COPD switch to LAMA/LABA plus ICS. The same approach as **GB13** was adopted with the addition of users with severe and moderate COPD.

GB16 – Combine Scenarios **GB1**, **GB4**, **GB7**, **GB10**, and **GB13.**

GB17– Combine Scenarios **GB2**, **GB5**, **GB8**, **GB11**, and **GB14**.

GB18 – Combine Scenarios **GB3**, **GB6**, **GB9**, **GB12**, and **GB15.**

Finally, budget expenditure on COPD therapy for each alternative scenario was forecasted.

Sensitivity analyses were conducted to test the robustness of results against scenarios including price reductions for LABALAMA combination therapies and/or preferred treatment with a particular LABA/LAMA product; and the number of units of LAMA/LABA products to be taken by those switching to these products.

A 25% price reduction was assumed for only Anoro Ellipta products, for only Ultibro products, and for both Anoro Ellipta and Ultibro products.

A preferred treatment was assumed whereby OPDP covered only Anoro Ellipta products or only Ultibro products.

A preferred treatment and price reduction were assumed whereby OPDP covered only Anoro Ellipta products with a 25% price reduction or only Ultibro products with a 25% price reduction.

Table 34 Sensitivity Analysis Scenarios

SENSITIVITY ANALYSIS SCENARIOS	ASSUMPTIONS
Reduced Price	
Anoro Ellipta	A 25% price reduction was assumed for Anoro Ellipta
Ultibro	A 25% price reduction was assumed for Ultibro
Both Anoro Ellipta and Ultibro	A 25% price reduction was assumed for both Anoro Ellipta and Ultibro
Preferred Treatment	
Anoro Ellipta	Only Anoro Ellipta was covered by OPDP
Ultibro	Only Ultibro was covered by OPDP
Reduced Price and Preferred Treatment	
Anoro Ellipta	Only Anoro Ellipta was covered by OPDP and a 25% price reduction was assumed for Anoro Ellipta
Ultibro	Only Ultibro was covered by OPDP and a 25% price reduction was assumed for Ultibro

In the additional sensitivity analysis, analysis was based on assuming that users who switch from drug therapy including a LAMA product to LAMA/LABA products will use the same number of units previously consumed of LAMA products and that users who switch from therapy not including a LAMA product, will use LAMA/LABA products half as much as their previous use of LABA products.

Findings

Current Usage and Expenditure

Table 35 COPD Therapy Users by Severity

	Users N(%)			
	ALL	**VERY SEVERE**	**SEVERE**	**MODERATE**
Total	215,952(100%)	35,601(100%)	35,296(100%)	145,055(100%)
Multiple Prescriptions				
Triple therapy ICS+LABA combo	51,720(24%)	15,220(43%)	10,295(29%)	26,205(18%)
Triple therapy dual	627(0%)	171(0%)	129(0%)	327(0%)
Combination therapy	50,122(23%)	6,789(19%)	8,673(25%)	34,660(24%)
Dual therapy ICS + LABA	806(0%)	90(0%)	136(0%)	580(0%)
Dual therapy ICS + LAMA	5,601(3%)	939(3%)	1,000(3%)	3,662(3%)
Dual therapy LAMA + LABA	859(0%)	188(1%)	112(0%)	559(0%)
Single therapy ICS	18,764(9%)	1,494(4%)	2,668(8%)	14,602(10%)

	Users N(%)			
	ALL	**VERY SEVERE**	**SEVERE**	**MODERATE**
Single therapy LABA	649(0%)	79(0%)	76(0%)	494(0%)
Single therapy LAMA	25,573(12%)	3,090(9%)	2,935(8%)	19,548(13%)
Single Prescription				
Multiple therapy - ICS+LABA combo + LAMA	3,484(2%)	843(2%)	569(2%)	2,072(1%)
Multiple therapy - ICS + LABA + LAMA	8(0%)	≤5(0%)	≤5(0%)	8(0%)
Combination therapy (ICS+LABA combo)	30,138(14%)	4,253(12%)	4,953(14%)	20,932(14%)
Multiple therapy - ICS + LABA	56(0%)	≤5(0%)	9(0%)	47(0%)
Multiple therapy - ICS + LAMA	652(0%)	78(0%)	100(0%)	474(0%)
Multiple therapy - LABA + LAMA	54(0%)	17(0%)	≤5(0%)	37(0%)
Single therapy - ICS	17,077(8%)	1,099(3%)	2,363(7%)	13,615(9%)
Single therapy - LABA	222(0%)	37(0%)	25(0%)	160(0%)
Single therapy - LAMA	9,540(4%)	1,214(3%)	1,253(4%)	7,073(5%)

Total number of users was 215,952; the majority (67%) of users were patients with moderate COPD.

Summary of Findings for COPD Therapy Users by Severity

- The total number of COPD therapy users was 215,952, ranging from 35,601 users with very severe COPD to 145,055 users with moderate COPD.
- Users of Triple therapy ICS+LABA combo with multiple prescriptions accounted for 43% of patients with very severe COPD, 29% of patients with severe COPD, and 18% of patients with moderate COPD.
- Users of Triple therapy dual with multiple prescriptions accounted for 0% of patients with very severe, severe, and moderate COPD.
- Users of Combination therapy ICS+LABA combo with multiple prescriptions accounted for 19% of patients with very severe COPD, 25% of patients with severe COPD, and 24% of patients with moderate COPD.

Table 36 COPD Therapy Units by Severity

	UNITS* N(%)			
	ALL	**VERY SEVERE**	**SEVERE**	**MODERATE**
COPD Therapy	112,162,457(100%)	22,091,355(100%)	20,011,200(100%)	70,059,902(100%)
ICS	20,864,672(19%)	2,125,620(10%)	3,100,740(15%)	15,638,312(22%)

	UNITS* N(%)			
	ALL	VERY SEVERE	SEVERE	MODERATE
LABA	1,400,040(1%)	246,900(1%)	210,480(1%)	942,660(1%)
LAMA	21,687,525(19%)	4,950,255(22%)	3,670,260(18%)	13,067,010(19%)
ICS+LABA	68,210,220(61%)	14,768,580(67%)	13,029,720(65%)	40,411,920 (58%)

UNITS* = per puff

Total number of COPD therapy units was 112.2 million; ICS+LABA accounted for 61% of units, while ICS, LABA, and LAMA individually accounted for 20% or less.

Summary of Findings for COPD Therapy Units by Severity

- The total number of COPD therapy units was 112.2 million. The number of units ranged from 20.0 million for patients with severe COPD to 70.1 million for patients with moderate COPD.
- Across all patient populations, ICS+LABA accounted for the greatest number of units, followed by LAMA and ICS, respectively.

Table 37 Number of Prescriptions by Severity

	PRESCRIPTIONS N			
	ALL	VERY SEVERE	SEVERE	MODERATE
COPD Therapy	1,115,115	240,213	196,268	678,634
ICS	133,911	13,611	20,252	100,048
LABA	15,114	2,791	2,263	10,060
LAMA	417,914	101,753	70,310	245,851
ICS+LABA	548,176	122,058	103,443	322,675

The most commonly prescribed COPD therapy was ICS+LABA across all patients, regardless of disease severity..

Summary of Findings for Number of Prescriptions by Severity

- The most commonly prescribed COPD therapy across all patients was ICS+LABA, followed by LAMA, ICS, and LABA, respectively.
- A total of 417,914 prescriptions for LAMA were filled; 101,753 for patients with very severe COPD, 70,310 for patients with severe COPD, and 245,851 for patients with moderate COPD.

Table 38 Total COPD Therapy Expenditure by Severity

	TOTAL COPD THERAPY EXPENDITURE* $ (%)			
	ALL	**VERY SEVERE**	**SEVERE**	**MODERATE**
COPD Therapy	$149,096,674(100%)	33,185,327(100%)	26,948,356(100%)	88,962,991(100%)
ICS	$12,063,335(8%)	1,306,818(4%)	1,861,776(7%)	8,894,742(10%)
LABA	$1,319,073(1%)	236,915(1%)	199,954(1%)	882,204(1%)
LAMA	$50,191,609(34%)	11,588,845(35%)	8,511,523(32%)	30,091,242(34%)
ICS+LABA	$85,522,656(57%)	20,052,748(60%)	16,375,104(61%)	49,094,803(55%)

* from April 1, 2012-March 31, 2013

NB: From April 1, 2011-March 31, 2012, total OPDP expenditure on COPD therapy was $141.6 million

From April 1, 2012-March 31, 2013, total COPD therapy expenditure by OPDP was $149.1 million for all patients, varying from $26.9 million for patients with severe COPD to $89.0 million for patients with moderate COPD.

Summary of Findings for Total COPD Therapy Expenditure by Severity

- Total COPD expenditure from April 1, 2012 to March 31, 2013 was $149.1 million, ranging from $1.3 million for LABA to $85.5 million for ICS+LABA.
- Expenditure for patients with moderate COPD was the greatest, ranging from $0.9 million for LABA to $49.1 million for ICS+LABA.
- Overall, LAMA accounted for 34% of all COPD therapy expenditure ($50.2 million).

Table 39 Average Cost per Unit by Severity

	AVERAGE COST PER UNIT * $			
	ALL	**VERY SEVERE**	**SEVERE**	**MODERATE**
Total COPD Therapy	$1.33	$1.50	$1.35	$1.27
ICS	$0.58	$0.61	$0.60	$0.57
LABA	$0.94	$0.96	$0.95	$0.94
LAMA	$2.31	$2.34	$2.32	$2.30
ICS+LABA	$1.25	$1.36	$1.26	$1.21

AVERAGE COSTS PER UNIT*= average cost per puff

From April 1, 2012-March 31, 2013, the average cost per unit was $1.31between $1.27 per unit for patients with moderate COPD to $1.50 per unit for patients with very severe COPD.

Summary of Findings for Average Cost per Unit by Severity

- LAMA had the highest average cost per unit at $2.31, while ICS had the lowest average cost per unit at $0.58.
- The average cost per unit of LAMA varied between $2.30 for patients with moderate COPD to $2.34 per unit for patients with very severe COPD.

Impact of Alternative Approaches to Reimbursement

Table 40 Budget Impact – Base Case Results

#	REIMBURSEMENT SCENARIO	IMPACT	TOTAL	% BUDGET IMPACT
Current Reimbursement				
			$149,096,674	
If a modest proportion (50%) **of LABA only and LAMA only users switch to LAMA/LABA**				
GB1	Only Very Severe	Expected total $	$149,388,831	**0.196%**
		Budget impact	+ $292,157	
GB2	At Least Severe	Expected total $	$149,620,265	**0.351%**
		Budget impact	+ $523,591	
GB3	At Least Moderate	Expected total $	$151,214,560	**1.420%**
		Budget impact	+ $2,117,886	
If almost all (99%) of LAMA and LABA users switch to LAMA/LABA				
GB4	Only Very Severe	Expected total $	$149,140,067	**0.029%**
		Budget impact	+ $43,393	
GB5	At Least Severe	Expected total $	$149,159,073	**0.042%**
		Budget impact	+ $62,399	
GB6	At Least Moderate	Expected total $	$149,301,953	**0.138%**
		Budget impact	+ $205,279	
If a modest proportion (60%) of ICS and LABA users switch to LAMA/LABA				
GB7	Only Very Severe	Expected total $	$149,532,219	**0.292%**
		Budget impact	+ $435,545	
GB8	At Least Severe	Expected total $	$150,407,536	**0.879%**
		Budget impact	+ $1,310,862	
GB9	At Least Moderate	Expected total $	$154,090,764	**3.350%**

		Budget impact	+ $4,994,090	
If a small proportion (20%) of ICS and LABA users switch to LAMA/LABA plus ICS				
GB10	Only Very Severe	Expected total $	$150,450,136	**0.908%**
		Budget impact	+ $1,353,462	
GB11	At Least Severe	Expected total $	$152,209,831	**2.088%**
		Budget impact	+ $3,113,157	
GB12	At Least Moderate	Expected total $	$159,006,555	**6.647%**
		Budget impact	+ $9,909,881	
If a modest (50%) proportion of ICS and LABA and LAMA users switch to LAMA/LABA plus ICS				
GB13	Only Very Severe	Expected total $	$151,679,926	**1.733%**
		Budget impact	+ $2,583,252	
GB14	At Least Severe	Expected total $	$153,162,203	**2.727%**
		Budget impact	+ $4,065,529	
GB15	At Least Moderate	Expected total $	$157,228,208	**5.454%**
		Budget impact	+ $8,131,534	
Combining all scenarios				
GB16	Only Very Severe	Expected total $	$153,804,482	**3.158%**
		Budget impact	+ $4,707,808	
GB17	At Least Severe	Expected total $	$158,172,212	**6.087%**
		Budget impact	+ $9,075,537	
GB18	At Least Moderate	Expected total $	$174,455,344	**17.008%**
		Budget impact	+ $25,358,670	

Disaggregated results by drug class are available in Appendix C2: Disaggregated Results, and allow consideration of the impact of differential reimbursement status by disease severity

Summary of Budget Impact – Base Case Results

- From April 1, 2012-March 31, 2013, total expenditure on COPD therapy was $149.1 million.
- All proposed scenarios would lead to an increase in total COPD therapy expenditure, ranging from a rise of $43,393 or 0.029% (GB4) to an increase of $25.4 million or 17.008% (GB18).
- If a modest proportion (50%) of LABA only and LAMA only users switch to LAMA/LABA (Scenarios GB1-GB3), this would lead to a small increase in total COPD therapy expenditure (a rise of 0.196% for only very severe, 0.351% for at least severe and 1.420% for at least moderate or an increase of $0.3 million, $0.5 million and $2.1 million respectively).
- If almost all (99%) of LAMA and LABA users switch to LAMA/LABA combination (Scenarios GB4-GB6), this would have a marginal impact on total costs (a rise in total COPD therapy expenditure of 0.029% for only very severe, 0.042% for at least severe and 0.138% for at least moderate or an increase of $43,393, $62,399 and $205,279 respectively).
- If a modest proportion (60%) of ICS and LABA users switch to LAMA/LABA combination (Scenarios GB7-GB9), this would lead to a rise in total costs ranging from 0.292% to 3.350% (an increase of $0.4 million for only very severe, $1.3 million for at least severe and $5.0 million for at least moderate).
- If a small proportion (20%) of ICS and LABA users switch to LAMA/LABA combination plus ICS (Scenarios GB10-GB12), this would lead to a greater rise in total costs ranging from 0.908% to 6.647% (an increase of $1.4 million for only very severe, $3.1 million for at least severe and $9.9 million for at least moderate).
- Similarly, if a modest proportion (50%) of ICS and LABA and LAMA users switch to LAMA/LABA plus ICS (Scenarios GB13-GB15), this would lead to a rise in total costs ranging from 1.733% to 5.454% (an increase of $2.6 million for only very severe, $4.1 million for at least severe and $8.1 million for at least moderate).
- Combining all scenarios (Scenarios GB1-GB15) would lead to a significant increase in OPDP expenditure ranging from an increase of $4.7 million to $25.4 million or 3.158% to 17.008%.

