NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Roflumilast for treating chronic obstructive pulmonary disease (review of technology appraisal guidance 244) [ID984]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Roflumilast for treating chronic obstructive pulmonary disease (review of technology appraisal guidance 244) [ID984]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Roflumilast for treating chronic obstructive pulmonary disease (review of technology appraisal guidance 244) [ID984]

Scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of roflumilast within its licensed indication for the maintenance treatment of severe chronic obstructive pulmonary disease.

Background

Chronic obstructive pulmonary disease includes chronic bronchitis, emphysema, chronic obstructive airways disease and chronic airflow limitation. Chronic obstructive pulmonary disease is characterised by consistent airways obstruction defined as FEV_1 (forced expiratory volume in 1 second) less than 80% predicted and FEV_1/FVC (forced volume capacity) ratio less than 70%. The impairment of lung function is usually progressive and is not fully reversible. Chronic obstructive pulmonary disease is associated with persistent and progressive breathlessness, a chronic productive cough and limited exercise capacity.

An estimated 1.2 million people in the UK have been diagnosed with chronic obstructive pulmonary disease, and 115,000 people are newly diagnosed each year.[1] The prevalence of this condition increases with age (rare before 35 years of age), and it is frequently associated with smoking. Chronic obstructive pulmonary disease caused nearly 30,000 deaths in the UK in 2012.[1] It is also a major cause of hospital admission.

For people with stable chronic obstructive pulmonary disease who are breathless and have limited exercise capacity, NICE clinical guideline 101 recommends initial therapy with a short-acting $beta_2$ agonist or a short-acting muscarinic antagonist. For people who remain breathless or have exacerbations despite use of short-acting bronchodilators, maintenance therapy may comprise long-acting muscarinic antagonists (LAMA), long-acting $beta_2$ agonists (LABA) or inhaled corticosteroids (ICS), either individually or in combination. The choice of therapy may be influenced by the severity of disease (FEV_1 above or below 50% predicted), response to treatment and tolerability of ICS. Theophylline should only be used after a trial of short- and long-acting bronchodilators, or in people who are unable to use inhaled therapy. In addition to drug therapy, NICE clinical guideline 101 recommends smoking cessation and pulmonary rehabilitation as part of the management of stable chronic obstructive pulmonary disease. In NICE technology appraisal 244, roflumilast was recommended for use only in the context of research. The guidance recommended that evidence should be generated on the benefits of roflumilast as an add-on to LAMA in combination with LABA and

ICS or LAMA in combination with LABA. Since TA244, the REACT trial has been published, in which roflumilast in combination with LABA and ICS, with or without LAMA, was compared with placebo.

The technology

Roflumilast (Daxas, AstraZeneca) is an orally administered long-acting selective phosphodiesterase-4 (PDE4) enzyme inhibitor which targets cells and mediators in the body believed to be important in chronic obstructive pulmonary disease.

Roflumilast has a marketing authorisation in the UK for maintenance treatment of severe chronic obstructive pulmonary disease (FEV_1 post bronchodilator less than 50% predicted) associated with chronic bronchitis in adults with a history of frequent exacerbations as an add on to bronchodilator treatment.

Intervention(s)	Roflumilast in combination with maintenance bronchodilator treatment (LABA, LABA/corticosteroid combination inhaler, LAMA, LAMA plus LABA/corticosteroid combination inhaler or LAMA plus LABA [if ICS not tolerated]).
Population(s)	Adults with severe chronic obstructive pulmonary disease (FEV_1 post bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations.
Comparators	• LAMA in combination with LABA and ICS • LAMA in combination with LABA • LAMA or LABA (with or without ICS) • Theophylline (in combination with inhaled maintenance bronchodilator treatment)
Outcomes	The outcome measures to be considered include: • lung function • incidence and severity of acute exacerbations, including hospitalisation • symptom control (e.g. shortness of breath) • mortality • adverse effects of treatment • health-related quality of life

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations	Related Technology Appraisals: 'Roflumilast for the management of severe chronic obstructive pulmonary disease' (2012). NICE Technology Appraisal 244. To be reviewed. Related Guidelines: 'Chronic obstructive pulmonary disease' (2010) NICE Clinical Guideline 101. Currently being updated. Date of publication to be confirmed. Related Quality Standards: 'Chronic obstructive pulmonary disease in adults' (2011). NICE quality standard 10. Related NICE Pathways: Chronic Obstructive Pulmonary Disease (2016) NICE pathway http://pathways.nice.org.uk/pathways/chronic-obstructive-pulmonary-disease

Related National Policy	Department of Health, NHS Outcomes Framework 2015-2016, Dec 2014. Domains 1–4. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/385749/NHS_Outcomes_Framework.pdf NHS England (2014) Our ambition to reduce premature mortality [accessed June 2016]. Chapter 6: respiratory disease. Department of Health (2011) An outcomes strategy for chronic obstructive pulmonary disease (COPD) and asthma in England [accessed June 2016]

References

1. British Lung Foundation (2016) Chronic obstructive pulmonary disease (COPD) statistics [accessed June 2016]

Appendix C

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Roflumilast for treating chronic obstructive pulmonary disease (review of technology appraisal guidance 244) [ID984]

Matrix of consultees and commentators

Consultees	**Commentators (no right to submit or appeal)**
Company • AstraZeneca UK (roflumilast) Patient/carer groups • Action on Smoking and Health (ASH) • British Lung Foundation • Muslim Council of Britain • Roy Castle Lung Cancer Foundation • South Asian Health Foundation • Specialised Healthcare Alliance Professional groups • Association of Respiratory Nurse Specialists • British Geriatrics Society • British Thoracic Society • Primary Care Respiratory Society UK • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal Pharmaceutical Society • United Kingdom Clinical Pharmacy Association Others • Department of Health • NHS England • Rhondda Cynon Taff LHB • Trafford Healthcare NHS Trust • Welsh Government	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Comparator companies • AstraZeneca UK (aclidinium, aclidinium/formoterol, formoterol, formoterol/budesonide,) • Boehringer Ingelheim (olodaterol, olodaterol/tiotropium, tiotropium) • Chiesi (formoterol, formoterol/budesonide) • GlaxoSmithKline (aclidinium, fluticasone/vilanterol, salmeterol, salmeterol/fluticasone, umeclidinium, umeclidinium/vilanterol) • Meda Pharmaceuticals (theophylline) • Merck Serono (theophylline)

Appendix C

Consultees	Commentators (no right to submit or appeal)
	• Mylan (salmeterol/fluticasone) • Napp Pharmaceuticals (theophylline, formoterol/fluticasone) • Novartis Pharmaceuticals (formoterol, glycopyrronium, indacterol, indacterol/glycopyrronium) • Orion Pharma (UK) (formoterol) • Sandoz (salmeterol/fluticasone) • Teva Pharma (formoterol/budesonide, salmeterol) <u>Relevant research groups</u> • British Association for Lung Research • Cochrane Airways Group • MRC Clinical Trials Unit • National Institute for Health Research • Policy Research Institute on Aging and Ethnicity <u>Associated Guideline groups</u> • National Clinical Guidelines Centre <u>Associated Public Health groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality and eliminating unlawful discrimination. Please let us know if we have missed any important organisations from the lists contained within the matrix and which organisations we should include who have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees
Organisations that accept an invitation to participate in the appraisal; the manufacturer(s) or sponsor(s) of the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England.

The manufacturer/sponsor of the technology is invited to make an evidence submission, respond to consultations and has the right to appeal against the Final Appraisal Determination (FAD).

All non-manufacturer/sponsor consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators
Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: manufacturers of comparator technologies; NHS Quality Improvement Scotland; the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines); other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*.

All non-manufacturers/sponsors commentators are invited to nominate clinical specialists or patient experts.

Evidence Review Group (ERG)
An independent academic group commissioned by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTA Programme) to assist the Appraisal Committee in reviewing the manufacturer/sponsor evidence submission to the Institute.

[1] Non manufacturer consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Roflumilast [ID984] for treating chronic obstructive pulmonary disease (review of technology appraisal guidance 244) [GID-TA10062]

AstraZeneca UK Ltd

Company evidence submission

File name	Version	Contains confidential information	Date
ID984_roflumilast_CompanyEvidenceSubmission_V01_300916_CIC	1.0	Yes	30th September 2016

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Abbreviations

ADL	Activities of daily living
AMP	Adenosine monophosphate
ATC	Anatomical Therapeutic Chemical
ATS	American thoracic society
BTS	British thoracic society
cAMP	Cyclic adenosine monophosphate
CAT	COPD Assessment Test
CFR	Case fatality rate
CHEST	American College of Chest Physicians
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
EMA	European Medicines Agency
ERS	European respiratory society
FDA	Food and Drugs Administration
FEV_1	Forced Expiratory Volume in the first second
FEV_6	Forced Expiratory Volume in the first 6 seconds
FVC	Forced vital capacity
GOLD	Global initiative for chronic obstructive lung disease
HCP	Health Care Practitioner
HIV	human immunodeficiency virus
HRQoL	Health related quality of life
ICS	Inhaled corticosteroid
ICTRP	International Clinical Trials Registry Platform
IQR	Inter quartile range
ITT	Intention to treat
IVRS	Interactive voice response system
LABA	Long-acting $beta_2$ agonist
LABA / ICS	Long-acting $beta_2$ agonist with an inhaled corticosteroid in a combination inhaler
LAMA	Long-acting muscarinic antagonist
LYG	Life years gained
LY	Life year
MACE	Major adverse cardiovascular events
MeSH	Medical Subject Headings
MCS	Mental component summary
mMRC	modified Medical Research Council dyspnoea scale
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NYHA	New York Heart Association
OR	Odds ratio
PCS	Physical component summary
PDE4	Phosphodiesterase-4
PP	Per protocol
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RE^2SPOND	Roflumilast Effect on Exacerbations in Patients on Dual [LABA / ICS] Therapy
REACT	Roflumilast and Exacerbations in patients receiving Appropriate Combination Therapy
RMP	Risk management plan
RR	Rate ratio
SABA	Short acting bronchodilators
SAMA	Short-acting muscarinic antagonist
SD	Standard deviation
SE	Standard error
SGRQ	St George's Respiratory Questionnaire
SmPC	Summary of product characteristics
SMR	Standardised mortality ratios

Vend	End of treatment period
TESAE	Treatment emergent serious adverse events
TEAE	Treatment emergent adverse events
VAS	Visual analogue scale

1 Executive summary

Disease background and unmet need

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease that is accompanied by exacerbations and comorbidities that contribute to the overall severity and cost of treatment [1]. Frequent exacerbations are associated with increased morbidity and mortality[3 6] a faster decline in lung function,[7] and poorer health status [8 9] when compared to patients whose disease is adequately controlled. Frequent exacerbations also increase the risk of future exacerbations, leading to a cycle of worsening disease that becomes a substantial burden to the patient and is associated with high costs to the health system.[10 11] Prevention of COPD exacerbations is therefore recognised as both a global and a UK priority.[1-3]

Bronchodilators (LABA and LAMA) and inhaled corticosteroids (ICS) are the mainstay of the pharmacological treatment for COPD.[1]Whilst current guidelines recommend combination inhaled triple therapy (LABA / LAMA / ICS) for the management of severe COPD,[1] treatment options and clinical guidance for patients who continue to have exacerbations despite inhaled triple therapy are limited.[1 2 5] This submission aims to address the unmet need for this patient group by seeking a recommendation for the use of roflumilast as an add-on to triple therapy in patients with FEV_1 < 50% predicted and chronic bronchitis who continue to have frequent exacerbations (≥ 2 / year). Due to the current lack of add-on treatments to triple inhaled therapy, both in terms of recommendations and use in clinical practice, the only relevant comparator for our submission is LABA / LAMA / ICS. Specifically, theophylline is not considered a relevant comparator due to negligible use in UK clinical practice [12] and lack of evidence demonstrating clinical efficacy in the patient group in question.

Roflumilast for the treatment of COPD

NICE previously recommended in technology appraisal 244 (TA244) that roflumilast is used in the context of research as part of a clinical trial for adults with severe COPD (FEV_1 < 50% predicted) associated with chronic bronchitis with a history of frequent exacerbations as an add-on to bronchodilator treatment[13] The NICE TA244 recommendations stated that the purpose of the research should be to generate robust evidence about the benefits of roflumilast as an add-on to LABA / LAMA / ICS or LAMA / LABA for people who are intolerant to ICS. Since the publication of TA244, the recommended study to investigate the benefits of roflumilast as add-on to LABA / LAMA / ICS has been conducted, and forms the basis of this submission.

Summaries of the decision problem, technology, clinical effectiveness analysis and cost effectiveness analysis are given below.

1.1 Statement of decision problem

This submission is seeking a recommendation for the use of roflumilast (an oral COPD-specific, non-steroidal anti-inflammatory agent), in a subgroup of adult patients with severe chronic obstructive pulmonary disease (COPD) as part of maintenance treatment; as add-on to triple therapy (inhaled corticosteroids [ICS], long-acting beta2 agonist [LABA] and long-acting muscarinic antagonist [LAMA]) in patients with FEV_1 < 50% predicted, symptoms of chronic bronchitis and frequent exacerbations (≥ 2 / year).

An overview of the scope of decision problem vs the scope of this submission is summarized in Table 1.

Table 1: The decision problem.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population(s)	Adults with severe COPD (FEV_1 post-bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations	Adult with severe COPD (FEV_1 post-bronchodilator < 50% predicted) associated with chronic bronchitis and a history of frequent exacerbations (≥2 exacerbations in the prior 12 months) despite triple therapy with LABA / LAMA / ICS	In line with current clinical evidence from the REACT trial, the positioning of roflumilast as add-on to triple therapy in patients with severe COPD and chronic bronchitis with a history of frequent exacerbations represents a subgroup of the current scope issued by NICE AstraZeneca believe this subgroup better reflects the recommendations for further research issued by NICE in their final guidance in 2012 and the unmet need for patients with severe COPD and chronic bronchitis with a history of frequent exacerbations.
Intervention	Roflumilast in combination with maintenance bronchodilator treatment (LABA, LABA / corticosteroid combination inhaler, LAMA, LAMA plus LABA / corticosteroid combination inhaler or LAMA plus LABA [if ICS not tolerated])	Roflumilast in combination with maintenance triple therapy, LABA / LAMA / ICS	Roflumilast will be positioned throughout the UK and Europe as add-on to triple therapy in patients with chronic bronchitis and a history of frequent exacerbations. AstraZeneca are seeking a recommendation for this subgroup only
Comparator (s)	• LAMA in combination with LABA and ICS • LAMA in combination with LABA	• LAMA in combination with LABA and ICS (LABA / LAMA / ICS)	As the scope of intervention is restricted to roflumilast in combination with LABA / LAMA / ICS, mono- and dual therapy comparators are not considered relevant

	• LAMA or LABA (with or without ICS) • Theophylline (in combination with inhaled maintenance bronchodilator treatment)		Theophylline is not considered as an appropriate comparator as it does not represent standard practice in the UK. Of COPD patients experiencing frequent exacerbations (≥2 exacerbations in the prior 12 months) despite treatment with ICS / LABA / LAMA, only 4.6% are also prescribed theophylline. In addition theophylline is associated with serious treatment limiting side effects which do not favour chronic usage
Outcomes	The outcome measures to be considered include: • lung function • incidence and severity of acute exacerbations, including hospitalisation • symptom control (e.g. shortness of breath) • mortality • adverse effects of treatment • health-related quality of life	The key outcome measures presented in the submission include: • rate of moderate to severe exacerbations (including hospitalisation) • rate of severe exacerbations (requiring hospitalisation) • lung function as measured by FEV_1 • mortality • health related quality of life • Adverse effects of treatment	N / A
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental	As per the scope of the decision problem	

	cost per quality-adjusted life year The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs will be considered from an NHS and Personal Social Services perspective.		
Subgroups to be considered	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator	The intervention and target population are in accordance with the marketing authorisation	No further subgroup analysis is provided. The target population is itself a subgroup of the licensed population and RE^{2}SPOND trial .
Special considerations including issues related to equity or equality			

1.2 Description of the technology being appraised

Table 2: Technology being appraised

UK approved name and brand name	Roflumilast; Daxas
Marketing authorisation / CE mark status	Roflumilast was granted UK marketing authorisation, via the centralised procedure, in July 2010 (market authorisation number EU / 1 / 10 / 636 / 001-007)
Indications and any restriction(s) as described in the summary of product characteristics	Roflumilast is indicated for maintenance treatment of severe chronic obstructive pulmonary disease (COPD) (FEV_1 post-bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add-on to bronchodilator treatment
Method of administration and dosage	Roflumilast is administered orally at a recommended dose of 500 micrograms (1 tablet) once daily

1.3 Summary of the clinical effectiveness analysis

The REACT trial provides the core clinical evidence for this submission. REACT is a randomised controlled clinical trial (RCT) that investigated the impact of roflumilast compared with placebo on the rate of moderate to severe exacerbations as add-on to LABA / ICS ± LAMA in patients with FEV_1 < 50%, chronic bronchitis and ≥2 exacerbations in the previous year. A high proportion (~70%) of study participants received concomitant LAMA therapy. The trial protocol therefore, closely reflected clinical practice in the UK, as well as the proposed positioning of roflumilast and the subgroup which is the focus of this submission document and appraisal.

The REACT dataset most relevant to the decision problem is the per protocol (PP) analysis of the pre-specified subgroup 'concomitant treatment with LAMA'. The PP analysis excluded patients with major protocol deviations, postbronchodilator FEV_1% predicted at >50% at V0 or not treated with LABA / ICS for at least 12 months prior to V0, or did not

use a fixed combination of LABA / ICS on a constant daily dose throughout the trial, being the most common violations. For this reason this study subgroup population included only those patients fulfilling the criteria of the target population under appraisal.

In the PP analysis (using negative binomial regression), the addition of roflumilast to LABA / LAMA / ICS significantly reduced the rate of moderate to severe exacerbations by 20.1% (roflumilast 0.858 vs placebo 1.075; rate ratio [RR] 0.799 [95% CI 0.670-0.952] p=0.0122) and by 34.1% (roflumilast 0.260 vs placebo 0.395; rate ratio [RR] 0.659 [95% CI 0.497–0.872] p=0.0035) for severe exacerbations. The rate of severe and moderate to severe exacerbation and / or exacerbations requiring antibiotic treatment were also significantly reduced in the roflumilast group compared with placebo in this population.

The most common adverse events associated with roflumilast treatment reported in the REACT trial were diarrhoea (10% vs 4% in the placebo arm), weight decrease (9% vs 3% in the placebo arm) and nausea (6% vs 2% in the placebo arm).

Comparative evidence

A systematic review was carried out to identify RCTs of roflumilast in combination with triple therapy or relevant comparators in patients with severe / very severe COPD, as defined in the pre-2013 GOLD report as stages III and IV.

Ten trials were identified, these included REACT and RESPOND which provided evidence for roflumilast. Three studies, REACT,[14] RE^{2}SPOND[15] and Cosio (2016)}[16] included treatments that were considered directly relevant to the decision problem under assessment (LABA / LAMA / ICS and add-on to LABA / LAMA / ICS including roflumilast). However, limitations and differences in study design between the RE^{2}SPOND and REACT trials that are outlined in Section 4.2, meant that RE^{2}SPOND was not considered to be an appropriate study for the decision problem, nor for

inclusion in an indirect comparison. The other trial considered potentially relevant to the roflumilast indication was the theophylline trial Cosio (2016).[16] However, as theophylline was excluded as a relevant comparator for the reasons outlined in Section 3.2 it was not considered further.

In summary, no comparative evidence was found to be relevant to the roflumilast indication and an indirect comparison was not required.

Strengths and Limitations

The REACT study was a well-designed RCT that directly addresses the target population for this appraisal.

The limitations of the REACT study are the lower than anticipated event rate, and that it did not follow-up all participants to the end of the study, which may have led to an underestimation of mortality risk.

1.4 Summary of the cost effectiveness analysis

In line with the NICE reference case, a cohort state transition (Markov) model with monthly cycles and a lifetime time horizon was developed with three states: severe COPD, very severe COPD, and death, as illustrated in Figure 1.

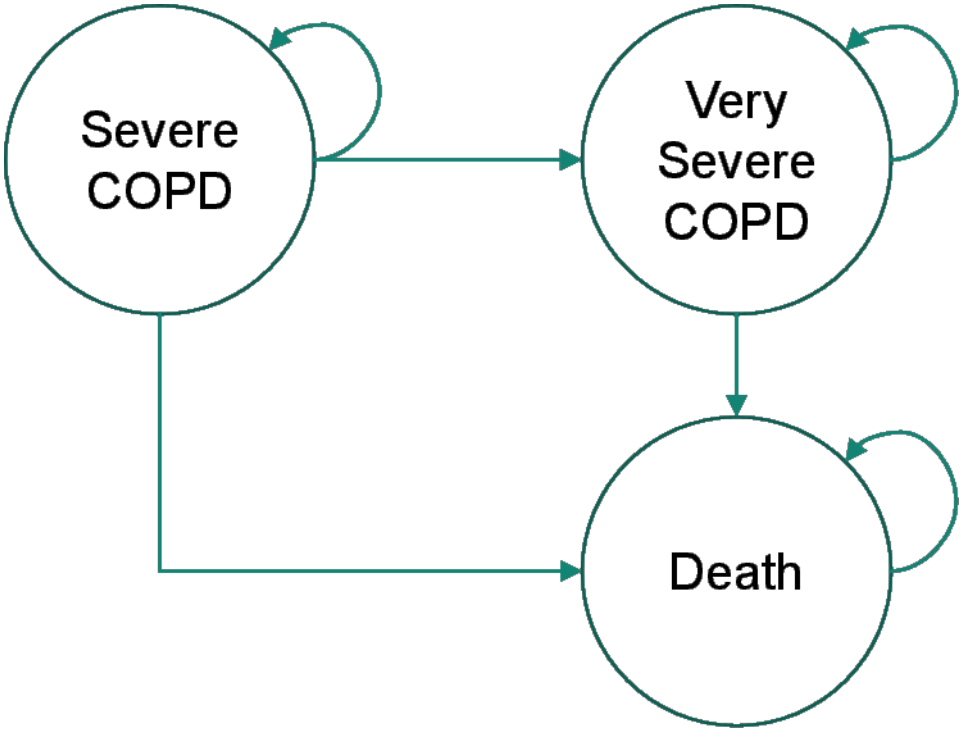


Figure 1: Model schematic

The progression from severe to very severe health states was modelled using a standard approach among studies in COPD. [17] [18] The model then uses individual patient level data from 1122 patients within REACT to predict the rate of moderate and severe exacerbations for patients treated with LABA / LAMA / ICS / roflumilast and LABA / LAMA / ICS alone.

The rate of mortality due to severe (i.e..hospitalised) exacerbations - the case fatality rate (CFR) - was obtained from the 2014 UK National COPD Audit Report[19] and background mortality is calculated using UK life tables and standardised mortality ratios (SMRs) that exclude hospital deaths.

Costs, resource use and utilities were identified through systematic reviews of published peer reviewed studies and supplemented with information taken from national databases. Rates of treatment emergent serious adverse events were taken from REACT and costs and utilities applied from the published literature. Owing to time constraints associated to the acquisition of roflumilast by AstraZeneca, it was not possible to build discontinuation into the economic model. Consequently, with the treatment

effect being inclusive of those patients who discontinued, the base case analysis, therefore, is a conservative estimate of the cost effectiveness of roflumilast.

The model was constructed and parameterised to enable both one-way and probabilistic sensitivity analysis (PSA) to assess the uncertainty in key model inputs. Where appropriate, uncertainty was characterised through the use of standard statistical distributions.

In the base case results LABA / LAMA / ICS / roflumilast accumulates total (discounted) costs of £22,930 and 6.14 quality-adjusted life years (QALYs). LABA / LAMA / ICS alone accumulates total (discounted) costs of £19,933 and 5.98 QALYs. This equates to LABA / LAMA / ICS / roflumilast producing an additional 0.16 QALYs at an incremental cost of £2,996 when compared to LABA / LAMA / ICS alone, generating a base-case incremental cost effectiveness ratio (ICER) of £18,774. Table 3 presents the base-case incremental cost effectiveness results in detail. This demonstrates that LABA / LAMA / ICS / roflumilast is cost effective at the £20,000 per QALY threshold.

Both probabilistic and deterministic sensitivity analyses were undertaken, which demonstrated the relative stability of the results to different assumptions and values. The analyses that lead to the largest change in values were when different health-related quality of life (HRQoL) utility values were used, although all the ICERs remained within the range considered cost effective by NICE.

In conclusion, the analyses undertaken demonstrate that roflumilast in addition to LABA / LAMA / ICS is a cost effective use of NHS resources for patients with severe and very severe COPD or in a mixed severity COPD population.

Table 3: Incremental cost effectiveness results

Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER vs baseline
LABA / LAMA / ICS / roflumilast	£22,930	8.95	6.14	£2,996	0.18	0.16	£18,774
LABA / LAMA / ICS	£19,933	8.77	5.98	-	-	-	-

ICER, incremental cost effectiveness ratio; QALYs, quality-adjusted life years

1.5 Conclusion

Taken together, the clinical evidence and economic evaluation demonstrate that the addition of roflumilast to LABA / LABA / ICS is a cost effective use of NHS resources to address an unmet need in a specific subgroup of patients with severe and very severe COPD.

2 The technology

This submission is seeking a recommendation for the use of roflumilast (an oral COPD-specific, non-steroidal anti-inflammatory agent) in a subgroup of adult patients with severe COPD as part of maintenance treatment; specifically, as add-on to triple therapy (ICS, LABA, and LAMA) in patients with FEV_1 < 50% predicted, symptoms of chronic bronchitis and frequent exacerbations (≥ 2 / year).

2.1 Description of the technology

Brand name: DAXAS▼
International nonproprietary name: roflumilast
Therapeutic class: Selective phosphodiesterase-4(PDE4) inhibitors
Pharmacotherapeutic group: drugs for obstructive airway diseases.[20]
Anatomical Therapeutic Chemical (ATC) code: R03DX07
Mode of action: COPD-specific, non-steroidal anti-inflammatory agent.

PDE4 is expressed in airway smooth muscle and many inflammatory cells involved in COPD pathogenesis [21]. In these pro-inflammatory and immune cells, PDE4 catalyses the breakdown of cAMP to AMP.[21] Cyclic AMP is an intracellular signalling molecule that inhibits the COPD-related pro-inflammatory function of cells.[22] By inhibiting PDE4 and increasing intracellular cAMP levels, roflumilast reduces COPD-related pro-inflammatory responses. For example, roflumilast (or its active metabolite, roflumilast N-oxide) reduces neutrophil adhesion, activation and production of reactive oxygen species, thereby helping to reduce inflammation and tissue remodelling in COPD.[21] Roflumilast has also been found to significantly reduce the number of neutrophils and eosinophils, as well as the number of soluble markers of neutrophilic and eosinophilic inflammatory activity in induced sputum samples of patients with COPD.[23]

2.2 Marketing authorisation / CE marking and health technology assessment

Roflumilast market authorisation

Roflumilast was granted UK marketing authorisation, via the centralised procedure, in July 2010 (market authorisation number EU / 1 / 10 / 636 / 001-007). Full market authorisation was granted with the standard commitment that the market authorisation holder will submit periodic safety update reports (as per Article 107c (7) of Directive 2001 / 83 / EC) and adhere to the agreed risk management plan (RMP). The European Public Assessment Report, which highlights the main issues discussed by the regulatory authorities, is provided in Appendix 1.

Globally, roflumilast is approved in all 31 European member states that fall under the remit of the European Medicines Agency and 58 other countries, including the USA. Appendix 2 lists all countries within which roflumilast has regulatory approval.

Roflumilast licence

In the UK roflumilast is indicated for maintenance treatment of severe COPD (FEV_1 post-bronchodilator < 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add-on to bronchodilator treatment. [20]

Roflumilast is contraindicated in patients:

- with moderate or severe hepatic impairment (Child-Pugh B or C)
- hypersensitivity to the active substance (roflumilast) or any of the excipients (lactose monohydrate, maize starch, povidone [K90], magnesium stearate, hypromellose, macrogol 4000, titanium dioxide [E171], iron oxide yellow [E172]).

It is recommended that roflumilast should not be used in patients:

- with severe immunological diseases (e.g. HIV infection, multiple sclerosis, lupus erythematosus, progressive multifocal leukoencephalopathy)
- with severe acute infectious diseases, cancers (except basal cell carcinoma)
- with immunosuppressive medicinal products (i.e. methotrexate, azathioprine, infliximab, etanercept, or oral corticosteroids to be taken long-term; except short-term systemic corticosteroids) with congestive heart failure (NYHA grades 3 and 4)
- treated with theophylline
- during pregnancy and / or breastfeeding
- of childbearing potential not using contraception
- with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption
- with a history of depression associated with suicidal ideation or behaviour
- new or worsening psychiatric symptoms, or suicidal ideation or suicidal attempt
- for the relief of acute bronchospasms.

Appendix 3 contains the Daxas▼ (roflumilast) product information, including the summary of product characteristics (SmPC).

Roflumilast has been launched in the UK and Astra Zeneca is now seeking a NICE recommendation for the use of roflumilast as a maintenance treatment in the following subgroup of patients:
Adult patients with severe COPD (FEV_1 post-bronchodilator < 50% predicted) associated with chronic bronchitis and a history of frequent exacerbations (≥2

exacerbations in the prior 12 months) as add-on to triple therapy with LABA / LAMA / ICS.

Health technology assessments

There are no other ongoing or planned health technology assessments for roflumilast in the UK.

2.3 Administration and costs of the technology

The recommended dose is 500 µg roflumilast (1 tablet) taken orally, once daily[20]. No dose adjustments are needed for special populations.

The list price of a 30-tablet pack is £37.71 and a 90-tablet pack is £113.14.[24]. This equates to a treatment cost of £1.26 per patient / day.

There is no patient access scheme for roflumilast.

2.4 Changes in service provision and management

Impact on service provision, management and cost

There are no additional tests, investigations or administration requirements for roflumilast that would impact service provision or management or cost. Furthermore, the technology does not require any additional NHS infrastructure to be put in place.

The DAXAS▼ SmPC specifies that body weight of underweight patients receiving roflumilast should be checked at each visit.[20] In the event of an unexplained and clinically concerning weight decrease, the intake of roflumilast should be stopped and body weight should be further followed-up.[20] In the UK, body weight and body mass index are already closely monitored in this patient group as part of the recommended standard of care[2] [25] Therefore, the SmPC requirement to monitor bodyweight of underweight patients receiving roflumilast will have no impact on service provision, management or cost.

Care setting

Patients with COPD are managed by multidisciplinary teams comprising, for example, a consultant respiratory physician, a respiratory community nurse and a general practitioner (team list is not exhaustive). It is anticipated that treatment with roflumilast will be initiated within secondary care and maintained in primary care. It is also expected that roflumilast will fall under the remit of the clinical commissioning groups.

Requirement for concomitant therapies

Roflumilast has a licensed indication as an add-on therapy for patients with severe COPD with chronic bronchitis who are receiving bronchodilators[20] however a more specific recommendation is being sought for use as add-on to triple therapy (LABA / LAMA / ICS). The marketing authorisation licence does not specify the use of any other concomitant therapies with the administration of roflumilast.

2.5 Innovation

Roflumilast is the only approved oral treatment with a specific anti-inflammatory mechanism of action that targets COPD inflammation. It is an innovative product as it provides a further step in the treatment pathway post-triple therapy (LABA / LAMA / ICS) where currently there is no treatment available. Roflumilast provides a treatment option for patients still exacerbating despite LABA / LAMA / ICS inhaled therapy; potentially reducing the need to long-term oral corticosteroid usage.

Roflumilast is expected to reduce exacerbations in this population and therefore reduce the comorbidities associated with frequent use of oral corticosteroids which is not captured in the QALY calculation.