Sensitivity Analysis Results

Table 41 Budget Impact - Sensitivity Analysis Results - Price Reduction

#	Impact	Base Case		Reduced $ Anoro Ellipta		Reduced $ Ultibro		Reduced $ (Both)	
		Total	%Budget Impact	Total	% Budget Impact	Total	% Budget Impact	Total	% Budget Impact
GB1	Expected total $	$149,388,831	**0.196%**	$149,240,599	**0.097%**	$149,241,692	**0.097%**	$149,093,460	**-0.002%**
	Budget impact	+ $292,157		+ $143,925		+ $145,018		- $3,214	
GB2	Expected total $	$149,620,265	**0.351%**	$149,328,925	**0.156%**	$149,331,072	**0.157%**	$149,039,732	**-0.038%**
	Budget impact	+ $523,591		+ $232,251		+ $234,398		-$56,943	
GB3	Expected total $	$151,214,560	**1.420%**	$149,937,200	**0.564%**	$149,946,615	**0.570%**	$148,669,256	**-0.287%**
	Budget impact	+ $2,117,886		+ $840,526		+ $849,941		- $427,419	
GB4	Expected total $	$149,140,067	**0.029%**	$149,109,853	**0.009%**	$149,110,076	**0.009%**	$149,079,881	**-0.011%**
	Budget impact	+ $43,393		+ $13,179		+ $13,402		- $16,793	
GB5	Expected total $	$149,159,073	**0.042%**	$149,112,519	**0.011%**	$149,112,862	**0.011%**	$149,066,338	**-0.020%**
	Budget impact	+ $62,399		+ $15,845		+ $16,188		- $30,336	

#	Impact	Base Case		Reduced $ Anoro Ellipta		Reduced $ Ultibro		Reduced $ (Both)	
		Total	%Budget Impact	Total	% Budget Impact	Total	% Budget Impact	Total	% Budget Impact
GB6	Expected total $	$149,301,953	**0.138%**	$149,166,713	**0.047%**	$149,167,710	**0.048%**	$149,032,552	**-0.043%**
	Budget impact	+ $205,279		+ $70,039		+ $71,036		- $64,122	
GB7	Expected total $	$149,532,219	**0.292%**	$149,019,783	**-0.052%**	$149,023,560	**-0.049%**	$148,511,125	**-0.393%**
	Budget impact	+ $435,545		- $76,891		- $73,114		- $585,549	
GB8	Expected total $	$150,407,536	**0.879%**	$148,638,826	**-0.307%**	$149,822,019	**0.486%**	$148,053,309	**-0.700%**
	Budget impact	+ $1,310,862		- $457,848		+ $725,345		- $1,043,365	
GB9	Expected total $	$154,090,764	**3.350%**	$149,743,852	**0.434%**	$150,946,049	**1.240%**	$146,599,136	**-1.675%**
	Budget impact	+ $4,994,090		+ $647,178		+ $1,849,374		- $2,497,538	
GB10	Expected total $	$150,450,136	**0.908%**	$150,279,324	**0.793%**	$150,280,583	**0.794%**	$150,109,771	**0.679%**
	Budget impact	+ $1,353,462		+ $1,182,650		+ $1,183,909		+ $1,013,097	
GB11	Expected total $	$152,209,831	**2.088%**	$151,816,736	**1.824%**	$151,819,633	**1.826%**	$151,426,537	**1.563%**

#	Impact	Base Case		Reduced $ Anoro Ellipta		Reduced $ Ultibro		Reduced $ (Both)	
		Total	%Budget Impact	Total	% Budget Impact	Total	% Budget Impact	Total	% Budget Impact
	Budget impact	+ $3,113,157		+ $2,720,062		+ $2,722,959		+ $2,329,863	
GB12	Expected total $	$159,006,555	**6.647%**	$157,754,059	**5.807%**	$157,763,291	**5.813%**	$156,510,794	**4.973%**
	Budget impact	+ $9,909,881		+ $8,657,385		+ $8,666,617		+ $7,414,120	
GB13	Expected total $	$151,679,926	**1.733%**	$150,781,060	**1.130%**	$150,787,685	**1.134%**	$149,888,819	**0.531%**
	Budget impact	+ $2,583,252		+ $1,684,386		+ $1,691,011		+ $792,145	
GB14	Expected total $	$153,162,203	**2.727%**	$152,250,980	**2.116%**	$152,257,697	**2.120%**	$151,346,475	**1.509%**
	Budget impact	+ $4,065,529		+ $3,154,306		+ $3,161,023		+ $2,249,801	
GB15	Expected total $	$157,228,208	**5.454%**	$154,828,093	**3.844%**	$154,845,784	**3.856%**	$152,445,669	**2.246%**
	Budget impact	+ $8,131,534		+ $5,731,419		+ $5,749,110		+ $3,348,995	
GB16	Expected total $	$153,804,482	**3.158%**	$152,043,923	**1.977%**	$152,056,900	**1.985%**	$150,296,360	**0.805%**
	Budget impact	+ $4,707,808		+ $2,947,249		+ $2,960,226		+ $1,199,686	

#	Impact	Base Case		Reduced $ Anoro Ellipta		Reduced $ Ultibro		Reduced $ (Both)	
		Total	%Budget Impact	Total	% Budget Impact	Total	% Budget Impact	Total	% Budget Impact
GB17	Expected total $	$158,172,212	**6.087%**	$154,761,289	**3.799%**	$155,956,587	**4.601%**	$152,545,695	**2.313%**
	Budget impact	+ $9,075,537		+ $5,664,615		+ $6,859,913		+ $3,449,020	
GB18	Expected total $	$174,455,344	**17.008%**	$165,043,220	**10.695%**	$166,282,752	**11.527%**	$156,870,711	**5.214%**
	Budget impact	+ $25,358,670		+ $15,946,546		+ $17,186,078		+ $7,774,037	

Summary of Budget Impact - Sensitivity Analysis Results - Price Reduction

- In the base case analysis, all scenarios would lead to an increase In OPDP expenditure. GB4 would result in the smallest increase in OPDP expenditure (an increase of $43,393 or 0.029%), while GB18 would lead to the greatest increase in costs (an increase of $25.4 million or 17.008%).
- In the reduced $ Anoro Ellipta scenario, all scenarios except for GB7 and GB8 would lead to an increase in OPDP expenditure. Both GB7 and GB8 would result in a reduction in OPDP expenditure (a reduction of $76,891 or -0.052% and a reduction of $457,848 or -0.307%, respectively).
- In the reduced $ Ultibro scenario, all scenarios except for GB7 would lead to an increase In OPDP expenditure. GB7 would result in a slight reduction in OPDP expenditure (a reduction of $73,114 or -0.049%).
- In the reduced $ Anoro Ellipta and Ultibro scenario, half of the 18 scenarios would lead to cost savings, with GB9 leading to the greatest amount saved (a reduction of $2.5 million or -1.675%).

Table 42 Budget Impact - Sensitivity Analysis Results- Preferred Treatment

#	Impact	Base Case		Anoro Ellipta Preferred		Ultibro Preferred	
		Total	%Budget Impact	Total	% Budget Impact	Total	% Budget Impact
GB1	Expected total $	$149,388,831	**0.196%**	$149,393,201	**0.199%**	$149,384,460	**0.193%**
	Budget impact	+ $292,157		+ $296,527		+ $287,786	
GB2	Expected total $	$149,620,265	**0.351%**	$149,628,855	**0.357%**	$149,611,675	**0.345%**
	Budget impact	+ $523,591		+ $532,181		+ $515,001	
GB3	Expected total $	$151,214,560	**1.420%**	$151,252,221	**1.446%**	$151,176,898	**1.395%**
	Budget impact	+ $2,117,886		+ $2,155,547		+ $2,080,224	
GB4	Expected total $	$149,140,067	**0.029%**	$149,140,958	**0.030%**	$149,139,176	**0.029%**
	Budget impact	+ $43,393		+ $44,284		+ $42,502	

#	Impact	Base Case		Anoro Ellipta Preferred		Ultibro Preferred	
		Total	%Budget Impact	Total	% Budget Impact	Total	% Budget Impact
GB5	Expected total $	$149,159,073	**0.042%**	$149,160,446	**0.043%**	$149,157,700	**0.041%**
	Budget impact	+ $62,399		+ $63,772		+ $61,026	
GB6	Expected total $	$149,301,953	**0.138%**	$149,305,942	**0.140%**	$149,297,965	**0.135%**
	Budget impact	+ $205,279		+ $209,268		+ $201,291	
GB7	Expected total $	$149,532,219	**0.292%**	$149,547,327	**0.302%**	$149,517,110	**0.282%**
	Budget impact	+ $435,545		+ $450,653		+ $420,436	
GB8	Expected total $	$150,407,536	**0.879%**	$150,424,927	**0.891%**	$150,390,144	**0.868%**
	Budget impact	+ $1,310,862		+ $1,328,253		+ $1,293,470	
GB9	Expected total $	$154,090,764	**3.350%**	$154,184,171	**3.412%**	$153,997,357	**3.287%**
	Budget impact	+ $4,994,090		+ $5,087,497		+ $4,900,683	
GB10	Expected total $	$150,450,136	**0.908%**	$150,455,172	**0.911%**	$150,445,100	**0.904%**
	Budget impact	+ $1,353,462		+ $1,358,498		+ $1,348,426	
GB11	Expected total $	$152,209,831	**2.088%**	$152,221,422	**2.096%**	$152,198,241	**2.080%**
	Budget impact	+ $3,113,157		+ $3,124,747		+ $3,101,567	
GB12	Expected total $	$159,006,555	**6.647%**	$159,043,484	**6.671%**	$158,969,627	**6.622%**
	Budget impact	+ $9,909,881		+ $9,946,810		+ $9,872,953	
GB13	Expected total $	$151,679,926	**1.733%**	$151,706,429	**1.750%**	$151,653,424	**1.715%**

#	Impact	Base Case		Anoro Ellipta Preferred		Ultibro Preferred	
		Total	%Budget Impact	Total	% Budget Impact	Total	% Budget Impact
	Budget impact	+ $2,583,252		+ $2,609,754		+ $2,556,750	
GB14	Expected total $	$153,162,203	**2.727%**	$153,189,069	**2.745%**	$153,135,336	**2.709%**
	Budget impact	+ $4,065,529		+ $4,092,395		+ $4,038,662	
GB15	Expected total $	$157,228,208	**5.454%**	$157,298,973	**5.501%**	$157,157,443	**5.406%**
	Budget impact	+ $8,131,534		+ $8,202,299		+ $8,060,769	
GB16	Expected total $	$153,804,482	**3.158%**	$153,856,391	**3.192%**	$153,752,574	**3.123%**
	Budget impact	+ $4,707,808		+ $4,759,717		+ $4,655,900	
GB17	Expected total $	$158,172,212	**6.087%**	$158,238,023	**6.131%**	$158,106,401	**6.043%**
	Budget impact	+ $9,075,537		+ $9,141,348		+ $9,009,727	
GB18	Expected total $	$174,455,344	**17.008%**	$174,698,095	**17.171%**	$174,212,593	**16.845%**
	Budget impact	+ $25,358,670		+ $25,601,421		+ $25,115,919	

Summary of Budget Impact - Sensitivity Analysis Results- Preferred Treatment

- In the Anoro Ellipta preferred scenario, all scenarios would lead to an increase in OPDP expenditure. GB4 would result in the smallest increase in OPDP expenditure (an increase of $44,284 or 0.030%), while GB18 would lead to the greatest increase in costs (an increase of $25.6 million or 17.171%).
- In the Ultibro preferred scenario, all scenarios would lead to an increase in OPDP expenditure. GB4 would result in the smallest increase in OPDP expenditure (an increase of $42,502 or 0.029%), while GB18 would lead to the greatest increase in costs (an increase of $25.1 million or 16.845%.

Table 43 Budget Impact - Sensitivity Analysis Results - Price Reduction and Preferred Treatment

#	Impact	Base Case		Reduced $ and Anoro Ellipta Preferred		Reduced $ and Ultibro Preferred	
		Total	%Budget Impact	Total	% Budget Impact	Total	% Budget Impact
GB1	Expected total $	$149,388,831	**0.196%**	$149,096,738	**0.000%**	$149,090,182	**-0.004%**
	Budget impact	+ $292,157		+ $64		- $6,492	
GB2	Expected total $	$149,620,265	**0.351%**	$149,046,174	**-0.034%**	$149,033,289	**-0.043%**
	Budget impact	+ $523,591		-$50,500		- $63,385	
GB3	Expected total $	$151,214,560	**1.420%**	$148,697,502	**-0.268%**	$148,641,009	**-0.306%**
	Budget impact	+ $2,117,886		- $399,172		- $455,665	
GB4	Expected total $	$149,140,067	**0.029%**	$149,080,548	**-0.011%**	$149,079,214	**-0.012%**
	Budget impact	+ $43,393		- $16,126		- $17,460	
GB5	Expected total $	$149,159,073	**0.042%**	$149,067,366	**-0.020%**	$149,065,310	**-0.021%**
	Budget impact	+ $62,399		- $29,308		- $31,364	
GB6	Expected total $	$149,301,953	**0.138%**	$149,035,540	**-0.041%**	$149,029,564	**-0.045%**
	Budget impact	+ $205,279		- $61,135		- $67,110	
GB7	Expected total $	$149,532,219	**0.292%**	$148,522,456	**-0.385%**	$148,499,794	**-0.400%**
	Budget impact	+ $435,545		- $574,218		- $596,881	
GB8	Expected total $	$150,407,536	**0.879%**	$148,066,353	**-0.691%**	$149,219,110	**0.082%**
	Budget impact	+ $1,310,862		- $1,030,321		+ $122,436	

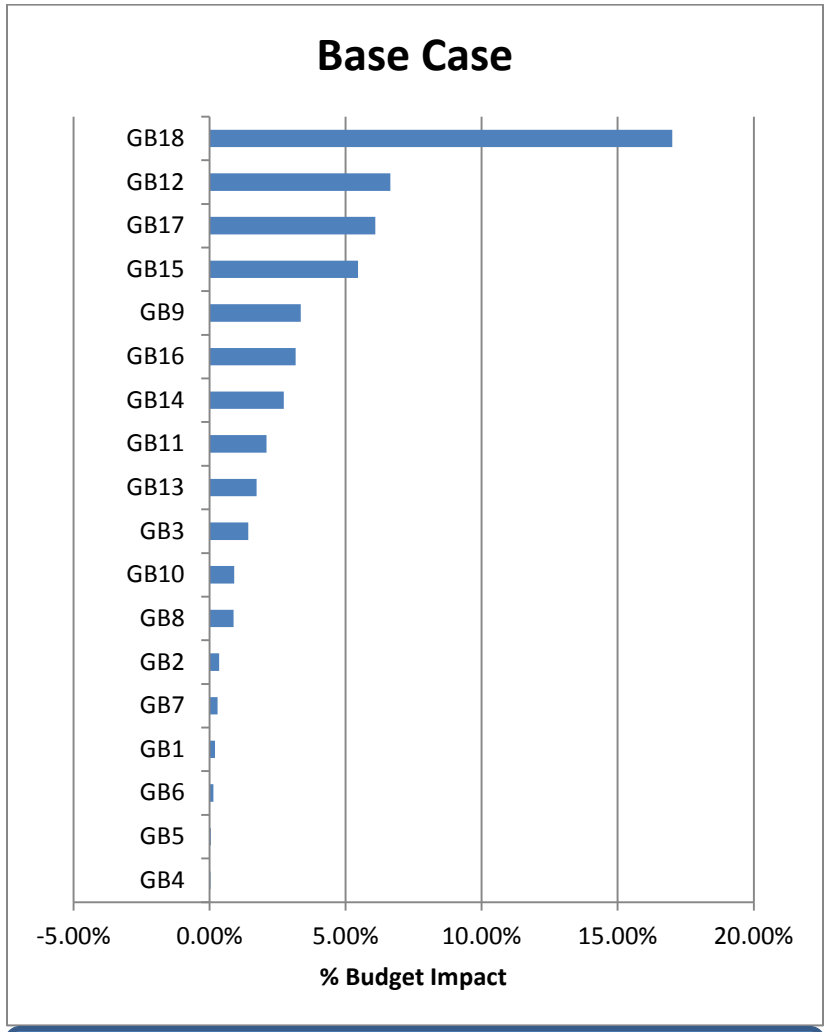
#	Impact	Base Case		Reduced $ and Anoro Ellipta Preferred		Reduced $ and Ultibro Preferred	
		Total	%Budget Impact	Total	% Budget Impact	Total	% Budget Impact
GB9	Expected total $	$154,090,764	**3.350%**	$146,669,192	**-1.628%**	$147,707,926	**-0.931%**
	Budget impact	+ $4,994,090		- $2,427,482		- $1,388,748	
GB10	Expected total $	$150,450,136	**0.908%**	$150,113,549	**0.682%**	$150,105,994	**0.677%**
	Budget impact	+ $1,353,462		+ $1,016,874		+ $1,009,320	
GB11	Expected total $	$152,209,831	**2.088%**	$151,435,230	**1.568%**	$151,417,845	**1.557%**
	Budget impact	+ $3,113,157		+ $2,338,556		+ $2,321,171	
GB12	Expected total $	$159,006,555	**6.647%**	$156,538,491	**4.991%**	$156,483,098	**4.954%**
	Budget impact	+ $9,909,881		+ $7,441,817		+ $7,386,424	
GB13	Expected total $	$151,679,926	**1.733%**	$149,908,695	**0.545%**	$149,868,942	**0.518%**
	Budget impact	+ $2,583,252		+ $812,021		+ $772,268	
GB14	Expected total $	$153,162,203	**2.727%**	$151,366,625	**1.522%**	$151,326,325	**1.495%**
	Budget impact	+ $4,065,529		+ $2,269,950		+ $2,229,651	
GB15	Expected total $	$157,228,208	**5.454%**	$152,498,743	**2.282%**	$152,392,595	**2.211%**
	Budget impact	+ $8,131,534		+ $3,402,069		+ $3,295,921	
GB16	Expected total $	$153,804,482	**3.158%**	$150,335,290	**0.831%**	$150,257,429	**0.779%**
	Budget impact	+ $4,707,808		+ $1,238,616		+ $1,160,755	
GB17	Expected total $	$158,172,212	**6.087%**	$152,595,051	**2.346%**	$153,675,183	**3.071%**