3 Health condition and position of the technology in the treatment pathway

Section summary:

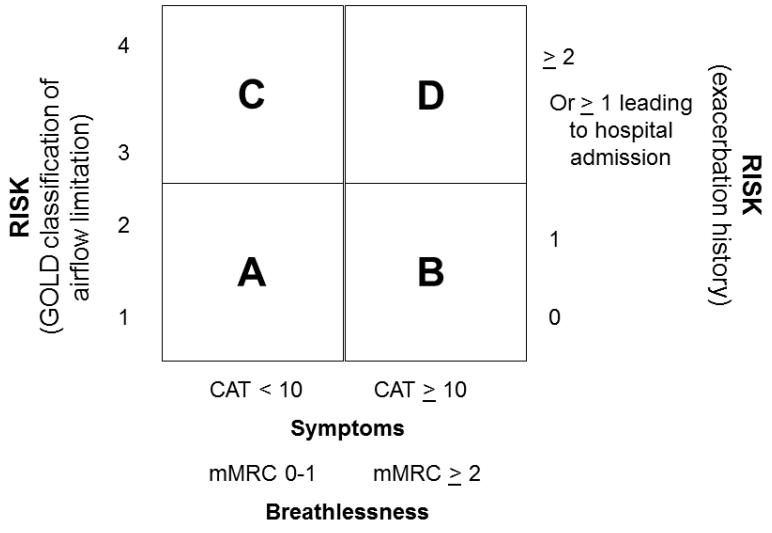
- COPD is characterised by a long-term progressive decline in persistent airflow limitation that is accompanied by exacerbations.
- Exacerbations significantly contribute to disease burden accelerating disease progression, increasing the risk of mortality and morbidity, and reducing quality of life (QoL)[1] placing a significant toll on patients, carers and health services. Therefore prevention and / or optimal treatment of exacerbations is a global and national priority.[2 3]
- Guidelines recommend LABA / LAMA / ICS as a treatment option in the management of severe COPD.[1] Treatment options for patients who continue to have exacerbations despite triple therapy (LABA / LAMA / ICS) are limited and guidance on how to best manage these patients is lacking.[1 4 5] This submission is addressing this unmet need by seeking a recommendation for the use of roflumilast as add-on to triple therapy with LABA / LAMA / ICS in those patients with FEV_1 <50% predicted and chronic bronchitis who continue to have frequent exacerbations (≥ 2 / year).
- Due to a lack of add-on treatment to triple therapy both in terms of recommendations and use in clinical practice, the only comparator relevant to the submission is LABA / LAMA / ICS.
- Theophylline is not considered a relevant comparator owing to: (i) its negligible use in UK clinical practice, [12] and (ii) lack of evidence demonstrating its effect on exacerbation rates as add-on to triple therapy in this patient group.

3.1 Overview of COPD

'COPD, a common preventable and treatable disease, is characterised by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases'.[1] COPD is also accompanied by exacerbations and comorbidities that contribute to the overall severity in individual patients.[1] Characteristic symptoms of COPD include chronic and progressive dyspnoea, cough, and sputum production that can be variable from day-to-day.[1]

Current guidelines grade disease severity A to D (Figure 2), according to a patient's symptoms (measured by COPD assessment test or modified Medical Research Council dyspnoea scale), exacerbation history and airflow limitation; prioritised in that order (Figure 2).[1]

Figure 2: The GOLD model of symptom / risk evaluation of COPD showing the criteria for patient classification in groups A–D[1]



CAT, COPD Assessment Test; mMRC, modified Medical Research Council dyspnoea scale

GOLD classification of airflow limitation in COPD is based on post-bronchodilator forced expiratory volume in 1 second (FEV_1) (Table 4).[1]

Table 4: Classification of severity of airflow limitation in COPD (in patients with FEV_1 / FVC < 0.70)[1]

GOLD classification	Disease severity	FEV_1 predicted
GOLD 1	Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3	Severe	$30\% \leq FEV_1 < 50$ predicted
GOLD 4	Very severe	$FEV_1 < 30\%$ predicted

FEV_1, forced expiratory volume in 1 second

Roflumilast is indicated in patients with severe airflow limitation ($FEV_1 < 50\%$ predicated) associated with chronic bronchitis and a history of exacerbations, which broadly overlaps with GOLD groups C and D. However, patients with less severe airflow may fall into groups C and D due to their high exacerbation risk and are not included in the licensed indication.

Aetiology, course and prognosis

Airflow limitation, the core pathological characteristic of COPD, results from small airways disease and / or parenchymal destruction;[1] the relative contribution of these two pathological mechanisms varies between patients resulting in disease heterogeneity. Patients with COPD are often assigned a clinical phenotype of chronic bronchitis or emphysema, reflecting the prevalent mechanism of airflow limitation. In addition, abnormal enhanced inflammatory responses, that usually develop due to long-term exposure to noxious particles and gases, play a key role in the pathophysiology of the disease. Consequently, COPD risk factors include smoking and exposure to other noxious gases (outdoor, occupational or indoor air pollution). Chronic inflammation causes the structural changes and narrowing of the small airways, while inflammatory processes contribute to the destruction of the lung parenchyma.[1]

Chronic bronchitis is a common clinical phenotype associated with COPD – published data report that 14–74% of COPD patients have chronic bronchitis.[26] Chronic bronchitis is defined 'as chronic productive cough for 3 months in each of 2 successive years, in a patient in whom other causes of productive chronic cough have been excluded'.[1] Chronic bronchitis may precede or follow the onset of airflow obstruction.

COPD is a progressive disease characterised by the gradual decline in lung function and occurrence of exacerbations (rapid and sustained worsening of symptoms beyond normal daily variation) – which significantly increase the burden of disease (discussed below). Exacerbations can be triggered by infection with bacteria or viruses, environmental pollutants, or by unknown factors[3 27] which leads to an increase in inflammation and symptoms.[3] Compared with patients without chronic bronchitis, patients with chronic bronchitis are likely to have more exacerbations and a higher proportion of patients have more frequent exacerbations.[28] This increased risk of exacerbations in chronic bronchitis is thought to be because these patients have chronic mucus hypersecretion, which makes them more likely to succumb to pulmonary infections than those without mucus hypersecretion.[29]

The risk of exacerbation increases with disease severity, and in turn, exacerbation events accelerate disease progression.[1] Exacerbations worsen patient health status, accelerate lung function decline and non-reversible lung damage, and increase the risk of hospitalisation, morbidity and mortality.[27 30] Furthermore the occurrence of a severe exacerbation increases the risk of subsequent events. A long-term cohort study of 73,106 patients hospitalised for the first time with COPD demonstrated how the median time between successive severe exacerbations decreases with every new severe exacerbation, from approximately 5.4 years from the first to the second, to less than 4 months from the ninth to the tenth.[8] The risk of another severe exacerbation peaks during the trimester following discharge from hospital, and the baseline rate of a severe exacerbation increases with every new severe exacerbation.

Frequent exacerbations are associated with increased morbidity and mortality,[3 6] a faster decline in lung function[7] and poorer health status[8 9] Every new severe exacerbation increases the risk of death, up to five times after their tenth COPD hospitalisation compared with after their first[8]

Reducing exacerbation frequency in these patients is therefore an important therapeutic aim, as 33% of patients with severe COPD, and 47% of patients with very severe COPD, experience ≥ 2 exacerbations per year (i.e. are frequent exacerbators), despite current treatment.[31] These patients have a considerably increased risk of death, and have significantly impaired quality of life (QoL). Prevention or optimal treatment of exacerbations is therefore a global and national priority.[2 3]

Burden of disease

COPD, especially more severe forms of the disease, is associated with significant risk of mortality and morbidity – impacting patients, carers and society.

- Mortality

It is predicted that by 2030 COPD will be the third leading cause of death worldwide.[32]

Owing to the variability of disease, patient smoking history and presence of co-morbidities, the impact of COPD on life expectancy is difficult to estimate. In a recent Danish study, life expectancy was reported to be 10.1 years shorter in patients with COPD compared with healthy participants who had never smoked.[33] Similar findings were reported in an analysis of Third National Health and Nutrition Examination survey data, which estimated a 9.3-year reduction in life expectancy in males 65 years of age who were smokers and had severe / very severe COPD (5.8-year reduction to COPD in addition to 3.5 years lost due to smoking).[34]

Three-year mortality rates in patients with severe (30% < FEV_1 < 50 % predicted) and very severe (FEV_1 < 30 % predicted) COPD are estimated at 15% and 24% respectively.[1] The risk of mortality is affected by specific features of the disease such as the presence of chronic bronchitis and the frequency of exacerbations. The symptoms of chronic bronchitis are also strongly associated with increased risk of death. Chronic cough and phlegm are associated with higher mortality compared with that which would be expected in the COPD population.[35-38]

Severe exacerbations increase mortality risk – both in the short and long-term. A UK study reported that 14% of patients died within 3 months of a hospital admission following an exacerbation and in the longer term, 77% of patients who were admitted died from COPD.[19 39] As previously mentioned, more frequent and more severe exacerbations are associated with higher mortality rates[40] - every new severe exacerbation increases the risk of death up to five times after the tenth COPD hospitalisation compared with after the first.[8] This high risk of death following an exacerbation reinforces the importance of preventing exacerbations in COPD patients.

- Morbidity

Morbidity due to COPD increases with age and occurrence of exacerbations.[32] In addition, patients with severe / very severe COPD typically have comorbid diseases that contribute to a high disease burden, overall morbidity and early mortality.

In the UK, an analysis of the primary care records of 1,204,100 people found that physician-diagnosed COPD is associated with increased risk of cardiovascular disease (OR 4.98, 95% CI: 4.85–5.81; p<0.001), stroke (OR 3.34, 95% CI: 3.21–3.48; p<0.001) and diabetes mellitus (OR 2.04, 95% CI: 1.97–2.12; p<0.001).[41] The highest relative risks were found in patients 35–44 years of age (probably due to healthy survivor bias), although the highest burden of comorbidities was found in the older age group (≥75 years), comprising 39% of the population with COPD.[41]

Exacerbations are associated with significant disease morbidity. A UK database study of 25,837 COPD patients over a 2-year period found that there was a 2.27-fold increased risk of myocardial infarction in the first 5 days immediately following an exacerbation (defined by the prescription of both steroids and antibiotics) (95% CI: 1.1–4.7; p=0.03), and a 1.26-fold increase in risk of stroke 1–49 days after exacerbation (95% CI: 1.0–1.6; p=0.05).[42] The increased risk of myocardial infarction and stroke following an exacerbation are thought to be due to increased systemic inflammation, although the increased airflow limitation during an exacerbation may also result in an increased burden on the heart, and increased $beta_2$-agonist use may also increase risk of adverse cardiac events in COPD.[42]

- Exacerbation and hospitalisations

As disease severity increases, so does the risk of exacerbation and consequently the rate of hospitalisation. In a UK study, exacerbation rates in GOLD C and D patients were 1.78 (95% CI: 1.74–1.82) and 2.51 (95% CI: 2.47–2.55) respectively (vs 0.83 [95% CI: 0.81–0.85] in GOLD A), while the rate of COPD-related hospitalisations was 0.44 (95% CI: 0.40–0.48) and 0.85 (95% CI: 0.81–0.89) (vs 0.35 [95% CI 0.31–0.40] in GOLD A) [43] Current GOLD guidelines estimate that patients with severe COPD (30% ≤ FEV_1 < 50 % predicted) have 1.1–1.3 exacerbations / year and 0.25–0.3 hospitalisations / year. This increases to 1.2–2.0 exacerbations / year and 0.4–0.54 hospitalisations / year in patients with very severe COPD (FEV_1 <30% predicted).[1] In a UK wide audit of secondary care patients admitted to hospital for COPD exacerbations, the length of hospital stay (from admission to discharge) was 5 days (median, IQR 3–10). [39]

The Continuing to Confront COPD International Patient Survey (a population based, cross-sectional survey of adults 40 years of age and over with COPD) collected responses from 305 UK patients with COPD and the data have been used estimate the economic impact of COPD.[44] Of the UK population surveyed (n=305, 35% of which reported as having severe or very severe COPD) 18% reported having at least 1 emergency department visit for

exacerbation in the past year and 15% had been hospitalised for exacerbations. Annual UK direct costs per patient were estimated at $3,224 (US dollars), with GP visits, specialist visits and inpatient hospitalisations contributing to the bulk of the cost (26%, 26%, 20% respectively).[44] Total UK indirect cost per patient was estimated to be $15,579, with 52% patients reporting that COPD prevented them from working.

- Quality of life

COPD has a direct impact on patients' QoL. Exertional dyspnoea (shortness of breath that worsens with exercise) often causes patients with COPD to unconsciously reduce their activities of daily living (ADL) so as to reduce the intensity of their distress. The reduction in ADLs leads to deconditioning (loss of exercise capacity, associated with loss of muscle mass) which in turn increases dyspnoea further.[45]

Studies have consistently shown that patients with COPD have significant decrements in their HRQoL.[46] The progression of COPD to more severe stages is associated with a corresponding decline in QoL. A study evaluating QoL using the St George's Respiratory Questionnaire (SGRQ) in 211 patients with COPD of differing severities demonstrated that QoL was worse in patients with more severe disease (GOLD airflow limitation 1–4).[47] SGRQ scores increased from 37.4 in moderate COPD (GOLD 2), to 53.0 in very severe COPD (GOLD 4). In the literature, utility values for severe COPD range between 0.63[48] and 0.82 [49] and consistently lower utility values have been reported for very severe COPD – between 0.52[50] and 0.74.[51]

Exacerbations have a significant short and long-term impact on QoL. A multicentre, single-arm study (n=421) demonstrated that acute exacerbations (defined as a change in respiratory symptoms lasting >24 hours) severely impacted health status in patients with COPD.[10] A clinically significant deterioration in SGRQ scores was observed in 71% of patients following early identification, 55% during the first week following onset of an acute exacerbation, and 37% during the second week. Patients with ≥ 2

exacerbations had no improvement in their SGRQ over the course of the study, whereas those with no or 1 exacerbation did show improvements over time.[10]

3.2 Clinical pathway of care

Data from a recent cohort study alludes to a substantial proportion of patients in the UK who have severe COPD (FEV_1 < 50% predicted), are treated with LABA / LAMA / ICS triple therapy and have frequent exacerbations (≥ 2 / year).[52] Currently, treatment options for patients who continue to have exacerbations despite triple therapy with LABA / LAMA / ICS are limited and guidance on how to best manage these patients is lacking.[1 2 5] To help address this unmet need, this submission is seeking a recommendation for the use of roflumilast as a treatment option for add-on to triple therapy with LABA / LAMA / ICS in those patients with FEV_1 < 50% predicted and chronic bronchitis who continue to have frequent exacerbations (≥ 2 / year). This positioning was endorsed by experts during a recent advisory board.[5] Furthermore, current GOLD guidelines suggest that roflumilast may be used to reduce exacerbations for patients with chronic bronchitis, severe and very severe COPD, and frequent exacerbations that are not adequately controlled by long-acting bronchodilators.[1]

The current NICE clinical guideline 101, 'Chronic obstructive pulmonary disease in over 16s: diagnosis and management' was published in 2010.[2] On reviewing latest clinical evidence in April 2016, NICE concluded that the guideline required updating. The timelines for the guideline update have not yet been confirmed, but the section on inhaled therapies has been identified as one of the sections for review and update. The GOLD guidelines, which were updated in 2016, incorporate the latest clinical evidence / data and are therefore currently considered to take precedence over the 2010 NICE guidance.[1 5 112]

GOLD 2016 guidelines are discussed in detail in Section 3.4. In brief, current guidelines recommend LABA / LAMA / ICS as an alternative treatment option

to first line recommendations, ICS / LABA dual therapy or LAMA monotherapy; in patients with COPD severity GOLD stage D.[1] As discussed in Section 3.1, GOLD stages C and D includes patients with FEV_1 < 50% predicted and with ≥2 exacerbations / year, and therefore encompasses the target population defined in the decision problem. It is proposed that roflumilast is used in this subgroup of patients, who also have chronic bronchitis, and continue to have frequent exacerbations, as an add-on LABA / LAMA / ICS.

Other possible treatments options used as either monotherapy or as add-on to first line or alternative treatment options for the management of patients with GOLD stage C and D, include:[1]

- Mucolytic, which may be beneficial for patients with chronic cough productive of sputum (GOLD stage D only)
- SABA and / or SAMA
- Theophylline (if long-acting bronchodilators are unavailable or unaffordable).

There is some evidence that low doses of theophylline may reduce the risk of exacerbation,[1] raising the suggestion that it may be a suitable comparator for roflumilast. However, based on the current clinical practice in the UK and review of recent literature, theophylline is not considered to be an appropriate comparator to roflumilast as an add-on treatment for patients with severe COPD, symptoms of chronic bronchitis and frequent exacerbations (≥2 / year) who remain uncontrolled on LABA / LAMA / ICS.

Theophylline use in the UK is low, especially as an add-on to triple therapy, with only 4.6% of patients experiencing frequent exacerbations (≥ 2 / year) receiving LABA / LAMA / ICS / theophylline.[12] Consequently theophylline is not considered to be part of standard of care and is therefore not an appropriate comparator.

In addition, there is no evidence on the use of theophylline as add-on to triple therapy and its impact on exacerbation rates in patients with severe COPD and frequent exacerbations. The theophylline study most relevant to the decision problem is a pilot clinical trial, in which patients with severe COPD were treated with oral low-dose theophylline added to ICS+LABA. In this placebo-controlled study theophylline failed to prevent exacerbations.[16] In fact, there was a trend (not statistically significant) of exacerbations being more frequent in the intervention group.

In addition to the lack of observed benefit in the target patient group, theophylline has been associated with a wide range of serious treatment-limiting side-effects, including seizures and cardiac arrhythmias.[1] Theophylline is difficult to use from a clinical perspective due its narrow therapeutic index, large number of drug–drug interactions, and prolonged half-life in certain populations (including the elderly).[1 22] These properties result in a requirement to monitor plasma theophylline levels when higher dosages are prescribed or when co-administered with a medication that reduces theophylline clearance.[53] These challenges are reflected in the GOLD guidelines which recommend that theophylline is considered only if long-acting bronchodialtors are not available or affordable.[1]

In light of the above, theophylline has been excluded from the decision problem as a comparator to roflumilast.

During the scoping process of the submission, other potential comparators to roflumilast were considered, including monotherapy and dual therapy (e.g. LAMA, LABA, LABA / LAMA, LABA / ICS). However, as this submission is only seeking a recommendation for the use of roflumilast as add-on to triple therapy, these comparators are out of scope, and thus not considered further.

3.3 Life expectancy, prevalence and incidence

No UK specific data were found on the life expectancy or epidemiology of people with severe COPD (FEV_1 < 50%) and chronic bronchitis experiencing frequent exacerbations while being treated with LABA / LAMA / ICS. However,

data on broader populations, presented below, provide some valuable insights.

Life expectancy and mortality

COPD is a major cause of mortality in the UK. In 2012, 29,776 people died from COPD in the UK; 5.3% of the total number deaths.[54] The UK mortality rate attributable to COPD is 58.14 per 100,000 person years.[55]

In assessing life expectancy according to disease severity, mortality models (created using the Third National Health and Nutrition Examination survey data) estimated > 5-year reduction in male life expectancy at 65 years of age in patients with severe / very severe COPD who were current or former smokers (Table 5).[34]

Table 5: Estimated reductions in life expectancy due to COPD in males 65 years of age.[34]

COPD disease severity*	**Estimated reduction in life expectancy (years) in patients with COPD vs those without COPD**		
	Current smokers‡	Former smokers	Never previously smoked
Stage 1: $FEV_1 \geq 80\%$ predicted	0.3	Not reported	Not reported
Stage 2: $50\% \leq FEV_1 < 80\%$ predicted	2.2	1.4	0.7
Stage 3 or 4† $30\% \leq FEV_1 < 50\%$ predicted	5.8	5.6	1.3

*COPD: FEV_1 / FVC < 70%, With or without chronic symptoms
†Stage 4 disease severity as defined in Shavelle 2009; note GOLD defines stage 4 severity as FEV_1 < 30% predicted
‡In addition to the 3.5 years lost due to smoking

These data provide an insight into reduced life expectancy of patients with severe / very severe COPD. However, the target population addressed in this submission incorporates a population with greater disease severity – namely those with FEV_1 < 50% predicted who are already on triple therapy (LABA / LAMA / ICS) with chronic bronchitis and frequent exacerbations, and therefore the impact on life expectancy may be greater. As discussed in Section 3.2, patients with frequent exacerbations have a greater mortality risk than those without frequent exacerbations.[8] A UK-wide audit of secondary care patients admitted to hospital with COPD exacerbations, conducted in 2008, reported inpatient and 90-day mortality rates of 7.7% and 14.0% respectively.[39] In addition, a Spanish study of survival following hospital admission for exacerbations reported in-hospital mortality rates of 11% and 1-year mortality rates of 43%.[40]

Prevalence and incidence

The British Lung Foundation estimates that 1.2 million people in the UK are living with diagnosed COPD;[54] this is expected to increase because of the aging population.

A recent UK study reported the overall prevalence of COPD as 33.6 (95% CI: 33.1–33.6) per 1,000 person-years (standardised for age and sex) in people ≥40 years of age.[52]. This study, which characterised a prevalent 2013 COPD cohort of 49,286 patients (≥ 40 years), found that a third of UK COPD patients had the most severe forms of the disease with GOLD C / D prevalence rates of 11.1 (95% CI: 10.9–11.2) per 1,000 person-years (standardised for age and sex). Further granular analysis found that 21.4% of COPD patients had FEV_1 of 30–50% and 4.2% had FEV_1 < 30%.[52] Analysis also showed that 25.5% of the UK COPD 2013 cohort had ≥ 2 exacerbations in the 12 months prior to the prevalence point, and that 28.6% of patients received treatment with LABA / LAMA / ICS.

Other UK epidemiological studies have reported GOLD C and D crude prevalence rates of 0.3% and 0.4% respectively (with an overall COPD prevalence rate of 1.7%)[56] and very severe prevalence rates of 0.3% (with overall COPD prevalence rate of 3.6%).[57] Another UK study conducted in 2010 reported a slightly higher prevalence of 1.7% (95% CI: 1.3–2.0) for severe / very severe COPD in people >40 years of age.[58]

3.4 Clinical guidance and guidelines

NICE clinical guideline 101 (published 2010),[2] 'Chronic obstructive pulmonary disease in over 16s: diagnosis and management', provides guidance on the management of COPD. However as mentioned in Section 3.2, this NICE guideline is currently undergoing an update and therefore more recent guidelines, namely the GOLD 2016 guideline, takes precedence in clinical practice.[1 5 112]

Within current NICE guidance (TA 244), roflumilast is recommended for use in the context of research as part of clinical trials in severe COPD (FEV_1 < 50% predicted) associated with chronic bronchitis, and with a history of frequent exacerbations, as add-on to bronchodilator treatment.[13] The objective of this recommendation was to enable the generation of robust evidence on the use of roflumilast as an add-on to LABA / LAMA / ICS therapy (or LAMA / LABA in those people who are intolerant to ICS).

Global guidelines

Global guidelines on COPD advise minimising the risk of disease progression through steps such as smoking cessation, vaccination, physical activity and rehabilitation.[1] These guidelines also highlight that pharmacological treatment can reduce COPD symptoms, reduce the frequency and severity of exacerbations and improve health status and exercise tolerance.[1]

GOLD guidelines classify COPD disease severity (A–D) based on symptoms, exacerbation history and airway limitation. The patient population for which roflumilast use is being reviewed as part of this appraisal falls within GOLD C and D disease severity categories. GOLD pharmacological treatment guidelines for the management of patients with stable COPD are summarised in Table 6. Of note, a PDE4 inhibitor (i.e. roflumilast) in combination with other therapies is recommended as an alternative treatment choice in patients with GOLD severity C and D.[1]

In brief, according to latest GOLD guidelines, the recommended treatment for patients in group C (few symptoms but a high risk of exacerbations) is either a fixed combination of ICS plus a LABA, or a LAMA. As a second choice, a combination of LABA and LAMA is recommended. If the patient has chronic bronchitis, then the addition of a PDE4 inhibitor (roflumilast) to one long-acting bronchodilator could be considered to reduce exacerbations. For patients in group D (many symptoms and high risk, based on either severe airflow limitation or frequent exacerbations), the first-choice medication is LABA / ICS, LAMA or LABA / LAMA / ICS. Second-choice options include LABA / LAMA / ICS triple therapy or, if the patient has chronic bronchitis, the addition of a PDE4 inhibitor to either LABA / ICS or LAMA.

Local UK guidelines

There are subtle variations between local UK guidelines. However, they are in general, aligned with the NICE clinical guideline 101 and GOLD 2016 guideline.[59-66]

Table 6: GOLD 2016 guidelines on initial pharmacologic management of COPD.[1]

Patient group (GOLD category)	**Recommended First choice***	**Alternative choice***	**Other possible treatments*** (used alone or in combinations with other options in recommended first choice and alternative choice columns)
A	SABA as required **or** SAMA as required	LABA **or** LAMA **or** SABA + SAMA	Theophylline†
B	LABA **or** LAMA	LAMA / LABA	SABA **and / or** SAMA as required Theophylline†
C	ICS / LABA **or** LAMA	LABA / LAMA **or** LABA / PDE4 inhibitor **or** LAMA / PDE4 inhibitor	SABA **and / or** SAMA as required Theophylline†
D	ICS / LABA **and / or** LAMA	ICS / LABA / LAMA **or** ICS / LABA / PDE4 inhibitor **or** LABA / LAMA **or** LAMA / PDE4 inhibitor	Carbocysteine N-acetycysteine SABA **and / or** SAMA as required Theophylline†

ICS, inhaled corticosteroid; LAMA, long-acting muscarinic antagonist ; LABA, long-acting beta2-agonist; PDE, phosphodiesterase; SAMA, short-acting muscarinic antagonist; SABA, short-acting beta2-agonist

* Medications are listed in alphabetical order, and therefore not necessarily in order of preference. † GOLD guidelines state theophylline can be used if long-acting inhaled bronchodilators are unavailable or unaffordable

Note: actual guidelines use the terminology ‘anticholinergic’ in place of ‘muscarinic antagonists’.’.

3.5 Issues relating to clinical practice

Based on a review of available local UK treatment guidelines, current clinical practice in the management of COPD is considered to be well-established. There are only very subtle variations between local UK guidelines.[59-65]These minor differences are not believed to be significant issues in current clinical practice.

All guidelines identified recommend triple therapy, LABA / LAMA / ICS as a treatment option for those patients with severe disease (FEV_1 < 50% predicted or GOLD sages C or D) and frequent exacerbations. However there is negligible information on the management of those patients who continue to have frequent exacerbations despite triple therapy. As discussed in Sections 3.2 and 3.3, although exact figures are not known, it can be inferred that there is a substantial proportion of patients who fall into this category, representing a high unmet need. A recommendation on the use of roflumilast as an add-on to triple therapy in patients with FEV_1 < 50% predicted, chronic bronchitis and frequent exacerbations (≥ 2 / year) would have substantial clinical impact and provide an additional treatment option for a proportion of the severe COPD population.

3.6 Assessment of equality issues

Not applicable.

4 Clinical effectiveness

Section summary

- The REACT trial provides the core clinical evidence for this submission
- The REACT trial is a RCT that investigated the impact of roflumilast compared with placebo on the rate of moderate to severe exacerbations as add-on to LABA / ICS ± LAMA in patients with FEV1< 50%, chronic bronchitis and ≥ 2 exacerbations in the previous year.
- The trial protocol closely reflected clinical practice in the UK, as well as the proposed positioning of roflumilast and target patient population under appraisal.
- The REACT dataset most relevant to the decision problem is the PP analysis of the pre-specified subgroup 'concomitant treatment with LAMA'. This study subgroup population included only those patients fulfilling the criteria of the target population under appraisal. Of those patients randomised to roflumilast, and placebo, 16.8% and 15.3% respectively had ≥ 1 major protocol deviation
- In the PP analysis, the addition of roflumilast to LABA / LAMA / ICS, significantly reduced the rate of moderate to severe exacerbations by 20.1% (roflumilast 0.858 vs placebo 1.075; RR 0.799 [95% CI: 0.670–0.952]; p=0.0122) and by 34.1% (roflumilast 0.260 vs placebo 0.395; RR 0.659 [95% CI: 0.497–0.872] p=0.0035) for severe exacerbations.
- The most common adverse events associated with roflumilast treatment reported in the REACT trial were diarrhoea (10% vs 4% in the placebo arm), weight decrease (9% vs 3% in the placebo arm) and nausea (6% vs 2% in the placebo arm).

4.1 Identification and selection of relevant studies

A systematic review was carried out to identify RCTs of roflumilast as an add-on to triple therapy (LABA / LAMA / ICS) in patients with severe / very severe COPD, as defined in the pre-2013 GOLD report as stages 3 and 4.

Search strategy

Searches were conducted on the 18th July 2016 in MEDLINE®, MEDLINE® Epub ahead of print and In-process, EMBASE (all OVID SP) and the Cochrane Central Register of Controlled Trials (CENTRAL). Search strategies combined free text and controlled vocabulary terms (Medical Subject Headings [MeSH] in MEDLINE and CENTRAL and EMTREE terms in EMBASE) for the disease and the comparators of interest. Designated filters to identify RCTs, as well as severity filters to target the search to patients with severe / very severe COPD, were used in MEDLINE and EMBASE search strategies. The searches were not limited by language, country or by year.

To identify unpublished literature, conference abstracts that were presented in the last 2 years were searched in five conference proceedings: American College of Chest Physicians (CHEST) World congress 2014 and 2016, CHEST annual meeting 2014 and 2015, American Thoracic Society (ATS) international conference 20145 and 2016, British Thoracic Society (BTS) winter meeting 2014 and 2015, and European Respiratory Society (ERS) annual congress 2014 and 2015.

Search strategies are provided in Appendix 4.

Abstracts and full papers were screened independently by two reviewers against the eligibility criteria presented in Table 7.

Study selection

Eligibility criteria are specified in terms of population, intervention,

comparators, outcomes and study design (PICOS) in Table 7. Studies were not excluded by outcomes until the full paper review stage.

As discussed in Section 3.3, theophylline is not considered to be an appropriate comparator and therefore has been excluded from the eligibility criteria used in the review.

Table 7: Eligibility criteria used in the review

Patients	Patients with severe / very severe COPD (defined as FEV_1 < 50% predicted level, corresponding to pre-2013 GOLD report stages III and IV)
Interventions	Roflumilast given as add-on to triple therapy
Comparators	LABA / LAMA / ICS
Outcomes	Annual rate of exacerbations Patients with ≥ 1 moderate / severe exacerbations Number of exacerbations requiring corticosteroids Time to first exacerbation Pre-bronchodilator FEV_1 mL mean change from baseline Post-bronchodilator FEV_1 mean change from baseline Mortality Quality of life Adverse events, and safety endpoints
Study design	RCTs Of at least 24 weeks (6 months) duration
Language restrictions	No language restriction

4.2 List of relevant randomised controlled trials

As defined in the search criteria, trials investigating the effect of roflumilast in combination with triple therapy (LABA / LAMA / ICS) in patients with severe COPD (FEV_1 < 50% predicted) were assessed for relevance. The systematic review searches identified two trials that were within the search criteria for the intervention roflumilast in combination with triple therapy:

1. The REACT trial (described below), which was published as a full paper by Martinez et al. in 2015.[14]
2. A randomised, open-controlled study of 108 patients. The systematic review identified this trial by a conference abstract presented by Sadigov and Huseynova at the 2015 American Thoracic Society

International Conference. The trial authors were contacted to obtain further information but no response was received and therefore this trial is not discussed further.

During the review, early results of the RE^{2}SPOND trial also became available and is described below.

Table 8: List of identified RCTs

Trial acronym (number)	Population	Intervention	Comparator	Primary study reference
REACT (RO-2455-404-RD; NCT01329029)	1. FEV_1 < 50% 2. Symptoms of chronic bronchitis 3. History of ≥ 2 exacerbations in previous year	Roflumilast + LABA + ICS ± LAMA	Placebo + LABA + ICS ± LAMA	Martinez 2015[14]
RE^{2}SPOND (ROF-MD-07 NCT01443845)	1. FEV_1 < 50% 2. Symptoms of chronic bronchitis 3. History of ≥ 2 exacerbations and / or hospitalisations in previous year	Roflumilast + LABA + ICS ± LAMA	Placebo + LABA + ICS ± LAMA	Rennard 2016 (design)[67] Martinez 2016 (results)[15]

REACT was a double-blind, RCT conducted in the EU (including the UK), Australia, Brazil, Canada, Israel, Republic of Korea, South Africa and Turkey. Key inclusion criteria were FEV_1 < 50%, chronic bronchitis and ≥ 2 exacerbations in the previous year. Patients were randomised to receive either roflumilast or placebo as add-on to LABA / ICS ± LAMA; 70% and 69% of patients in each treatment arm received concomitant LAMA, respectively. Concomitant treatment with LAMA was a pre-specified subgroup for analysis.[14] The REACT study is therefore considered relevant for this submission and is discussed in further detail below.