#	Impact	Base Case Total	Base Case %Budget Impact	Reduced $ and Anoro Ellipta Preferred Total	Reduced $ and Anoro Ellipta Preferred % Budget Impact	Reduced $ and Ultibro Preferred Total	Reduced $ and Ultibro Preferred % Budget Impact
	Budget impact	+ $9,075,537		+ $3,498,377		+ $4,578,509	
GB18	Expected total $	$174,455,344	17.008%	$157,052,770	5.336%	$157,867,496	5.883%
	Budget impact	+ $25,358,670		+ $7,956,096		+ $8,770,822	

Summary of Budget Impact - Sensitivity Analysis Results - Price Reduction and Preferred Treatment

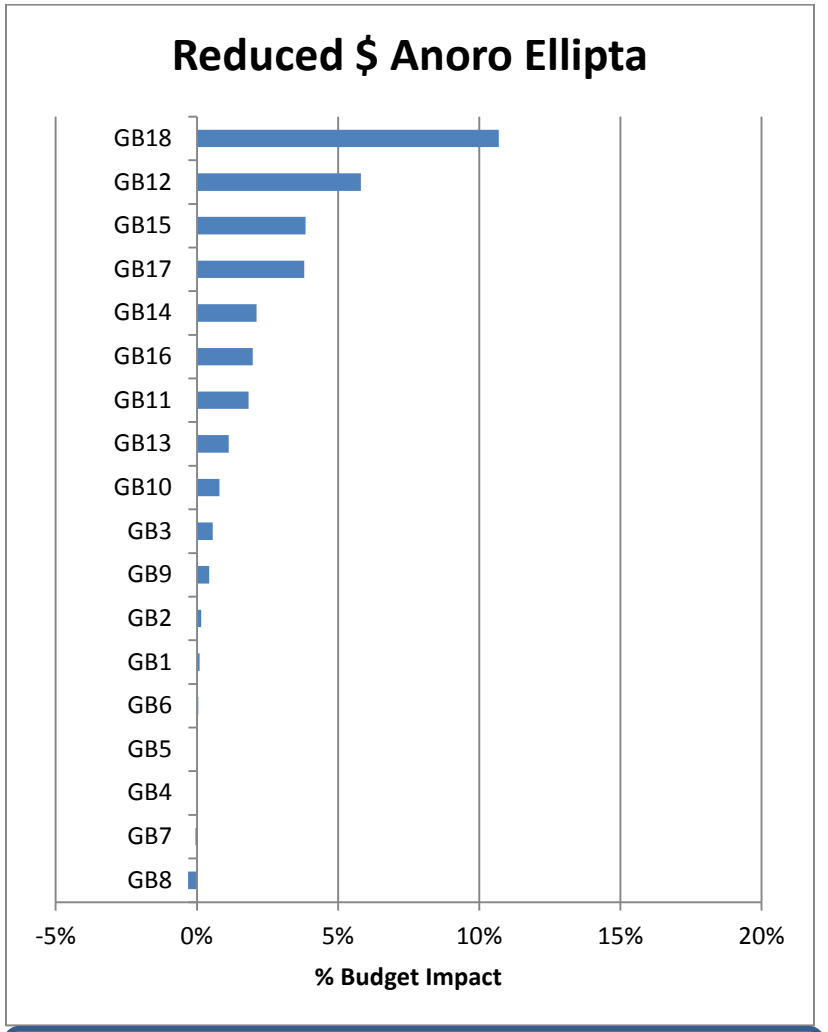
- In the reduced $ and Anoro Ellipta preferred scenario, almost half of the 18 scenarios would lead to cost savings, with GB9 leading to the greatest amount saved (a reduction of $2.4 million or - 1.628%).
- Similarly, in the reduced $ and Ultibro preferred scenario, almost half of the 18 scenarios would lead to cost savings, with GB9 leading to the greatest amount saved (a reduction of $1.4 million or -0.931%.

Figure 7 % Budget Impact - Base Case



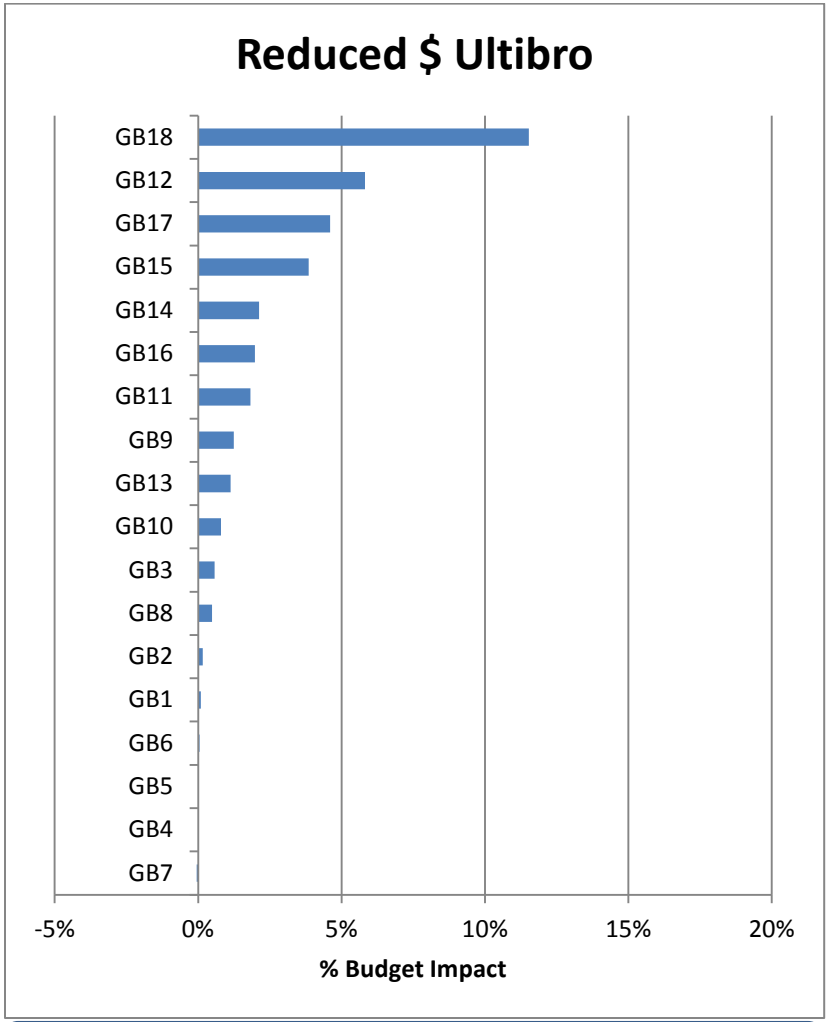
All scenarios would lead to an increase In OPDP expenditure

Figure 8 % Budget Impact - Reduced $ Anoro Ellipta



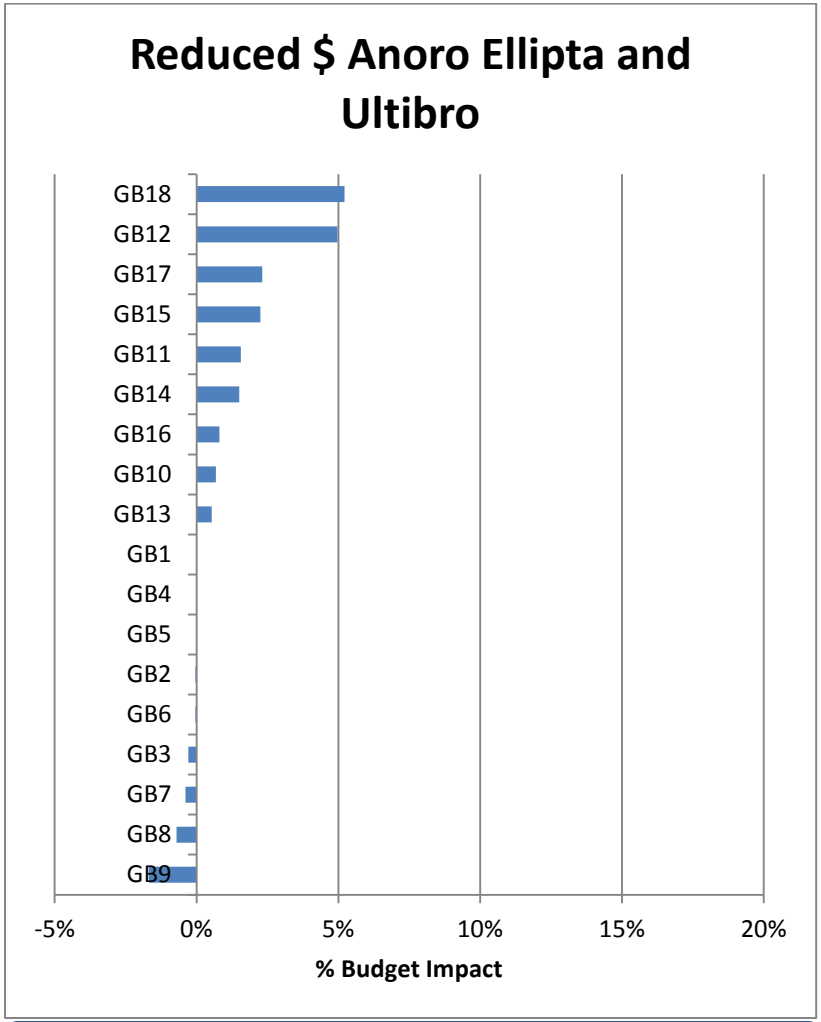
GB7 and GB8 would lead to a slight reduction In expenditure

Figure 9 % Budget Impact - Reduced $ Ultibro



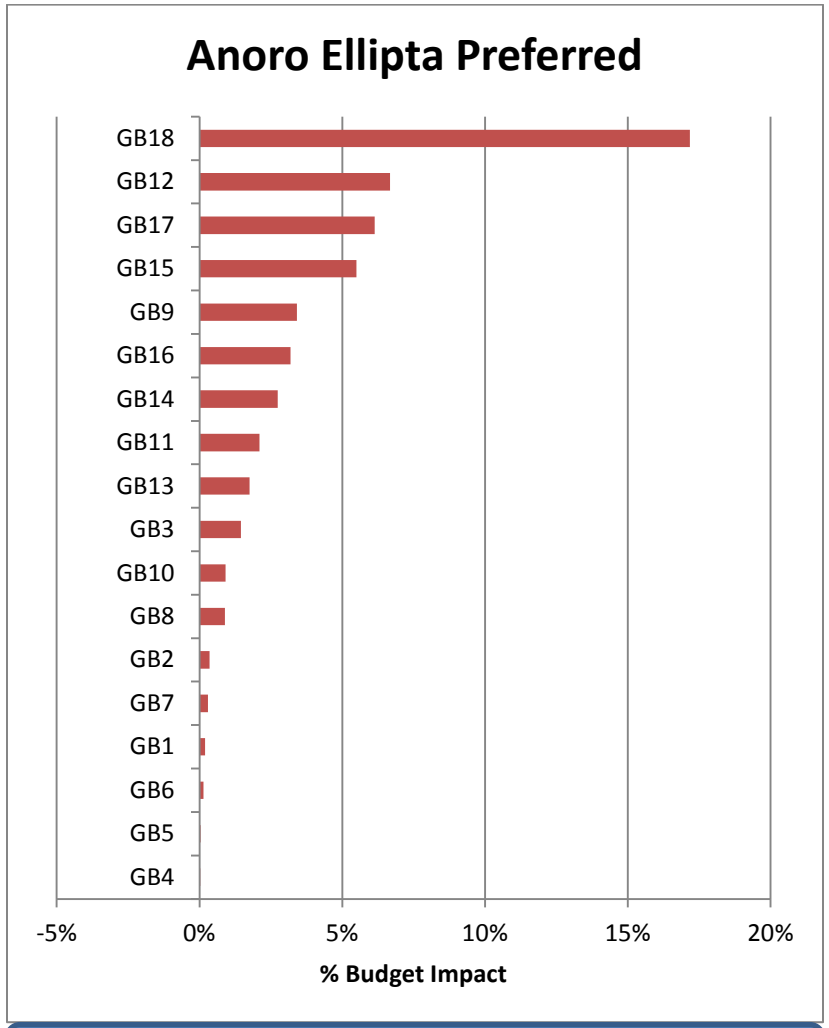
All scenarios except GB7 would lead to a rise in expenditure

Figure 10 % Budget Impact - Reduced $ Anoro Ellipta and Ultibro



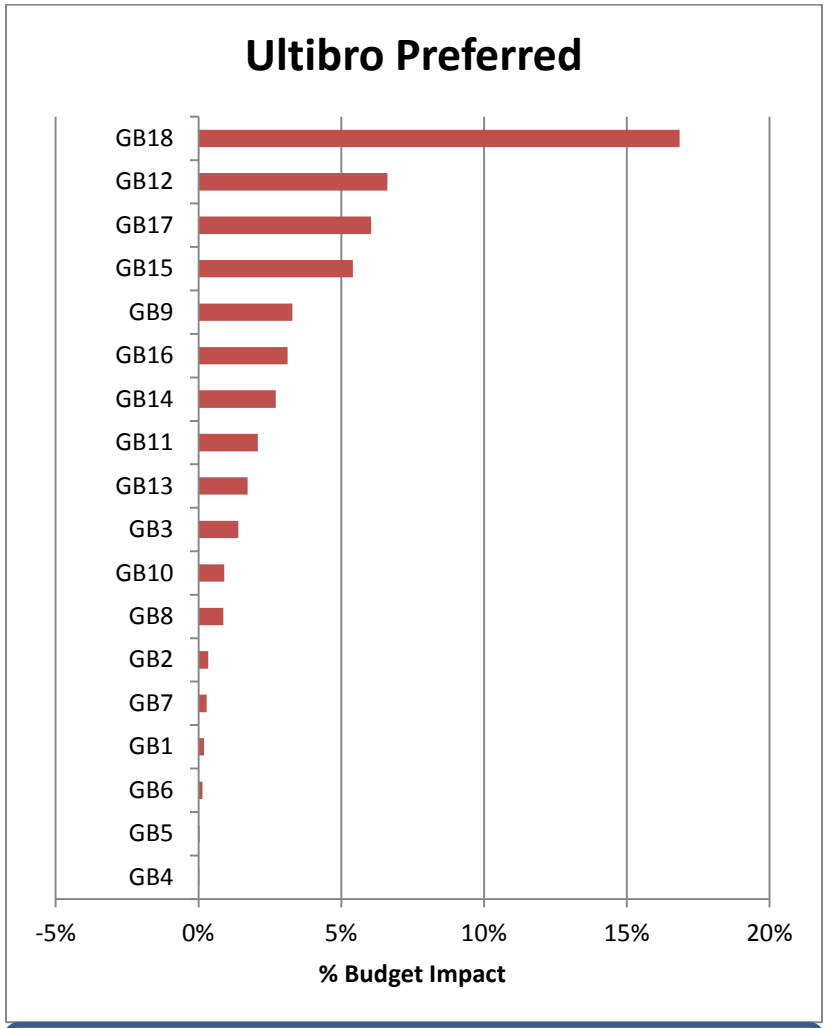
GB9 would lead to the greatest amount saved, followed by GB8