RE^{2}SPOND was a double-blind, RCT conducted in the US, Argentina, Canada, Chile, Colombia, Italy, Malaysia, Mexico, Peru Philippines Romania,

Russia, Serbia, Spain, Taiwan, Thailand and Ukraine. Like REACT, patients were randomised to receive either roflumilast or placebo as add-on to LABA / ICS ± LAMA. Key inclusion criteria were FEV_1 < 50%, chronic bronchitis and ≥ 2 exacerbations and / or hospitalisations in the previous year.[67]

REACT and RE^{2}SPOND could both be seen as relevant studies for the decision problem. However due to a number of trial limitations and issues with trial design (explained below) RE^{2}SPOND is not representative of clinical practice in the UK. It is therefore considered not appropriate for inclusion in the evidence base in the appraisal of roflumilast as add-on to triple therapy (LABA / LAMA / ICS) for patients in the UK and is not presented in detail in this submission.

RE^{2}SPOND trial limitations and issues with trial design:

1. **The protocol stipulated LABA / ICS dosing according to FDA licence.** The REACT study permitted the maximum EMA-approved, and therefore the maximum UK-approved, dose of fluticasone / salmeterol (fluticasone / salmeterol 500 / 50 µg [1 inhalation twice daily]), whereas the maximum dose of LABA / ICS permitted in the RE^{2}SPOND study was based on the lower maximum FDA-approved (fluticasone / salmeterol 250 / 50 µg [1 inhalation twice daily]).[15]. Consequently, background therapy in the RE^{2}SPOND study was not aligned with UK clinical practice.

2. **A low proportion of patients were on triple therapy.** Only 47% of patients in each treatment arm were on LAMA therapy.

3. **Inclusion criteria specified ICS / LABA therapy for a minimum of 3 months prior to entry into the study.** RE^{2}SPOND inclusion criteria specified dual ICS / LABA therapy for a minimum of 3 months prior to inclusion into the trial (compared with 12 months for REACT). Therefore the RE^{2}SPOND trial population does not reflect the target patient population of the decision problem (i.e. patients uncontrolled on ICS / LABA+LAMA therapy, who continue to have frequent exacerbations).

4. **Low proportion of Western European patients.** The RE^{2}SPOND study recruited only one patient from Italy and 12 from Spain (RE^{2}SPOND CSR, data on file). There were no patients recruited from the UK or other Western European countries.

5. **Formulation used in RE^{2}SPOND is not approved for use in the UK.** The RE^{2}SPOND trial used a US FDA-approved non-film coated tablet whereas the REACT trial used the EMA-approved enteric film coated tablet.[15] Although bioequivalence studies have been conducted, these studies have not been recognised by the FDA.

RE^{2}SPOND is therefore not considered appropriate for the assessment of roflumilast as add-on to triple therapy in UK patients with severe COPD, chronic bronchitis and frequent exacerbations:

- The patient profile of the RE^{2}SPOND population does not reflect accurately that of the target population in this decision problem (i.e. inclusion criteria prevented demonstration that patients were uncontrolled on ICS / LABA ± LAMA, proportion of patients on triple therapy was relatively low, a very small proportion of the study population were from Western Europe)

- The RE^{2}SPOND trial conditions do not reflect UK clinical practice (i.e. lower LABA / ICS dosing, different tablet formulation)

To conclude, REACT is the most relevant trial to the decision problem and as such is presented as the primary trial in this submission.

4.3 Summary of methodology of the relevant randomised controlled trials

This section focuses on the REACT study which has been identified as the sole RCT relevant to the decision problem.

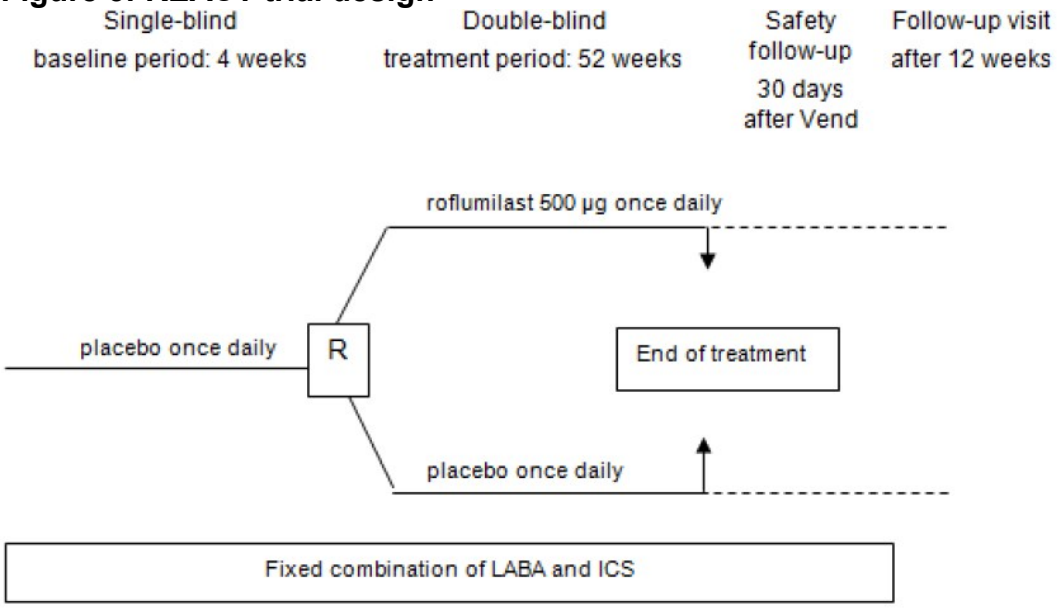
Trial design

REACT (NCT01329029) was a 1-year double-blind, placebo controlled, parallel group phase 3 / 4 trial. Patients (n=1,945) with severe COPD (FEV_1 < 50% predicted) with symptoms of chronic bronchitis and ≥ 2 exacerbations in the previous year were randomly assigned in a 1:1 ratio to either roflumilast or placebo. Detailed inclusion and exclusion criteria are described below. Study drug was added to a background of LABA / ICS fixed combination; tiotropium (LAMA) was also permitted.

Patients were assigned to study drugs in a 1:1 ratio with a block size of 4 by a computerised central randomisation system, the Interactive Voice Response System-Interactive Web Response System. Both patients and investigators were masked to treatment assignment.

The trial schema is illustrated in Figure 3. Briefly, the trial consisted of a 4-week, single-blind baseline period during which patients received placebo. Visits were at weeks –4, –2 (optional) and 0. This was followed by a 52-week double-blind treatment period during which patients received either roflumilast or placebo. Visits were at Week 4, 12, 20, 28, 40 and 52. After the treatment phase, there was a 12-week follow-up period with a final visit at week 64. For those patients who were experiencing an adverse event at the end of the double-blind treatment phase (i.e. when they stopped study drug treatment) there was also safety follow-up at 30 days.

Figure 3: REACT trial design



R; Randomisation, Vend; end of treatment period

Eligibility criteria

Inclusion criteria were:

- history of COPD (according to GOLD 2009 for at least 12 months prior to baseline) associated with symptoms of chronic bronchitis (chronic product cough for 3 months in each of the 2 years prior to baseline)
- post-bronchodilator FEV_1 / FVC ratio < 0·70
- post-bronchodilator FEV_1 of ≤ 50% predicted
- age ≥ 40 years
- smoking history ≥ 20 pack-years
- history of ≥ 2 moderate or severe exacerbations (separated by at least 10 days) in the previous year. Moderate exacerbations were defined as requiring oral or parenteral glucocorticosteroids, and severe as requiring hospitalisation and / or leading to death
- pre-treatment with inhaled ICS and LABA combination for at least 12 months before baseline; and at a constant dose (the maximum

approved dose of the combination) as a fixed combination in the 3 months prior to baseline

- placebo tablet compliance of 80–125% during the 4-week baseline observation period
- total cough and sputum score of ≥ 14 (sum of daily scores on 4-point scales for cough and sputum) during the week preceding the randomisation visit.

Exclusion criteria that would affect read-out parameters of the trial included:

- COPD exacerbation that was ongoing during the baseline period
- lower respiratory tract infection that was not resolved 4 weeks prior to baseline
- diagnosis of asthma or other major lung disease
- participation in a pulmonary rehabilitation program or completion of a program within 3 months preceding the baseline.

A full list of inclusion and exclusion criteria are given in Appendix 4.

Settings and locations where the data were collected

The trial was carried out in 21 countries, including: the UK, Australia, Austria, Belgium, Brazil, Canada, Denmark, France, Germany, Greece, Hungary, Israel, Italy, Republic of Korea, Netherlands, Poland, Russia, Slovak Republic, South Africa, Spain, and Turkey. The UK recruited 107 patients, of which 51 were randomised (22 to roflumilast and 29 to placebo).

Patients were recruited from secondary care (outpatient clinics, hospitals, specialised pulmonologists) and primary care (family doctors / general practitioners).

Trial drugs and concomitant medications

Patients received either roflumilast (500 µg) or placebo once daily. Both roflumilast and placebo were supplied as identical yellow triangular tablets. There was no dose titration and the protocol did not permit dose adjustments. In addition to the study drug, all patients continued with a fixed-dose LABA / ICS combination, at the maximum approved dosage. Patients who were already taking an inhaled LAMA (tiotropium bromide) prior to the start of the trial were allowed to continue this treatment.

If a patient had an exacerbation during the study that required additional treatment, they could receive 40 mg prednisolone / day, administered systemically for 7–14 days. Additional antibiotic therapy was allowed in cases of purulent sputum or suspected bacterial infection.

The following treatments were not permitted during the study: oral and parenteral glucocorticosteroids (except to treat acute exacerbations), LABA or ICS monotherapy, short-acting muscarinic antagonists, and any short-acting β2 agonists (with the exception of salbutamol) or oral β2 agonists.

Primary and secondary outcomes

The primary endpoint was the rate of moderate or severe COPD exacerbations per patient per year. This endpoint is central to the decision problem and appraisal. Moderate exacerbations were defined as requiring oral or parenteral glucocorticosteroids and severe exacerbations as requiring hospitalisations and / or leading to death.

Key secondary endpoints were: change in post-bronchodilator FEV_1 over the 52-week treatment period and the rate of severe COPD exacerbations per patient per year.

A complete list of endpoints is given in Table 9.

Table 9: All primary and secondary endpoints

Primary endpoint:

- Rate of moderate or severe COPD exacerbations per patient per year. Moderate exacerbations are defined as requiring oral or parenteral glucocorticosteroids and severe as requiring hospitalisation and / or leading to death

Key-secondary endpoints:

- Change from randomisation (V2) over 52 weeks of treatment in post-bronchodilator FEV_1 [L]
- Rate of severe COPD exacerbations per patient per year

Other secondary endpoints:

COPD exacerbations

The COPD categories analysed include: mild; moderate; severe; moderate or severe; mild, moderate or severe; COPD exacerbations treated with systemic glucocorticosteroids and / or antibiotics; COPD exacerbations treated with antibiotics only; moderate or severe and / or treated with antibiotics and case report form COPD exacerbations. The following endpoints will be evaluated:

- Rate of COPD exacerbations per patient per year (all categories except 'moderate or severe', which is done in the primary endpoint and mild, treated with antibiotics only)
- Proportion of patients experiencing a COPD exacerbation (all categories except mild, treated with antibiotics only)
- Time to first COPD exacerbation (all categories except mild, treated with antibiotics only)
- Number of COPD exacerbation days (all categories)
- Duration of COPD exacerbations (all categories)
- Time to second COPD exacerbation of moderate or severe COPD exacerbations
- Time to third COPD exacerbation of moderate or severe COPD exacerbations
- Number needed to treat to avoid one 'moderate or severe' COPD exacerbation
- Frequency of COPD exacerbations (all categories)

Lung function endpoints (post-bronchodilator)

Change from randomisation (V2) over 52 weeks of treatment for:

- FVC [L]
- Forced expiratory flow at 25% to 75% of vital capacity (FEF25-75% [L / s])
- Forced expiratory volume in the first 6 seconds (FEV_6 [L])
- FEV_1 / FVC [%]

Diary endpoints

- Use of rescue medication (change from randomisation [W0 = last week prior to randomisation] over 52 weeks of treatment)
- COPD symptom scores: score sum, cough, sputum (change from randomisation [W0] over 52 weeks of treatment)
- Proportion of symptom-free days
- Proportion of rescue medication-free days

Quality of life

- COPD Assessment Test (change from randomisation [V2] over 52 weeks of treatment)

Mortality

- Time to mortality due to any cause
- Time to mortality due to a COPD exacerbation

MACE

Major adverse cardiovascular events, a composite endpoint including cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke, will be evaluated according to criteria pre-defined by a MACE Adjudication Committee. The following will be evaluated:

- Number and proportion of patients with MACE
- Number and proportion of patients with each individual component of MACE
- Time to first MACE and time to first occurrence of each individual component of

MACE
Time to trial withdrawal • Time to withdrawal during the treatment period • Time to withdrawal due to a COPD exacerbation during the treatment period • Time to trial withdrawal due to an adverse event during the treatment period
Pharmacokinetics and pharmacodynamics: • Pharmacokinetic profiles of roflumilast and roflumilast N-oxide • Individual and population pharmacokinetic parameters for roflumilast, roflumilast N-oxide and 'tPDE4i', including covariate effects • The relationship between the pharmacokinetic profiles or pharmacokinetic parameters and relevant safety and efficacy parameters
Safety: • Adverse events • Changes in laboratory values • Changes in vital signs including blood pressure and heart rate • Changes in physical examination findings including electrocardiograms • Changes in body weight and body mass index

COPD, chronic obstructive pulmonary disease; FEF, forced expiratory flow; FEV_1, forced expiratory volume in 1 second; FEV_6, forced expiratory volume in 6 seconds; MACE, major adverse cardiovascular event; tPDE4i, total PDE4 inhibition

The REACT trial design is summarised in Table 10.

Table 10: Overview of the REACT trial design

Trial number (acronym)	REACT
Location	Australia Austria, Belgium, Brazil, Canada, Denmark, France, Germany, Greece, Hungary, Israel, Italy, Republic of Korea, Netherlands, Poland, Russia, Slovak Republic, South Africa, Spain, Turkey, and the UK
Trial design	1-year double-blind, placebo controlled, parallel group phase 3-4 trial, comprising a 4-week baseline period, 52-week double-blind treatment period, and a 12-week follow-up period.
Eligibility criteria for participants	Key inclusion criteria were: • history of COPD associated with symptoms of chronic bronchitis • post-bronchodilator FEV_1 / FVC ratio < 0·70 • post-bronchodilator FEV_1 of ≤ 50% predicted • age ≥ 40 years • smoking history ≥ 20 pack-years • 2 moderate or severe exacerbations (separated by at least 10 days) in the previous year • pre-treatment with inhaled ICS and LABA combination for at least 12 months before baseline; and at a fixed dose for 3 months prior to baseline
Settings and locations where the data were collected	The trial was carried out in 21 countries, including the UK. 105 patients were recruited in the UK, of which 55 were randomised
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) Intervention(s) Permitted and disallowed concomitant medication	Trial drugs were roflumilast (500 µg) or placebo, taken orally, once daily. Roflumilast n=969; placebo n=966 Permitted concomitant medication included LAMA. In addition, 40 mg prednisolone / day and antibiotic therapy were permitted to manage exacerbations and purulent sputum / suspected bacterial infection, respectively Disallowed concomitant medications included oral and parenteral glucocorticosteroids (except to treat acute exacerbations), LABA or ICS monotherapy, short-acting muscarinic antagonists, and any SABA (with the exception of salbutamol) or oral β2 agonists
Primary outcomes (including scoring methods and timings of assessments)	The primary endpoint was the rate of moderate or severe COPD exacerbations per patient per year. (Moderate exacerbations were defined as requiring oral or parenteral glucocorticosteroids and severe exacerbations as requiring hospitalisations and / or leading to death)
Secondary outcomes (including scoring methods and timings of assessments)	Key secondary endpoints were change in post-bronchodilator FEV_1 over the 52-week treatment period and the rate of severe COPD exacerbations per patient per year Other secondary endpoints included rate and time to exacerbations, post-bronchodilator lung function endpoints, COPD assessment test (specifically over the

	52-week treatment period), mortality, major adverse cardiovascular events, time to withdrawal, and pharmacokinetics / pharmacodynamics. Safety endpoints included adverse events, changes in vital signs, changes in physical examination, changes in bodyweight and body mass index
Pre-planned subgroups	There were 21 pre-planned subgroups, of which concomitant treatment with LAMA is considered to be relevant to this decision problem

COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting beta2 agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting beta2 agonist

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

The primary analysis of the REACT trial is summarised in Table 11 and is described in detail below.

Table 11: Summary of primary analysis for the REACT study

Hypothesis objective	**Statistical analysis**	**Sample size, power calculation**	**Data management, patient withdrawals**
Determine treatment difference between roflumilast and placebo on the rate of moderate or severe COPD exacerbations in patients of interest* and on LABA / ICS background therapy	ITT analyses using a Poisson regression model including correction for over dispersion (primary) and a negative binomial model to account for possible over dispersion in the Poisson regression model (pre-planned sensitivity)	967 patients / treatment arm, assuming rate of 1.25 moderate or severe exacerbations / year in placebo group and a 20% rate reduction with roflumilast, study power is 90% to detect treatment difference (with α of 0.05)	ITT included data up until a patient discontinued the trial Sensitivity analysis was also conducted to investigate the impact of premature withdrawal from the study

* with FEV1 <50%, symptoms of chronic bronchitis, ≧ 2 exacerbations in the previous year

REACT study: Hypothesis and Statistical tests

The null hypothesis for the primary analysis was that there is no difference between roflumilast and placebo with regard to the rate of moderate to severe COPD exacerbations in patients with FEV_1 < 50%, symptoms of chronic bronchitis, and ≥ 2 exacerbations in the previous year on LABA / ICS ± LAMA background therapy.

In line with the study hypothesis, the primary analysis of the REACT study looked at the impact of roflumilast on LABA / ICS ± LAMA background therapy. However, as this submission seeks recommendation for the use of roflumilast in combination with LABA / ICS+LAMA triple therapy, the critical population for this assessment is the pre-specified LABA / LAMA / ICS subgroup – this subgroup is discussed in detail in Section 4.8.

The primary endpoint was analysed using a Poisson regression model for comparability with previous studies, with an accompanying pre-specified negative binomial analysis. The rate of moderate to severe exacerbations was the dependant variable, with an offset variable for the natural logarithm of duration in the study. Treatment was included as an independent variable. The Poisson model assumes events are independent of each other. Therefore, a Pearson Chi-Square correction was applied in order to account for potential over dispersion resulting from lack of independence of the events and / or zero inflation. However as Keene et al. (2007)[68] explain and Suissa et a. (2006) illustrate,[69] in the Poisson regression model, estimates of treatment effect are unaffected by use of an over dispersion adjustment as only the estimates of standard error are increased. In contrast, the pre-specified negative binomial model assumes that individuals' exacerbations follow a Poisson process with an underlying rate that is distributed as a gamma distribution. Therefore, the alternative negative binominal analysis (which accounts for over dispersion) of the primary endpoint was included as pre-specified analysis for the full analysis dataset (intention to treat, ITT).

Secondary endpoints were analysed using the Poisson regression model and / or negative binomial regression model.

Primary analysis: trial population

The primary analysis for the primary outcome (and subgroup analyses) used the ITT analysis and a Poisson regression model. The ITT analysis assigned patients to the treatment group based on the study drug to which they were randomised and includes all:

- randomised patients who took at least 1 dose of study drug following randomisation

- data until a patient discontinued (prematurely or as scheduled) the trial.

A PP analysis of the primary endpoint was also pre-specified to assess the robustness of the results. This analysis included all patients without any major protocol deviations (Table 12) including patients terminating early (provided there were no major protocol violations).

Missing data: exacerbation events

The statistical analysis plan incorporated a detailed approach to handling missing data regarding exacerbations.

The trial collected start and end dates for exacerbations. Where the start date of an exacerbation was incomplete or missing, it was to be imputed as the end day –9 days. Incomplete or missing end dates were replaced by the start date +9 days. If both dates were missing, these were replaced by the start and end date of:

- the respective adverse event (in the case of a severe exacerbation)

- use of concomitant medication to treat the exacerbation (in the case of a moderate exacerbation).

The statistical plan incorporated a sensitivity analyses to investigate the impact of drop-out on primary and key secondary endpoints. Patients who discontinued treatment prematurely were to be contacted by telephone in order to establish the number of moderate to severe exacerbations since discontinuation. The statistical analysis plan stipulated that if exacerbation information could not be obtained via telephone contact for ≥ 10% of patients who prematurely discontinued, an additional analysis would be performed. In this case, for patients with missing information (regarding post drop-out exacerbations), the dependent variable was to be replaced with the number of exacerbations leading to hospitalisation (i.e. severe exacerbations) and / or

treated with systemic glucocorticosteroids (i.e. moderate exacerbations) in the previous year, and the time in trial was to be replaced as 1 year.

Sample size and study power

The REACT study protocol specified that 1,934 patients would be randomised into two treatment arms (967 patients / treatment arm). The sample size was determined based on the following assumptions:

- a rate of 1.25 moderate to severe COPD exacerbations per patient per year (primary endpoint) in the placebo group
- a 20% rate reduction in the roflumilast group (i.e. 1.00 moderate to severe exacerbations per year).

With the above assumptions, a sample size of 967 patients per treatment group was calculated to provide a 90% study power to detect a treatment difference for the primary endpoint with a two-sided significance level of 5% (using a Poisson regression model, corrected for over dispersion).

Subgroup analysis

Of the 12 subgroup analyses pre-specified in the statistical plan, concomitant treatment with LAMA is central to this submission. This submission seeks a recommendation for use of roflumilast as add-on therapy to LABA / LAMA / ICS, consequently the following clinical discussion and economic assessment focusses heavily on the LAMA subgroup.

As per the primary analysis, subgroup analyses of the primary endpoint used the ITT analysis and Poisson regression model. In addition, analyses using the PP study population and the negative binomial regression model have been conducted for the concomitant treatment with LAMA subgroup.

Analysis of secondary endpoints and multiple comparisons

The statistical analysis plan stipulated that if a statistically significant treatment difference was demonstrated for the primary endpoint, key secondary

endpoints were to be tested in a predefined order (as listed above in Section 4.3). If significant differences between treatments were not achieved for primary or key secondary outcomes, subsequent analyses were regarded as exploratory. Owing to this hierarchal approach to testing the primary and key secondary endpoints, no adjustment of the α (5% two-sided) was required.

4.5 Participant flow in the relevant randomised controlled trials

Participant flow

In the REACT trial a total of 2,712 patients were screened (Takeda; data on file 2015);[70] of these 2,708 were enrolled in the trial and 1,945 were randomised (973 to the roflumilast treatment arm and 972 to placebo).

Patient disposition is summarised in Figure 4. Reasons for non-randomisation included violation of inclusion criteria, met exclusion criteria, failure to meet randomisation criteria, or discontinuation during the baseline period for other reasons.

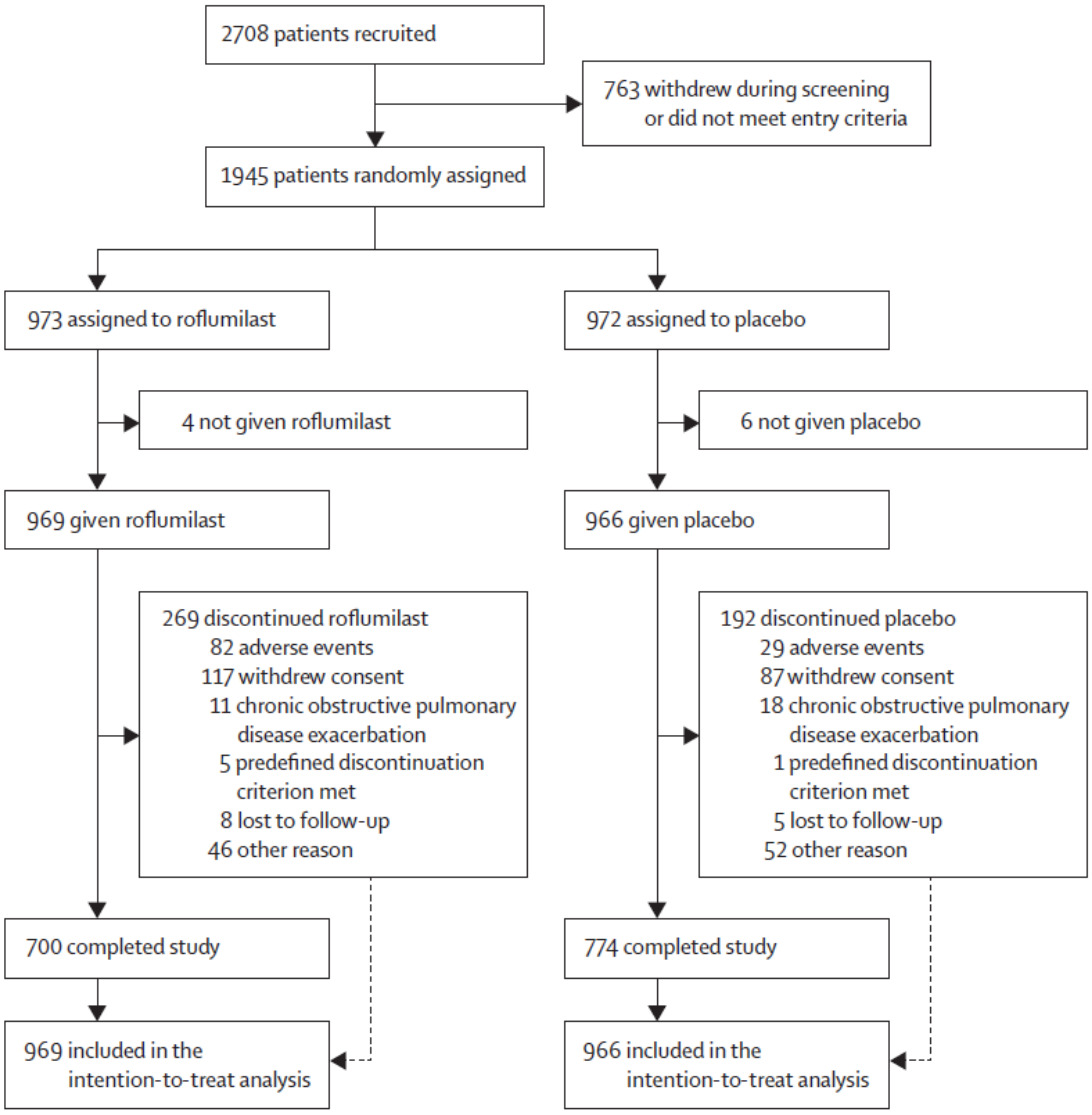
Of those patients who were randomised, 969 received at least 1 dose of roflumilast and 966 received at least 1 dose of placebo; these patients comprised the ITT study population. Ten patients did not receive any study medication; reasons for this included tablets dispensed at randomisation being returned on the same day, randomisation by mistake, and no drug dispensed at randomisation.

A total of 269 patients in the roflumilast treatment group and 192 patients in the placebo group discontinued prematurely. Reasons for discontinuation from the roflumilast group were: adverse events (82), withdrawal of consent (117), COPD exacerbation (11), lost to follow-up (8), predefined discontinuation criteria met (5), other (46). Reasons for discontinuation from the placebo group were: adverse events (29), withdrawal of consent (87), COPD exacerbation (18), lost to follow-up (5), predefined discontinuation criteria met (1), other (52).[14] Of 51 UK patients randomised to treatment (22 to roflumilast,

29 to placebo), 8 of the roflumilast patients and 12 of the placebo patients discontinued prematurely.

One patient was randomised to roflumilast but received placebo for the entire trial, and was therefore analysed in the placebo group for the safety analysis set.

Figure 4: Patient disposition of the REACT trial



Of the 1945 randomised patients, 163 in the roflumilast group and 149 in the placebo group had ≥ 1 major protocol deviation and were excluded from the PP analysis set. Major protocol deviations are listed in Table 12. The most

common protocol violation (57 patients in roflumilast group, 48 in the placebo group) was post-bronchodilator FEV_1 > 50% predicted at V0.

Table 12: Major protocol deviations (all randomised patients; Takeda data on file 2015)[70]

	Roflumilast (N=973) n (%)	Placebo (N=972) n (%)	Total (N=1945) n (%)
Number of patients with ≥ 1 major protocol deviation	163 (16.8)	149 (15.3)	312 (16.0)
Total number of major protocol deviations	203	188	391
Protocol deviation breakdown			
Postbronchodilator FEV_1 % predicted >50% at V0	57 (5.9)	48 (4.9)	105 (5.4)
Not pre-treated with LABA / ICS for at least 12 months prior to V0, or did not use a fixed combination of LABA / ICS on a constant daily dose throughout the trial	41 (4.2)	37 (3.8)	78 (4.0)
Total cough and sputum score < 14 during the last week prior to randomisation	30 (3.1)	31 (3.2)	61 (3.1)
Use of prohibited medication during the trial	21 (2.2)	15 (1.5)	36 (1.9)
Non-compliance during baseline period	8 (0.8)	16 (1.6)	24 (1.2)
Less than 2 documented moderate or severe COPD exacerbations within 1 year prior to V0	11 (1.1)	8 (0.8)	19 (1.0)
Issues with site noncompliance	8 (0.8)	9 (0.9)	17 (0.9)
Postbronchodilator FEV_1 / FVC > 70% at V0	7 (0.7)	3 (0.3)	10 (0.5)
Randomised but not treated	4 (0.4)	6 (0.6)	10 (0.5)
Premature unblinding	4 (0.4)	5 (0.5)	9 (0.5)
Misallocation resulting in at > 1 dose of incorrect treatment	4 (0.4)	0	0 4 (0.2)
Medical history of asthma and / or other relevant lung disease, or lower respiratory tract infection unresolved 4 weeks prior to V0	2 (0.2)	2 (0.2)	4 (0.2)
Smoking history < 20 pack years	2 (0.2)	2 (0.2)	4 (0.2)
Current participation in a pulmonary rehabilitation program or completion of a pulmonary rehabilitation program within 3 months preceding the baseline visit V0	2 (0.2)	1 (0.1)	3 (0.2)
Moderate or severe COPD exacerbation and / or a COPD exacerbation treated with antibiotics between visits V0 and V2	0	0 3 (0.3)	3 (0.2)
History of COPD less than 12 months	2 (0.2)	0	0 2 (0.1)
Randomised to placebo but received commercial DAXAS▼ during trial period	0	2 (0.2)	2 (0.1)

Percentages were based on the total number of patients in the treatment group.

This table includes patients who were deemed major protocol violators at the blinded data review meeting. n=number of patients with at least one event in the specified category. V0 = start of the single-blind baseline period

Patient characteristics

The participants were well matched at baseline between the two treatment groups. Baseline demographics are summarised in Table 13. Of particular relevance, the numbers of patients were receiving concomitant treatment with LAMA were similar in each treatment arm (roflumilast n=677, placebo n=669). Baseline characteristics of the PP population of the LABA / LAMA / ICS subgroup, which is of particular relevance to this submission, are summarised in Table 14.

Table 13: Baseline characteristics of participants in the REACT study in the ITT population[14]

Baseline characteristic	Roflumilast	Placebo
REACT (n=1,935)	50.1% (n= 969)	49.9% (n= 966)
Age, mean years (SD)	65 (8.4)	65 (8.4)
Male sex n (%)	718 (74%)	725 (75%)
Body-mass index, kg / m^2, mean (SD)	26.5 (5.47)	26.6 (5.36)
Cigarette pack-years, mean (SD)	48 (24.6)	48 (23.6)
Smoking status, n (%)		
Current smoker	411(42%)	432 (45%)
Former smoker	558 (58%)	534 (55%)
Pre-bronchodilator FEV_1, L mean (SD)	1.0 (0.31)	1.0 (0.32)
Post-bronchodilator FEV_1, L mean (SD)	1.1 (0.33)	1.1 (0.32)
% of predicted pre-bronchodilator FEV_1 %, mean (SD)	33.3 (9.08)	33.6 (9.00)
% of predicted post-bronchodilator FEV_1 %, mean (SD)	35.4 (9.25)	35.5 (8.76)
Post-bronchodilator FEV_1 / FVC % mean (SD)	40.2 (10.81)	40.1 (10.26)
COPD severity n (%)		
Mild	2 (<1%)	0
Moderate	18 (2%)	16 (2%)
Severe	658 (68%)	677 (70%)
Very severe	291 (30%)	273 (28%)
Concomitant treatment with LAMA* n (%)	677 (70%)	669 (69%)
CAT score mean (SD)	20.4 (7.22)	19.8 (6.88)
MRC score mean (SD)	2.2 (0.97)	2.1 (0.94)
No. exacerbations in the prior year† n (%)		
< 2 exacerbations	6 (<1%)	4 (<1%)
2 exacerbations	855 (88%)	859 (89%)
> 2 exacerbations	103 (11%)	100 (10%)
History of cardiovascular disease	414 (43%)	440 (46%)

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; LAMA, long-acting muscarinic antagonist; CAT, Chronic Obstructive Pulmonary Disease Assessment Test; MRC, Medical Research Council.