Figure 11 % Budget Impact - Anoro Ellipta Preferred



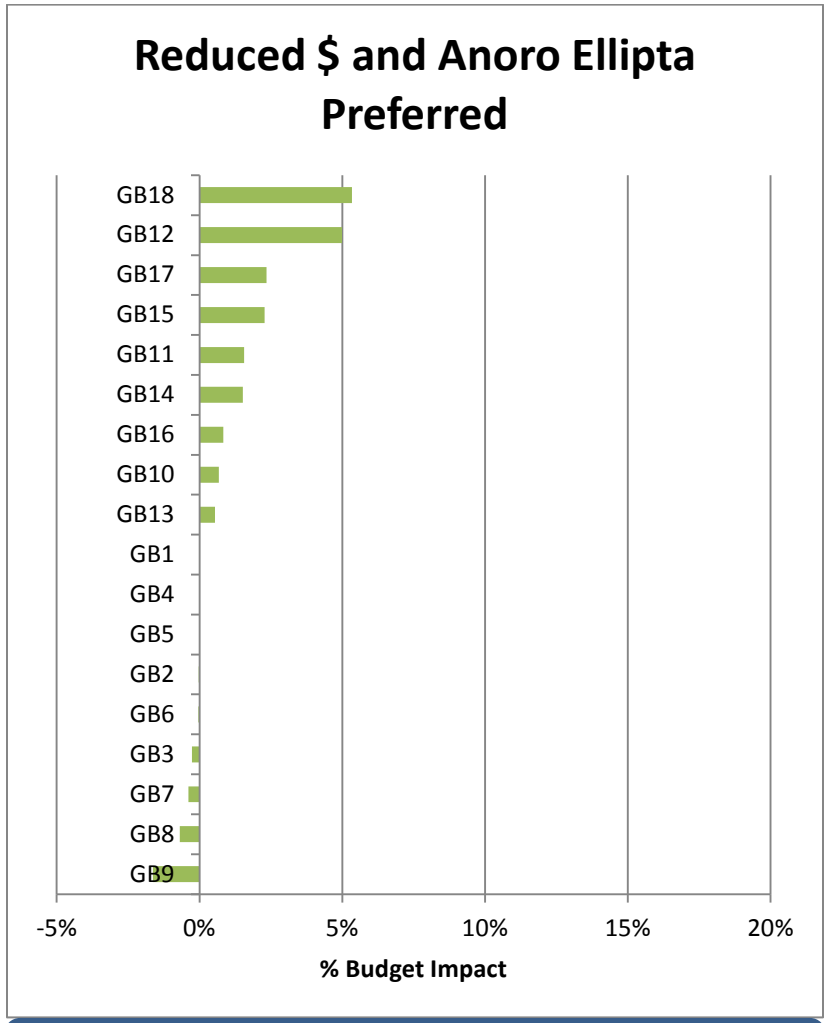
All scenarios would lead to a rise in expenditure

Figure 12 % Budget Impact - Ultibro Preferred



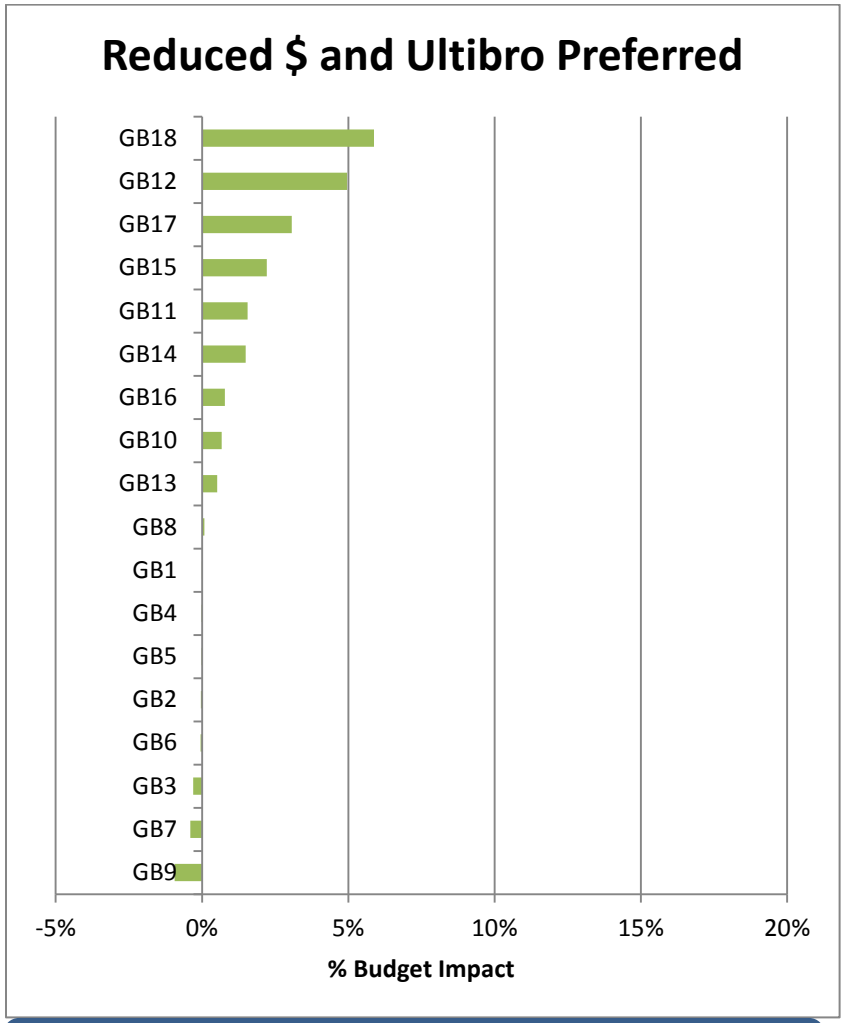
All scenarios would lead to an increase in OPDP expenditure

Figure 13 % Budget Impact - Reduced $ and Anoro Ellipta Preferred



GB9 would lead to the greatest amount saved, followed by GB8

Figure 14 % Budget Impact - Reduced $ and Ultibro Preferred



GB9 would lead to the greatest amount saved, followed by GB7

Summary of Figures 7 to 14

The analysis is most sensitive to price reduction and preferred therapy; scenarios including a price reduction to both Anoro Ellipta and Ultibro or both a price reduction and preferred therapy would lead to a small absolute reduction in OPDP expenditure.

Table 44 Budget Impact - Sensitivity Analysis Results – Revised Units of LAMA/LABA Products

#	Impact	Base Case			
		Total	%Budget Impact	Total	% Budget Impact
GB1	Expected total $	$149,388,831	**0.196%**	$149,388,831	**0.196%**
	Budget impact	+ $292,157		$292,157	
GB2	Expected total $	$149,620,265	**0.351%**	$149,620,265	**0.351%**
	Budget impact	+ $523,591		$523,591	
GB3	Expected total $	$151,214,560	**1.420%**	$151,214,560	**1.420%**
	Budget impact	+ $2,117,886		$2,117,886	
GB4	Expected total $	$149,140,067	**0.029%**	$149,035,416	**-0.041%**
	Budget impact	+ $43,393		-$61,258	
GB5	Expected total $	$149,159,073	**0.042%**	$149,004,069	**-0.062%**
	Budget impact	+ $62,399		-$92,605	
GB6	Expected total $	$149,301,953	**0.138%**	$148,860,737	**-0.158%**
	Budget impact	+ $205,279		-$235,937	

#	Impact	Base Case Total	Base Case %Budget Impact	Total	% Budget Impact
GB7	Expected total $	$149,532,219	0.292%	$147,490,031	-1.078%
	Budget impact	+ $435,545		-$1,606,643	
GB8	Expected total $	$150,407,536	0.879%	$145,699,083	-2.279%
	Budget impact	+ $1,310,862		-$3,397,592	
GB9	Expected total $	$154,090,764	3.350%	$139,107,508	-6.700%
	Budget impact	+ $4,994,090		-$9,989,166	
GB10	Expected total $	$150,450,136	0.908%	$149,769,407	0.451%
	Budget impact	+ $1,353,462		$672,733	
GB11	Expected total $	$152,209,831	2.088%	$150,643,243	1.037%
	Budget impact	+ $3,113,157		$1,546,569	
GB12	Expected total $	$159,006,555	6.647%	$154,015,033	3.299%
	Budget impact	+ $9,909,881		$4,918,359	
GB13	Expected total $	$151,679,926	1.733%	$150,017,211	0.617%
	Budget impact	+ $2,583,252		$920,537	
GB14	Expected total $	$153,162,203	2.727%	$151,497,146	1.610%
	Budget impact	+ $4,065,529		$2,400,472	
GB15	Expected total $	$157,228,208	5.454%	$153,123,503	2.701%

#	Impact	Base Case Total	Base Case %Budget Impact	Total	% Budget Impact
	Budget impact	+ $8,131,534		$4,026,829	
GB16	Expected total $	$153,804,482	3.158%	$149,314,200	0.146%
	Budget impact	+ $4,707,808		$217,526	
GB17	Expected total $	$158,172,212	6.087%	$150,077,110	0.658%
	Budget impact	+ $9,075,537		$980,436	
GB18	Expected total $	$174,455,344	17.008%	$149,934,645	0.562%
	Budget impact	+ $25,358,670		$837,971	

Summary of Budget Impact - Sensitivity Analysis Results - Revised Units of LAMA/LABA Products

In the sensitivity analysis relating to revised units of LAMA/LABA prodcuts, 3 scenarios would lead to cost savings. For all of the scenarios combined, the increase in budget associated with the funding of LAMA/LABA products fell from $25,358,670 to $837,971.

Overall Conclusions and Summary

Assuming general benefit (GB) for LAMA/LABA combination products in patients with COPD, regardless of severity of disease, will lead to an increase in total OPDP expenditure.

Switching almost all (99%) of LAMA and LABA users to LAMA/LABA combination product, whereby users of LAMA and LABA (dual therapy) or single prescription, multiple therapy (LAMA and LABA) switch to LAMA/LABA combination, would have a marginal impact in total costs (a rise in total COPD therapy expenditure of 0.029% for only very severe, 0.042% for at least severe and 0.138% for at least moderate). This scenario yields a small absolute rise in costs.

If a small proportion (20%) of ICS and LABA users switch to LAMA/LABA combination, whereby users of combination therapy (ICS+LABA), dual therapy (ICS + LABA), single prescription ICS+LABA combo, or single prescription, multiple therapy - ICS + LABA switch to LAMA/LABA combination, this would lead to a greater rise in total costs ranging from 0.908% to 6.647% (an increase of $1.4 million for only very

severe, $3.1 million for at least severe and $9.9 million for at least moderate).

If a modest proportion (20%-60%) of LABA only, LAMA only, and LABA and LAMA users switch to LAMA/LABA; a proportion of ICS and LABA users switch to LAMA/LABA or LAMA/LABA plus ICS; and a proportion ICS and LABA and LAMA users switch to LAMA/LABA plus ICS, this would result in the greatest increase in OPDP costs ranging from 3.158% to 17.008% (an increase of $4.7 million for only very severe, $9.1 million for at least severe and $25.4 million for at least moderate).

The analysis is most sensitive to price reduction and preferred therapy; scenarios including a price reduction to both Anoro Ellipta and Ultibro or a price reduction to a preferred therapy would lead to a small absolute reduction in OPDP expenditure.

A sensitivity analysis whereby the number of units of LAMA/LABA products was assumed to be based on previous use of LAMA and LABA/ICS products forecasted a small budget increase of less than 1%

Conclusions

Assuming GB for LAMA/LABA combination product in patients with COPD, regardless of severity of disease, would lead to an increase in total expenditure on COPD therapy. Scenarios involving LAMA and LABA users switching to LAMA/LABA combination yield a small absolute rise in COPD costs. In many cases, negotiating price reductions and a preferred therapy would lead to a small reduction in OPDP expenditure. If the use of LAMA/LABA products was similar to previous use of LAMA products and was half the use of LABA/ICS products, the increase in budget would be minimal.

Appendix C – Appendices

Appendix C1: Model Details

Scenarios GB1-GB3 (If a modest proportion (50%) of LABA only and LAMA only users switch to LAMA/LABA)

In Scenarios **GB1 – GB3**, for users on single therapy (LAMA or LABA) or single prescription, single therapy (LAMA or LABA), 50% switch to combination therapy (LAMA/LABA). The following assumptions were made:

Table 44 Scenarios GB1-GB3 - Assumptions

Assumptions (Scenarios GB1-GB3)
A proportion of COPD patients who are users of single therapy (LAMA or LABA) or single prescription, single therapy (LAMA or LABA) will switch to combination therapy (LAMA/LABA)
Approximately 50% of those currently taking a LAMA or LABA alone will switch to LAMA/LABA
Users use half the number of units for LAMA/LABA as they did for LABA and the same number of units as for LAMA. The number of units will be split equally (50-50) between Anoro Ellipta and Ultibro

The following table illustrates how users on single therapy (LAMA or LABA) or single prescription, single therapy (LAMA or LABA) switched to combination therapy (LAMA/LABA).

Table 45 Scenarios GB1-GB3 - Details of LABA Only and LAMA Only Users Switching to LAMA/LABA

Details of Switch to Combination Product		
Users on LABA only and LAMA only whose initial therapy is:		**Will switch to:**
SEREVENT	50MCG	Anoro Ellipta/Ultibro
FORADIL	12MCG	Anoro Ellipta/Ultibro
SEREVENT DISKUS	50MCG	Anoro Ellipta/Ultibro
OXEZE	12MCG	Anoro Ellipta/Ultibro
OXEZE	6MCG	Anoro Ellipta/Ultibro
SPIRIVA	18MCG	Anoro Ellipta/Ultibro

Of those who will switch to combination product, the proportion will be divided as follows:

Table 46 Scenarios GB1-GB3 - How the Switch to LAMA/LABA will be Divided

How the Switch to LAMA/LABA will be divided by COPD Severity			
Combination therapy:	**Very Severe**	**Severe**	**Moderate**
Anoro Ellipta	0.5	0.5	0.5
Ultibro	0.5	0.5	0.5

Scenarios GB4-GB6 (If almost all (99%) of LAMA and LABA users switch to LAMA/LABA)
In Scenarios **GB4 – GB6**, for users on LAMA and LABA (dual therapy) or single prescription, multiple therapy (LAMA and LABA), 99% switch to combination therapy (LAMA/LABA). The following assumptions were made:

Table 47 Scenarios GB4-GB6 - Assumptions

Assumptions (Scenarios GB4-GB6)
A proportion of COPD patients who are users of LAMA and LABA (dual therapy) or single prescription, multiple therapy (LAMA and LABA) will switch to combination therapy (LAMA/LABA)
Approximately 99% of patients currently on LAMA and LABA will switch over to LAMA/LABA
Users use the same number of units for LAMA/LABA as they did for LABA, units are split equally (50-50) between Anoro Ellipta and Ultibro

The following table illustrates how users on LAMA and LABA (dual therapy) or single prescription, multiple therapy (LAMA and LABA) would switch to combination therapy (LAMA/LABA).

Table 48 Scenarios GB4-GB6 - Details of LAMA and LABA Users Switching to LAMA/LABA

Details of Switch to Combination Product		
Users on LABA and LAMA whose initial therapy is:		**Will switch to:**
SEREVENT	50MCG	Anoro Ellipta/Ultibro
FORADIL	12MCG	Anoro Ellipta/Ultibro
SEREVENT DISKUS	50MCG	Anoro Ellipta/Ultibro
OXEZE	12MCG	Anoro Ellipta/Ultibro
OXEZE	6MCG	Anoro Ellipta/Ultibro

Of those who will switch to combination product, the proportion will be divided as follows:

Table 49 Scenarios GB4-GB6 - How the Switch to LAMA/LABA will be Divided

How the Switch to LAMA/LABA will be divided by COPD Severity			
Combination therapy:	**Very Severe**	**Severe**	**Moderate**
Anoro Ellipta	0.5	0.5	0.5
Ultibro	0.5	0.5	0.5

Scenarios GB7-GB9 (If a modest proportion (60%) of ICS and LABA users switch to LAMA/LABA)

In Scenarios **GB7 – GB9**, for users on combination therapy (ICS+LABA), dual therapy (ICS + LABA), single prescription ICS+LABA combo, or single prescription, multiple therapy - ICS + LABA, 60% would switch to combination therapy (LAMA/LABA). The following assumptions were made:

Table 50 Scenarios GB7-GB9 - Assumptions

Assumptions (Scenarios GB7-GB9)
A proportion of COPD patients who are users of combination therapy (ICS+LABA), dual therapy (ICS + LABA), single prescription ICS+LABA combo, or single prescription, multiple therapy - ICS + LABA will switch to combination therapy (LAMA/LABA)
Approximately 60% of current users of ICS and LABA will switch to LAMA/LABA
Users use the same number of units for LAMA/LABA as they did ICS+LABA for combo users and of LABA for dual users. The number of units are split equally (50-50) between Anoro Ellipta and Ultibro and halved

The following table illustrates how users on LAMA and LABA (dual therapy) or single prescription, multiple therapy (LAMA and LABA) would switch to combination therapy (LAMA/LABA).