*Patients were classified as receiving concomitant treatment with LAMA if they used this therapy during baseline and at least 80% of the duration of the treatment period.

†Historical exacerbations were counted as the number of exacerbations in the past year that led to hospital admission and / or needed treatment with systemic glucocorticosteroids in the year before baseline visit; percentages do not add up to 100% in this section because of missing data

Table 14: Baseline characteristics of participants in the REACT study in the concomitant LAMA subgroup (LABA / LAMA / ICS) PP population[71]

Baseline characteristic	Roflumilast	Placebo
REACT (n= 1,122), n (%)	565 (50.4%)	557 (49.6%)
Age, n (%)		
≤ 65 years	296 (52.4%)	302 (54.2%)
➢ 65 years	269 (47.6%)	255 (45.8%)
Male sex n (%)	418 (74%)	418 (75%)
Body-mass index, n (%)		
< 18.5 kg / m^2	28 (5.0%)	26 (4.7%)
18.5 – < 25 kg / m^2	220 (38.9%)	195 (35.0%)
25 – < 30 kg / m^2	183 (32.4%)	194 (34.8%)
≥ 30 kg / m^2	134 (23.7%)	142 (25.5%)
Smoking status, n (%)		
Current smoker	224 (39.7%)	231 (41.5%)
Former smoker	341 (60.4%)	326 (58.5%)
Cigarette pack years		
<40	226 (40.0%)	214 (38.4%)
≥40	339 (60.0%)	343 (61.6%)
COPD severity n (%)		
Moderate (FEV_1 50 - < 80%)	3 (0.5%)	3(0.5%)
Severe (FEV_1 30 – < 50%)	380 (67.2%)	386 (69.3%)
Very severe (FEV_1 < 30%)	182 (32.2%)	168 (30.2%)
COPD severity group, n (%)		
GOLD C – high risk, less symptoms	37 (6.6%)	35 (6.3%)
GOLD D – high risk more symptoms	528 (93.5%)	522 (93.7%)
CAT total score n (%)		
< 10	37 (6.6%)	35 (6.3%)
≥ 10	528 (93.4)	522 (93.7%)
MRC score n (%)		
<2	124 (22%)	137 (24.6)
≥2	431 (76.3)	414 (74.3)
No. exacerbations in the prior year n (%)		
2 exacerbations	492 (87.1%)	489 (87.8%)
≥ 2 exacerbations	73 (12.9%)	68 (12.2%)
History of cardiovascular condition n (%)	264 (46.7%)	256 (46.0%)
History of ischaemic heart disease n (%)	15 (2.7%)	21 (3.8%)

4.6 Quality assessment of the relevant randomised controlled trials

The risk of bias assessment for the REACT trial is provided in Table 15. The REACT study has already undergone peer-review and has been published in the Lancet (Martinez 2015).[14]

Selection bias

Patients were randomised to treatment using a well-established computerised central randomisation system – the Interactive Voice Response System – Interactive Web Response System. Patients were randomised in a 1:1 ratio with a block size of 4. The risk of selection bias is therefore considered to be low.

Baseline characteristics (discussed in Section 4.5), which included markers of prognosis, were closely matched between the two patient groups. The percentage of patients with severe COPD was 68% in the roflumilast group and 70% in the placebo group and the proportion of patients with very severe COPD was 30% and 28% respectively. In addition, 88% of roflumilast patients and 89% of placebo patients had 2 exacerbations in the previous year, and 11% and 10% respectively had > 2 exacerbations.

Performance bias

The sponsor and investigators were unblinded during the single-blind baseline period. However, importantly, during the double-blind 52- week treatment phase all parties (patients, investigators and sponsor) were masked to treatment assignment until the end of follow-up. The blind was broken for 9 patients during the trial (Takeda 2015 data on file):[70]

- 4 patients were unblinded due to suspected unexpected adverse reactions
- 3 patients were unblinded due to investigator errors

- 1 patient was unblinded due to request from international ethics committee after the patient died due to cardiac arrest

- 1 patient was unblinded due to a severe elevation of transaminases value of unknown cause, which was later confirmed to be caused by biliary lithiasis which resulted in surgery.

Both placebo and roflumilast treatments were supplied as yellow triangular tablets.

Based on the above review the risk of performance bias is considered to be low.

Detection bias

Exacerbation rate was the primary outcome of interest. It was assumed that the rate of exacerbations would be 1.25 / year in the placebo group and 20% lower in the roflumilast group. Over the treatment period (52 weeks) it is considered very unlikely that investigators or patients would be able to determine treatment allocation, due to the relatively low number of estimated events over the study period. The risk of detection bias is therefore considered to be low.

Attrition bias

The specified primary analysis was an ITT population set and PP population analyses were included as sensitivity analyses. The ITT analysis is considered to be the most appropriate analysis by which to assess clinical effectiveness, as it more closely mirrors actual practice than PP analysis (which is a closer measure of efficacy). Methods for imputing missing data were clearly described in the clinical trial protocol.

There was no unexpected imbalance in drop-out rates between groups in the REACT study. Patient withdrawal rates were similar between the two treatment groups, although more patients withdrew in the 12 weeks of the double-blind treatment period in the roflumilast group compared with the

placebo group.[14] This finding is consistent with previous roflumilast studies, which demonstrated that adverse events associated with roflumilast are mostly transient and resolve with continued treatment.[72] To fully address the risk of attrition bias, a sensitivity analysis of the primary endpoint to drop-out was pre-specified in the statistical plan.

Based on the above review the risk of attrition bias is considered to be low.

Reporting bias

Study outcomes and analyses relevant to the decision problem, which are discussed in detail in subsequent sections (namely exacerbation rates in patients receiving LABA / ICS ± LAMA), were all pre-specified in the approved protocol. Therefore, the risk of reporting bias is considered to be low.

Table 15: Risk of bias assessment REACT trial publication

Question	**Yes / No / Not clear** **How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes. Randomisation was carried out by an IVRS web response system using computerised central randomisation system
Risk	Low
Was the concealment of treatment allocation adequate?	Yes. All parties masked to treatment assignment. Interactive voice response system-interactive web response system used and patients received identical tablets in both treatment and control group
Risk	Low
Were the groups similar at the outset of the study in terms of prognostic factors e.g. severity of disease?	Yes. No imbalances in baseline characteristics
Risk	Low
Blinding of care providers, participants and outcome assessors to treatment allocation?	Yes. Participants and care-givers blinded. Patients received identical pills
Risk	Low
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No. No large imbalances in patients lost to follow up
Risk	Low
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. No evidence to suggest more outcomes measured than reported
Risk	Low
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data	Not clear. An ITT analysis was conducted but no information is given on accounting for missing data
Risk	Unclear

Reflection of clinical practice

The design of the clinical trial closely reflects clinical practice in England and Wales of the management of patients with severe COPD (FEV_1 < 50% predicted), who remain breathless and continue to have exacerbations. Study participants were treated with a background therapy of the maximum UK approved LABA / ICS dose with / without LAMA. This background treatment closely reflects patient management as per GOLD, NICE and local guidelines as discussed in detail in Section 3.[2 59-61 63]

4.7 Clinical effectiveness results of the relevant randomised controlled trials

The REACT trial investigated a large number of endpoints. Primary and key secondary endpoints that are of particular relevance to the decision problem and appraisal are summarised in Table 16. Other secondary endpoints are summarised in Appendix 5.

As discussed in Section 4.4 the pre-specified primary analysis of the trial used the ITT population and a Poisson regression model to determine exacerbation rates in patients receiving roflumilast vs placebo as add-on to LABA / ICS ± LAMA. However this analysis is not the most appropriate or relevant for the decision problem, for the following reasons, and which are discussed in more detailed below:

- The Poisson regression model is not considered to be the most suitable approach for the analysis of exacerbation rates – the negative binomial model compared is more appropriate.[73]
- The ITT population does not accurately reflect the target population in the decision problem – the PP population is more appropriate
- This submission seeks a recommendation for the use of roflumilast as add-on to triple therapy therefore the pre-specified concomitant treatment therapy with LAMA subgroup (LABA / LAMA / ICS) is more relevant than the whole LABA / ICS ± LAMA trial population.

Each of these issues are discussed in more detail below.

- Poisson regression model vs negative binomial regression model

As discussed in Section 4.4, the Poisson regression model was originally selected as the primary analysis for consistency and comparability with pivotal roflumilast studies (Calverley 2009).[72] Unfortunately, due to a low event rate, the pre-specified Poisson regression model used in the primary analysis may not be the optimal model for the REACT study population. The sample size calculation assumed an event rate of 1.25 moderate to severe exacerbations per patient per year in the placebo group, with a 20% reduction in the roflumilast group (resulting in a rate of 1.00 exacerbation per patient per year with roflumilast), an over dispersion factor of 2 and a mean exposure time of 287 days. The correction for over dispersion and the mean exposure time were estimated from data of previous trials (BY217 / M2-124 and BY217 / M2-125 with roflumilast in a comparable setting. Using a Poisson regression model with a two-sided significance level of 5%, and the calculated sample size of 967 patients per treatment group, the study power amounted to 90%. However, the event rate observed was substantially lower (0.927 in the placebo group against an assumed rate of 1.25). This lower than assumed event rate reduced the study power from 90% to 79.7%.

As discussed in Section 4.4 the negative binomial regression model has some advantages over the Poisson model, as it uses a less simplistic assumption about variability from patient to patient than does the Poisson model. It allows a different exacerbation rate for each patient consistent with the fact that COPD patients differ in their tendency to exacerbate. Keene et al. (2008) re-analysed data from the TRISTAN and ISOLDE studies, and concluded that the negative binomial approach provides a better model for analysing exacerbation rates, making it the statistical method of choice.[68] In support of this, the negative binomial regression method has previously been used for the analysis of exacerbation rates in the TORCH study[74] and more recently, the WISDOM study.[75]

To conclude, the negative binomial regression model is considered to be more appropriate than the Poisson regression model for the analysis of REACT.

- ITT vs PP study population

The ITT population included randomised patients who took at least 1 dose of study drug following randomisation and incorporated all data until the patient discontinued (prematurely or as scheduled) the trial. The PP population, however, included only those patients without major protocol violations (note: patients who discontinued treatment were included in the PP population provided there were no major protocol violations). As shown in Table 12, the most common violations were that patients: (i) had post-bronchodilator $FEV_1 \geq 50\%$; (ii) had not been treated with ICS / LABA for the prior year; (iii) had a low cough and sputum score; and (iv) had fewer than 2 exacerbations in the prior year. All of these violations exclude these patients (16.0%) from meeting either the licence criteria for roflumilast and / or the decision problem criteria for this technology appraisal. Therefore AstraZeneca have restricted the population used in the cost effectiveness analysis and focussed subsequent clinical discussion to those in the PP population in keeping with the decision problem being assessed.

- LABA / ICS ± LAMA vs LABA / LAMA / ICS

As mentioned above this submission is seeking a recommendation on the use of roflumilast in combination with LABA / LAMA / ICS. Therefore, the pre-specified concomitant treatment with LAMA subgroup provides the most relevant data, compared with the whole study population which includes patients on dual and triple therapy. For completeness, data on the primary trial population, LABA / ICS ± LAMA is summarised below. The key clinical efficacy discussion on the LABA / LAMA / ICS subgroup is covered in Section 4.8. The cost effectiveness analysis is also restricted to the LABA / LAMA / ICS subgroup, in keeping with the decision problem being assessed.

Primary endpoint: moderate to severe exacerbations

In the primary ITT analysis LABA / ICS ± LAMA, using the Poisson model, the frequency of moderate to severe exacerbations was 13.2% lower in the roflumilast group compared with placebo (0.805 [95%CI: 0.72–0.895] vs 0.927 [95%CI: 0.843–1.020], RR 0.868 [95% CI: 0.753–1.002]) on a background of LABA / ICS ± LAMA. However, this difference narrowly missed statistical significance (p=0.0529). The ITT analysis using a negative binomial regression model revealed a statistically and clinically significant reduction of 14.2% in the rate of moderate to severe COPD exacerbations in patients treated with roflumilast vs placebo (0.823 [95% CI: 0.738–0915] vs 0.959 [95% CI: 0.867–1.061]; RR 0.858 [95% CI; 0.740–0.995], p=0.0424.

In the pre-specified PP analysis, a 19.4% statistically significant reduction was observed in moderate to severe exacerbation event rates, favouring roflumilast vs placebo as add-on to LABA / ICS ± LAMA (0.742 [95% CI: 0.659–0.836] vs 0.921 [95% CI: 0.831–1.021], RR 0.806 [95% CI: 0.688–0.943], p=0.0070, Poisson regression model) (Table 16).

Table 16: REACT: Primary and secondary endpoint data of relevance to the decision problem[14]

Analysis	**Roflumilast (ITT n=969, PP n=810)**	**Placebo ITT n=966, PP n=823)**	**Roflumilast vs placebo**
Primary endpoint: Moderate to severe COPD exacerbation rate (mean per patient year (95% CI); number of patients with ≥1 exacerbation			
Primary analysis: Poisson regression, ITT*	0.805 (0.724–0.895); n=380	0.927 (0.843–1.020); n=432	RR 0.868 (0.753–1.002), p=0.0529
Pre-specified analysis Poisson regression, PP* Negative binomial regression, ITT†	0.742 (0.659–0.836); n=310 0.823 (0.738–0917); n=380	0.921 (0.831–1.021); n=369 0.959 (0.867–1.061); n=432	RR 0.806 (0.688–0.943); p=0.0070 RR 0.858 (0.740–0.995) p=0.0424
Key secondary endpoint: severe COPD exacerbation rate (mean rate per patient year (95% CI); number of patients with ≥1 severe exacerbation.			
Negative binomial regression, ITT†	0.239 (0.201–0.283); n=151	0.315 (0.270–0.368); n=192	RR 0.757 (0.601–0.952) p=0.0175
Negative binomial regression, PP†	0.218 (0.180–0.264); n=120	0.326 (0.277–0.385); n=167	RR 0.668 (0.518–0.861) p=0.0018
Key secondary endpoint: Lung function, mean change from baseline to week 52; no. patients with data available			
Post-bronchodilator FEV_1, ITT, mL	52 (6.4); n=928	–4 (6.2); n=941	Difference 56 (38–73); p<0.0001
Post-bronchodilator FVC, ITT, mL	36 (11.4); n=928	–57 (11.1); n=941	Difference 92 (61–124); p<0.0001
Other secondary endpoints: exacerbation rate mean rate per patient year (95% CI); number of patients with at least one exacerbation			
Leading to hospital admission Negative binomial regression, ITT†	0.238 (0.200–0.283); n=150	0.313 (0.268–0.365); n=190	RR 0.761 (0.604–0.960); p=0.0209

PP, per protocol; RR, rate ratio; HR, hazard ratio; FEV_1. forced expiratory volume in 1 second; FVC, forced vital capacity; ITT, intention to treat; CAT, Chronic Obstructive Pulmonary Disease Assessment Test

Data in second and third columns are mean rate per patient per year (95% CI), median (IQR), or mean change (SE); data in final column are RR (95% CI), or mean difference (95% CI) and p values

*Estimated exacerbation rates based on a Poisson regression model including a correction for over dispersion

†Estimated exacerbation rates based on a negative binomial regression model excluding correction for over dispersion

Secondary endpoints

A key secondary endpoint of particular relevance to the decision problem is summarised in Table 16. Results for other secondary endpoints are summarised in Appendix 6.

A key secondary endpoint of particular relevance to the decision problem is the rate of severe exacerbations. Severe exacerbations were defined as exacerbations that required hospitalisation and / or lead to death. Due to the low event rate (and as per the statistical plan), this endpoint was analysed by negative binomial regression. In the PP analysis, the rate of severe exacerbations was significantly reduced by 33.2% in the roflumilast group compared with the placebo group on a background of LABA / ICS ± LAMA (Table 16).

Treatment with roflumilast was also associated with a significant improvement in post-bronchodilator FEV_1 and FVC (Table 16). The observed improvement in post-bronchodilator FEV_1, which equates to ~5% of the baseline value, was considered by investigators unlikely to have modified the patients' degree of breathlessness, but potentially to have contributed to the reduction in exacerbations.[14]

Results for other secondary endpoints are summarised in Appendix 6. Although not all secondary endpoints achieved statistical significance, there was a consistent trend that roflumilast reduced exacerbation rates and time to second and third moderate to severe exacerbations. These data compliment the primary analysis, and add further weight to the beneficial effects of roflumilast in this target patient group.

4.8 Subgroup analysis

This submission is seeking a recommendation for the use of roflumilast in combination with LABA / LAMA / ICS, to address an identified unmet need in the target patient group (patients with severe COPD, with chronic bronchitis

and frequent exacerbations, see Section 3.2). Consequently, the pre-specified 'concomitant treatment with LAMA' subgroup in the REACT trial, which provides data on the impact of roflumilast as add-on to LABA / LAMA / ICS, is critical for this assessment.

Over two-thirds of the REACT study population received concomitant treatment with LAMA in addition to LABA / ICS (677 / 969 [70%] in the roflumilast group and 669 / 966 [69%] in the placebo group). Analyses of the LABA / LAMA / ICS subgroup are summarised in Table 17.

As discussed in Section 4.7, the ITT population includes a substantial proportion of patients with protocol violations that excludes them from the target population for which the recommendation is sought. Therefore, in the context of this submission, AstraZeneca has identified the PP population to be more appropriate (than the ITT population) as it is more closely aligns with the target population defined in the decision problem. In the PP analysis (using the negative binomial regression model), compared with placebo, roflumilast as add-on to LABA / LAMA / ICS significantly reduced the rate of:[76]

- moderate to severe exacerbations by 20.1% (roflumilast 0.858 vs placebo 1.075; RR 0.799 [95% CI: 0.670–0.952]; p=0.0122)
- severe exacerbations by 34.1% (roflumilast 0.260 vs placebo 0.395; RR 0.659 [95% CI: 0.497–0.872]; p=0.0035).

To conclude, in the PP population, roflumilast as add-on therapy to LABA / LAMA / ICS significantly reduces the rate of moderate to severe exacerbations in patients with severe COPD, with symptoms of chronic bronchitis and a high frequency of exacerbations (≥ 2 in previous year). As this PP sub-group population is most relevant to the decision problem, the cost effectiveness analysis has been restricted to this dataset.

Table 17: Mean rate (95% CI) of COPD exacerbations per patient per year with concomitant LAMA treatment[14 76]

	Roflumilast **ITT: LABA / LAMA / ICS N=677;** **PP: LABA / LAMA / ICS N=565**	**Placebo** **ITT: LABA / LAMA / ICS N=669;** **PP: LABA / LAMA / ICS N=557**	**Roflumilast vs placebo**
Moderate to severe exacerbation			
ITT population, Poisson regression model	0.901 (0.799–1.016); n=286	1.023 (0.918–1.141); n=320	RR 0.881 (0.749–1.036); p=0.1252
PP population, negative binomial regression model	0.858 (0.754–0.978), n=235	1.075 (0.954–1.211) n= 271	RR 0.799 (0.670–0.952); p=0.0122
Severe exacerbation			
ITT population, negative binomial regression model	0.287 (0.237–0.347); n=125	0.374 (0.315–0.443); n=152	RR 0.767 (0.595–0.989); p=0.0406
PP population, negative binomial regression model	0.260 (0.21–0.322); n=99	0.395 (0.329–0.475); n =132	RR 0.659 (0.497–0.872); p=0.0035
Moderate exacerbation			
ITT population, negative binomial regression model	0.631 (0.550–0.725); n=212	0.676 (0.564–0.770); n=242	RR 0.934 (0.773–1.128); p=0.4775
PP population, negative binomial regression model	0.593 (0.511–0.689); n= 177	0.669 (0.582–0.769); n= 204	0.886 (0.722–1.087); p=0.2457

4.9 Meta-analysis

Not applicable.

4.10 Indirect and mixed treatment comparisons

Search strategy

A systematic review was carried out to identify RCTs of roflumilast or relevant comparators in combination with triple therapy in patients with severe / very severe COPD, as defined in the pre-2013 GOLD report as stages III and IV. Methods of the systematic review were as described in Section 4.1.

Study selection

Eligibility criteria are specified in terms of population, intervention, comparators, outcomes and study design (PICOS) in Table 18. Studies were not excluded by outcomes until the full paper review stage.

The systematic review for indirect and mixed treatment comparisons was conducted with a broader scope than the review for RCTs (see Section 4.1) to incorporate any and all potential comparators in the severe to very severe COPD population. They are included here for completeness; however the only comparator of relevance to this submission is LABA / LAMA / ICS. As discussed in Section 3.3 theophylline (a methylxanthine) is not considered to be an appropriate comparator.

Table 18: Eligibility criteria used in the systematic review

Population	Patients with severe / very severe COPD (defined as FEV_1 <50% predicted level, corresponding to pre-2013 GOLD report stages III and IV) (Include patients with emphysema or bronchitis. Exclude asthma patients)
Comparators / Interventions	Roflumilast given as add-on to triple therapy LABA / LAMA LABA / ICS LABA / LAMA / ICS LABA / ICS / Methylxanthines LABA / LAMA / Methylxanthines LABA / ICS / LAMA / Methylxanthines
Outcomes	Annual rate of exacerbations Patients with ≥1 moderate / severe exacerbations No. exacerbations requiring corticosteroids Time to first exacerbation Pre-bronchodilator FEV_1 mean change from baseline Post-bronchodilator FEV_1 mean change from baseline Mortality Quality of life Adverse events, and safety endpoints
Study design	RCTs [of at least 24 weeks (6 months) duration] (Pooled study designs to be included)
Language	No language limit

Identified trials

The PRISMA diagram, detailing the numbers of studies excluded at each stage of the review, is provided in Appendix 4.

Table 19: Trials identified by the systematic review

Study ID	Population FEV_1 % predicted	Treatments	Treatment type summary	Primary reference
Altaf 2016	<50%	Salmeterol / fluticasone	LABA / ICS	Altaf 2016[77]
		Formoterol / budesonide	LABA / ICS	
		Formoterol / fluticasone	LABA / ICS	
Calverley 2010	30%≤FEV_1 <50%	Beclomethasone / formoterol	LABA / ICS	Calverley 2010[78]
		Budesonide / formoterol	LABA / ICS	
Cosio 2016	<50%	Salmeterol / fluticasone propionate / theophylline	LABA / ICS / methylxanthines	Cosio 2016[16]
		Salmeterol / fluticasone propionate	LABA / ICS	
FLAME	25%≤FEV_1<60%	Indacaterol / glycopyrronium	LABA / LAMA	Wedzicha 2016[79]
		Salmeterol / fluticasone	LABA / ICS	
FORWARD	30%≤FEV_1 <50%	Formoterol / tiotropium / beclomethasone	LABA / LAMA / ICS	Wedzicha 2014[80]
		Formoterol / tiotropium	LABA / LAMA	
ILLUMINATE	40-80%	Indacaterol / glycopyrronium	LABA / LAMA	Vogelmeier 2013[81]
		Salmeterol / fluticasone	LABA / ICS	
LANTERN	30%≤FEV_1<80%	Indacaterol / glycopyrronium	LABA / LAMA	Zhong 2015[82]
		Salmeterol / fluticasone	LABA / ICS	
REACT	≤50%	Roflumilast / LABA / LAMA / ICS	LABA / LAMA / ICS / roflumilast	Martinez 2015m[14]
		LABA / LAMA / ICS	LABA / LAMA / ICS	
RESPOND	≤50%	LABA / LAMA / ICS / roflumilast	LABA / LAMA / ICS / roflumilast	Martinez 2016[15]
		LABA / LAMA / ICS	LABA / LAMA / ICS	
WISDOM	<50%	Salmeterol / tiotropium / fluticasone propionate	LABA / LAMA / ICS	Magnussen 2014[75]
		Salmeterol / tiotropium	LABA / LAMA	

Ten trials were identified. Only two of these studies (REACT and RESPOND) included treatments that are relevant to the decision problem under assessment (LABA / LAMA / ICS and LABA / LAMA / ICS / roflumilast). Due limitations and differences in study design compared to REACT (outlined in Section 4.2) RESPOND was considered not appropriate for the decision problem and for inclusion in an indirect comparison. As described in Section 4.2 we also identified a conference abstract but not enough information was available to determine inclusion.

For the comparator trials the only trial considered potentially relevant to the roflumilast indication was the theophylline trial Cosio 2016.[16]

Oral low-dose theophylline added to ICS / LABA failed to prevent exacerbations in severe COPD patients. COPD exacerbations were not reduced by the combination of oral low-dose theophylline and ICS / LABA in patients with severe COPD, neither in the ITT nor the PP analysis. In fact, there was a trend of exacerbations being more frequent in the intervention group, although not statistically significant, probably due to the small sample size.

Given that theophylline comparator is not considered relevant for the reason outlined above (Section 3.3) we have not considered the Cosio 2016 trial further.

Methods of analysis and presentation of results

For the reasons outlined above none of the trials identified in the review were considered relevant to the roflumilast indication. Therefore an indirect comparison was not carried out.

4.11 Non-randomised and non-controlled evidence

Not applicable

4.12 Adverse reactions

The REACT study[14] has been identified as the only relevant RCT for this decision problem and appraisal. Adverse events were reported by 648 (67%) of 968 patients receiving roflumilast and 572 (59%) of 967 patients receiving placebo. Serious adverse events were reported by 249 (26%) patients and 285 (30%) patients in the

roflumilast and placebo groups respectively. This overall adverse event rate was similar to that reported in less severely affected patients in Rabe et al. 2010[21] and in a previous 12-month study of roflumilast (Calverley et al. 2009).[72] The majority of adverse reactions reported by patients receiving roflumilast were mild or moderate and occurred mainly within the first weeks of therapy and mostly resolved on continued treatment.[20]

Common adverse events, that occurred in at least 2.5% of patients in either treatment group, are summarised in Table 20. The most common patient-reported adverse events in the roflumilast group were diarrhoea (10% vs 4% in the placebo arm), weight decrease (9% vs 3% in the placebo arm) and nausea (6% vs 2% in the placebo arm).

There was no increase in the incidence of pneumonia or other pulmonary infections during treatment with roflumilast (4%) compared with placebo (5%). However, the rate of pneumonia in both groups was higher than reported in previous roflumilast studies[72] reflecting the known risk of ICS for COPD-related pneumonia in this population.[83]

Table 20: Adverse events occurring in at least 2.5% of patients in either treatment group in the REACT study[14]

	Roflumilast group (n=969)	Placebo group (n=967)	Difference between groups (95% CI)
COPD exacerbation	145 (15%)	185 (19%)	–4.2% (–5.08 to 3.23)
Diarrhoea	99 (10%)	35 (4%)	6.6% (5.50 to 7.71)
Weight decrease	88 (9%)	27 (3%)	6.3% (5.22 to 7.38)
Nausea	55 (6%)	15 (2%)	4.1% (3.24 to 5.02)
Nasopharyngitis	52 (5%)	52 (5%)	0% (–0.04 to 0.03)
Headache	40 (4%)	21 (2%)	2.0% (1.34 to 2.58)
Pneumonia	39 (4%)	45 (5%)	–0.6% (–0.98 to –0.27)
Decreased appetite	36 (4%)	5 (1%)	3.2% (2.42 to 3.99)
Insomnia	29 (3%)	15 (2%)	1.4% (0.91 to 1.98)
Back pain	27 (3%)	14 (1%)	1.3% (0.83 to 1.85)
Upper abdominal pain	25 (3%)	10 (1%)	1.5% (1.00 to 2.10)
Hypertension	24 (3%)	27 (3%)	–0.3% (–0.56 to –0.06)

Data are n (%) unless otherwise indicated. Adverse events were reported independently of the investigator causality assessments. Patients might have had more than one adverse event. One patient assigned to the roflumilast accidentally received placebo for the entire duration of the study and was therefore included in the placebo group for the safety analysis.

Body weight was a pre-specified safety endpoint and an identified safety issue of concern. The mean weight loss in the roflumilast group was 2.65 kg (SD 4.37 kg) compared with 0.15 kg (SD 3.69 kg) in the placebo group. This magnitude of weight loss associated with roflumilast use was consistent with previous studies and equated to a ~4% reduction in body weight from baseline (mean weight at baseline of the ITT population of the roflumilast group was 75.07 kg SD 17.275 kg). During the 12-week end-of-treatment follow-up period, patients stopped taking study drug but were able to take commercially available roflumilast. This follow-up group was comprised of patients who completed the study as scheduled. Of the follow-up group who were originally randomised to roflumilast, 94% (620 / 657) discontinued treatment and 6% (37 / 657) continued on commercial roflumilast. Bodyweight partially recovered during the 3-month follow-up in the roflumilast treated patients who discontinued the study treatment and appeared relatively stable in those who continued on commercial roflumilast (Table 21).

Table 21: Key safety outcomes[14]

	Roflumilast group	Placebo group
Bodyweight changes (n=968 roflumilast group; n=966 placebo group)		
Change in bodyweight (kg) during double-blind treatment period	–2.65 (4.37); n=938†	–0.15 (3.69); n=944†
Change in bodyweight (kg) post-randomisation to end of follow-up‡ Roflumilast in post-treatment period No roflumilast in post-treatment period	 0.28 (1.58); n=36† 1.10 (2.61); n=612†	 –1.62 (2.49); n=48† 0.11 (2.60); n=679†
Mortality (n=969 roflumilast group; n=966 placebo group)		
Deaths*	17 (2%)	18 (2%)
Primary cause of death* COPD exacerbation Adverse event	 7 (1%) 10 (1%)	 7 (1%) 11 (1%)
Major adverse cardiovascular events (n=969 roflumilast group; n=966 placebo group)		
Composite major CV events	16 (2%)	16 (2%)
Major adverse CV event due to CV death (incl. death from undetermined cause)	9 (1%)	7 (1%)
Major adverse CV event due to non-fatal myocardial infarction	3 (<1%)	6 (1%)
Major adverse CV event due to non-fatal stroke	4 (<1%)	3 (<1%)

CV, cardiovascular.
Data are n (%) or mean (SD). One patient assigned to roflumilast received placebo for the entire study and was therefore included in the placebo group for the safety analysis. The total numbers of patients for the mortality and major CV event analyses are based on the full analysis population of patients, whereas bodyweight is based on the safety population.
*Analysis includes deaths during the double-blind treatment period only.
† The number of patients with bodyweight measurements available.
‡ Analysis includes data from the entire observations period.

Other end-points related to key safety outcomes are summarised in Table 21. The number of patients who died or had a major adverse cardiovascular event did not differ between the two treatment groups. During market authorisation, the CHMP flagged psychiatric disorders as a potential safety concern. In the REACT study depression was reported by 2% (19 / 968) of patients in the roflumilast group and 1.1% (11 / 967) in the placebo group.[70]

In the REACT study, patients who received roflumilast reported the anticipated range of pharmacologically predictable side effects.

4.13 Overview of roflumilast in relation to the decision problem

The REACT trial provides the core clinical evidence for this decision problem and appraisal.

REACT is a well-designed RCT trial that investigated the impact of roflumilast compared with placebo on moderate to severe exacerbation rates as add-on therapy in the target patient group of interest – patients with severe COPD, with symptoms of chronic bronchitis and a high frequency of exacerbations (≥ 2 in previous year) despite treatment with LABA / ICS ± LAMA. A high proportion of study participants were on concomitant LAMA therapy. The trial protocol closely reflected clinical practice in the UK, as well as the proposed positioning of roflumilast and target patient population for appraisal.

The PP population of the LAMA subgroup accurately reflects the target population specified in the decision problem, and thus the cost effectiveness analysis in Section 5 has been restricted to this population. In this population of patients with severe COPD (FEV_1 < 50% predicted) and chronic bronchitis, with frequent exacerbations (≥ 2 / year) despite treatment with LABA / LAMA / ICS, roflumilast as add-on to triple therapy significantly reduced the rate of moderate to severe exacerbations by 20.1% (roflumilast 0.858 vs placebo 1.075; RR 0.799 [95% CI: 0.670–0.952]; p=0.0122).[76]

The most common adverse events associated with roflumilast treatment reported in the REACT trial were diarrhoea (10% vs 4% in the placebo arm), weight decrease (9% vs 3% in the placebo arm) and nausea (6% vs 2% in the placebo arm). Weight decrease has been identified as an adverse event of concern and a series of risk management measures have been put in place to address this; namely close monitoring of patient weight and ceasing treatment in event of an unexplained and clinically concerning weight decrease.[20] During market authorisation, regulatory bodies highlighted psychiatric disorders as a potential safety concern. In the REACT study depression was reported by 2% (19 / 968) of patients in the roflumilast group and 1.1% (11 / 967) in the placebo group.[70]. Roflumilast is not recommended in patients with a history of depression associated with suicidal ideation or behaviour. In addition, risk minimisation materials (HCP and patient education) have been put in place to further address this risk.

A key limitation of the REACT study is the lower than anticipated event rate. As discussed above, use of the pre-specified negative binomial regression model over the Poisson model in the analyses helps to address this issue. This is because the negative binomial model uses a less simplistic assumption about exacerbation variability from patient to patient than the Poisson model. Another limitation was that the study did not follow-up all participants to the end of the study which may have led to an underestimation of mortality risk.

As discussed in Section 3.2, exacerbations accelerate disease progression, impact QoL, increase the risk of future exacerbations and increase mortality risk – and the greater the severity of the exacerbation the greater the impact. In the UK rates of exacerbations in GOLD C and D patients were estimated to 1.78 (95% CI: 1.74–1.82) and 2.51 (95% CI: 2.47–2.55) respectively (vs 0.83 95% CI: 0.81–0.85 in GOLD A), while the rate of COPD-related hospitalisations were 0.44 (95% CI: 0.40–0.48) and 0.85 (95% CI: 0.81–0.89) (vs 0.35 95% CI: 0.31–0.40 in GOLD A).[43] In addition, another UK study reported that 14% of patients died within 3 months of a hospital admission following an exacerbation and in the longer term 77% of patients who were admitted to hospital died from COPD.[19 39] Therefore, based on observations and data from the REACT trial, the addition of roflumilast to existing LABA / LAMA / ICS treatment in uncontrolled patients with severe COPD, symptoms of chronic bronchitis with frequent exacerbations is expected to have clinically important implications and justifies the proposition to target this high-risk patient group.[14]

As previously discussed, there are no UK epidemiology data on people with severe COPD (FEV_1 < 50%) and chronic bronchitis experiencing frequent exacerbations while treated with LABA / LAMA / ICS. However, data on broader populations provide some valuable insights. A UK cohort study found that nearly a quarter of COPD patients had FEV_1 < 50%. In addition, 28.6% of this cohort were on LABA / LAMA / ICS therapy and 25.5% had ≥ 2 exacerbations in the 12 months prior to the prevalence point.[52] As triple therapy is recommended only for patients with severe disease[1 2] and exacerbation risk also increases worsening airflow limitation,[1] these data imply that there remains a substantial proportion of patients with severe COPD

who continue to have frequent exacerbations despite tripe therapy (LABA / LAMA / ICS). The REACT trial demonstrated that for these patients who also have chronic bronchitis, addition of roflumilast to triple therapy can provide a clinically significant benefit.

Roflumilast is not considered to be a life-extending treatment at the end of life.

4.14 Ongoing studies

Searches were carried out for ongoing RCTs that could provide additional evidence for roflumilast in this indication. This was restricted to data likely to be available in the next 12 months. Sources searched were: NIH clinicaltrials.gov and WHO International Clinical Trials Registry Platform (ICTRP).

No relevant trials were identified.

5 Cost effectiveness

Section summary:

- To support the economic evaluation of roflumilast, a cohort state transition (Markov) model with monthly cycles has been developed to assess the cost effectiveness of roflumilast in the target population.
- The estimation of moderate and severe exacerbations (as separate endpoints) is based on analyses conducted in the REACT study, using a negative binomial regression. The model estimated the rate of moderate and severe exacerbations whilst controlling for COPD severity and treatment arm and excluding the subgroup of patients without concomitant LAMA use.
- In the base case incremental cost effectiveness analysis, LABA / ICS / LAMA / roflumilast accumulates total (discounted) costs of £22,930 and 6.14 QALYs. LABA / LAMA / ICS alone accumulates total (discounted) costs of £19,933 and 5.98 QALYs. This equates to LABA / LAMA / ICS / roflumilast producing an additional 0.16 QALYs at an incremental cost of £2,996 when compared to LABA / LAMA / ICS alone.
- This generates a base case ICER of £18,774 and demonstrates that LABA / LAMA / ICS / roflumilast is cost effective at the £20,000 per QALY threshold.
- Probabilistic sensitivity results are highly comparable to the base case deterministic results demonstrating that the model is stable. LABA / LAMA / ICS / roflumilast has a 72% probability of being cost effective at £20,000 per QALY gained increasing to 100% at £30,000 per QALY gained.
- This demonstrates that the addition of roflumilast to LABA / LAMA / ICS is a cost effective use of NHS resources to address an unmet need for patients with severe and very severe COPD.

5.1 Published cost effectiveness studies

Method

Search strategy

A systematic review was undertaken in May 2015 and updated in July 2016 to identify and summarise studies that reported cost effectiveness of roflumilast as an add-on treatment to triple therapy compared to other comparators. In the original review conducted in May 2015, systematic searches were carried out in four electronic databases: EMBASE, MEDLINE, EconLit and NHS EED between 2004 and 2015. As the updating of NHS EED in Cochrane library ceased after April 2015 searches were not performed in this database during the update of the review (2015–2016). The search strategies were designed to capture data from eight countries: UK, US, Canada, Germany, France, Italy, Spain and Australia. The search strategies are presented in Appendix 7.

Study selection

Inclusion criteria are provided in Table 22. PRISMA diagrams present the selection process graphically in the original and the updated review (Figure 5 and Figure 6). A single reviewer screened and identified references based on titles and abstracts. Two reviewers independently assessed the full text articles for inclusion and a third reviewer was consulted where there were differences between results. As a common search strategy was used to identify cost effectiveness and cost / resource use studies, relevant records were divided at the full-text review stage. Data were extracted by a single reviewer for the full text article that met the inclusion criteria and were validated by a second reviewer.

Table 22: Published cost effectiveness studies systematic review – inclusion criteria

	Inclusion criteria
Patients	Severe / very severe COPD (defined as FEV_1 <50% predicted level, corresponding to pre-2013 GOLD report stages III and IV)
Interventions	Roflumilast given as add-on to triple therapy
comparators	• LABA / LAMA • LABA / ICS • LABA / ICS / LAMA • LABA / ICS / Methylxanthines • LABA / LAMA / Methylxanthines • LABA / ICS / LAMA / Methylxanthines • LABA / ICS / placebo • LABA / ICS / LAMA / placebo
Outcomes	• Cost-utility analyses, • Cost effectiveness analyses, • Cost benefit analyses or • Cost minimisation analyses
Geography	UK, US, Canada, Germany, France, Italy, Spain and Australia
Language	English only
Date restriction	2004-current

Figure 5: Published cost effectiveness studies systematic review – PRISMA diagram (Original review 2004–2015)

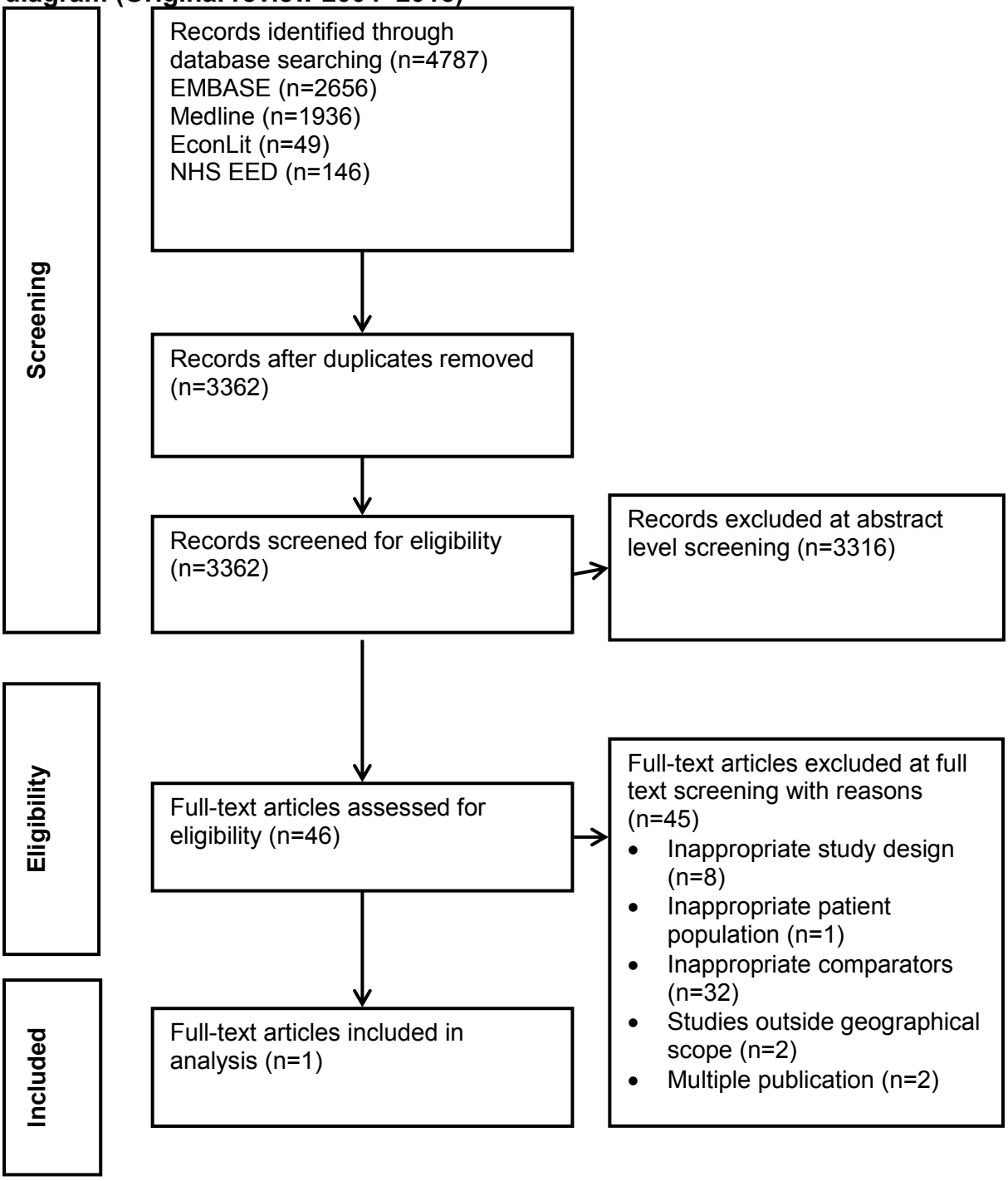
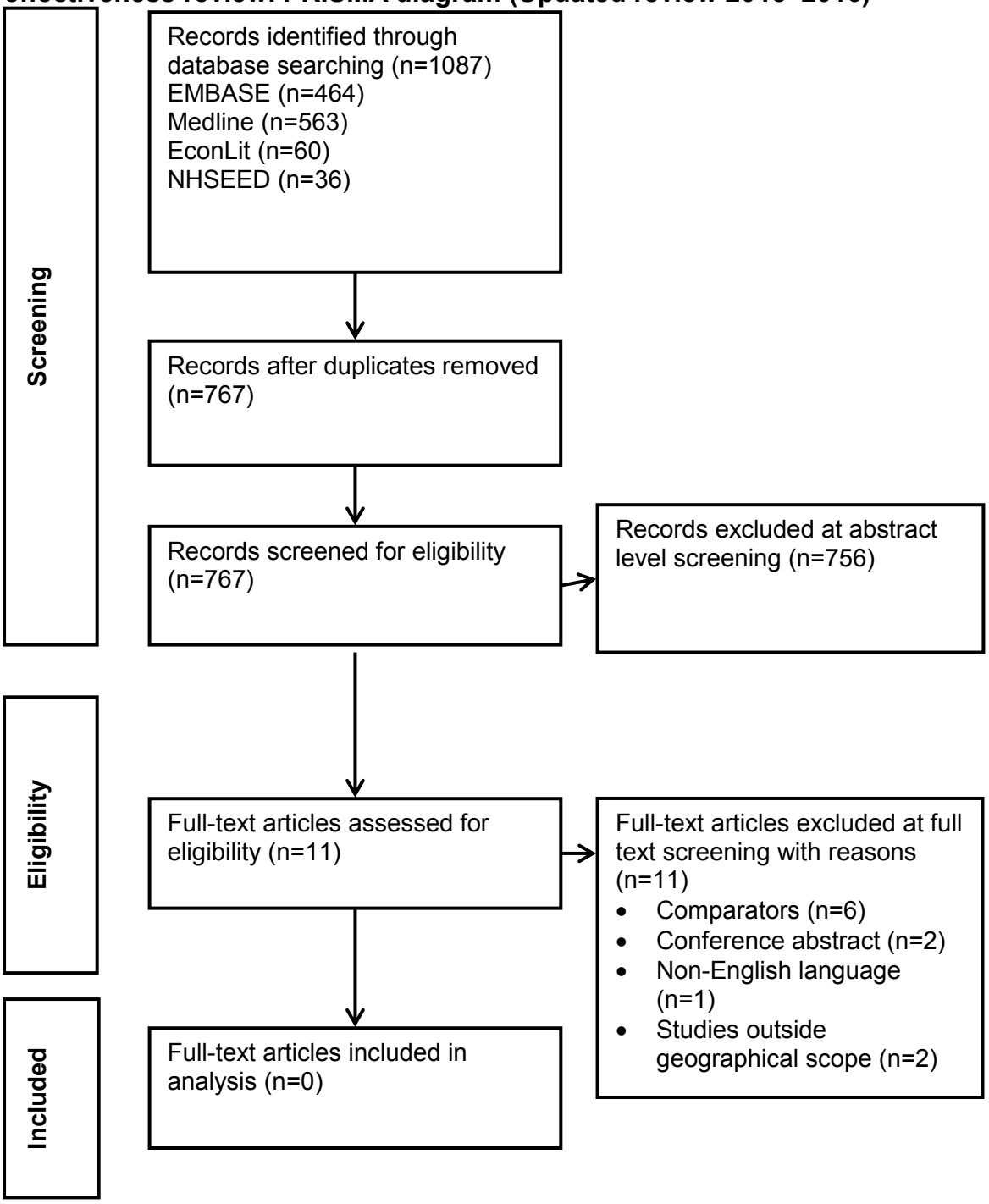


Figure 6: Published cost effectiveness studies systematic review – cost-effectiveness review. PRISMA diagram (Updated review 2015–2016)



Included studies

One published cost effectiveness study was identified that met the inclusion criteria. Hertel (2012)[17] developed a Markov model to predict cost effectiveness of various combinations of a LAMA, LABA, ICS and roflumilast in two fully incremental analyses that were conducted separately for ICS-tolerant and ICS-intolerant patients with severe COPD.

The model included five Markov states: severe COPD, first-line regimen; severe COPD, second-line regimen; very severe COPD, first-line regimen; very severe COPD, second-line regimen; and death. The severe and very severe health states were based on the GOLD criteria. The average age of patients in the cohort at the start of the model was 64 years. The baseline characteristics of the modeled cohort were obtained from the pooled analysis of the M2–124 and M2–125 clinical trials of roflumilast.[72] Model results are presented in Table 23.

Table 23: Published cost effectiveness studies systematic review – summary of included studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs	Cost	ICER (per QALY gained)
Hertel	2012	Cohort-transition Markov model; cycle length of 1 month; time horizon of 30 years	Severe COPD patients (64 years) at the start of the model	<u>ICS-tolerant patients</u> LABA / LAMA / ICS / roflumilast: 5.51 LAMA / LABA / ICS: 5.48	<u>ICS-tolerant patients</u> LABA / LAMA / ICS / roflumilast: £23,230 LAMA / LABA / ICS: £22,816	£16,566
				<u>ICS-intolerant patients</u> LAMA / LABA / roflumilast: 5.22 LAMA / LABA: 5.19	<u>ICS-intolerant patients</u> LAMA / LABA / roflumilast: £22,222 LAMA / LABA: £21,814	£13,764

In this analysis, LABA / LAMA / ICS / roflumilast is the optimal intervention generating an ICER per QALY gained of £16,566 and £13,764 for ICS tolerant patients and ICS intolerant patients respectively.

A quality assessment of this study was performed using Drummond and Jefferson (1996) checklist,[84] and this is provided in Appendix 8. The model is clear and transparent in terms of study design. The research question, perspective taken, comparators chosen and form of economic evaluation chosen are clearly stated and justified. Details relating to data (primary outcomes, resources and costs) used in the model for the economic evaluation are clearly given. The model choice and key parameters used for the model are clearly explained. Analysis and interpretation of results are also appropriate. Details of statistical tests and confidence intervals for stochastic data are not clearly stated (the type of distributions assigned to key model parameters is unclear). Overall, the model is reliable but lacks transparency in some analysis and results presentation.

5.2 De novo analysis

Patient population

This analysis is concerned with the addition of roflumilast to triple therapy in patients with severe to very severe COPD (FEV_1% predicted < 50%) and ≥ 2 moderate or severe COPD exacerbations within the previous year. REACT compared LABA ± LAMA / ICS / roflumilast against LABA ± LAMA / ICS. The modelling therefore focusses on those patients in REACT who received concomitant LAMA. Of REACT trial participants 69% were treated with concomitant LAMA (ITT: 677 / 969 patients in the roflumilast arm and 669 / 966 patients in the comparator arm; PP: 565 / 810 patients in the roflumilast arm and 557 / 823 patients in the comparator arm).

As discussed in Section 4, the analyses presented here are based on the PP analysis. A total of 312 (~16.0%) patients experienced at least one major protocol deviation and were excluded from the PP analysis. The proportion of patients with protocol deviations was similar across treatment groups, with many relating to 'post-bronchodilator FEV_1 % predicted > 50% at visit zero (105 patients, 5.4%). Other violations included 'not pre-treated with LABA / ICS for at least 12 months', 'total

cough and sputum score <14 during the last week prior to randomisation', and 'less than 2 documented moderate or severe COPD exacerbations within 1 year prior to visit zero '. Further details of protocol violations are provided in Table 12. The ITT population therefore includes a large proportion of patients whose COPD and treatment status are other than those of the patient population relevant to the decision problem (i.e. moderate COPD, with <2 exacerbations in the previous year, and without 12 months' treatment without LABA / ICS etc.).

The base case population characteristics are outlined in Table 24.

Table 24: Base-case population characteristics

Baseline characteristic	Baseline value	Source
Age (years)	64.70	REACT[14]
Male (%)	74.60%	REACT[14]
Mean height males (cm)	172.74	REACT (Data on file)
Mean height females (cm)	161.67	REACT (Data on file)

Model structure

A cohort state transition (Markov) model with monthly cycles has been developed. Due to the short cycle length, half-cycle corrections have not been applied. The model includes three states: severe COPD, very severe COPD and death. COPD states in the model are based on the severity of COPD as defined by GOLD lung function criteria i.e. using post-bronchodilator FEV_1% predicted value relative to the normal population.[85]} The threshold for severe COPD is below 50% and the threshold for very severe COPD is below 30% FEV_1 predicted. In each cycle the model predicts the proportion of patients who progress from severe COPD to very severe COPD or die. Patients in either COPD state are at risk of suffering exacerbations which may be moderate to severe. The principle analyses reported below is for patients who enter the model in the severe COPD state (very severe patients and a mixed population are entered in a scenario analysis). Table 25 outlines a number of the key features of the analysis. The model schematic is presented in Figure 7.

Table 25: Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	40 years	Lifetime analysis. No patients remain alive in model
Were health effects measured in QALYs; if not, what was used?	Yes	NICE reference case
Discount of 3.5% for utilities and costs	Yes	NICE reference case
Perspective (NHS / PSS)	NHS and PSS	NICE reference case

PSS, personal social services; QALYs, quality-adjusted life years

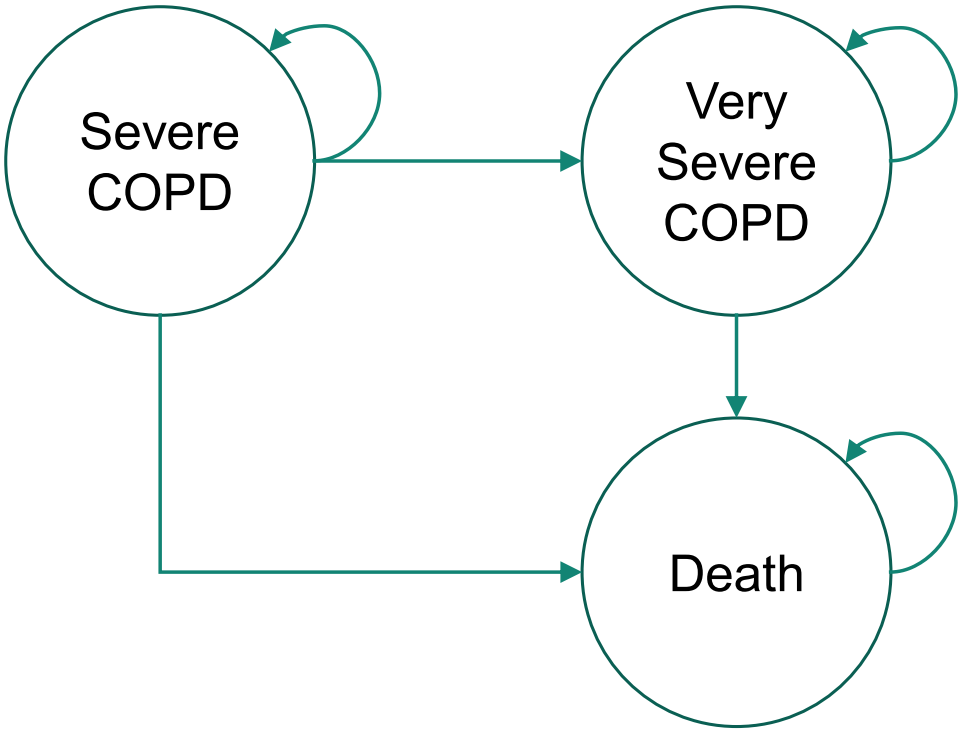


Figure 7: Model schematic

Although this model structure is similar to those used in the NICE TA 244,[13] Samyshkin et al. 2014,[18] and in the NICE COPD clinical guidelines[2] an updated structure was required in order to include differential moderate and severe exacerbation rates and to focus on roflumilast as add-on to triple therapy rather than dual therapy.

Intervention technology and comparators

The European Medicines Agency summary of product characteristics for roflumilast states "'Daxas▼ [roflumilast] is indicated for maintenance treatment of severe chronic obstructive pulmonary disease (COPD) (FEV_1 post-bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add-on to bronchodilator treatment."[20]

In this analysis roflumilast as add-on to triple therapy (LABA / LAMA / ICS / roflumilast) in severe and very severe COPD patients is compared against triple therapy (LABA / LAMA / ICS). Other comparators as listed in the NICE scope are not included. Rationale for their exclusion is provided in Section 3.2.

5.3 Clinical parameters and variables

Disease progression

COPD is a progressive disease, such that once patients have transitioned to very severe in the model, there is no possibility of this being reversed. Therefore, other than mortality, the only state transition probabilities required are those for severe to very severe COPD, and from either COPD state to death.

The progression from severe to very severe COPD health states depends on predicted FEV_1 values for the general population and estimated FEV_1 decline in patients with COPD.

Prediction of FEV_1 percent of normal value

In order to estimate the predicted FEV_1 values for the general population, equations from a study of 251 healthy non-smoking males and females were implemented.[86] These equations are detailed below:

$$FEV_1(males), L = (0.0414 \times height) - (0.0244 \times age) - 2.190$$

$$FEV_1(females), L = (0.0342 \times height) - (0.0255 \times age) - 1.578$$

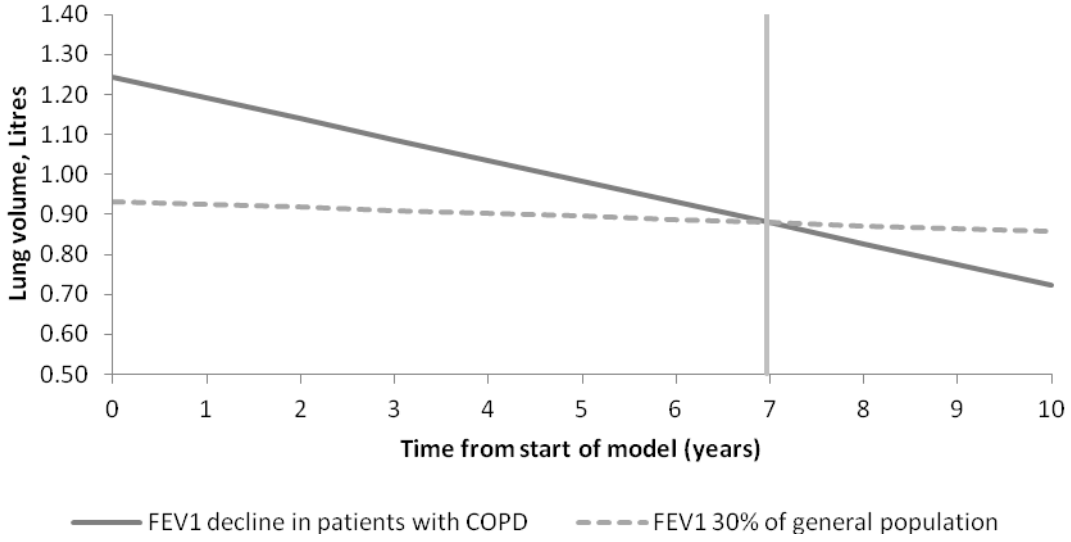
Given the population base case characteristics, baseline predicted FEV_1 values for males and females are calculated as 3.38 and 2.30 litres respectively.

Estimated lung function decline in patients with COPD

FEV_1 declines naturally within the general population with age.[85] The Lung Health Study[87] measured lung function over 5 years in patients with mild to moderate COPD (FEV_1% between 50% and 90% of the value predicted for their age).[87]. This study demonstrated that FEV_1 for patients with COPD declines at a rate of 52 ml per year. The model adopts this rate of FEV decline for all COPD patients.

Transition probabilities for progression from the severe to very severe COPD state are calculated using the estimated time to the 30% of predicted post-bronchodilator FEV_1% threshold. The estimated time in the severe COPD state is shown in Figure 8 as the time between the start of the model and the time until the average FEV_1 of the cohort reaches the 30% FEV_1 threshold. Monthly transition probabilities are the reciprocal of this average estimated time as in previous models.[88] This is estimated for males and females separately and weighted dependent on the proportion of males and females included in the model. With the base case population characteristics applied to Crapp et al.'s reference equations (which estimate a baseline lung volume of 1.24 L), the predicted average time to very severe COPD is 6.97 years, with a monthly transition probability from severe to very severe COPD of 1.20%.

Figure 8: Calculation of average time to very severe COPD state



Lung function improvement

In REACT roflumilast / ICS / LABA / LAMA treatment resulted in a 56 ml (95% CI: 38-73) improvement in post-bronchodilator FEV_1 over 52 weeks compared to patients treated with ICS / LABA / LAMA.[14] It is possible that some degree of reduction in exacerbation rates seen in REACT may be attributable to lung function improvement.[14] Samyshkin et al. applied an empirical adjustment to the roflumilast exacerbation rate ratio in recognition of this.[18] Rather than use such an adjustment in the base case, the lung function benefit of treatment with roflumilast is excluded.

In scenario analyses lung function benefit as observed in REACT is applied, with the duration this is sustained over also varied. With lung function benefit applied, the patients treated with roflumilast enjoy lower rates of progression to very severe COPD for a specified period.

Exacerbations

As well as disease progression, in each model cycle patients can experience either a moderate or severe exacerbation. Moderate exacerbations in REACT were defined as those that require treatment with oral or parenteral corticosteroids whilst severe exacerbations are defined as those that cause hospital admission or lead to death. Different baseline rates of moderate and severe exacerbations are applied dependent on patients' COPD health state.

Prediction of exacerbation rates

The primary endpoint in REACT was the rate of moderate or severe COPD exacerbations per patient per year, analysed using both Poisson and negative binomial regressions (see Section 4.3). REACT used Poisson regression for comparability with previously published trials. In addition, negative binomial regression was a pre-specified analysis in the trial to account for possible over dispersion in the Poisson regression model. Negative binomial regression likely offers a more precise estimate, particularly as exacerbations in patients who received placebo were less frequent in REACT than was expected when the trial

was designed. The negative binomial analyses confirmed a significant reduction in moderate or severe exacerbations, and per protocol analyses also resulted in significant reductions for the severe endpoint when analysed separately from moderate exacerbations.

The REACT trial analyses provided exacerbation rates across all patients rather than adjusting for GOLD stage (COPD state) or treatment with triple therapy (concomitant LAMA). The model is based on analyses that control for GOLD stage and LAMA use, allowing cost effectiveness analyses to focus on the target population of patients treated with background triple therapy.

In the de novo economic model, two approaches have been considered for the estimation of moderate and severe exacerbations separately based on analyses conducted in the REACT study, both using negative binomial regression. As a significant reduction in the rate of severe exacerbations was confirmed in these analyses and as severe exacerbations have more important consequences than do moderate exacerbations, we estimated the rate of exacerbations separately for moderate and severe exacerbations. The first approach, used in the model base case, controlled for COPD severity and treatment arm and excluded the subgroup of patients without concomitant LAMA use. In the second approach, used in scenario analyses, all patients (in the PP population) were included with concomitant LAMA use adjusted for as a covariate, along with COPD severity and treatment arm.

Across all analyses a stronger (and significant) effect of roflumilast was found in terms of reductions of severe than of moderate exacerbations (Table 26) although with narrower CI in the case where LAMA is included as a covariate.

Table 26: Moderate and severe COPD exacerbation rate ratios

Exacerbations	Rate ratio*	Lower 95% confidence interval	Upper 95% confidence interval
LAMA strata only (N=1122)			
Moderate exacerbations	0.887	0.723	1.087
Severe exacerbations	0.656	0.496	0.868
LAMA as covariate (N=1633)			
Moderate exacerbations	0.861	0.722	1.028
Severe exacerbations	0.657	0.511	0.845

*rate ratio of less than 1 represents a favourable outcome for roflumilast

LAMA strata only

RRs, coefficients and 95% CIs for all covariates included in the negative binomial regressions for both moderate and severe exacerbations are detailed in Table 27 and Table 28 respectively.

Table 27: Moderate exacerbation negative binomial risk model (LAMA strata only)

Exacerbations	RR*	Coefficient	Lower 95% CI	Upper 95% CI
Intercept	-	-0.836	-1.309	-0.362
Roflumilast use	0.887	-0.120	-0.324	0.083
Very severe COPD	1.579	0.457	-0.018	0.933

*Rate ratio = exp(coefficient); rate ratio < 1 represents a favourable outcome for reference category.

In this analysis, moderate exacerbations are 11% lower for patients using roflumilast compared to the comparator and 58% higher for patients with very severe COPD compared to those with severe COPD. The rate of moderate exacerbations among severe COPD patients is 0.43, and among very severe patients it is 0.68.

Table 28: Severe exacerbation negative binomial risk model (LAMA strata only)

Exacerbations	Rate ratio*	Coefficient	Lower 95% confidence interval	Upper 95% confidence interval
Intercept	-	-1.743	-2.476	-1.011
Roflumilast use	0.656	-0.422	-0.702	-0.142
Very severe COPD	2.351	0.855	0.116	1.594

*Rate ratio = exp(coefficient); rate ratio < 1 represents a favourable outcome for reference category.

In this analysis, severe exacerbations are 34% lower for patients using roflumilast compared to the comparator and 135% higher for patients with very severe COPD compared to those with severe COPD. The rate of severe exacerbations among severe COPD patients is 0.17, and 0.41 among very severe patients.

LAMA as covariate

RRs, coefficients and 95% CI for all covariates included in the negative binomial regressions for both moderate and severe exacerbations are detailed in the Table 29 and Table 30 respectively.