Table 51 Scenarios GB7-GB9 - Details of ICS and LABA Users Switching to LAMA/LABA

Details of Switch to Combination Product		
Users on ICS and LABA whose initial therapy is:		**Will switch to:**
ADVAIR DISKUS	100MCG	Anoro Ellipta/Ultibro
ADVAIR DISKUS	250MCG	Anoro Ellipta/Ultibro
ADVAIR DISKUS	500MCG	Anoro Ellipta/Ultibro
ADVAIR DISKUS (INH AEM)	125MCG	Anoro Ellipta/Ultibro
ADVAIR DISKUS (INH AEM)	250MCG	Anoro Ellipta/Ultibro
SYMBICORT	100/6MG	Anoro Ellipta/Ultibro
SYMBICORT	200/6MG	Anoro Ellipta/Ultibro
ZENHALE	50-5MCG	Anoro Ellipta/Ultibro
ZENHALE	100-5MCG	Anoro Ellipta/Ultibro
ZENHALE	200-5MCG	Anoro Ellipta/Ultibro
SEREVENT	50MCG	Anoro Ellipta/Ultibro
FORADIL	12MCG	Anoro Ellipta/Ultibro
SEREVENT DISKUS	50MCG	Anoro Ellipta/Ultibro
OXEZE	12MCG	Anoro Ellipta/Ultibro
OXEZE	6MCG	Anoro Ellipta/Ultibro

Of those who will switch to combination product, the proportion will be divided as follows:

Table 52 Scenarios GB7-GB9 - How the Switch to LAMA/LABA will be Divided

How the Switch to LAMA/LABA will be divided by COPD Severity			
Combination therapy:	**Very Severe**	**Severe**	**Moderate**
Anoro Ellipta	0.5	0.5	0.5
Ultibro	0.5	0.5	0.5

Scenarios GB10-GB12 (If a small proportion (20%) of ICS and LABA users switch to LAMA/LABA plus ICS)

In Scenarios **GB10 – GB12**, for users on combination therapy (ICS+LABA), dual therapy (ICS + LABA), single prescription ICS+LABA combo, or single prescription, multiple therapy - ICS + LABA, 20% would switch to combination therapy (LAMA/LABA) plus ICS. The following assumptions were made:

Table 53 Scenarios GB10-GB12 - Assumptions

Assumptions(Scenarios GB10-GB12)
A proportion of COPD patients who are users of combination therapy (ICS+LABA), dual therapy (ICS + LABA), single prescription ICS+LABA combo, or single prescription, multiple therapy - ICS + LABA will switch to combination therapy (LAMA/LABA) plus ICS
Approximately 20% of current users of ICS and LABA will switch to LAMA/LABA combination with an ICS
Users use the same number of units for LAMA/LABA as they did for ICS+LABA for combo users and LABA for dual users. The number of units are split equally (50-50) between Anoro Ellipta and Ultibro and halved

The following table illustrates how users on combination therapy (ICS+LABA), dual therapy (ICS + LABA), single prescription ICS+LABA combo, or single prescription, multiple therapy - ICS + LABA would switch to combination therapy (LAMA/LABA) plus ICS.

Table 54 Scenarios GB10-GB12 - Details of ICS and LABA Users Switching to LAMA/LABA Plus ICS

Details of Switch to Combination Product Plus ICS		
Users on ICS and LABA whose initial therapy is:		**Will switch to:**
ADVAIR DISKUS	100MCG	Anoro Ellipta/Ultibro + Fluticasone
ADVAIR DISKUS	250MCG	Anoro Ellipta/Ultibro + Fluticasone
ADVAIR DISKUS	500MCG	Anoro Ellipta/Ultibro + Fluticasone
ADVAIR DISKUS (INH AEM)	125MCG	Anoro Ellipta/Ultibro + Fluticasone
ADVAIR DISKUS (INH AEM)	250MCG	Anoro Ellipta/Ultibro + Fluticasone
SYMBICORT	100/6MG	Anoro Ellipta/Ultibro + Budesonide
SYMBICORT	200/6MG	Anoro Ellipta/Ultibro + Budesonide
ZENHALE	50-5MCG	Anoro Ellipta/Ultibro +Fluticasone/Budesonide
ZENHALE	100-5MCG	Anoro Ellipta/Ultibro +Fluticasone/Budesonide
ZENHALE	200-5MCG	Anoro Ellipta/Ultibro +Fluticasone/Budesonide

Of those who will switch to combination product plus ICS, the proportion will be divided as follows:

Table 55 Scenarios GB10-GB12 - How the Switch to LAMA/LABA will be Divided

How the Switch to LAMA/LABA plus ICS will be divided by COPD Severity			
Combination therapy plus ICS:	**Very Severe**	**Severe**	**Moderate**
Anoro Ellipta plus ICS	0.5	0.5	0.5
Ultibro plus ICS	0.5	0.5	0.5

Scenarios GB13-GB15 (If a modest proportion (50%) of ICS and LABA and LAMA users switch to LAMA/LABA plus ICS)

In Scenarios **GB13 – GB15**, for users on triple therapy combo (ICS+LABA plus LAMA), triple therapy - dual therapy (ICS + LABA + LAMA), single prescription ICS+LABA combo + LAMA, or single prescription, multiple therapy - ICS + LABA + LAMA, 50% would switch to combination therapy (LAMA/LABA) plus ICS. The following assumptions were made:

Table 56 Scenarios GB13-GB15 - Assumptions

Assumptions(Scenarios GB13-GB15)
A proportion of COPD patients who are users of triple therapy combo (ICS+LABA plus LAMA), triple therapy - dual therapy (ICS + LABA + LAMA), single prescription ICS+LABA combo + LAMA, or single prescription, multiple therapy - ICS + LABA + LAMA will switch to combination therapy (LAMA/LABA) plus ICS
Approximately 50% of those currently taking ICS and LABA and LAMA will switch to LAMA/LABA combination with an ICS
The number of units for triple therapy combo users and triple therapy dual users are now split equally (50-50) between Anoro Ellipta and Ultibro and halved

The following table illustrates how users on triple therapy combo (ICS+LABA plus LAMA), triple therapy - dual therapy (ICS + LABA + LAMA), single prescription ICS+LABA combo + LAMA, or single prescription, multiple therapy - ICS + LABA + LAMA would switch to combination therapy (LAMA/LABA) plus ICS.

Table 57 Scenarios GB13-GB15 - Details of ICS and LABA and LAMA Users Switching to LAMA/LABA Plus ICS

Details of Switch to Combination Product Plus ICS		
Users on ICS and LABA and LAMA whose initial therapy is:		**Will switch to:**
ADVAIR DISKUS	100MCG	Anoro Ellipta/Ultibro + Fluticoasone
ADVAIR DISKUS	250MCG	Anoro Ellipta/Ultibro + Fluticoasone
ADVAIR DISKUS	500MCG	Anoro Ellipta/Ultibro + Fluticoasone
ADVAIR DISKUS (INH AEM)	125MCG	Anoro Ellipta/Ultibro + Fluticoasone
ADVAIR DISKUS (INH AEM)	250MCG	Anoro Ellipta/Ultibro + Fluticoasone
SYMBICORT	100/6MG	Anoro Ellipta/Ultibro + Budesonide
SYMBICORT	200/6MG	Anoro Ellipta/Ultibro + Budesonide
ZENHALE	50-5MCG	Anoro Ellipta/Ultibro +Fluticasone/Budesonide
ZENHALE	100-5MCG	Anoro Ellipta/Ultibro +Fluticasone/Budesonide
ZENHALE	200-5MCG	Anoro Ellipta/Ultibro +Fluticasone/Budesonide

Of those who will switch to combination product plus ICS, the proportion will be divided as follows:

Table 58 Scenarios GB13-GB15 - How the Switch to LAMA/LABA plus ICS will be Divided

How the Switch to LAMA/LABA plus ICS will be divided by COPD Severity			
Combination therapy plus ICS:	**Very Severe**	**Severe**	**Moderate**
Anoro Ellipta plus ICS	0.5	0.5	0.5
Ultibro plus ICS	0.5	0.5	0.5

Combining Scenarios GB1-GB15 (Scenarios GB16-GB18)

In Scenarios GB16-GB18, Scenarios GB1-GB15 are combined. Current users on single therapy (LAMA or LABA) or single prescription, single therapy (LAMA or LABA), LAMA and LABA (dual therapy) or single prescription, multiple therapy (LAMA and LABA) may switch to combination therapy (LAMA/LABA). As well, current users on combination therapy (ICS+LABA), dual therapy (ICS + LABA), single prescription ICS+LABA combo, or single prescription, multiple therapy - ICS + LABA may switch to combination therapy (LAMA/LABA) or combination therapy (LAMA/LABA) plus ICS. Also, current users on single therapy triple therapy combo (ICS+LABA plus LAMA), triple therapy - dual therapy (ICS + LABA + LAMA), single prescription ICS+LABA combo + LAMA, or single prescription, multiple therapy - ICS + LABA + LAMA may switch to combination therapy (LAMA/LABA) plus ICS.

Assumptions and details for switching to combination product and combination product plus ICS can be found in GB1-GB15 assumptions and details.

Appendix C2: Disaggregated Results by Disease Severity

The following tables present the forecasted expenditure and budget impact for each alternative approach to reimbursement.

Table 59 Scenarios GB1-GB3 Results

If a modest proportion of LABA only and LAMA only users switch to LAMA/LABA	Base Case	GB1 Only Very Severe	GB2 At Least Severe	GB3 At Least Moderate
ICS	$12,063,355	$12,063,335	$12,063,335	$12,063,335
LABA	$1,319,073	$1,301,972	$1,284,925	$1,170,995
LAMA	$50,191,609	$49,319,384	$48,427,214	$42,276,356
ICS+LABA	$85,522,658	$85,522,656	$85,522,656	$85,522,656
LAMA/LABA		$1,181,483	$2,322,134	$10,181,217
Total	**$149,096,674**	**$149,388,831**	**$149,620,265**	**$151,214,560**
Budget Impact				
$		+ **$292,157**	+ **$523,591**	+ **$2,117,886**
%		↑0.196%	↑0.351%	↑1.420%

GB1 would lead to a 0.196% increase in COPD therapy expenditure, while GB2 and GB3 would lead to a 0.351% and 1.420% increase respectively.

Summary of Scenarios GB1-GB3 Results

If a modest proportion (50%) of LABA only and LAMA only users switch to LAMA/LABA (GB1-GB3), whereby current users of single therapy (LAMA or LABA) or single prescription, single therapy (LAMA or LABA) switch to combination therapy (LAMA/LABA), this would lead to a small increase in total COPD therapy expenditure (a rise of 0.196% for only very severe, 0.351% for at least severe and 1.420% for at least moderate or an increase of $0.3 million, $0.5 million and $2.1 million respectively).

Table 60 Scenarios GB4-GB6 Results

If almost all (99%) of LAMA and LABA users switch to LAMA/LABA	Base Case	GB4 Only Very Severe	GB5 At Least Severe	GB6 At Least Moderate
ICS	$12,063,355	$12,063,335	$12,063,335	$12,063,335
LABA	$1,319,073	$1,235,019	$1,189,608	$947,247
LAMA	$50,191,609	$50,077,781	$50,011,695	$49,688,787

If almost all (99%) of LAMA and LABA users switch to LAMA/LABA	Base Case	GB4 Only Very Severe	GB5 At Least Severe	GB6 At Least Moderate
ICS+LABA	$85,522,658	$85,522,656	$85,522,656	$85,522,656
LAMA/LABA		$241,276	$371,778	$1,079,927
Total	**$149,096,674**	**$149,140,067**	**$149,159,073**	**$149,301,953**
Budget Impact				
$		+ **$43,393**	+ **$62,399**	+ **$205,279**
%		↑0.029%	↑0.042%	↑0.138%

GB4 would lead to a 0.029% increase in COPD therapy expenditure, while GB5 and GB6 would lead to a 0.042% and 0.138% increase respectively.

Summary of Scenarios GB4-GB6 Results

If almost all (99%) of LAMA and LABA users switch to LAMA/LABA combination (GB4-GB6), whereby users of LAMA and LABA (dual therapy) or single prescription, multiple therapy (LAMA and LABA) switch to combination therapy (LAMA/LABA), this would have a marginal impact in total costs (a rise in total COPD therapy expenditure of 0.029% for only very severe, 0.042% for at least severe and 0.138% for at least moderate or an increase of $43,393, $62,399 and $205,279 respectively).

Table 61 Scenarios GB7-GB9 Results

If a modest proportion (60%) of ICS and LABA users switch to LAMA/LABA	Base Case	GB7 Only Very Severe	GB8 At Least Severe	GB9 At Least Moderate
ICS	$12,063,355	$12,036,182	$11,992,560	$11,822,922
LABA	$1,319,073	$1,295,084	$1,259,017	$1,098,832
LAMA	$50,191,609	$50,191,609	$50,191,609	$50,191,609
ICS+LABA	$85,522,658	$81,924,968	$77,547,443	$61,010,890
LAMA/LABA		$4,084,374	$9,416,907	$29,966,511
Total	**$149,096,674**	**$149,532,219**	**$150,407,536**	**$154,090,764**
Budget Impact				
$		+ **$435,545**	+ **$1,310,862**	+ **$4,994,090**
%		↑ 0.292%	↑ 0.879%	↑ 3.350%

GB7 would lead to a 0.292% increase in COPD therapy expenditure, while GB8 and GB9 would lead to a 0.879% and 3.350% increase respectively.

Summary of Scenarios GB7-GB9 Results

If a modest proportion (60%) of ICS and LABA users switch to LAMA/LABA combination (GB7-GB9), whereby users of combination therapy (ICS+LABA), dual therapy (ICS + LABA), single prescription ICS+LABA combo, or single prescription, multiple therapy - ICS + LABA switch to combination therapy (LAMA/LABA), this would lead to a rise in total costs ranging from 0.292% to 3.350% (an increase of $0.4 million for only very severe, $1.3 million for at least severe and $5.0 million for at least moderate).

Table 62 Scenarios GB10-GB12 Results

If a small proportion (20%) of ICS and LABA users switch to LAMA/LABA plus ICS	Base Case	GB10 Only Very Severe	GB11 At Least Severe	GB12 At Least Moderate
ICS	$12,063,355	$13,262,565	$14,721,740	$20,234,175
LABA	$1,319,073	$1,311,077	$1,299,054	$1,245,659
LAMA	$50,191,609	$50,191,609	$50,191,609	$50,191,609
ICS+LABA	$85,522,658	$84,323,427	$82,864,252	$77,352,067
LAMA/LABA		$1,361,458	$3,133,176	$9,983,044
Total	**$149,096,674**	**$150,450,136**	**$152,209,831**	**$159,006,555**
Budget Impact				
$		+ **$1,353,462**	+ **$3,113,157**	+ **$9,909,881**
%		↑ 0.908%	↑ 2.088%	↑ 6.647%

GB10 would lead to a 0.908% increase in COPD therapy expenditure, while **GB11** and **GB12** would lead to a 2.088% and 6.647% increase respectively.

Summary of Scenarios GB10-GB12 Results

If a small proportion (20%) of ICS and LABA users switch to LAMA/LABA combination plus ICS (GB10-GB12), whereby users of combination therapy (ICS+LABA), dual therapy (ICS + LABA), single prescription ICS+LABA combo, or single prescription, multiple therapy - ICS + LABA switch to combination therapy (LAMA/LABA) plus ICS, this would also lead to a greater rise in total costs ranging from 0.908% to 6.647% (an increase of $1.4 million for only very severe, $3.1 million for at least severe and $9.9 million for at least moderate).

Table 63 Scenarios GB13-GB15 Results

If a modest proportion (50%) of ICS and LABA and LAMA users switch to LAMA/LABA plus ICS	Base Case	GB13 Only Very Severe	GB14 At Least Severe	GB15 At Least Moderate
ICS	$12,063,355	$19,091,637	$23,631,251	$34,398,191
LABA	$1,319,073	$1,280,158	$1,250,219	$1,178,940
LAMA	$50,191,609	$45,649,346	$42,575,833	$34,845,875
ICS+LABA	$85,522,658	$78,494,355	$73,954,741	$63,187,800
LAMA/LABA		$7,164,431	$11,750,158	$23,617,402
Total	**$149,096,674**	**$151,679,926**	**$153,162,203**	**$157,228,208**
Budget Impact				
$		+ **$2,583,252**	+ **$4,065,529**	+ **$8,131,534**
%		↑ 1.733%	↑ 2.727%	↑ 5.454%

GB13 would lead to a 1.733% increase in COPD therapy expenditure, while **GB14** and **GB15** would lead to a 2.727% and 5.454% increase respectively.

Summary of Scenarios GB13-GB15 Results

Similarly, if a modest proportion (50%) of ICS and LABA and LAMA users switch to LAMA/LABA plus ICS (GB13-GB15), whereby users of triple therapy combo (ICS+LABA plus LAMA), triple therapy - dual therapy (ICS + LABA + LAMA), single prescription ICS+LABA combo + LAMA, or single prescription, multiple therapy - ICS + LABA + LAMA switch to combination therapy (LAMA/LABA) plus ICS, would lead to a rise in total costs ranging from 1.733% to 5.454% (an increase of $2.6 million for only very severe, $4.1 million for at least severe and $8.1 million for at least moderate).

Table 64 Scenarios GB16-GB18 Results

Combining Scenarios GB1-GB15	Base Case	GB16 Only Very Severe	GB17 At Least Severe	GB18 At Least Moderate
ICS	$12,063,355	$20,263,713	$26,218,880	$42,328,618
LABA	$1,319,073	$1,147,018	$1,006,532	$365,381
LAMA	$50,191,609	$44,663,291	$40,631,523	$26,427,800
ICS+LABA	$85,522,658	$73,697,438	$63,321,123	$30,505,445
LAMA/LABA		$14,033,023	$26,994,153	$74,828,101
Total	**$149,096,674**	**$153,804,482**	**$158,172,212**	**$174,455,344**
Budget Impact				
$		+ **$4,707,808**	+ **$9,075,537**	+ **$25,358,670**

Combining Scenarios GB1-GB15	Base Case	GB16	GB17	GB18
		Only Very Severe	At Least Severe	At Least Moderate
%		↑ 3.158%	↑ 6.087%	↑ 17.008%

GB16 would lead to a 3.158% increase in COPD therapy expenditure, while **GB17** and **GB18** would lead to a 6.087% and 17.008% increase respectively.

Summary of Scenarios GB16-GB18 Results

A policy combining all scenarios (GB1-GB15), whereby patients on single therapy (LAMA or LABA) or single prescription, single therapy (LAMA or LABA), LAMA and LABA (dual therapy) or single prescription, multiple therapy (LAMA and LABA) switch to combination therapy (LAMA/LABA); patients on combination therapy (ICS+LABA), dual therapy (ICS + LABA), single prescription ICS+LABA combo, or single prescription, multiple therapy - ICS + LABA switch to combination therapy (LAMA/LABA) or combination therapy (LAMA/LABA) plus ICS; and patients on triple therapy combo (ICS+LABA plus LAMA), triple therapy - dual therapy (ICS + LABA + LAMA), single prescription ICS+LABA combo + LAMA, or single prescription, multiple therapy - ICS + LABA + LAMA switch to combination therapy (LAMA/LABA) plus ICS, would lead to a significant rise in total costs ranging 3.158% to 17.008% (an increase of $4.7 million for only very severe, $9.1 million for at least severe and $25.4 million for at least moderate).

Appendix D – Reimbursement Based Economic Evaluation

Research Question

RQ4. Based on the results from the economic model above, what is the cost-effectiveness of reimbursing LAMA/LABA combination therapies?

Methods

For the budget impact analysis detailed above, three assumptions were made based on expert opinion regarding the impact of covering LAMA/LABA combination therapies, as follows:

1. 50% of current users of LAMA or LABA monotherapies would move to LAMA/LABA combination therapies.
2. 60% of current users of ICS/LABA combination therapies would move to LAMA/LABA combination therapies.
3. 99% of users of LAMA/LABA dual therapies would move to LAMA/LABA combination therapies.

Using the above budget impact analysis, a reimbursement based economic evaluation was conducted to estimate the number of users of each therapy affected, with or without coverage of the LAMA/LABA combination therapies. The estimated costs and QALYs for each therapy were weighted by the proportion of users with and without the change in coverage. As such, this analysis estimated the average costs and QALYs with and without coverage of LAMA/LABA combination therapies and assessed the cost effectiveness of coverage.

Primary analysis assumed coverage of both Ultibro and Anoro Ellipta. Secondary analyses assumed coverage of only one of these, with and without a negotiated price reduction. Results were derived for price reductions of 20% and 40%. In addition, threshold analysis was conducted to identify the price reuction required for a policy of reimbrusment to be optimal.

No analyses were conducted for LAMA monotherapies, as expert opinion suggested that there would be no change in use of these products even if more monotherapies were covered.

All analyses were based on estimates of costs and QALYs from the de novo economic evaluation for Males aged 70.

Results

For all disease severities, a reimbursement strategy covering both LAMA/LABA combination therapies would lead to more costs and less QALYs than a strategy of not covering either therapy for each disease severity. This finding held for strategies involving coverage of only one of the therapies with or without a 20% price reduction. With a 40% price reduction, covering Ultibro would lead to cost savings for all disease severities (Table 65).

Table 65 Average Costs and QALYs per Patient Under Different Reimbursement Strategies

Coverage for LAMA/LABA Combination Therapies	Costs			QALYs		
	Moderate	Severe	Very Severe	Moderate	Severe	Very Severe
Without coverage	$16,359	$17,607	$17,464	5.46	3.76	2.66
With coverage for both	$18,339	$20,113	$20,160	5.40	3.70	2.60
With coverage (Ultibro only)	$16,786	$18,048	$17,863	5.45	3.75	2.65
With coverage (Anoro Ellipta only)	$19,893	$22,178	$22,458	5.35	3.65	2.55
With 20% price reduction (Ultibro only)	$15,833	$17,309	$17,221	5.45	3.75	2.65
With 20% price reduction (Anoro Ellipta only)	$18,966	$21,467	$21,844	5.35	3.65	2.55
With 40% price reduction (Ultibro only)	$14,880	$16,570	$16,579	5.45	3.75	2.65
With 40% price reduction (Anoro Ellipta only)	$18,038	$20,755	$21,231	5.35	3.65	2.55

If only one LAMA/LABA product was covered and decision makers were unable to negotiate a price reduction, a policy of not covering either (Ultibro or Anoro Ellipta) would be dominant (Table 66):

Table 66 Cost Effectiveness of Different Reimbursement Strategies with No Price Reductions

Coverage for LAMA/LABA Combination Therapies	Costs	QALYs	Sequential Incremental Cost per QALY
Without coverage	$16,704	4.818	
With coverage (Ultibro Only) (AT LEAST VERY SEVERE)	$16,758	4.817	**Dominated by no coverage**
With coverage (Ultibro Only) (AT LEAST SEVERE)	$16,827	4.815	**Dominated by no coverage**
With coverage for both (AT LEAST VERY SEVERE)	$17,069	4.810	**Dominated by no coverage**
With coverage (Ultibro Only) (AT LEAST MODERATE)	$17,129	4.806	**Dominated by no coverage**
With coverage (Anora Elipta Only) (AT LEAST VERY SEVERE)	$17,380	4.803	**Dominated by no coverage**
With coverage for both (AT LEAST SEVERE)	$17,461	4.800	**Dominated by no coverage**
With coverage (Anora Elipta Only) (AT LEAST SEVERE)	$18,095	4.785	**Dominated by no coverage**
With coverage for both (AT LEAST MODERATE)	$18,863	4.757	**Dominated by no coverage**
With coverage (Anora Elipta Only) (AT LEAST MODERATE)	$20,597	4.708	**Dominated by no coverage**

If decision makers were willing to pay at least $36,438 per QALY gained, a policy not covering LAMA/LABAs would be optimal even if decision makers were able to negotiate a price reduction of 20% for one or both products, (Table 46). If decision makers were not willing to pay $36,438 per QALY gained, the optimal policy would be to reimburse Ultibro for patients with at least moderate COPD.

Table 67 Cost Effectiveness of Different Reimbursement Strategies with 20% Price Reductions for Single Coverage

Coverage for LAMA/LABA Combination Therapies	Costs	QALYs	Sequential Incremental Cost per QALY
With 20% price reduction (Ultibro Only) (AT LEAST MODERATE)	$16,252	4.806	
Without coverage	$16,704	4.818	$36,438
With 20% price reduction (Ultibro Only) (AT LEAST SEVERE)	$16,624	4.815	Subject to extended dominance
With 20% price reduction (Ultibro Only) (AT LEAST VERY SEVERE)	$16,671	4.817	Subject to extended dominance
With coverage (Ultibro Only) (AT LEAST MODERATE)	$17,129	4.806	Dominated by no coverage
With 20% price reduction (Anora Elipta Only) (AT LEAST VERY SEVERE)	$17,297	4.803	Dominated by no coverage
With 20% price reduction (Anora Elipta Only) (AT LEAST SEVERE)	$17,900	4.785	Dominated by no coverage
With coverage for both (AT LEAST MODERATE)	$18,863	4.757	Dominated by no coverage
With 20% price reduction (Anora Elipta Only) (AT LEAST MODERATE)	$19,746	4.708	Dominated by no coverage
With coverage (Anora Elipta Only) (AT LEAST MODERATE)	$20,597	4.708	Dominated by no coverage

If decision makers were willing to pay at least $84,129 per QALY gained, a policy not covering LAMA/LABAs would be optimal even if decision makers were able to negotiate a price reduction of 20% for one or both products, Table 46). If decision makers were not willing to pay as much as $84,129 per QALY gained, the optimal policy would be to reimburse Ultibro for patients with at least moderate COPD.

Table 68 Cost Effectiveness of Different Reimbursement Strategies with 40% Price Reductions for Single Coverage

Coverage for LAMA/LABA Combination Therapies	Costs	QALYs	Sequential Incremental Cost per QALY
With 40% price reduction (Ultibro Only) (AT LEAST MODERATE)	$15,374	4.806	
Without coverage	$16,704	4.818	$84,129
With 40% price reduction (Ultibro Only) (AT LEAST SEVERE)	$16,422	4.815	Subject to extended dominance
With 40% price reduction (Ultibro Only) (AT LEAST VERY SEVERE)	$16,584	4.817	Subject to extended dominance
With coverage (Ultibro Only) (AT LEAST MODERATE)	$17,129	4.806	Dominated by no coverage

Coverage for LAMA/LABA Combination Therapies	Costs	QALYs	Sequential Incremental Cost per QALY
With 40% price reduction (Anora Elipta Only) (AT LEAST VERY SEVERE)	$17,214	4.803	Dominated by no coverage
With 40% price reduction (Anora Elipta Only) (AT LEAST SEVERE)	$17,706	4.785	Dominated by no coverage
With coverage for both (AT LEAST MODERATE)	$18,863	4.757	Dominated by no coverage
With 40% price reduction (Anora Elipta Only) (AT LEAST MODERATE)	$18,895	4.708	Dominated by no coverage
With coverage (Anora Elipta Only) (AT LEAST MODERATE)	$20,597	4.708	Dominated by no coverage

Given the results in Tale 55 and 56, a threshold analysis was conducted to assess the minimum price reduction for Ultibro required for its reimbursement to be optimal. If decision makers were able to negotiate a price reduction of 29%, the strategy of reimbursing Ultibro for at least moderate disease would be optimal assuming a threshold value of a QALY of $50,000.

Conclusions

Based on current list prices, assuming that use of LAMA products is not expected to increase and that there is continued willingness to reimburse LAMA therapies, an optimal policy, assuming a willingness to pay of $50,000 per QALY, would be to list only Seebri.

Based on current list prices without any price reductions, assuming a willingness to pay of $50,000 per QALY, it is not cost effective to fund either of the LAMA/LABA combination products. If decision makers can negotiate a price reduction of at least 29%, reimbursement of Ultibro for patients with at least moderate disease would be optimal. Under no price reduction scenario would it be worthwhile to reimburse Anoro Ellipta.

References

1. Oostenbrink JB, Rutten-van Molken MP, Monz BU, FitzGerald JM. Probabilistic Markov model to assess the cost-effectiveness of bronchodilator therapy in COPD patients in different countries. Value Health. 2005 Jan;8(1):32-46.

2. Hoogendoorn M, Kappelhoff BS, Overbeek JA, Wouters EF, Rutten-van Molken MP. Which long-acting bronchodilator is most cost-effective for the treatment of COPD? Neth J Med. 2012 Oct;70(8):357-64.

3. Hoogendoorn M, Al MJ, Beeh KM, Bowles D, Graf von der Schulenburg JM, Lungershausen J, et al. Cost-effectiveness of tiotropium versus salmeterol: the POET-COPD trial. Eur Respir J. 2013 Mar;41(3):556-64.

4. Hertel N, Kotchie RW, Samyshkin Y, Radford M, Humphreys S, Jameson K. Cost-effectiveness of available treatment options for patients suffering from severe COPD in the UK: a fully incremental analysis. Int J Chron Obstruct Pulmon Dis. 2012;7:183-99. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3325000

5. Gani R, Griffin J, Kelly S, Rutten-van MM. Economic analyses comparing tiotropium with ipratropium or salmeterol in UK patients with COPD. Prim Care Respir J. 2010 Mar;19(1):68-74.

6. Rutten-van Molken MP, Oostenbrink JB, Miravitlles M, Monz BU. Modelling the 5-year cost effectiveness of tiotropium, salmeterol and ipratropium for the treatment of chronic obstructive pulmonary disease in Spain. Eur J Health Econ. 2007 Jun;8(2):123-35. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1913175

7. Maniadakis N, Tzanakis N, Fragoulakis V, Hatzikou M, Siafakas N. Economic evaluation of tiotropium and salmeterol in the treatment of chronic obstructive pulmonary disease (COPD) in Greece. Curr Med Res Opin. 2006 Aug;22(8):1599-607.

8. National Clinical Guideline Centre. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care. London: National Clinical Guideline Centre; 2010 Jun. [cited 2013 Dec 3]. Available from: http://guidance.nice.org.uk/CG101/Guidance/pdf/English

9. Price D, Asukai Y, Ananthapavan J, Malcolm B, Radwan A, Keyzor I. A UK-based cost-utility analysis of indacaterol, a once-daily maintenance bronchodilator for patients with COPD, using real world evidence on resource use. Applied Health Economics and Health Policy. 2013;11(3):259-74.

10. Price D, Gray A, Gale R, Asukai Y, Mungapen L, Lloyd A, et al. Cost-utility analysis of indacaterol in Germany: A once-daily maintenance bronchodilator for patients with COPD. Respiratory Medicine. 2011;105(11):1635-47.

11. Oostenbrink JB, Al MJ, Oppe M, Rutten-Van Molken MPMH. Expected value of perfect

information: An empirical example of reducing decision uncertainty by conducting additional research. Value in Health. 2008;11(7):1070-80.

12. Naik S, Kamal KM, Keys PA, Mattei TJ. Evaluating the cost-effectiveness of tiotropium versus salmeterol in the treatment of chronic obstructive pulmonary disease. Clinicoecon Outcomes Res. 2010;2:25-36. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3169962

13. Oba Y. Cost-effectiveness of long-acting bronchodilators for chronic obstructive pulmonary disease. Mayo Clin Proc. 2007 May;82(5):575-82.

14. Guillermo AJ, Thuresson P-O, Machnicki G, Mungapen L, Kraemer M, Asukai Y, et al. The Cost-Effectiveness and Budget Impact of Introducing Indacaterol into the Colombian Health System. Value in Health Regional Issues. 2012;1(2):165-71.

15. Garattini L, Koleva D, Casadei G. Modeling in pharmacoeconomic studies: funding sources and outcomes. Int J Technol Assess Health Care. 2010 Jul;26(3):330-3.

16. Canadian Agency for Drugs and Technologies in Health. Guidelines for the economic evaluation of health technologies: Canada [Internet]. 3. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2006. [cited 2013 Jun 12]. Available from: http://www.cadth.ca/media/pdf/186_EconomicGuidelines_e.pdf

17. Decramer M, Celli B, Tashkin DP, Pauwels RA, Burkhart D, Cassino C, et al. Clinical trial design considerations in assessing long-term functional impacts of tiotropium in COPD: the UPLIFT trial. COPD. 2004;1(2):303-12.