Table 29: Moderate exacerbation negative binomial risk model (LAMA as covariate)

Exacerbations	RR*	Coefficient	Lower 95% CI	Upper 95% CI
Intercept	-	-1.098	-1.540	-0.656
Roflumilast use	0.861	-0.150	-0.326	0.027
Very severe COPD	1.519	0.418	-0.002	0.838
LAMA use	1.369	0.314	0.100	0.510

*Rate ratio = exp(coefficient); rate ratio < 1 represents a favourable outcome for reference category.

The rate of moderate exacerbations in the triple therapy arm for severe COPD patients is 0.45 per patient per year, rising to approximately 0.70 for very severe COPD patients. In this analysis, moderate exacerbations are 14% lower for roflumilast compared to the comparator.

Table 30: Severe exacerbation negative binomial risk model (LAMA as covariate)

Exacerbations	Rate ratio*	Coefficient	Lower 95% CI	Upper 95% CI
Intercept	-	-2.210	-2.859	-1.561
Roflumilast use	0.657	-0.420	-0.672	-0.168
Very severe COPD	1.726	0.546	-0.066	1.159
LAMA use	2.151	0.766	0.466	1.065

*Rate ratio = exp(coefficient); rate ratio < 1 represents a favourable outcome for reference category.

The rate of severe exacerbations in the triple therapy arm for severe COPD patients is 0.24 per patient per year, rising to approximately 0.40 for very severe COPD

patients. In this analysis, severe exacerbations are 34% lower for roflumilast compared to the comparator.

Mortality

Within the model mortality occurs through one of two routes; case fatality due to severe exacerbation or in stable COPD based on all cause general population mortality rates with adjustment for the impact of stable COPD and exacerbation specific mortality.

Severe exacerbation mortality

The rate of mortality due to severe exacerbations - the case fatality rate (CFR) - was obtained from the 2014 UK National COPD Audit Report.[19] 576 of 13,414 (4.3%, SE 0.18%) patients died during an admission to hospital for a severe exacerbation. In order to avoid possible overestimation of severe exacerbation mortality when the cohort age is below that in the UK National COPD Audit Report (72 years for both males and females, and when the greater proportion of the modelled cohort remains at risk), an adjustment to the CFR by age is applied, following Samyshkin 2014[18] The ratio of the age specific risk of death in the general population to the risk of death at the age of 72 years has been used to adjust the reported CFR. For example, the ratio of the risk of death for patients 70 years of age compared to those 72 years of age is 0.78. The CFR for patients 72 years of age, adjusted accordingly, is 3.4%. These adjustment ratios and associated adjusted CFRs are illustrated in Table 31. Adjustments are made for all ages in the model.

Table 31: Adjusted severe exacerbation CFR

Age, years	64	70	72	75	80	85
Adjustment ratio	0.48	0.78	1	1.33	2.29	4.13
Hospital CFR	2.1%	3.4%	4.3%	5.7%	9.8%	17.8%

This adjustment leads to proportionately higher CFRs for patients of more than 72 years of age due to the increasing mortality rate in the general population with advancing age, but these greater fatality rates apply when the remaining cohort in

the model is diminished due to prior cumulative mortality among the initial cohort of patients entered in the model at age 64 years.

Background mortality

Background mortality for the severe and very severe COPD health states is calculated using UK life tables and standardised mortality ratios (SMRs) that exclude hospital deaths. Samyshkin (2014)[18] estimated these SMRs as 2.5 and 3.85 respectively and these adjusted SMRs are adopted in the base case. These SMRs were calculated by taking all-cause mortality SMRs of 3.1 and 5.0 from a Swedish study[37] and deducting within the model the estimated exacerbation mortality rates from the SMR implied all-cause mortality. In our analysis however, both the CFR (4.3% vs 7.7%) and rate of severe exacerbations are lower than those used in Samyshkin 2014.[18] Revision of the adjustment of the SMRs could be expected to result in SMRs closer to the unadjusted values derived from Ekberg-Aronsson 2005. As the CFR and background mortality are from separate populations, however, re-adjustment may not necessarily improve the parameter estimates for the model. A scenario analysis assesses the importance of the SMR values applied in the model.

5.4 Measurement and valuation of health effects

Health-related quality of life data from clinical trials

QoL data were collected in REACT using the COPD Assessment Test (CAT). There was a significant difference in quality of life between baseline and the end of the treatment period in both trial arms with no significant difference between the treatments.

Table 32: Change in CAT score[14]

	Roflumilast arm (mean, SE)	Comparator arm (mean, SE)	Difference (mean difference, 95% CI, p-value)
Change in CAT score	–1.270 (0.156)	–0.985 (0.152)	–0.285 (–0.711 to 0.142) p=0.191

Mapping

Hoyle et al. have developed an algorithm to estimate EQ-5D based preference weights (utilities) based on CAT.[89] In the authors' view their algorithm is likely to underestimate utilities for both low HRQoL (utility<0.5) and at near full health (utility≥0.9). Mapped CAT-based utility data would require further analyses to derive relevant parameter estimates for the model. CAT data is not considered in this analysis.

Health-related quality of life studies

Method

Search strategy

A systematic review was undertaken in May 2015 and updated in July 2016 to identify evidence of humanistic burden of disease in severe and very severe COPD patients. The search for HRQoL data was undertaken in two electronic databases: MEDLINE and EMBASE. The search strategies were designed to capture data from eight countries: UK, US, Canada, Germany, France, Italy, Spain and Australia. The search strategies are presented in Appendix 9.

Study selection

Inclusion criteria are provided in Table 33. PRISMA diagrams present the selection process graphically in the original and updated review (Figure 9 and Figure 10). A single reviewer screened and identified references based on titles and abstracts. Two reviewers independently assessed the full text articles for inclusion and a third reviewer was consulted where there were differences between results. Data were extracted by a single reviewer for the full text article that met the inclusion criteria and were validated by a second reviewer.

Table 33: Published HRQoL studies systematic review - inclusion criteria

	Inclusion criteria
Patients	Adults with severe or very severe COPD (FEV_1 post-bronchodilator < 50% predicted value)
Interventions / comparators	No intervention or pharmacological interventions
Outcomes	Any of the following instruments: • SF-36, SF-12, SF-6D • EQ-5D • SGRQ • CAT • CRQ / CRQ-SAS or • TDI
Study types	• Minimum study population of 50 individuals with COPD with HRQL results • Cross-sectional or longitudinal design
Geography	US, UK, Germany, France, Italy, Spain, Australia or Canada
Language	English only
Date range	2004-current

CAT, COPD Assessment Test; COPD, Chronic obstructive pulmonary disease; CRQ, Chronic Respiratory Questionnaire; FEV_1, Forced expiratory volume in 1 second; HRQL, Health-related quality of life; SGRQ, St George's Respiratory Questionnaire; TDI, Transition Dyspnoea Index.

Figure 9 Published HRQoL studies systematic review – PRISMA diagram (Original review 2004-2015)

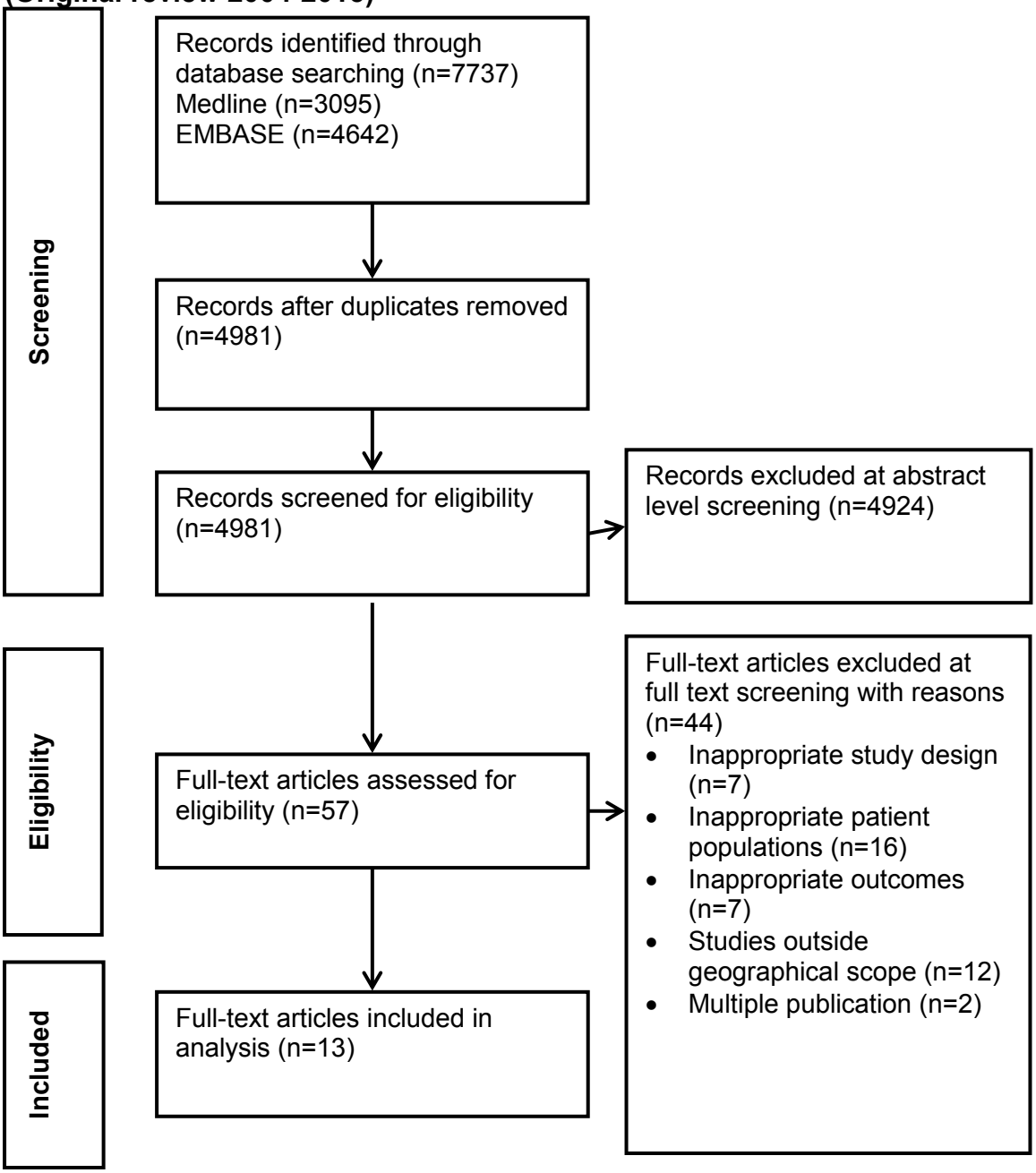
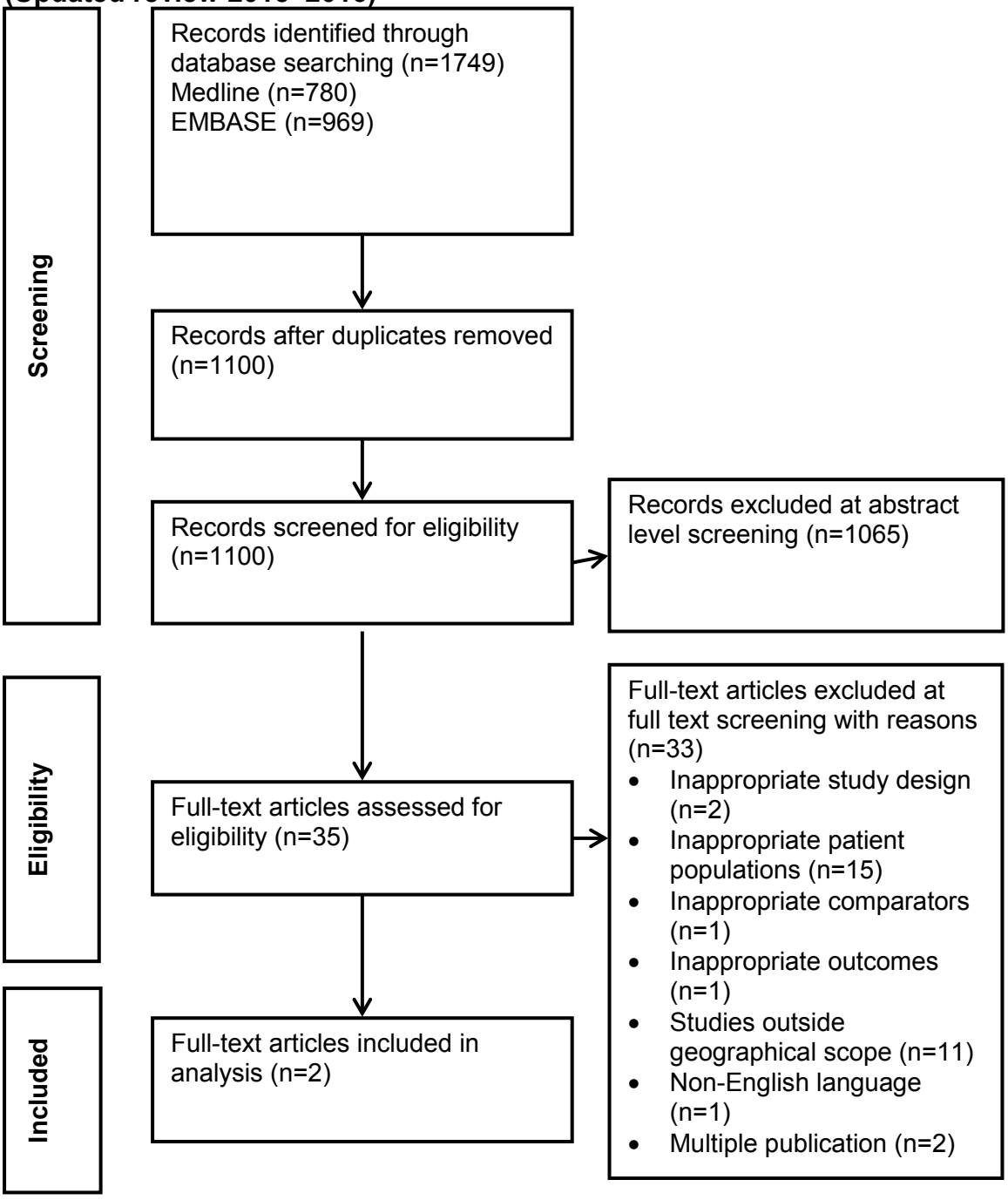


Figure 10 Published HRQoL studies systematic review - PRISMA diagram (Updated review 2015–2016)



Included studies

In total, 15 studies were identified from the electronic databases that measured and reported HRQL of severe and very severe COPD patients. Of these, none were conducted only in the UK. However, two studies - Rutten-van Molken 2006[90] and Menn 2010[91] - specifically used the EQ-5D UK value set. Five studies - Jones

2011,[92] Janson 2013,[93] Fletcher 2011,[94] Rutten-van Molken 2006,[90] and Punekar 2007[95] - were conducted multi-nationally, four - Rodriquez Gonzalez-Moro 2009,[96] Lopez-Campos 2015,[97] Miravitlles 2014,[98] and Martin 2008[99] in Spain, two each in the US (Lin 2014,[51] Solem 2013[100]) and Germany (Menn 2010,[91] Wacker 2016[101]) and one each in Italy (Di Marco 2006)[102] and France (Burgel 2012)[103]. In all but two studies (Fletcher 2011,[94] Rodriquez Gonzalez-Moro 2009[96]) disease severity was based on the GOLD criteria.

Two different types of disease-specific (CAT, SQRQ) and generic HRQL (SF-12, EQ-5D) instruments were utilised in the included studies. Of 15 studies, eight (Fletcher 2011,[94] Lin 2014,[51] Menn 2010,[91] Miravitlles 2014[98] Rutten-van Molken 2006,[90] Solem 2013,[100] Wacker 2016,[101] Punekar 2007[95]) reported EQ-5D utility values and one of the studies (Menn 2010[91]) also reported SF-6D utility values. SF-12 scores were reported in four studies: Jones 2011,[92] Janson 2013,[93] Menn 2010,[91] Martin 2008.[99] These utilities values are presented in Table 34. Six studies (Fletcher 2011,[94] Lin 2014,[51] Menn 2010,[91] Rutten-van Molken 2006,[90] Miravittles 2014,[98] Wacker, 2016[101]) presented EQ-5D VAS scores in addition to EQ-5D time trade-off values. Two COPD-specific HRQoL instruments, SGRQ and CAT, were used in seven studies and these are presented in Table 34. Six (Burgel 2013,[103] Di Marco 2006,[102] Jones 2011,[92] Rutten-van Molken 2006,[90] Solem 2013,[100] Wacker 2016[101]) used SGRQ and two (Lopez-Campos 2015,[97] Wacker 2016[101]) used CAT. Two or more HRQL instruments were used in six studies (Jones 2011,[92] Rutten-van Molken 2006,[90] Wacker 2016,[101] Solem 2013,[100] Menn 2010,[91] Miravittles 2014[98])

Table 34: Published HRQoL studies systematic review – summary of health state utility values

Author (Year)	Country	Population	HRQL Instrument	Disease Severity	Sample size	Mean utility score	SD
Menn *et al.* (2010)[91]	Germany	Minimum age of 45, prior diagnosis of COPD and sufficient knowledge of German language, admitted for an exacerbation	SF-6D	Severe	34	0.61	0.13
				Very Severe	83	0.54	0.08
Fletcher *et al*. (2011)*[94]	Multi-national (Germany, UK, US)	45-67 years, reporting a physician diagnosis of COPD	EQ-5D	Severe	521	0.41	0.02
Lin *et al.* (2014)[51]	US	Patients with a diagnosis of COPD, based on the GOLD spirometric criteria and ≥40 years of age	EQ-5D	Severe	165	0.76	0.17
				Very Severe	50	0.74	0.15
Menn *et al.* (2010)[91]	Germany	Minimum age of 45, prior diagnosis of COPD and sufficient knowledge of German language admitted for an exacerbation	EQ-5D German value set	Severe	34	0.62	0.26
				Very Severe	83	0.6	0.26
Menn *et al.* (2010)[91]	Germany	Minimum age of 45, prior diagnosis of COPD and sufficient knowledge of German language admitted for an exacerbation	EQ-5D UK value set	Severe	34	0.46	0.31
				Very Severe	83	0.44	0.31
Miravitlles *et al.* (2014)[98]	Spain	Aged ≥40 years, with a diagnosis of COPD of >12 months confirmed by spirometry	EQ-5D [GOLD 2007]	Severe	145	0.72	0.29
				Very Severe	66	0.57	0.35
			EQ-5D [GOLD 2013]	Severe	30	0.88	0.25
				Very Severe	222	0.66	0.31

Punekar (2007) [c95]	Multi-national	40 years of age or older with COPD, emphysema, and / or chronic bronchitis and a history of smoking who were personally seen by a physician during or immediately after the consultation	Severe / very severe		EQ-5D	PCP:0.62 RSL 0.64	PCP: 0.56-0.68 RS: 0.61-0.67
Rutten-van Mölken *et al.* (2006)[90]	Multi-national (13 countries; details not provided)	COPD patients, ≥ 40 years of age, cigarette smoking history of at least 10 pack-years	EQ-5D UK Value set	Severe	513	0.75	0.731-0.768 [a]
			US value set			0.803	0.79-0.816 [a]
			UK value set	Very Severe	91	0.647	0.598-0.695 [a]
			US value set			0.731	0.699-0.762 [a]
Solem *et al.* (2013)[100]	US	Adults (≥40 years of age) who had been diagnosed with severe or very severe COPD	EQ-5D	Severe	190	0.707	0.174
				Very Severe	124	0.623	0.234
Wacker *et al.* (2016),[101] Karch *et al.* (2016)[104]	Germany	Patients ≥ 40 years of age with physician diagnosed COPD or chronic bronchitis	EQ-5D	Severe	874	0.81	0.21 [b]
				Very Severe	249	0.74	0.24 [b]

EQ, EuroQol; GOLD, Global Initiative for Chronic Obstructive Lung Disease; PCP, primary care physician; RS, respiratory specialist; SD, Standard Deviation; SF, Short Form.

[*]Disease severity by Medical Research Council Dyspnea Scale

[a] 95% confidence interval reported

[b] Unadjusted means

Table 35: Published HRQoL studies systematic review – Summary of HRQoL results

Author (Year)	Country	Population	HRQL Instrument	Disease Severity	Sample size	Mean	SD
Jones *et al.* (2011)[92]	Multi-national (Germany, France, Spain, UK)	Age 40-80 years of age with an established COPD history	SF-12	Severe	551	PCS: 35.7	PCS: 8.7
						MCS: 47	MCS: 12
				Very Severe	144	PCS: 31.7	PCS: 8.6
						MCS: 43.7	MCS: 12.9
Janson *et al.* (2013)[93]	Multi-national (18 countries specified)	Population-based sample not institutionalised, ≥40 years of age	SF-12	Severe	257	PCS: 38	PCS: -
						MCS: 49	MCS: -
				Very Severe	40	PCS: 35	PCS: -
						MCS: 45	MCS: -
Martin *et al* (2008)[99]	Spain	≥ 40 years of age with a previously confirmed diagnosis of COPD (via history or spirometry) seeking consultation related to their pulmonary condition	SF12	Severe	1523	PCS: 30.6	PCS: 9.5
						MCS: 43.9	MCS: 13
Menn *et al.* (2010)[91]	Germany	Minimum age of 45 years, prior diagnosis of COPD and sufficient knowledge of German language admitted for an exacerbation	SF-12	Severe	34	PCS: 28	PCS: 8
						MCS: 47	MCS: 11
				Very Severe	83	PCS: 27	PCS: 5
						MCS: 39	MCS: 10
Burgel *et al.* (2013)[103]	France	COPD that's spirometry diagnosed, in stable condition	SGRQ	Severe	110	49.3 [a]	34.5-60.2 [a]
				Very Severe	60	63.6 [a]	45.6-70.9 [a]
Di Marco *et al.* (2006)[102]	Italy	COPD diagnosis via ATS criteria	SGRQ	Severe	59	46.6	2.9
				Very Severe	29	53.5	1.7
Jones *et al.* (2011)[92]	Multi-national (Germany, France,	40-80 years of age with an established COPD history	SGRQ	Severe	551	50.2	18.6

	Spain, UK)			Very Severe	144	58.6	17.7
Rutten-van Mölken *et al.* (2006)[90]	Multi-national (13 countries; details not provided)	COPD patients, age ≥ 40 years, cigarette smoking history of at least 10 pack-years	SGRQ	Severe	513	46.51	45.08-47.93 [b]
				Very Severe	91	57.31	54.37-60.24 [b]
Solem *et al.* (2013)[100]	US	Adults (≥40 years of age) who had been diagnosed with severe or very severe COPD	SQRQ	Severe	190	61.1	19
				Very Severe	124	70.1	21.3
Wacker *et al.* (2016); [101]Karch *et al.* (2016)[104]	Germany	Patients ≥ 40 years with physician diagnosed COPD or chronic bronchitis	SGRQ	Severe	874	48.6	17.9 [c]
				Very Severe	249	58.4	18 [c]
Fletcher *et al*. (2011)*[94]	Multi-national (Germany, UK, US)	45-67 years of age, reporting a physician diagnosis of COPD	EQ-5D VAS	Severe	521	45.9	-
Lin *et al.* (2014)[51]	US	Patients with a diagnosis of COPD, based on the GOLD spirometric criteria and ≥40 years of age	EQ-5D VAS	Severe	165	65.7	20.2
				Very Severe	50	61.1	19.7
Menn *et al.* (2010)[91]	Germany	Minimum age of 45 years, prior diagnosis of COPD and sufficient knowledge of German language admitted for an exacerbation	EQ-5D VAS	Severe	34	42	16
				Very Severe	83	37	13
Rodriguez Gonzalez-Moro *et al.* (2009)**[96]	Spain	Outpatient men or women, older than 40 years, diagnosed with moderate (stage II) or severe／very severe COPD (stage III／IV)	EQ-5D VAS	Severe / very severe	-	45.9	44.9-46.7 [b]
Rutten-van Mölken *et al.* (2006)[90]	Multi-national (13 countries; details not provided)	COPD patients, ≥ 40 years of age, cigarette smoking history of at least 10 pack-years	EQ-5D VAS	Severe	513	62.45	60.97-63.92 [b]
				Very Severe	91	57.84	54.52-61.16 [b]

Wacker *et al.* (2016); [101]Karch *et al.* (2016)[104]	Germany	Patients ≥ 40 years of age with physician diagnosed COPD or chronic bronchitis	EQ-5D VAS	Severe	874	52.2	18.8 [c]
				Very Severe	249	45.5	17.8 [c]
Lopez-Campos *et al.* (2015)[97]	Spain	Patients diagnosed with COPDs reported in their medical records, >40 years of age who were smokers or ex-smokers with a history of >10 pack-years	CAT	Severe	-	17.6	7
				Very Severe	-	21.8	6.9
Wacker *et al.* (2016); [101]Karch *et al.* (2016)[104]	Germany	Patients ≥ 40 years of age with physician diagnosed COPD or chronic bronchitis	CAT	Severe	874	19.4	7.2 [c]
				Very Severe	249	22.1	6.8 [c]

ATS, American thoracic society; CAT, COPD assessment test; EQ, EuroQol; GOLD, Global Initiative for Chronic Obstructive Lung Disease; MCS, Mental component summary; PCS, Physical component summary; SD, Standard deviation; SF, Short form; SGRQ, St. george's respiratory questionnaire; VAS, Visual analogue scale

[*]Disease severity by Medical Research Council (MRC) Dyspnea Scale. [**] Disease severity by Spanish Society of Chest Diseases and Thoracic Surgery (SEPAR)

[a] Median and interquartile range are reported. [b] 95% confidence interval reported.[c] Unadjusted means

Adverse reactions

The model includes pneumonia (the most common serious adverse event), along with the three most common adverse events of any grade (diarrhoea, weight decrease, nausea) observed in REACT. The rates of both treatment emergent serious adverse events (TESAEs) and treatment emergent adverse events (TEAEs) are provided in Table 36 and Table 37. Given that the majority of TEAEs are of grade 1 and 2 severity, which is not significant enough to impact costs or disutilities, the base case applies rates for TESAEs only. Adverse events rates (for the trial period only) are applied in the first cycle of treatment. As noted in the SmPC (Appendix 2) "The majority of these adverse reactions were mild or moderate. These adverse reactions mainly occurred within the first weeks of therapy and mostly resolved on continued treatment." Furthermore, it is assumed that that the majority of patients with uncontrolled adverse reactions will discontinue treatment and given that in REACT 95.3% of TEAEs occurred within the first year post-treatment initiation, long-term adverse events are not anticipated (Data on file; REACT Clinical Study Report). Scenario analyses assess the impact of either including all TEAEs, or excluding them from the analysis.

Owing to time constraints associated to the acquisition of roflumilast by AstraZeneca, it was not possible to build discontinuation into the economic model. Consequently, with the treatment effect being inclusive of those patients who discontinued, the base case analysis is a conservative estimate of the cost effectiveness of roflumilast.

Table 36: Occurrence of TESAEs

TEAE	Roflumilast arm (mean, SE)	Comparator arm (mean, SE)
Diarrhoea	0.21% (0.15%)	0.21% (0.15%)
Weight loss	0.41% (0.21%)	0.00% (0.00%)
Nausea*	0.00% (0.00%)	0.00% (0.00%)
Pneumonia	3.41% (0.58%)	3.21% (0.57%)

*Serious nausea did not occur in ≥2 patients and as such is not reported. This is equal to zero.

Table 37: Occurrence of TEAEs

TEAE	Roflumilast arm (mean, SE)	Comparator arm (mean, SE)
Diarrhoea	10.23% (0.97%);	3.62% (0.60%)
Weight loss	9.09% (0.92%)	2.79% (0.53%)
Nausea	5.68% (0.74%);	1.55% (0.40%)
Pneumonia	4.03% (0.63%)	4.65% (0.68%)

Health-related quality of life data used in cost effectiveness analysis

HRQoL weights (utilities) are applied in the model for COPD health states, exacerbations, and TEAE. It is assumed that all utilities are constant over time.

COPD health state utilities and exacerbation disutilities

Due to their reduced lung function, patients with COPD suffer impaired HRQoL.[85] Rutten-van Molken et al. (2006) sampled 1,235 patients across 13 countries including 513 patients with severe COPD and 91 patients with very severe COPD using the EQ-5D questionnaire, and UK general population preference weights (EQ-5D UK tariff).[90] A difference between COPD severity classifications was demonstrated when adjusting for factors known or expected to impact HRQoL, such as comorbidities (Table 38).

Table 38: Rutten van Molken 2006 utility scores

Severity	Mean	SE	Upper 95% CI	Lower 95% CI
Severe COPD	0.750	0.009	0.768	0.731
Very severe COPD	0.647	0.025	0.695	0.598

A subsequent analysis sampled 239 Dutch adults, also based on EQ-5D, but used the Dutch time trade-off tariff. In this analysis the authors also analysed the quality of life decrements patients experienced due to exacerbations. These health state utilities and disutilities are shown in Table 39. The decrements for exacerbations represent the aggregate reduction in quality of life across exacerbations rather than annual utility values.

Table 39: Rutten van Molken 2009 utility scores

Severity	Mean	SE	Upper 95% CI	Lower 95% CI
Severe COPD	0.717	0.008	0.733	0.701
Very severe COPD	0.522	0.008	0.538	0.506
Moderate exacerbations	-0.010	0.007	0.004[#]	-0.024
Severe exacerbations	-0.042	0.009	-0.024	-0.060

[#]capped at 0 in the model to ensure application as a disutility

In the base case, COPD health state utilities from Rutten-van Molken et al. (2006) are used as these are derived using UK general population preference weights which are in line with the NICE clinical guideline cost effectiveness model.[2] Rutten-van Molken et al. (2009) provides the decrements for exacerbations, as although these are using patient preference rather than population preferences their use of the EQ-5D ensures they are applicable and broadly in line with the NICE reference case. The former estimates higher utilities for the COPD health states than Rutten-van Molken (2009) especially for very severe COPD. A series of scenario analyses assesses the impact of using alternative sources of utility weights in a scenario analysis, including using a US study.

TEAE disutilities

Although the vast majority of TEAEs within REACT are of grade 1 and 2 severities, to be conservative the utility loss due to each TEAE is assumed to be 0.042. This is equal to that of a severe exacerbation from Rutten-van Molken 2009.[50]

Summary

A summary of the utility values applied in the analysis are detailed in Table 40.

Table 40: Summary of utility values for cost effectiveness analysis

State	Utility value: mean (SE)	95% CI	Reference in submission (section and page number)	Justification
Severe COPD	0.750 (0.009)	0.731 to 0.768	Table 38	UK general population weights
Very severe COPD	0.647 (0.025)	0.598 to0.695	Table 38	UK general population weights
Moderate exacerbations	-0.010 (0.007)	0 to 0.024	Table 39	EQ-5D TTO
Severe exacerbations	-0.042 (0.009)	-0.060 to -0.024	Table 39	EQ-5D TTO
TEAE	-0.042	NA	NA	Conservative assumption

5.5 Cost and healthcare resource use identification, measurement and valuation

Table 41 lists the monthly maintenance, exacerbation and adverse event costs used in the cost effectiveness model.

Table 41: List of resource use and associated costs in the economic model

Resource use	Cost
Maintenance	
Severe COPD monthly maintenance	£32.57
Very severe COPD monthly maintenance	£106.90
Exacerbations	
Moderate exacerbations	£103.85
Severe exacerbations	£1,724.43
Adverse events	
Diarrhoea, weight loss and nausea	£44.00
Pneumonia	£2518.00

Resource identification, measurement and valuation studies

Methods

Search strategy

A systematic review was undertaken in May 2015 and updated in July 2016 to identify and summarise studies that reported relevant cost and healthcare resources use data. Systematic searches were initially carried out in four electronic databases: Embase, Medline, EconLit and NHS EED between 2004 and 2015. However, owing to a large volume of literature, only studies published after 2012 were included. Due to the reason specified earlier, searches were not performed in NHS EED during the updated review (2015-2016). The search strategies were designed to capture data from eight countries: UK, US, Canada, Germany, France, Italy, Spain and Australia. The search strategies are presented in Appendix 8.

Study selection

Inclusion criteria are provided in Table 42. PRISMA diagrams present the selection process graphically in the original and updated review (Figure 11 and Figure 12). A single reviewer screened and identified references based on titles and abstracts. Two reviewers independently assessed the full text articles for inclusion and a third reviewer was consulted where there were differences between results. As a common search strategy was used to identify cost effectiveness and cost / resource use studies, relevant records were divided at the full-text review stage. Data were extracted by a single reviewer for the full text article that met the inclusion criteria and were validated by a second reviewer.