18. Oba Y. Cost-Effectiveness of salmeterol, fluticasone, and combination therapy for COPD. American Journal of Managed Care. 2009;15(4):225-32.

19. Dalal AA, Shah MB, D'Souza AO, Lunacsek OE, Nagar SP, Crater GD. Observational study of the outcomes and costs of initiating maintenance therapies in patients with moderate exacerbations of COPD. Respir Res. 2012;13:41. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3490761

20. Yu AP, Guerin A, de Leon DP, Ramakrishnan K, Wu EQ, Mocarski M, et al. Clinical and economic outcomes of multiple versus single long-acting inhalers in COPD. Respir Med. 2011 Dec;105(12):1861-71.

21. Dalal AA, Roberts MH, Petersen HV, Blanchette CM, Mapel DW. Comparative cost-effectiveness of a fluticasone-propionate/salmeterol combination versus anticholinergics as initial maintenance therapy for chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2011;6:13-22. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3034283

22. Dalal AA, Roberts MH, Petersen HV, Blanchette CM, Mapel DW. Comparative cost-effectiveness of a fluticasone-propionate/salmeterol combination versus anticholinergics as initial maintenance therapy for chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon

Dis. 2011;6:13-22. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3034283

23. Dalal AA, Shah M, D'Souza AO, Mapel DW. COPD-related healthcare utilization and costs after discharge from a hospitalization or emergency department visit on a regimen of fluticasone propionate-salmeterol combination versus other maintenance therapies. Am J Manag Care. 2011 Mar;17(3):e55-e65.

24. Hernandez C, Casas A, Escarrabill J, Alonso J, Puig-Junoy J, Farrero E, et al. Home hospitalisation of exacerbated chronic obstructive pulmonary disease patients. Eur Respir J. 2003 Jan;21(1):58-67.

25. Chaplin S, Turner A. Glycopyrronium (Seebri Breezhaler): Once-daily LAMA for COPD. Prescriber. 2013;24(21):30-4.

26. Dalal AA, Shah MB, D'Souza AO, Lunacsek OE, Nagar SP, Crater GD. Observational study of the outcomes and costs of initiating maintenance therapies in patients with moderate exacerbations of COPD. Respiratory Research. 2012;13:41.

27. Guarascio AJ, Ray SM, Finch CK, Self TH. The clinical and economic burden of chronic obstructive pulmonary disease in the USA. ClinicoEconomics and Outcomes Research. 2013;5(1):235-45.

28. Cazzola M, Rogliani P, Matera MG. Aclidinium bromide/formoterol fumAarate fixed-dose combination for the treatment of chronic obstructive pulmonary disease. Expert Opinion on Pharmacotherapy. 2013;14(6):775-81.

29. Tashkin DP. Tiotropium for the treatment of chronic obstructive pulmonary disease. Clinical Practice. 2013;10(2):141-55.

30. van AP. Zone in on: Drug spending: Generic-drug incursion and reduced demand contribute to modest gains. Pharmaceutical Technology. 2012;36(5):26.

31. Gross NJ, Hanania NA. The COPD pipeline XII. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2011;8(5):387-91.

32. Gross NJ. The COPD pipeline X. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2011;8(3):244-7.

33. Dalal AA, Shah MB, D'Souza AO, Lunacsek OE, Nagar SP, Crater GD. Observational study of the outcomes and costs of initiating maintenance therapies in patients with moderate exacerbations of COPD. Respiratory Research. 2012;13:41.

34. Park HY, Man SFP, Sin DD. Inhaled corticosteroids for chronic obstructive pulmonary disease. BMJ (Online). 2012;345(7882).

35. Gross NJ. The copd pipeline xviii. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2011;9(5):571-3.

36. Halpern R, Baker CL, Su J, Woodruff KB, Paulose-Ram R, Porter V, et al. Outcomes associated with initiation of tiotropium or fluticasone/salmeterol in patients with chronic obstructive pulmonary disease. Patient Preference and Adherence. 2011;5:375-88.

37. Mapel DW, Roberts MH. New Clinical insights into chronic obstructive pulmonary disease and their implications for pharmacoeconomic analyses. Pharmacoeconomics. 2012;30(10):869-85.

38. Dalal AA, Roberts MH, Petersen HV, Blanchette CM, Mapel DW. Comparative cost-effectiveness of a futicasone-propionate/salmeterol combination versus anticholinergics as initial maintenance therapy for chronic obstructive pulmonary disease. International Journal of COPD. 2011;6(1):13-22.

39. Kozma CM, Paris AL, Plauschinat CA, Slaton T, Mackowiak JI. Comparison of resource use by COPD patients on inhaled therapies with long-acting bronchodilators: a database study. BMC pulmonary medicine. 2011;11:61.

40. Chatterjee A, Shah M, D'Souza AO, Bechtel B, Crater G, Dalal AA. Observational study on the impact of initiating tiotropium alone versus tiotropium with fluticasone propionate/salmeterol combination therapy on outcomes and costs in chronic obstructive pulmonary disease. Respiratory Research. 2012;13:15.

41. Roberts MH, Dalal AA. Clinical and economic outcomes in an observational study of COPD maintenance therapies: Multivariable regression versus propensity score matching. International Journal of COPD. 2012;7:221-33.

42. Kozma CM, Paris AL, Plauschinat CA, Slaton T, Mackowiak JI. Comparison of resource use by COPD patients on inhaled therapies with long-acting bronchodilators: A database study. BMC pulmonary medicine. 2011;11.

43. Dalal AA, Candrilli SD, Davis KL. Outcomes and costs associated with initial maintenance therapy with fluticasone propionate-salmeterol xinafoate 250 microg/50 microg combination versus tiotropium in commercially insured patients with COPD. Managed care (Langhorne, Pa). 2011;20(8):46-55.

44. Dalal AA, Shah M, D'Souza AO, Mapel DW. COPD-related healthcare utilization and costs after discharge from a hospitalization or emergency department visit on a regimen of fluticasone propionate-salmeterol combination versus other maintenance therapies. American Journal of Managed Care. 2011;17(3):e55-e65.

45. Yu AP, Guerin A, de Leon DP, Ramakrishnan K, Wu EQ, Mocarski M, et al. Clinical and economic outcomes of multiple versus single long-acting inhalers in COPD. Respiratory Medicine. 2011;105(12):1861-71.

46. Cao Z, Zou KH, Baker CL, Su J, Paulose-Ram R, Durden E, et al. Respiratory-related medical expenditure and inpatient utilisation among COPD patients receiving long-acting bronchodilator therapy. Journal of Medical Economics. 2011;14(2):147-58.

47. Gross NJ. The COPD pipeline VIII. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2011;8(1):52-4.

48. Gross N. The COPD pipeline V. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2010;7(4):307-9.

49. White P. COPD in primary care: A time of opportunity. British Journal of General Practice. 2010;60(576):477-8.

50. Vestbo J. Choice of medications when treating stable COPD. Clinical Respiratory Journal. 2010;4(4):195-6.

51. Gross NJ. The COPD pipeline II. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2010;7(1):76-8.

52. Alifano M, Cuvelier A, Delage A, Roche N, Lamia B, Molano LC, et al. Treatment of COPD: From pharmacological to instrumental therapies. European Respiratory Review. 2010;19(115):7-23.

53. Dalal AA, Petersen H, Simoni-Wastila L, Blanchette CM. Healthcare costs associated with initial maintenance therapy with fluticasone propionate 250 mug/salmeterol 50 mug combination versus anticholinergic bronchodilators in elderly US Medicare-eligible beneficiaries with COPD. Journal of Medical Economics. 2009;12(4):339-47.

54. Simoni-Wastila L, Blanchette CM, Qian J, Yang H, Zhao L, Zuckerman IH, et al. Burden of chronic obstructive pulmonary disease in medicare beneficiaries residing in long-term care facilities. American Journal Geriatric Pharmacotherapy. 2009;7(5):262-70.

55. Mamary AJ, Criner GJ. Tiotropium bromide for chronic obstructive pulmonary disease. Expert Review of Respiratory Medicine. 2009;3(3):211-20.

56. Miravitlles M, Brosa M, Velasco M, Crespo C, Gobartt E, Diaz S, et al. An economic analysis of pharmacological treatment of COPD in Spain. Respiratory Medicine. 2009;103(5):714-21.

57. Tashkin DP. The role of tiotropium in the hospital management of exacerbation of chronic obstructive pulmonary disease. Respiratory Care. 2008;53(12):1657-9.

58. Chambers S, Schachter M, Price D, Kassianos G, Gaw A, Kirby M, et al. Tiotropium - Advancing the treatment of COPD. Drugs in Context. 2008;4(1):15-28.

59. Akazawa M, Hayflinger DC, Stanford RH, Blanchette CM. Economic assessment of initial maintenance therapy for chronic obstructive pulmonary disease. American Journal of Managed Care. 2008;14(7):438-48.

60. Reddy CB, Kanner RE. Is combination therapy with inhaled anticholinergics and beta2-adrenoceptor agonists justified for chronic obstructive pulmonary disease? Drugs and Aging. 2007;24(8):615-28.

61. Herrick TM, Million RP. Tapping the potential of fixed-dose combinations. Nature Reviews Drug Discovery. 2007;6(7):513-4.

62. Patients with severe COPD may benefit from the addition of an inhaled corticosteroid. Formulary. 2007;42(3):178-83.

63. Varkey B. Weighing the benefits and risks of inhaled corticosteroids. Current Opinion in Pulmonary Medicine. 2007;13(2):89.

64. Saha S, Siva R, Brightling CE, Pavord ID. COPD: An inhaled corticosteroid-resistant, oral corticosteroid-responsive condition. European Respiratory Journal. 2006;27(4):863-5.

65. Molken MRV, Lee TA. Economic modeling in chronic obstructive pulmonary disease. Proceedings of the American Thoracic Society. 2006;3(7):630-4.

66. Sullivan SD, Briggs A. Improving survival in chronic obstructive pulmonary disease: Assessing the value of life-saving therapy. Proceedings of the American Thoracic Society. 2006;3(7):617-8.

67. Shaya FT, El Khoury AC, Samant ND, Scharf SM. Utilization of health care resources in a high-risk medicaid population with chronic obstructive pulmonary disease. P and T. 2006;31(5):261-8.

68. Jones D. Long-acting inhaled bronchodilators for COPD--lack of logic continues. The New Zealand medical journal. 2005;118(1222):U1669.

69. Krpke C. Tiotropium effective in treatment of COPD. American Family Physician. 2005;72(11).

70. Jones D. Long-acting inhaled bronchodilators for COPD - Lack of logic continues. New Zealand Medical Journal. 2005;118(1222).

71. Rich A. Corticosteroids and chronic obstructive pulmonary disease in the Nursing Home. Journal of the American Medical Directors Association. 2005;6(3 Suppl):S67-S74.

72. Fishman AP. One hundred years of chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine. 2005;171(9):941-8.

73. Cooper CB, Tashkin DP. Recent developments in inhaled therapy in stable chronic obstructive pulmonary disease. British Medical Journal. 2005;330(7492):640-4.

74. Bryan J. Novel inhaler devices: Balancing innovation against price is important. Pharmaceutical Journal. 2005;274(7338):241-2.

75. Izquierdo-Alonso JL, De Miguel-Diez J. Economic impact of pulmonary drugs on direct costs of stable chronic obstructive pulmonary disease. COPD. 2004;1(2):215-23.

76. Lee TA, Weiss KB, Sullivan SD, Sin DD, Golmohammadi K, Jacobs P. Cost-effectiveness of inhaled corticosteroids in chronic obstructive pulmonary disease (multiple letters). American Journal of Medicine. 2004;117(8):618-9.

77. Mundy C, Kirkpatrick P. Tiotropium bromide. Nature Reviews Drug Discovery. 2004;3(8):643-4.

78. ZuWallack AR, ZuWallack RL. Tiotropium bromide, a new, once-daily inhaled anticholinergic bronchodilator for chronic-obstructive pulmonary disease. Expert Opinion on Pharmacotherapy. 2004;5(8):1827-35.

79. Friedman M, Menjoge SS, Anton SF, Kesten S. Healthcare costs with tiotropium plus usual care versus usual care alone following 1 year of treatment in patients with Chronic Obstructive Pulmonary Disorder (COPD). Pharmacoeconomics. 2004;22(11):741-9.

80. Hutton SF. Tiotropium (Spiriva) for COPD. American Family Physician. 2004;69(12):2901-2.

81. Cazzola M, Matera MG. Long-Acting Bronchodilators Are the First-Choice Option for the Treatment of Stable COPD. Chest. 2004;125(1):9-11.

82. De BW. Inhaled salmeterol/fluticasone propionate combination in chronic obstructive pulmonary disease. American Journal of Respiratory Medicine. 2002;1(4):283.

83. New in the marketplace. Drugs and Therapy Perspectives. 2005;18(11):26.

84. Faulkner MA, Hilleman DE. The economic impact of chronic obstructive pulmonary disease. Expert Opinion on Pharmacotherapy. 2002;3(3):219-28.

85. Frith P, McKenzie D, Pierce R. Management of chronic obstructive pulmonary disease in the twenty-first century. Internal Medicine Journal. 2001;31(9):508-11.

86. Pingleton SK. Pulmonary medicine. Journal of the American Medical Association. 1996;275(23):1849-50.

87. Rogol PR, Hahn DL, Kerstjens HAM, Brand PLP, Postma DS. Bronchodilator therapy with or without inhaled corticosteroid therapy for obstructive airways disease. New England Journal of Medicine. 1993;328(14):1044-5.

88. Najafzadeh M, Marra CA, Lynd LD, Sadatsafavi M, FitzGerald JM, McManus B, et al. Future impact of various interventions on the burden of COPD in Canada: a dynamic population model. PLoS One. 2012;7(10):e46746. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3469627

89. Hettle R, Wouters H, Ayres J, Gani R, Kelly S, Lion M, et al. Cost-utility analysis of tiotropium versus usual care in patients with COPD in the UK and Belgium. Respir Med. 2012 Dec;106(12):1722-33.

90. Menn P, Leidl R, Holle R. A lifetime Markov model for the economic evaluation of chronic obstructive pulmonary disease. Pharmacoeconomics. 2012 Sep 1;30(9):825-40.

91. Hoogendoorn M, Rutten-van Molken MP, Hoogenveen RT, Al MJ, Feenstra TL. Developing and applying a stochastic dynamic population model for chronic obstructive pulmonary disease.

Value Health. 2011 Dec;14(8):1039-47.

92. Zaniolo O, Iannazzo S, Pradelli L, Miravitlles M. Pharmacoeconomic evaluation of tiotropium bromide in the long-term treatment of chronic obstructive pulmonary disease (COPD) in Italy. Eur J Health Econ. 2012 Feb;13(1):71-80.

93. Hoogendoorn M, Rutten-van Molken MP, Hoogenveen RT, van Genugten ML, Buist AS, Wouters EF, et al. A dynamic population model of disease progression in COPD. Eur Respir J. 2005 Aug;26(2):223-33.

94. Spencer M, Briggs AH, Grossman RF, Rance L. Development of an economic model to assess the cost effectiveness of treatment interventions for chronic obstructive pulmonary disease. Pharmacoeconomics. 2005;23(6):619-37.

95. Borg S, Ericsson A, Wedzicha J, Gulsvik A, Lundback B, Donaldson GC, et al. A computer simulation model of the natural history and economic impact of chronic obstructive pulmonary disease. Value Health. 2004 Mar;7(2):153-67.

96. Chandra K, Blackhouse G, McCurdy BR, Bornstein M, Campbell K, Costa V, et al. Cost-effectiveness of interventions for chronic obstructive pulmonary disease (COPD) using an Ontario policy model. Ont Health Technol Assess Ser. 2012;12(12):1-61. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3384363

97. Hettle R, Wouters H, Ayres J, Gani R, Kelly S, Lion M, et al. Cost-utility analysis of tiotropium versus usual care in patients with COPD in the UK and Belgium. Respir Med. 2012 Dec;106(12):1722-33.

98. Najafzadeh M, Marra CA, Lynd LD, Sadatsafavi M, FitzGerald JM, McManus B, et al. Future impact of various interventions on the burden of COPD in Canada: a dynamic population model. PLoS One. 2012;7(10):e46746. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3469627

99. Zaniolo O, Iannazzo S, Pradelli L, Miravitlles M. Pharmacoeconomic evaluation of tiotropium bromide in the long-term treatment of chronic obstructive pulmonary disease (COPD) in Italy. Eur J Health Econ. 2012 Feb;13(1):71-80.

100. Dalal AA, Shah M, D'Souza AO, Crater GD. Rehospitalization risks and outcomes in COPD patients receiving maintenance pharmacotherapy. Respir Med. 2012 Jun;106(6):829-37.

101. Hoogendoorn M, Rutten-van Molken MP, Hoogenveen RT, Al MJ, Feenstra TL. Developing and applying a stochastic dynamic population model for chronic obstructive pulmonary disease. Value Health. 2011 Dec;14(8):1039-47.

102. Mapel DW, Schum M, Lydick E, Marton JP. A new method for examining the cost savings of reducing COPD exacerbations. Pharmacoeconomics. 2010;28(9):733-49.

103. Dal NR, Eandi M, Pradelli L, Iannazzo S. Cost-effectiveness and healthcare budget impact in Italy

of inhaled corticosteroids and bronchodilators for severe and very severe COPD patients. Int J Chron Obstruct Pulmon Dis. 2007;2(2):169-76. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2695615

104. Lee KH, Phua J, Lim TK. Evaluating the pharmacoeconomic effect of adding tiotropium bromide to the management of chronic obstructive pulmonary disease patients in Singapore. Respir Med. 2006 Dec;100(12):2190-6.

105. Spencer M, Briggs AH, Grossman RF, Rance L. Development of an economic model to assess the cost effectiveness of treatment interventions for chronic obstructive pulmonary disease. Pharmacoeconomics. 2005;23(6):619-37.

106. Hettle R, Wouters H, Ayres J, Gani R, Kelly S, Lion M, et al. Cost-utility analysis of tiotropium versus usual care in patients with COPD in the UK and Belgium. Respiratory Medicine. 2012;106(12):1722-33.

107. Zaniolo O, Iannazzo S, Pradelli L, Miravitlles M. Pharmacoeconomic evaluation of tiotropium bromide in the long-term treatment of chronic obstructive pulmonary disease (COPD) in Italy. European Journal of Health Economics. 2012;13(1):71-80.

108. Neyt M, Devriese S, Thiry N, Van den BA. Tiotropium's cost-effectiveness for the treatment of COPD: A cost-utility analysis under real-world conditions. BMC pulmonary medicine. 2010;10.

109. Lee K-H, Phua J, Lim T-K. Evaluating the pharmacoeconomic effect of adding tiotropium bromide to the management of chronic obstructive pulmonary disease patients in Singapore. Respiratory Medicine. 2006;100(12):2190-6.

110. Spencer M, Briggs AH, Grossman RF, Rance L. Development of an economic model to assess the cost effectiveness of treatment interventions for chronic obstructive pulmonary disease. Pharmacoeconomics. 2005;23(6):619-37.

111. Jones PW, Wilson K, Sondhi S. Cost-effectiveness of salmeterol in patients with chronic obstructive pulmonary disease: An economic evaluation. Respiratory Medicine. 2003;97(1):20-6.

112. Najafzadeh M, Marra CA, Sadatsafavi M, Aaron SD, Sullivan SD, Vandemheen KL, et al. Cost effectiveness of therapy with combinations of long acting bronchodilators and inhaled steroids for treatment of COPD. Thorax. 2008 Nov;63(11):962-7.

113. Najafzadeh M, Marra CA, Sadatsafavi M, Aaron SD, Sullivan SD, Vandemheen KL, et al. Cost effectiveness of therapy with combinations of long acting bronchodilators and inhaled steroids for treatment of COPD. Thorax. 2008;63(11):962-7.

114. Nielsen R, Kankaanranta H, Bjermer L, Lange P, Arnetorp S, Hedegaard M, et al. Cost effectiveness of adding budesonide/formoterol to tiotropium in COPD in four Nordic countries. Respiratory Medicine. 2013;107(11):1709-21.

115. Neyt M, Devriese S, Thiry N, Van den BA. Tiotropium's cost-effectiveness for the treatment of

COPD: a cost-utility analysis under real-world conditions. BMC Pulm Med. 2010;10:47. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2954895

116. Neyt M, Devriese S, Thiry N, Van den BA. Tiotropium's cost-effectiveness for the treatment of COPD: a cost-utility analysis under real-world conditions. BMC pulmonary medicine. 2010;10:47.

117. Gaebel K, Blackhouse G, Robertson D, Xie F, Assasi N, McIvor A, et al. Triple Therapy for Moderate-to-Severe Chronic Obstructive Pulmonary Disease. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2010 May. [cited 2013 Dec 3]. Available from: http://www.cadth.ca/index.php/en/hta/reports-publications/search/publication/1690

118. Mittmann N, Hernandez P, Mellstrm C, Brannman L, Welte T. Cost effectiveness of budesonide/formoterol added to tiotropium bromide versus placebo added to tiotropium bromide in patients with chronic obstructive pulmonary disease: Australian, Canadian and Swedish healthcare perspectives. Pharmacoeconomics. 2011;29(5):403-14.

119. Najafzadeh M, Marra CA, Sadatsafavi M, Aaron SD, Sullivan SD, Vandemheen KL, et al. Cost effectiveness of therapy with combinations of long acting bronchodilators and inhaled steroids for treatment of COPD. Thorax. 2008 Nov;63(11):962-7.

120. Nielsen R, Kankaanranta H, Bjermer L, Lange P, Arnetorp S, Hedegaard M, et al. Cost effectiveness of adding budesonide/formoterol to tiotropium in COPD in four Nordic countries. Respir Med. 2013 Nov;107(11):1709-21.

121. Neyt M, Devriese S, Thiry N, Van den BA. Tiotropium's cost-effectiveness for the treatment of COPD: a cost-utility analysis under real-world conditions. BMC Pulm Med. 2010;10:47. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2954895

122. Gani R, Griffin J, Kelly S, Rutten-van MM. Economic analyses comparing tiotropium with ipratropium or salmeterol in UK patients with COPD. Prim Care Respir J. 2010 Mar;19(1):68-74.

123. Hertel N, Kotchie RW, Samyshkin Y, Radford M, Humphreys S, Jameson K. Cost-effectiveness of available treatment options for patients suffering from severe COPD in the UK: a fully incremental analysis. Int J Chron Obstruct Pulmon Dis. 2012;7:183-99. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3325000

124. Hoogendoorn M, Al MJ, Beeh KM, Bowles D, Graf von der Schulenburg JM, Lungershausen J, et al. Cost-effectiveness of tiotropium versus salmeterol: the POET-COPD trial. Eur Respir J. 2013 Mar;41(3):556-64.

125. Hoogendoorn M, Al MJ, Beeh K-M, Bowles D, Von Der Schulenburg JMG, Lungershausen J, et al. Cost-effectiveness of tiotropium versus salmeterol: The POET-COPD trial. European Respiratory Journal. 2013;41(3):556-64.

126. Hertel N, Kotchie RW, Samyshkin Y, Radford M, Humphreys S, Jameson K. Cost-effectiveness of available treatment options for patients suffering from severe COPD in the UK: A fully

incremental analysis. International Journal of COPD. 2012;7:183-99.

127. Hoogendoorn M, Kappelhoff BS, Overbeek JA, Wouters EF, Rutten-van Molken MP. Which long-acting bronchodilator is most cost-effective for the treatment of COPD? Neth J Med. 2012 Oct;70(8):357-64.

128. Hoogendoorn M, Kappelhoff BS, Overbeek JA, Wouters EF, Rutten-van Molken MP. Which long-acting bronchodilator is most cost-effective for the treatment of COPD? The Netherlands journal of medicine. 2012;70(8):357-64.

129. Maniadakis N, Tzanakis N, Fragoulakis V, Hatzikou M, Siafakas N. Economic evaluation of tiotropium and salmeterol in the treatment of chronic obstructive pulmonary disease (COPD) in Greece. Current Medical Research and Opinion. 2006;22(8):1599-607.

130. Naik S, Kamal KM, Keys PA, Mattei TJ. Evaluating the cost-effectiveness of tiotropium versus salmeterol in the treatment of chronic obstructive pulmonary disease. ClinicoEconomics and Outcomes Research. 2010;2(1):25-36.

131. Oba Y. Cost-effectiveness of long-acting bronchodilators for chronic obstructive pulmonary disease. Mayo Clinic Proceedings. 2007;82(5):575-82.

132. Oostenbrink JB, Rutten-Van Molken MPMH, Monz BU, FitzGerald JM. Probabilistic Markov model to assess the cost-effectiveness of bronchodilator therapy in COPD patients in different countries. Value in Health. 2005;8(1):32-46.

133. Rutten-van Molken MP, Oostenbrink JB, Miravitlles M, Monz BU. Modelling the 5-year cost effectiveness of tiotropium, salmeterol and ipratropium for the treatment of chronic obstructive pulmonary disease in Spain. Eur J Health Econ. 2007 Jun;8(2):123-35. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1913175

134. Rutten-Van Molken MPMH, Oostenbrink JB, Miravitlles M, Monz BU. Modelling the 5-year cost effectiveness of tiotropium, salmeterol and ipratropium for the treatment of chronic obstructive pulmonary disease in Spain. European Journal of Health Economics. 2007;8(2):123-35.

135. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2007 Sep 15;176(6):532-55.

136. Scanlon PD, Connett JE, Waller LA, Altose MD, Bailey WC, Buist AS, et al. Smoking cessation and lung function in mild-to-moderate chronic obstructive pulmonary disease. The Lung Health Study. Am J Respir Crit Care Med. 2000 Feb;161(2 Pt 1):381-90.

137. Crapo RO, Morris AH, Gardner RM. Reference spirometric values using techniques and equipment that meet ATS recommendations. American Review of Respiratory Disease. 1981;123(6):659-64.

138. Jenkins CR, Jones PW, Calverley PM, Celli B, Anderson JA, Ferguson GT, et al. Efficacy of

salmeterol/fluticasone propionate by GOLD stage of chronic obstructive pulmonary disease: analysis from the randomised, placebo-controlled TORCH study. Respir Res. 2009;10:59. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2714501

139. Price D, Gray A, Gale R, Asukai Y, Mungapen L, Lloyd A, et al. Cost-utility analysis of indacaterol in Germany: A once-daily maintenance bronchodilator for patients with COPD. Respiratory Medicine. 2011;105(11):1635-47.

140. Ekberg-Aronsson M, Pehrsson K, Nilsson JA, Nilsson PM, Lofdahl CG. Mortality in GOLD stages of COPD and its dependence on symptoms of chronic bronchitis. Respir Res. 2005;6:98. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1224873

141. Statistics Canada. Life Tables, Canada, Provinces and Territories, 2009 to 2011. 2012. In. Ottawa.

142. Stone RA, Lowe D, Potter JM, Buckingham RJ, Roberts CM, Pursey NJ. Managing patients with COPD exacerbation: does age matter? Age Ageing. 2012 Jul;41(4):461-8.

143. Spencer M, Briggs AH, Grossman RF, Rance L. Development of an economic model to assess the cost effectiveness of treatment interventions for chronic obstructive pulmonary disease. Pharmacoeconomics. 2005;23(6):619-37.

144. Rutten-van Molken MP, Oostenbrink JB, Tashkin DP, Burkhart D, Monz BU. Does quality of life of COPD patients as measured by the generic EuroQol five-dimension questionnaire differentiate between COPD severity stages? Chest. 2006 Oct;130(4):1117-28.

145. Rutten-van Molken MP, Hoogendoorn M, Lamers LM. Holistic preferences for 1-year health profiles describing fluctuations in health: the case of chronic obstructive pulmonary disease. Pharmacoeconomics. 2009;27(6):465-77.

146. Borg S, Ericsson A, Wedzicha J, Gulsvik A, Lundback B, Donaldson GC, et al. A computer simulation model of the natural history and economic impact of chronic obstructive pulmonary disease. Value Health. 2004 Mar;7(2):153-67.

147. Stahl E, Lindberg A, Jansson SA, Ronmark E, Svensson K, Andersson F, et al. Health-related quality of life is related to COPD disease severity. Health Qual Life Outcomes. 2005;3:56. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1215504

148. Samyshkin Y, Kotchie RW, Mork AC, Briggs AH, Bateman ED. Cost-effectiveness of roflumilast as an add-on treatment to long-acting bronchodilators in the treatment of COPD associated with chronic bronchitis in the United Kingdom. Eur J Health Econ. 2014 Jan;15(1):69-82. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3889819

149. Hoogendoorn M, Hoogenveen RT, Rutten-van Molken MP, Vestbo J, Feenstra TL. Case fatality of COPD exacerbations: a meta-analysis and statistical modelling approach. Eur Respir J. 2011 Mar;37(3):508-15.

150. Atsou K, Chouaid C, Hejblum G. Simulation-based estimates of effectiveness and cost-

effectiveness of smoking cessation in patients with chronic obstructive pulmonary disease. PLoS One. 2011;6(9).

151. Oostenbrink JB, Rutten-Van Molken MPMH, Monz BU, FitzGerald JM. Probabilistic Markov model to assess the cost-effectiveness of bronchodilator therapy in COPD patients in different countries. Value in Health. 2005;8(1):32-46.

152. O'Reilly JF, Williams AE, Rice L. Health status impairment and costs associated with COPD exacerbation managed in hospital. International Journal of Clinical Practice. 2007;61(7):1112-20.

153. Goossens LM, Nivens MC, Sachs P, Monz BU, Rutten-van Molken MP. Is the EQ-5D responsive to recovery from a moderate COPD exacerbation? Respir Med. 2011 Aug;105(8):1195-202.

154. Menn P, Weber N, Holle R. Health-related quality of life in patients with severe COPD hospitalized for exacerbations - comparing EQ-5D, SF-12 and SGRQ. Health and Quality of Life Outcomes. 2010;8.

155. Paterson C, Langan CE, McKaig GA, Anderson PM, Maclaine GDH, Rose LB, et al. Assessing patient outcomes in acute exacerbations of chronic bronchitis: The measure your medical outcome profile (MYMOP), medical outcomes study 6-item general health survey (MOS-6A) and EuroQol (EQ-5D). Quality of Life Research. 2000;9(5):521-7.

156. Hoogendoorn M, Rutten-Van Molken MPMH, Hoogenveen RT, Al MJ, Feenstra TL. Developing and applying a stochastic dynamic population model for chronic obstructive pulmonary disease 181. Value in Health. 2011;14(8):1039-47.

157. Bank of Canada. Inflation Calculator. 2014. Bank of Canada. 9-1-2014.

158. Mittmann N, Kuramoto L, Seung SJ, Haddon JM, Bradley-Kennedy C, FitzGerald JM. The cost of moderate and severe COPD exacerbations to the Canadian healthcare system. Respiratory Medicine. 2008;102(3):413-21.

159. Lange P, Marott JL, Vestbo J, Olsen KR, Ingebrigtsen TS, Dahl M, et al. Prediction of the clinical course of chronic obstructive pulmonary disease, using the new GOLD classification: a study of the general population. Am J Respir Crit Care Med. 2012 Nov 15;186(10):975-81.

160. By A, Sobocki P, Forsgren A, Silfverdal SA. Comparing health outcomes and costs of general vaccination with pneumococcal conjugate vaccines in Sweden: a Markov model. Clin Ther. 2012 Jan;34(1):177-89.

161. Jin Y, Marrie TJ, Carriere KC, Predy G, Houston C, Ness K, et al. Variation in management of community-acquired pneumonia requiring admission to Alberta hospitals. Alberta Centre for Health Services Research; 2002 Nov. [cited 2014 Apr 24]. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2869937

162. Canadian Agency for Drugs and Technologies in Health. *Guidelines for the economic evaluation of health technologies: Canada*. 3rd Edition. Ottawa: Canadian Agency for Drugs and

Technologies in Health; 2006.

163. Jansson SA, Andersson F, Borg S, Ericsson A, Jonsson E, Lundback B. Costs of COPD in Sweden according to disease severity. Chest. 2002 Dec;122(6):1994-2002.

164. Ontario Ministry of Health and Long-Term Care. Ontario drug benefit formulary/comparative drug index. Toronto: Ontario Ministry of Health and Long-Term Care; 2014.

165. Torrance G, Walker V, Grossman R, Mukherjee J, Vaughan D, La FJ, et al. Economic evaluation of ciprofloxacin compared with usual antibacterial care for the treatment of acute exacerbations of chronic bronchitis in patients followed for 1 year. Pharmacoeconomics. 1999 Nov;16(5 Pt 1):499-520.