Table 42: Published cost and resource use systematic review - inclusion criteria

	Inclusion criteria
Patients	Severe / very severe COPD (defined as FEV_1 <50% predicted level, corresponding to pre-2013 GOLD report stages III and IV)
Interventions / comparators	No intervention or pharmacological interventions
Outcomes	• Direct and indirect costs (E.g. cost of treatment, hospitalisations, exacerbations, medication, general practitioner or specialist visits, inpatient and outpatient care, rehabilitation, productivity losses due to absenteeism, impairment, caregiver costs, etc.) • Resource utilisation (including resource use per patient with exacerbations and non-exacerbation)
Geography	UK, US, Canada, Germany, France, Italy, Spain and Australia
Language	English only
Date restriction	2012-current

COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease

Figure 11 Published cost and resource use systematic review – PRISMA diagram (Original review 2012–2015)

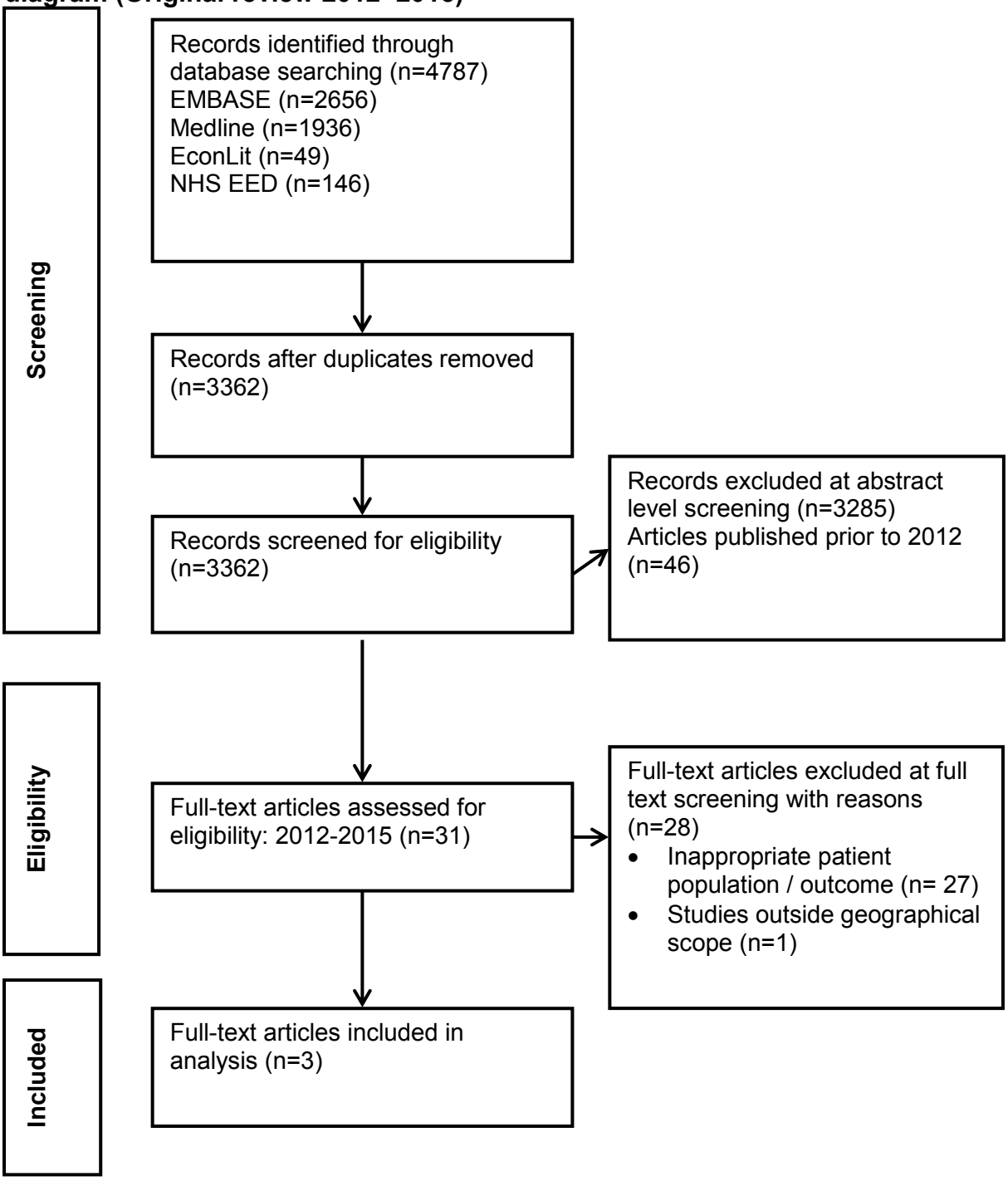
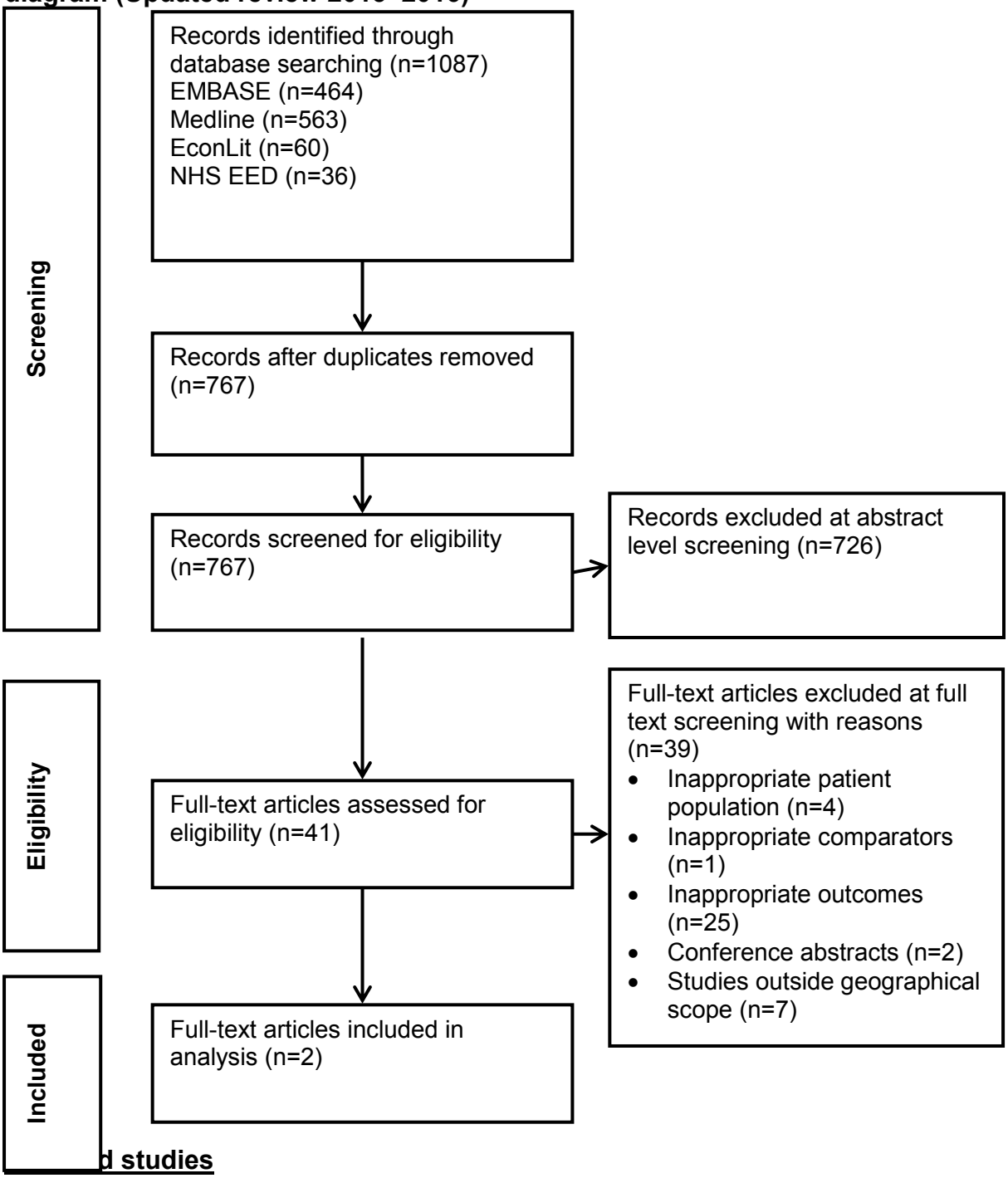


Figure 12 Published cost and resource use systematic review – PRISMA diagram (Updated review 2015–2016)



d studies

Five studies were identified in total that report data on cost and resource use of severe and very severe COPD patients. Of the five studies, three (Punekar 2014,[105] Punekar 2015,[106] Thomas 2014[107]} were conducted in the UK and the remaining two were conducted in Germany (Wacker 2016[101]) and Canada (Maleki-Yazdi 2012[108] Three studies (Punekar 2015,[106] Thomas 2014, [107], Wacker 2016[101]) reported

resource use data and these are presented in Table 43. Four studies (Maleki-Yazdi 2012,[108] Punekar 2014,[105] Punekar 2015,[106], Wacker 2016[101]) estimated costs relating to the population of interest; these are provided in Table 44.

Table 43: Published cost and resource use systematic review - resource use summary

Author, Year	Country	Study design	Population	n	Resource item	Mean	Range, SD	Unit
Punekar, 2015*	UK	Retrospective cohort study (data from primary care electronic medical records)	Whole population	7,881				
			Stage 3 (Severe)	1,754	GP surgery visits	12.64	-	Per year
					GP out of office visits	0.18		
					GP administrative contacts	29.02		
					GP surgery correspondence	1.36		
					GP practice nurse visits	4.83		
					GP home visits	0.32		
					Moderate exacerbations	0.6		
					Severe exacerbations	0.14		
					Non-COPD hospitalisation	0.47		
			Stage 4 (Very severe)	285	GP surgery visits	12.22	-	Per year
					GP out of office visits	0.3		
					GP administrative contacts	30.74		
					GP surgery correspondence	1.22		
					GP practice nurse visits	5.03		
					GP home visits	0.38		
					Moderate exacerbations	0.86		
					Severe exacerbations	0.19		
					Non-COPD hospitalisation	0.52		

Thomas, 2014	United Kingdom	Retrospective observational study	Whole population	511	Drug treatment - any LABA (single agent or combination LABA-ICS device)	403 (79%)	-	Number (%) / observation period
					Drug treatment - any LAMA	295 (58%)		
					Drug treatment - any ICS (single agent or combination LABA-ICS device)	413 (81%)		
			Severe COPD	145	Primary care COPD contacts	Median: 3.33	IQR: 2.33-5.00	Per year
					Secondary care COPD visits	Median: 0.33	IQR: 0.00-1.00	
					COPD hospitalisations	Median: 0	0.00-0.00	
					Patients hospitalised for COPD	14.3 (10%)	-	Number (%) of patients / year
					Length of hospital stay	Median: 5	IQR: 2-9	Days
			Very severe COPD	52	Primary care COPD contacts	Median: 3.67	IQR: 2.67-6.42	Per year
					Secondary care COPD visits	Median: 1.00	IQR: 0.00-2.08	Per year
					COPD hospitalisations	Median: 0.00	IQR: 0.00-0.33	Per year
					Patients hospitalised for COPD	8.3 (16%)	-	Number (%) of patients / year
					Length of hospital stay	Median: 6	IQR: 3-11	Days
Wacker, 2016**	Germany	Cross-sectional and observational study	Whole population	2139				
			COPD Grade 3	810	*Outpatient services (3 months)*	95.8	-	% User in 3 months

					Outpatient visits	6.1	5.5	N visits in 3 months, unadjusted
					General Practitioner	2.4	2.8	
					Specialist	3.7	4	
					Inpatient services (12 months)	41.9	-	% User in 12 months
					Length of hospital stay	7	15.9	Days
					Prescribed medication (7 days)	99.5	NA	% User in 7 days
					Prescribed drugs	6.6	3.2	N drugs in 7 days
			COPD Grade 3, Participants <65 years	352	Work absenteeism: retired	51.4	-	%, unadjusted
					Work absenteeism: employed	31.8	-	%, unadjusted
					Sick days (12 months)	70.6	-	% with sick days, in 12 months
					Sick days (12 months)	34.1	53.9	Days, in 12 months
			COPD Grade 4	224	*Outpatient services (3 months)*	96		%, in 3 months, unadjusted
					Outpatient visits	5.4	4.3	N visits, in 3 months, unadjusted
					General Practitioner	2.2	2	
					Specialist	3.3	3.3	
					Inpatient services (12 months)	54.3	-	% in 12 months, unadjusted
					Length of hospital stay	11.4	20.1	Days, unadjusted
					Prescribed medication (7 days)	99.1	-	% in 7 days, unadjusted
					Prescribed drugs	7	3.3	N drugs in 7 days

			COPD Grade 4, Participants <65 years	133	Work absenteeism: retired	72.2	-	%, unadjusted
					Work absenteeism: employed	15.8	-	%, unadjusted
					Sick days (12 months)	76.2	-	% with sick days, in 12 months, unadjusted
					Sick days (12 months)	40.1	71	Days, in 12 months, unadjusted

COPD, Chronic obstructive pulmonary disease; ICS, Inhaled corticosteroid; LABA, Long-acting beta agonist; LAMA, long-acting muscarinic antagonist.

* Resource use did not include medication costs.

**All analyses are unadjusted.

Table 44: Published cost and resource use systematic review – cost summary

Author, Year	Country	Study design	Population	n	Type of Cost	Mean value	Range, SD	Cost unit
Maleki-Yazdi, 2012	Canada	Chart review and patient survey	Whole population	285	Medications	**CAD (2009)** 1,755.00		Per year per patient
					ER visits	53.00		
					Hospitalisations	1,497.00		
					Ambulance	25.00		
					Rehabilitation programs	22.00		
					Medical devices	27.00		
					Healthcare professionals	306.00		
					Procedures	145.00		
					Patient travel to health care professional	46.00		
					Direct costs	3,895.00		
					Patient's missed time from work	179.00		
					Caregiver's missed time from work	73.00		
					Indirect costs	252.00		
					Total costs	4,147.00		
			GOLD 3 (severe COPD)	94	AECOPD-related cost	2,414.00		
					Maintenance-related cost	2,984.00		
					Total COPD-related cost	5,398.00		
			GOLD 4 (very severe COPD)	11	AECOPD-related cost	2,631.00		
					Maintenance-related cost	3,511.00		
					Total COPD related cost	6,141.00		

Punekar , 2014 *	United Kingdom	Retrospective cohort study (data from primary care electronic medical records)	Whole population	58,589	-	**GBP; 2011 (Medication costs only taken from 2012);**	-	Per patient per year
			GOLD Stage 3	15,497	Exacerbations	319.65		
					Non-COPD hospitalisations	672.90		
					GP surgery contact	1,297.33		
					Total costs	2,289.88		
			GOLD Stage 3; No exacerbation	7,013	Exacerbations	0.00		
					Non-COPD hospitalisations	428.50		
					GP surgery contact	1,073.42		
					Total costs	1,501.92		
			GOLD Stage 3; 1 exacerbation	3,855	Exacerbations	347.98		
					Non-COPD hospitalisations	710.18		
					GP surgery contact	1,331.90		
					Total costs	2,390.06		
			GOLD Stage 3; 2 or more exacerbations	4,629	Exacerbations	789.53		
					Non-COPD hospitalisations	1,018.99		
					GP surgery contact	1,614.04		
					Total costs	3,422.57		
			GOLD Stage 4	3,377	Exacerbations	445.53		
					Non-COPD hospitalisations	775.20		
					GP surgery contact	1,418.44		
					Total costs	2,639.17		
			GOLD Stage 4;	1,152	Exacerbations	0.00		

			No exacerbation		Non-COPD hospitalisations	405.51		
					GP surgery contact	1,100.32		
					Total costs	1,505.83		
			GOLD Stage 4; 1 exacerbation	814	Exacerbations	351.51		
					Non-COPD hospitalisations	682.12		
					GP surgery contact	1,308.08		
					Total costs	2,341.71		
			GOLD Stage 4; Two or more exacerbations	1,411	Exacerbations	871.16		
					Non-COPD hospitalisations	1,137.25		
					GP surgery contact	1,747.82		
					Total costs	3,756.23		
Punekar, 2015 *	United Kingdom	Retrospective cohort study (data from primary care electronic medical records)	Whole population	7,881		**GBP; 2011**		
			Stage 3 (Severe)	1,754	*Management costs*		-	Per patient per year, 12 month period post-diagnosis
					Exacerbations	227.00		
					Non-COPD hospitalisations	656.00		
					GP visits	1,268.00		
					Total management costs	2,151.00		
					Exacerbations	228.00		Per patient per year, 24 month period post-diagnosis
					Non-COPD hospitalisations	642.00		
					GP visits	1,222.00		
					Total management costs	2,092.00		
					Total management costs MRC Grade 1	1,469.00		

					Total management costs MRC Grade 2	1,662.00		
					Total management costs MRC Grade 3	2,041.00		
					Total management costs MRC Grade 4	2,514.00		
					Total management costs MRC Grade 5	3,492.00		
			Stage 4 (Very severe)	285	*Management costs*			Per patient Per year, 12 month period post-diagnosis
					Exacerbations	260.00		
					Non-COPD hospitalisations	642.00		
					GP visits	1,355.00		
					Total management costs	2,258.00		
					Exacerbations	313.00		Per patient per year, 24 month period post-diagnosis
					Non-COPD hospitalisations	711.00		
					GP visits	1,268.00		
					Total management costs	2,293.00		
					Total management costs MRC Grade 1	1,590.00		
					Total management costs MRC Grade 2	2,058.00		
					Total management costs MRC Grade 3	2,090.00		
					Total management costs MRC Grade 4	2,394.00		

					Total management costs MRC Grade 5	2,334.00		
Wacker, 2016 **	Germany	Cross-sectional and observational study	Whole population	2,139		**EUR; 2012**		
			COPD Grade 3	810	Outpatient costs	868.00	802.00	In 12 months, unadjusted
					Inpatient costs	4,139.00	9,356.00	
					Medication costs	2,731.00	2,998.00	
					Total direct costs	7,747.00	10,336.00	
					Adjusted direct costs	7,801.00	7058.00-8653.00	Per year
			COPD Grade 3, Participants <65 years	352	Sick days (12 months)	1,889.00	6,019.00	Days, in 12 months, unadjusted
					Premature retirement (12 months)	19,090.00	18,582.00	In 12 months, unadjusted
					Total indirect costs (12 months)	21,144.00	17,560.00	In 12 months, unadjusted
					Adjusted indirect costs: human capital approach	22,687.00	19,927.00-26494	Per year
					Indirect costs: human capital approach	22,489.00	19,854.00-25,690.00	Per year, recycled predictions
					Indirect costs: friction cost approach	918.00	699.00-1,160.00	
			COPD Grade 4	224	Outpatient costs	803.00	683.00	In 12 months, unadjusted
					Inpatient costs	6,699.00	11,869.00	
					Medication costs	2,900.00	2,959.00	

					Total direct costs	10,409.00	12,662.00	
					Adjusted direct costs	10,770.00	8,973.00-12,694.00	Per year
			COPD Grade 4, Participants <65 years	133	Sick days (12 months)	1,123.00	5,548.00	In 12 months, unadjusted
					Premature retirement (12 months)	26,798.00	16,699.00	
					Total indirect costs (12 months)	27,921.00	15,779.00	
					Adjusted indirect costs: human capital approach	33,795.00	28,561.00-41,870.00	Per year
					Indirect costs: human capital approach	33,783.00	28,225.00-41,537.00	Per year, recycled predictions
					Indirect costs: friction cost approach	467.00	207.00-767.00	

AECOPD, Acute exacerbation of chronic obstructive pulmonary disease; COPD, Chronic obstructive pulmonary disease, ER, Emergency room; MRC: Medical research council

*COPD management costs excluded non-exacerbation-related medication costs

** Over-the-counter pharmaceuticals, non-pharmacy medicines, dietary supplements, and vitamins were excluded.

Applicability of NHS Reference Costs

Stable severe and very severe COPD are generally managed in the community via GP visits. NHS reference costs are applied to severe (hospitalised) exacerbations. The weighted average cost of HRG Code DZ65 "Chronic Obstructive Pulmonary Disease or Bronchitis" non-elective short stay and non-elective long stay are used to provide a cost for this event. Also, the HRG code ASS02 "See and treat and convey" has been used to provide a cost for ambulance transport to hospital for a severe exacerbation.

Intervention and comparators' costs and resource use

The unit costs of LAMA, LABA / ICS, roflumilast and prednisolone (used in the treatment of moderate exacerbations) are detailed in Table 45. Drug costs, dose requirements and days of treatment are from the British National Formulary.[24]

Table 45: Drug unit costs

Technology	Pack size	Pack cost	Cost per dose
Roflumilast			
Roflumilast 500 µg	30	£37.71	£1.26
Roflumilast 500 µg	90	£113.14	£1.26
Average cost			£1.26
LAMA			
Spiriva® 18µg	30	£33.50	£1.12
LABA / ICS			
Symbicort (200 / 6) (×2)	120	£38.00	£0.63
Symbicort (400 / 12)	60	£38.00	£0.63
Seretide 500	60	£40.92	£0.68
Average cost (×2)[¥]			£1.30
Prednisolone[#]			
Prednisolone 5 mg	28	£1.24	£0.04
Prednisolone 25 mg	56	£75.00	£1.34
Combined cost (30 mg dose)			£1.38

[#] lowest pill burden for patients via this combination; [¥] unit cost doubled to ensure correct dosage

Table 46 summarises the calculated average monthly cost applied in the cost effectiveness analysis. The monthly cost of LABA / LAMA / ICS / ROF is calculated as £111.72 whilst LABA / LAMA / ICS alone is £73.48.

Table 46: Monthly drug costs applied in cost effectiveness analysis

Technology	Daily cost	Days of treatment per month	Cost per cycle
Roflumilast	£1.26	30.42[#]	£38.24
LAMA	£1.12	30.42[#]	£33.97
LABA / ICS	£1.30	30.42[#]	£39.51
Prednisolone 30 mg	£1.38	7	£9.69
Prednisolone 30 mg	£1.38	14	£19.37
[#]number of days in each model cycle equivalent to 365 / 12			

Health-state unit costs and resource use

The model includes costings for three broad categories:

- COPD maintenance
- COPD exacerbations
- Treatment emergent adverse events

COPD maintenance

Monthly maintenance cost calculations for severe and very severe COPD are detailed in Table 47. The cost per month for maintenance of patients with severe and very severe COPD is calculated as £32.57, and £106.90 respectively. Patients with stable severe and very severe COPD are managed in the community. BMJ Best Practice (2016)[109] states that stable COPD patients should be assessed at 6-month intervals, and we assume patients in both severe and very severe COPD states visit a GP twice a year. Other maintenance resource use was assumed to be the same as in Samyshkin 2014,[18] in which resource use estimates were based on Oostenbrink et al. conducted alongside a clinical trial.[110] These resource use assumptions were also used elsewhere.[17]

Table 47: Severe and very severe COPD monthly maintenance cost

Component	Severe COPD resource use	Very severe COPD resource use	Cost per use	Cost per month (severe COPD)	Cost per month (very severe COPD)	Resource use reference	Cost reference
GP consultation	2 per year	2 per year	£44.00	£7.33	£7.33	BMJ Best Practice	PSSRU 2015
Spirometry	2 days per year	4 days per year	£50.05[#]	£8.34	£16.68	Oostenbrink 2005	Samyshkin 2014
Influenza vaccination	75% of patients	75% of patients	£6.29	£0.39	£0.39	Oostenbrink 2005	BNF July 2016
Oxygen therapy	1.22 days per month	6.08 days per month	£13.56[¥]	£16.50	£82.49	Oostenbrink 2005	Oostenbrink 2005
Total monthly cost				£32.57	£106.90		

[#] indexed to 2015; [¥] indexed to 2015 and converted at PPP exchange rate

COPD exacerbations

BMJ Best Practice for COPD states that patients with frequent exacerbations should be followed at 2-week to 1-month intervals.[109] Thomas et al. 2014[107] reports primary care contacts by exacerbation frequency (none, infrequent and frequent). The median number of primary care contacts per year is less than recommended in BMJ Best Practice. The model applies an assumption that the ratio of contacts (Table 48) between non-exacerbators, infrequent exacerbators and frequent exacerbators can be applied to the recommended number of primary care visits to estimate the number of visits for patients without exacerbations (recommended two contacts per year), and with moderate and severe exacerbations. Standard errors are set such that the lower 95% CI is equal to half that of the mean. The total cost for "excess" primary care visits is applied at the time of the modelled exacerbation.

Table 48: "Excess" primary care contacts due to exacerbations

	Non-exacerbators	**Infrequent exacerbators**	**Frequent exacerbators**
Median number of primary care contacts per year	1.33	2.67	6.67
Ratio compared to non-exacerbators	1.00	2.01	5.02
	Non-exacerbators	**Moderate exacerbations**	**Severe exacerbations**
Number of primary care contacts per year	2.00	4.03	10.03
"Excess" number of primary care contacts per year applied in model (mean, SE)	0.00	2.03 (0.61)	8.03 (2.42)

Cost calculations for moderate and severe COPD exacerbations are as in Table 49 and Table 50. The cost per moderate exacerbation is calculated as £103.85 whilst the cost for severe exacerbations is calculated as £1,724.43. This is applied in the month that the exacerbation occurs.

Table 49: Moderate COPD exacerbation costs

Component	Mean value	Cost per use	Cost per exacerbation	Resource use reference	Cost reference
Excess GP consultations (per year)	2.03	£44.00	£89.32	See Table 49	PSSRU 2015
Prednisolone (7 days) ~	50%	£9.69	£4.84	Assumption	See Table 46
Prednisolone (14 days) ~	50%	£19.37	£9.69	Assumption	See Table 46
Total cost			£103.85		

Table 50: Severe COPD exacerbation costs

Component	Mean value	Cost per use	Cost per exacerbation	Resource use reference	Cost reference
Excess GP consultations (per year)	8.03	£44.00	£353.32	See Table 49	PSSRU 2015
Hospital admission (%)	100%	£1,183.06	£1,183.06	By definition	NHS Ref Costs (DZ65)*
Ambulance transport (%)	90%	£223.02	£209.72	Assumption	NHS Ref Costs (ASS02)
Total cost			£1,724.43		

*weighted average of non-elective inpatient short stay and long stay

Adverse reaction unit costs and resource use

The majority of TEAEs in REACT were minor.[14] Although these are likely to have negligible resource and cost implications, the cost of each has been assumed to be equivalent to that of a GP consultation (£44). Pneumonia by contrast is costed at £2,518.00, the weighted average of HRG DZ11 "Lobar, Atypical or Viral Pneumonia", non-elective inpatient short stay and non-elective inpatient long stay.

Miscellaneous unit costs and resource use

Not applicable.

5.6 Summary of base-case de novo analysis inputs and assumptions

Summary of base-case de novo analysis inputs

A summary of the key variables included in the cost effectiveness analysis are provide in Table 51.

Table 51: Summary of variables applied in the base case analysis

Variable	Value (SE)	Measurement of uncertainty distribution	Reference to section in submission
Baseline characteristics			
Age	64.70	NA	Section 5.2
Male	74.60%	NA	Section 5.2
Mean height males	172.74 cm	NA	Section 5.2
Mean height females	161.67 cm	NA	Section 5.2
FEV_1% predicted (severe COPD patients) at start of model	40%	NA	Section 5.2
Progression from severe to very severe COPD			
FEV_1 decline per annum	0.052 (0.008)	Gamma	Section 5.3
Roflumilast lung function improvement	0.000	NA	Section 5.3
Monthly transition probability	1.20%	NA	Section 5.3
Exacerbation rates (annual)			
LABA / LAMA / ICS / roflumilast	Negative binominal regression		Section 5.3
LABA / LAMA / ICS	Negative binominal regression		Section 5.3
Mortality			
Severe exacerbations CFR	Table 31	NA	Section 5.3
Background mortality	Corrected UK life tables	NA	Section 5.3

LABA / LAMA / ICS / roflumilast TESAEs			
Diarrhoea	0.21%(0.15%)	Beta	Section 5.4
Weight loss	0.41%(0.21%)	Beta	Section 5.4
Nausea*	0.00% (0.00%)	Beta	Section 5.4
Pneumonia	3.41% (0.58%)	Beta	Section 5.4
LABA / LAMA / ICS TESAEs			
Diarrhoea	0.21% (0.15%)	Beta	Section 5.4
Weight loss	0.00% (0.00%)	Beta	Section 5.4
Nausea*	0.00% (0.00%)	Beta	Section 5.4
Pneumonia	3.21% (0.57%)	Beta	Section 5.4
HRQoL			
Severe COPD	0.750 (0.009)	Beta	Section 5.4
Very severe COPD	0.647 (0.025)	Beta	Section 5.4
Moderate exacerbations	-0.010 (0.007)	Beta	Section 5.4
Severe exacerbations	-0.042 (0.009)	Beta	Section 5.4
TEAEs	-0.042	NA	Section 5.4
Monthly Drug Costs			
Roflumilast	£38.24	NA	Section 5.5
LAMA	£33.97	NA	Section 5.5
LABA / ICS	£39.51	NA	Section 5.5
Prednisolone 30mg	£9.69	NA	Section 5.5
Prednisolone 30mg	£19.37	NA	Section 5.5
Other Costs			
Severe COPD monthly maintenance	£32.57	Applied to individual components	Section 5.5
Very severe COPD monthly maintenance	£106.90		Section 5.5
Moderate exacerbations	£103.85		Section 5.5
Severe exacerbations	£1,724.43		Section 5.5
Adverse events	£44.00	NA	Section 5.5
CI, confidence interval			

Assumptions

The effect of certain assumptions in the model (e.g. exclusion of lung function benefit), may differ between instances where patients are modelled as staring in severe rather than very severe COPD.

The main assumptions within the model are:

- Differences in exacerbation rate ratios between the analyses based on excluding patients not treated with LAMA and those controlling for LAMA use are not supported by any apparent interaction effect. The difference in the

base case treatment effects, though due to chance, provide conservative estimates of effect and are assumed for the model base case.

- Lung function benefit due to treatment with roflumilast is assumed to be ignorable for the base case analyses, despite patients remaining at risk for progression from severe to very severe COPD.
- The average FEV_1% predicted for severe COPD patients at the start of model is the midpoint of the FEV_1% range for severe COPD (30% to 50%).
- The use of an independent source for exacerbation mortality allows for an appropriate adjustment of the SMRs as applied from Samyshkin 2014.
- Applying the adverse events rates for the entire trial period in the first month is appropriate as long-term adverse events are not anticipated.
- All TEAE disutilities are equal to that of a severe exacerbation.
- Severe and very severe COPD patients have two GP visits a year for general maintenance.
- That the relative difference in rates of primary care contacts in Thomas et al. 2014 between non-exacerbators, infrequent exacerbators and frequent exacerbators can be applied to the number of primary care visits recommended in BMJ Best Practice for non exacerbators (two p.a.) to estimate the number of visits for patients with moderate and severe exacerbations.
- During a moderate exacerbation 50% of patients will be treated with a 7-day course of prednisolone and 50% of patients will be treated with a 14-day course.
- During a severe exacerbation event 90% of patients will be transported to hospital by ambulance.

- Costs of diarrhoea, weight loss and nausea adverse event management can be represented by a GP consultation (£44).

5.7 Base-case results

Base case incremental cost effectiveness analysis results

LABA / LAMA / ICS / roflumilast accumulates total (discounted) costs of £22,930 and 6.14 QALYs. LABA / LAMA / ICS alone accumulates total (discounted) costs of £19,933 and 5.98 QALYs. This equates to LABA / LAMA / ICS / roflumilast producing an additional 0.16 QALYs at an incremental cost of £2,996 when compared to LABA / LAMA / ICS alone. This generates a base case ICER of £18,774. Table 52 presents the base case incremental cost effectiveness results in detail. This demonstrates that LABA / LAMA / ICS / roflumilast is cost effective at the £20,000 per QALY threshold.

Table 52: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
LABA / LAMA / ICS / roflumilast	£22,930	8.95	6.14	£2,996	0.18	0.16	£18,774
LABA / LAMA / ICS	£19,933	8.77	5.98	-	-	-	-

LYG, life years gained

Clinical outcomes from the model

Comparison of rate ratios observed in the trial (median exposure to treatment was 364 days for both arms of REACT) and those generated by the model (in the first year) are shown in Table 53. As REACT contained both severe and very severe COPD patients, a mixed population has been applied in the model to generate these results.

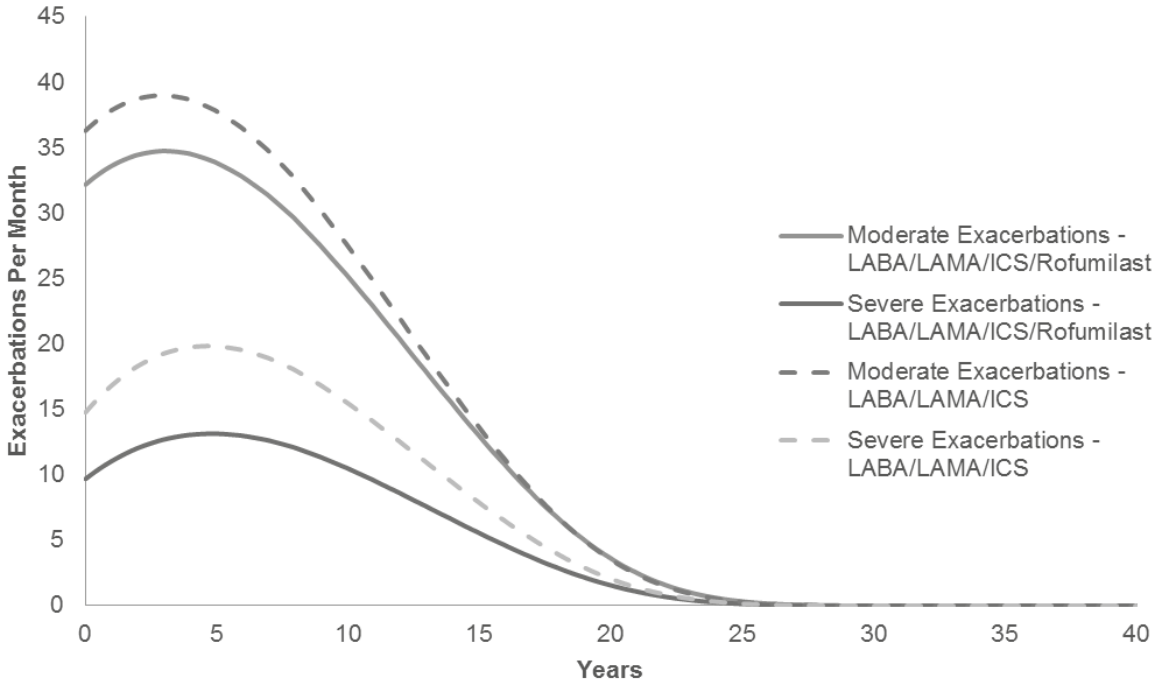
Table 53: Clinical outcomes (exacerbation rate ratios)

Exacerbations	Trial	Model	Difference (%)
Moderate or Severe	0.810	0.810	0.01%
Moderate	0.879	0.887	0.87%
Severe	0.688	0.656	4.66%

This demonstrates the high predictive ability of the model to replicate the trial. The minor differences in rate ratios are likely due to other facets of the model such as the transition between severe and very severe COPD which may be different between the model and trial.

Proportion of the cohort in the health state over time (Markov trace)

Markov traces for the proportion of the cohort in each health state, for LABA / LAMA / ICS / roflumilast and LABA / LAMA / ICS are provided in Figures 13 and 14. There are minor differences between the health states driven by a higher proportion of patients in the dead state for LABA / LAMA / ICS due to more deaths from a higher severe exacerbation rate. Differences in the number of moderate and severe exacerbations over time for the cohort of patients are provided in Figure 15



, peaking approximately 5 years in as patients' transition from severe to very severe COPD.

Figure 13: LABA / LAMA / ICS / roflumilast Markov trace

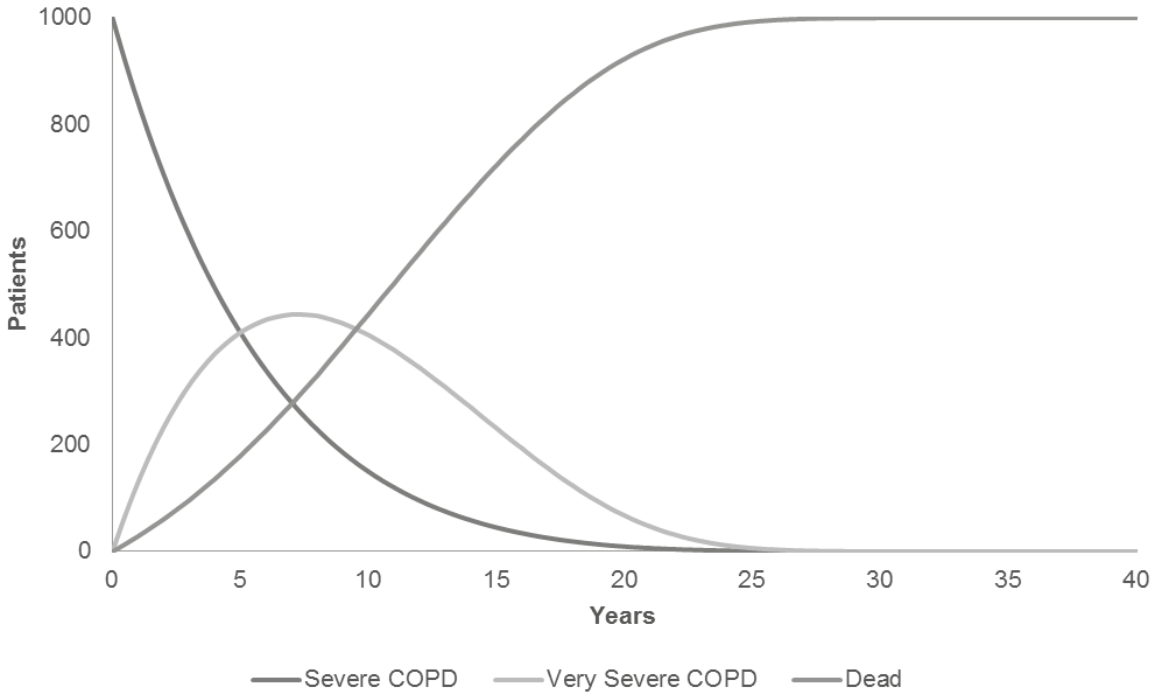


Figure 14: LABA / LAMA / ICS Markov trace

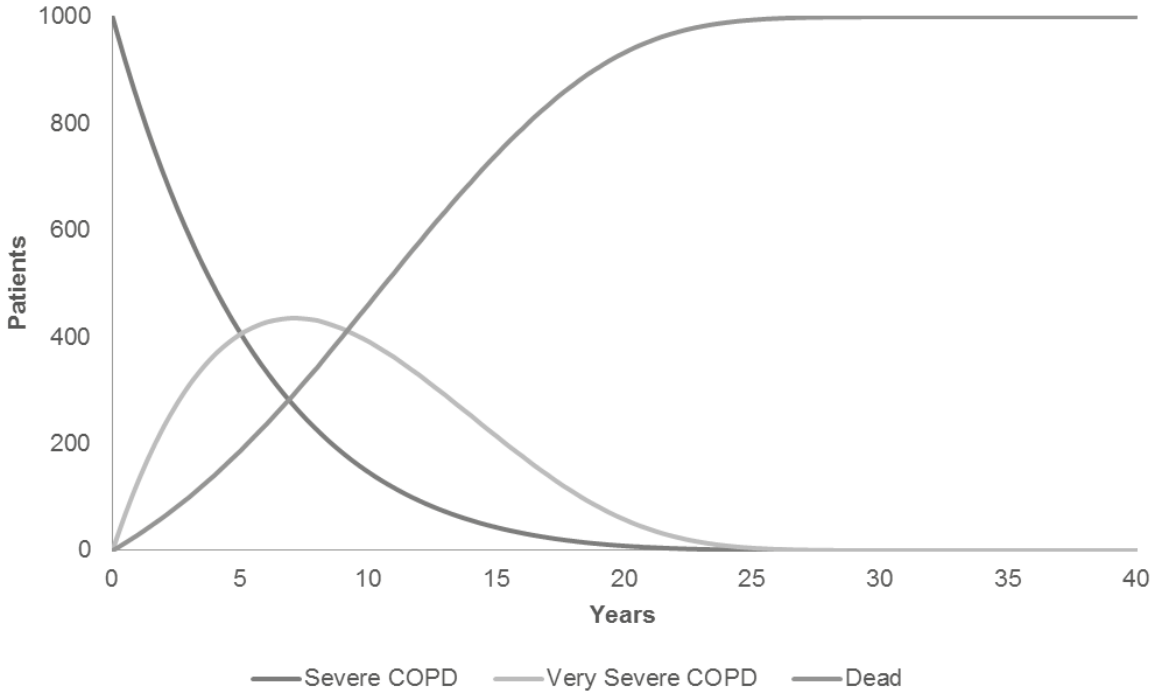


Figure 15: Number of exacerbations per month

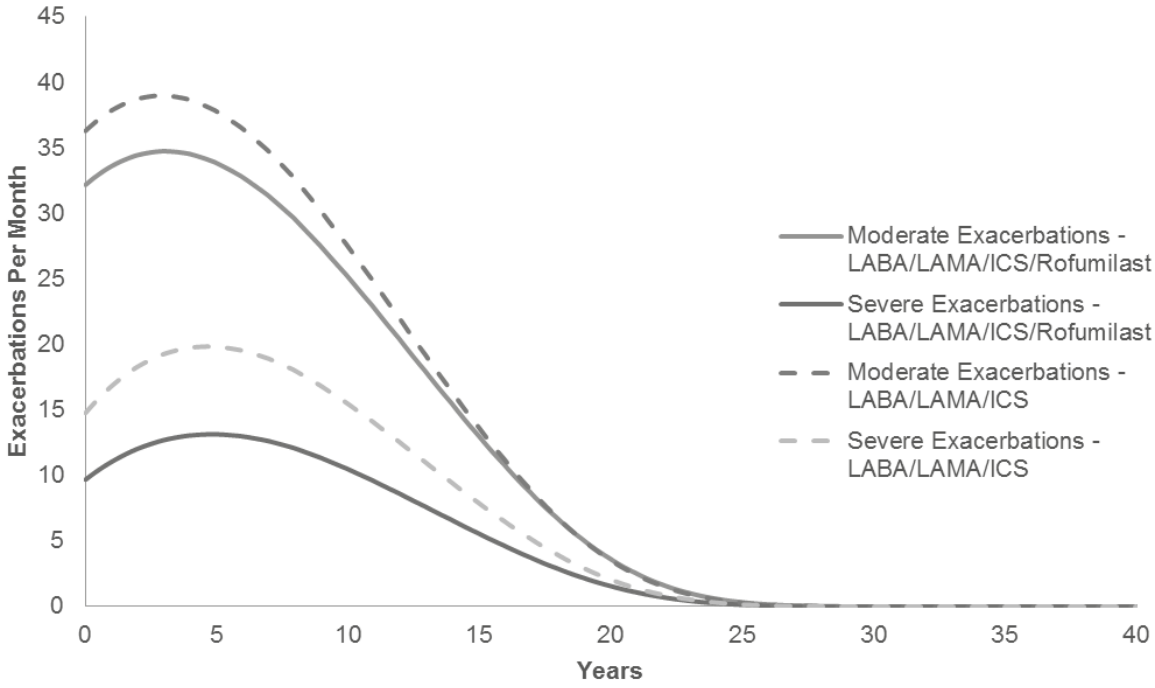
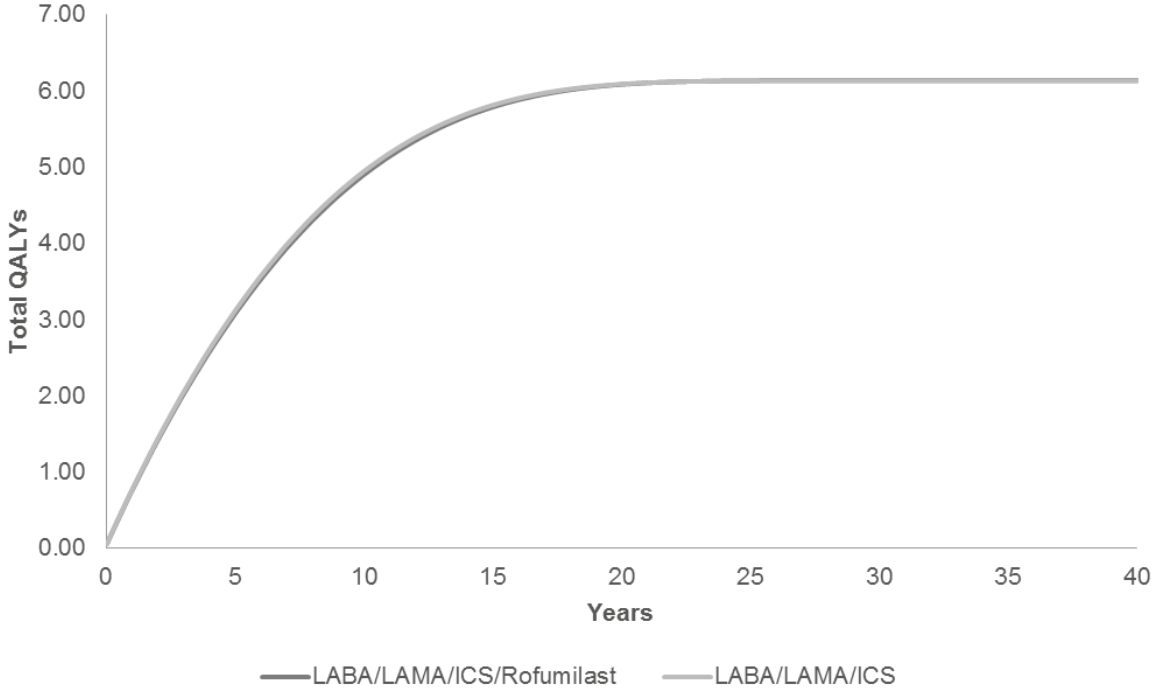


Figure 16 details how (discounted) QALYs accrue over the time horizon of the cost effectiveness model. The majority of QALYs are accrued over the first 15 years.

Figure 16: LAMA strata base-case QALY accrual over time



Disaggregated results of the base case incremental cost effectiveness analysis

Disaggregated results for QALYs by health state and costs by health state (including disaggregating treatment costs) are detailed in Table 54 and QALY, quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 55, respectively.

A number of conclusions can be drawn here:

- LABA / LAMA / ICS / roflumilast accumulates more QALYs than LABA / LAMA / ICS due to fewer severe exacerbations and an increased life expectancy as fewer patients die due to severe exacerbations.
- TEAEs have a negligible impact on both total QALYs and total costs.
- 25% of the absolute incremental difference in costs and 24% of the absolute incremental different in QALYs is due COPD exacerbations.

Table 54: LAMA strata base-case - summary of QALY gain by health state

Health state	QALY intervention	QALY comparator	Increment	Absolute increment	% Absolute increment
COPD Severity					
Severe COPD	3.400	3.377	0.023	0.023	14.58%
Very severe COPD	2.857	2.760	0.097	0.097	60.65%
Exacerbations					
Moderate exacerbations	-0.044	-0.049	0.004	0.004	2.81%
Severe exacerbations	-0.072	-0.107	0.035	0.035	21.79%
Adverse events					
TEAEs	-0.002	-0.001	0.000	0.000	0.16%
Total	6.139	5.980	0.160	0.160	100%

QALY, quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 55: LAMA strata base-case - summary of costs by health state

Health state	Cost intervention	Cost comparator	Increment	Absolute increment	% Absolute increment
Technology costs					
COPD treatments	£11,996.91	£7,731.07	£4,265.84	£4,265.84	71.63%
COPD Severity					
Severe COPD	£1,771.64	£1,759.48	£12.17	£12.17	0.20%
Very severe COPD	£5,664.28	£5,471.73	£192.55	£192.55	3.23%
Exacerbations					
Moderate exacerbations	£459.45	£506.16	£-46.71	£46.71	0.78%
Severe exacerbations	£2951.40	£4384.13	-£1432.73	£1432.73	24.06%
Adverse events					
TEAEs	£85.93	£80.64	£5.29	£5.29	0.09%
Total	£22,929.61	£19,933.19	£2,996.42	£5955.29	100%

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

5.8 Sensitivity analyses

Probabilistic sensitivity analysis

The model was constructed and parameterised to enable probabilistic sensitivity analysis (PSA) to assess the uncertainty in the model inputs. Where appropriate,

uncertainty has been characterised through the use of standard statistical distributions. The following parameters were made probabilistic:

- FEV_1 decline per annum (Gamma)
- Exacerbation regression equations (Normal)
- TEAE and TSEAE rates (Beta)
- Resource use (Beta or Gamma)
    - except prednisolone use, hospital admission and ambulance transport
- Unit costs (Gamma)
    - expect spirometry, influenza vaccination and oxygen therapy
- COPD health state utilities (Beta)
- COPD exacerbation disutilities (Beta)
- Standardised mortality ratios (Gamma)
- Severe exacerbation case fatality rate (Beta).

The PSA involved undertaking 10,000 simulations, each involved a random draw from each distribution and provided an estimate of the expected costs, life years (Lys) and QALYs associated with each comparator.

Probabilistic results

LABA / LAMA / ICS / roflumilast accumulates total (discounted) costs of £23,075 and 6.19 QALYs. LABA / LAMA / ICS alone accumulates total (discounted) costs of £20,042 and 6.03 QALYs. This equates to LABA / LAMA / ICS / roflumilast producing an additional 0.16 QALYs at an incremental cost of £3,033 when compared to LABA / LAMA / ICS alone. This generates an ICER of £18,425.

These probabilistic results are highly comparable to the base case deterministic results demonstrating that the model is stable. Table 56 presents the probabilistic incremental cost effectiveness results in detail with the individual simulation scatter plot detailed in Figure 17. LABA / LAMA / ICS / roflumilast has 72% probability of being cost effective at £20,000 per QALY gained increasing to 100% at £30,000 per

QALY gained. The CEAC and CEAF are detailed in Figure 18 and Figure 19 respectively.

Table 56: LAMA strata base-case probabilistic results

Technologies	Total costs (£)	95% CI	Total QALYs	95% CI	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
LABA / LAMA / ICS / roflumilast	£23,068	£19,809 to £26,749	6.19	5.50 to 6.93	£3,030	0.16	£18,575
LABA / LAMA / ICS	£20,035	£17,040 to £23,485	6.02	5.35 to 6.73	-	-	-

Figure 17: LAMA strata base-case incremental cost effectiveness scatter plot

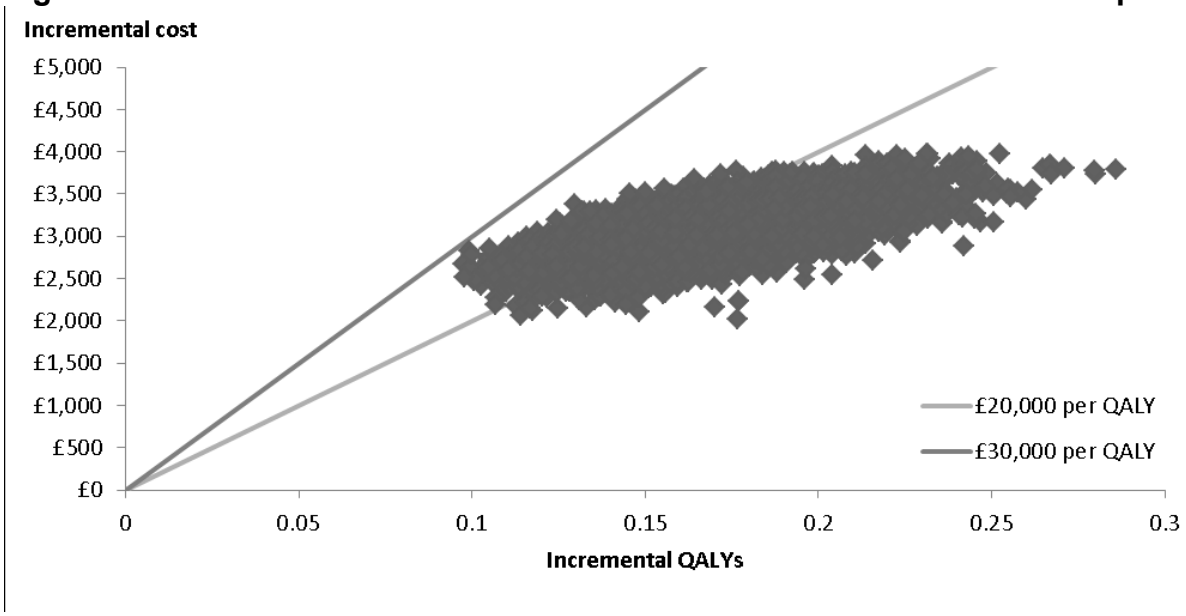


Figure 18: LAMA strata base-case cost effectiveness acceptability curve

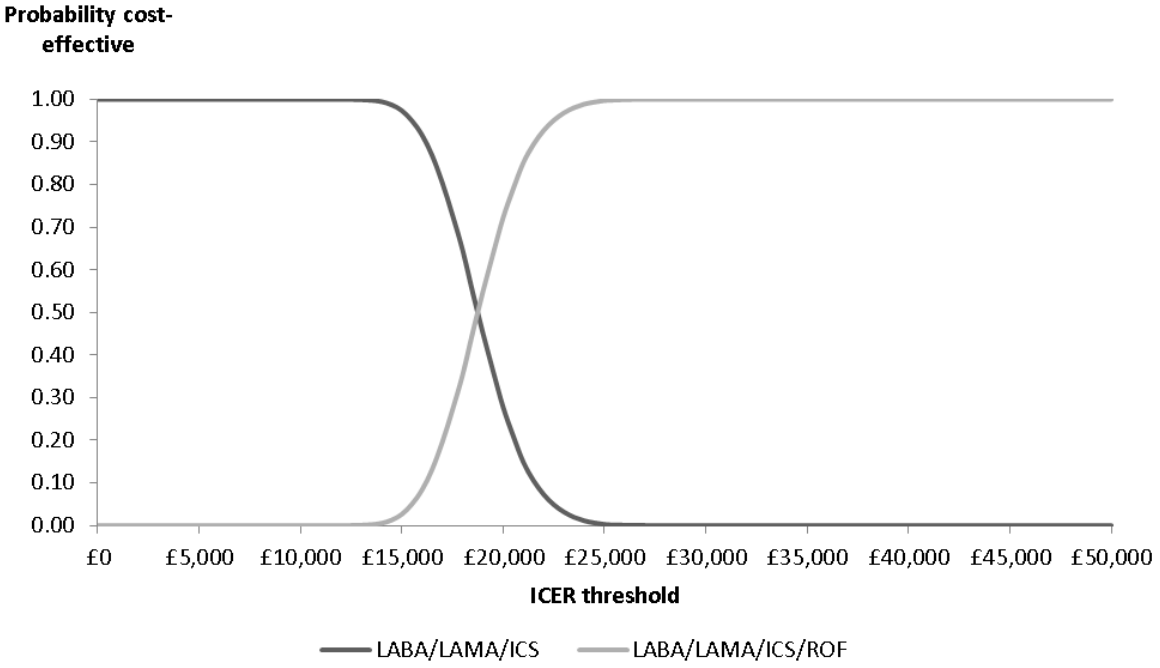
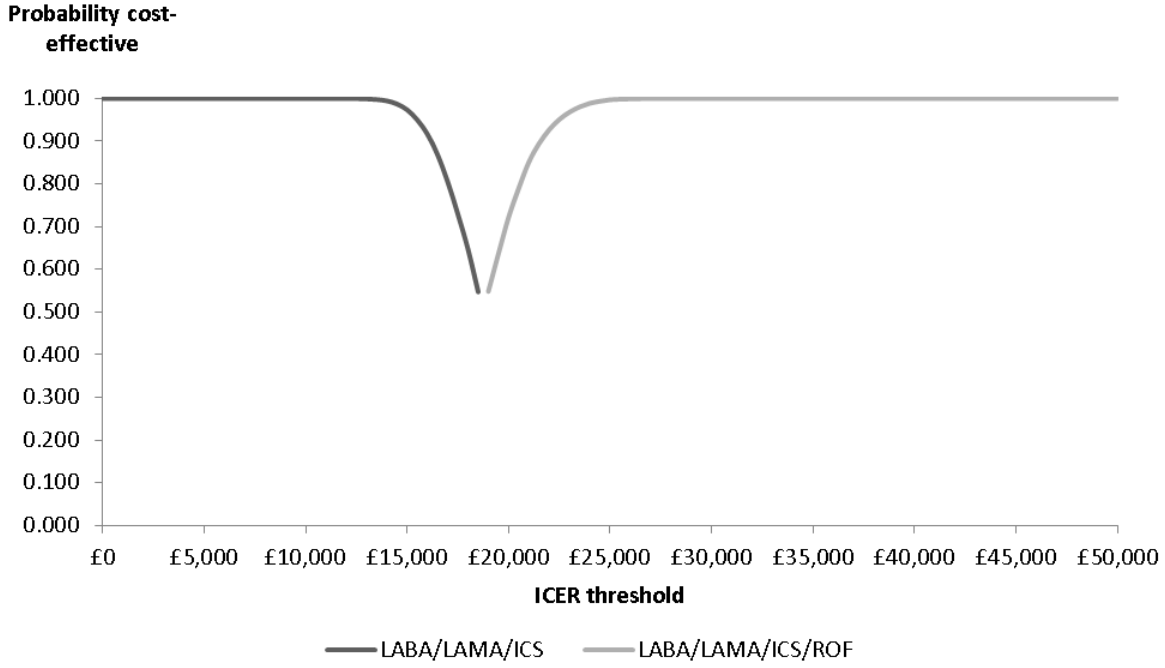


Figure 19: LAMA strata base-case cost effectiveness acceptability frontier

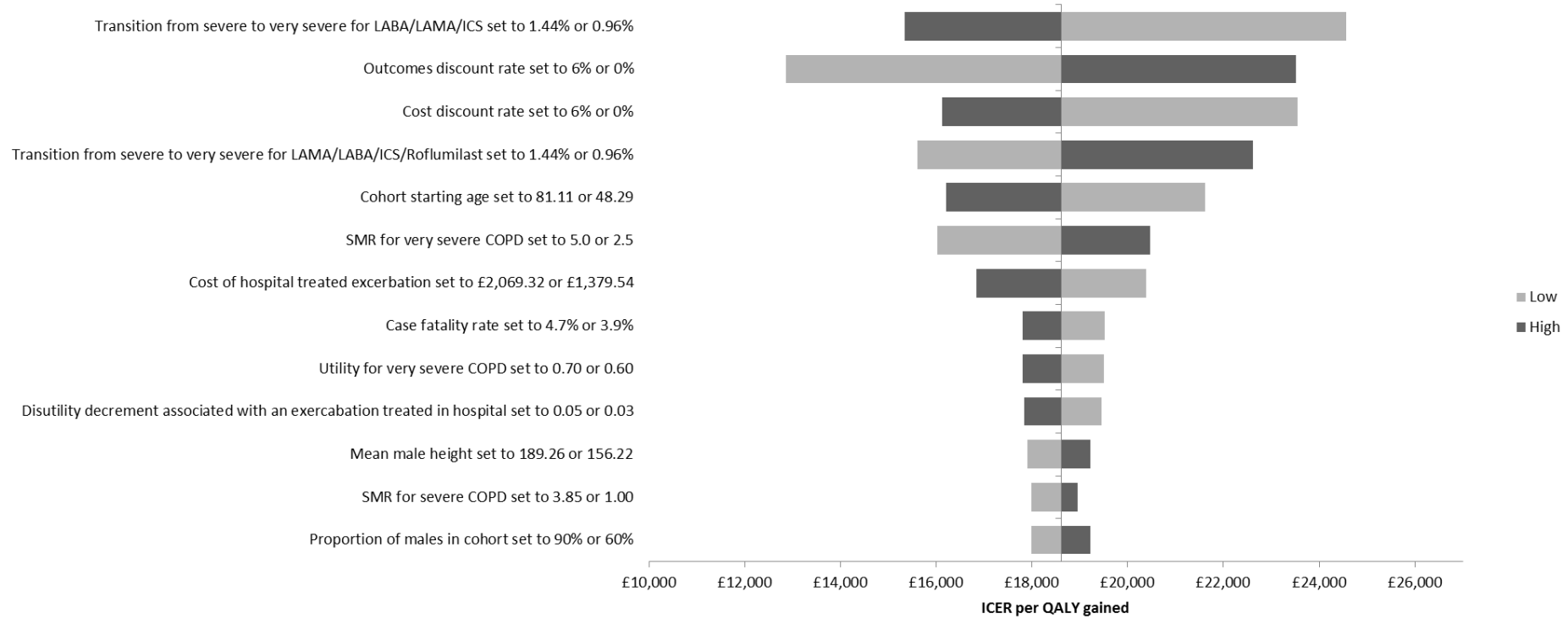


Deterministic sensitivity analysis

In order to understand the importance of each parameter in the model and the parameters' individual impact on the cost, effectiveness and cost effectiveness results, a series of deterministic sensitivity analyses were undertaken. Each parameter was set to either the upper and lower limits of the 95% CI, 20% higher or lower than the base case value (where a 95% CI was not available) or standard upper and lower limits (i.e. cost and outcomes discount rates were set to 6% and 0%) , holding all other parameters constant.

The most influential parameter is the monthly transition probability for LABA / LAMA / ICS. Although these changes in monthly transitions (± 0.24%) may seem minor they are equivalent to 17 additional or fewer months in the severe COPD state. Other influential parameters are discount rates and the monthly transition probability for LABA / LAMA / ICS / roflumilast. In all analyses the ICER remains under £25,000 per QALY gained.

Figure 20: LAMA strata base-case tornado diagram



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Scenario analysis

In order to understand the importance of key assumptions within the model on the cost, effectiveness and cost effectiveness results, a number of scenario analyses were undertaken.

Due to the importance of the two scenarios below, full deterministic (excluding a one-way sensitivity analysis) and probabilistic results are presented as in the base case results

- Assuming that 100% of patients enter the model with very severe COPD.
- Assuming a mixed population of severe and very COPD patients as in REACT.

For all below scenarios, results are provided for the severe COPD, very severe and mixed COPD population based on the proportion reported in REACT.

- Exacerbation rates are based on the LAMA covariate analysis.
- Set SMRs to unadjusted levels.
- Including lung function benefit for roflumilast and applying adjusted rate ratios for two different time periods (1 year, 5 years).
- Using alternative sources for COPD related HRQoL values.
- Addition of TEAEs and the removal of TRAEs.

Patients starting the model with very severe COPD

In the initial analysis, all patients start in the severe COPD state. However, to assess the impact of this assumption an analysis was undertaken where patients start in the very severe COPD state.

LABA / LAMA / ICS / roflumilast accumulates total (discounted) costs of £26,014 and 5.18 QALYs. LABA / LAMA / ICS alone accumulates total (discounted) costs of £23,671 and 4.99 QALYs. This equates to LABA / LAMA / ICS / roflumilast producing

an additional 0.19 QALYs at an incremental cost of £2,343 when compared to LABA / LAMA / ICS alone. This generates a base-case ICER of £12,337. Table 57 below presents the base-case incremental cost effectiveness results in detail. This demonstrates that LABA / LAMA / ICS / roflumilast is cost effective at the £20,000 per QALY threshold.

Table 57: Very severe COPD scenario analysis deterministic results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
LABA / LAMA / ICS / roflumilast	£26,014	8.23	5.18	£2,343	0.22	0.19	£12,337
LABA / LAMA / ICS	£23,671	8.01	4.99	-	-	-	-

Proportion of the cohort in the health state over time (Markov trace)

Markov traces for the proportion of the cohort in each health state, for LABA / LAMA / ICS / roflumilast and LABA / LAMA / ICS are provided in Figure 21 and Figure 22.

As in the base case analysis, there are minor differences between the health states driven by a higher proportion of patients in the dead state for LABA / LAMA / ICS due to more deaths from a higher severe exacerbation rate. Differences in the number of moderate and severe exacerbations over time for the cohort of patients are provided in Figure 23. In this analysis, the number of exacerbations is higher than previously as the rate of exacerbations for patients in the very severe COPD population is higher than in the severe COPD population.

Figure 21: Very severe COPD scenario analysis – LABA / LAMA / ICS / roflumilast Markov trace

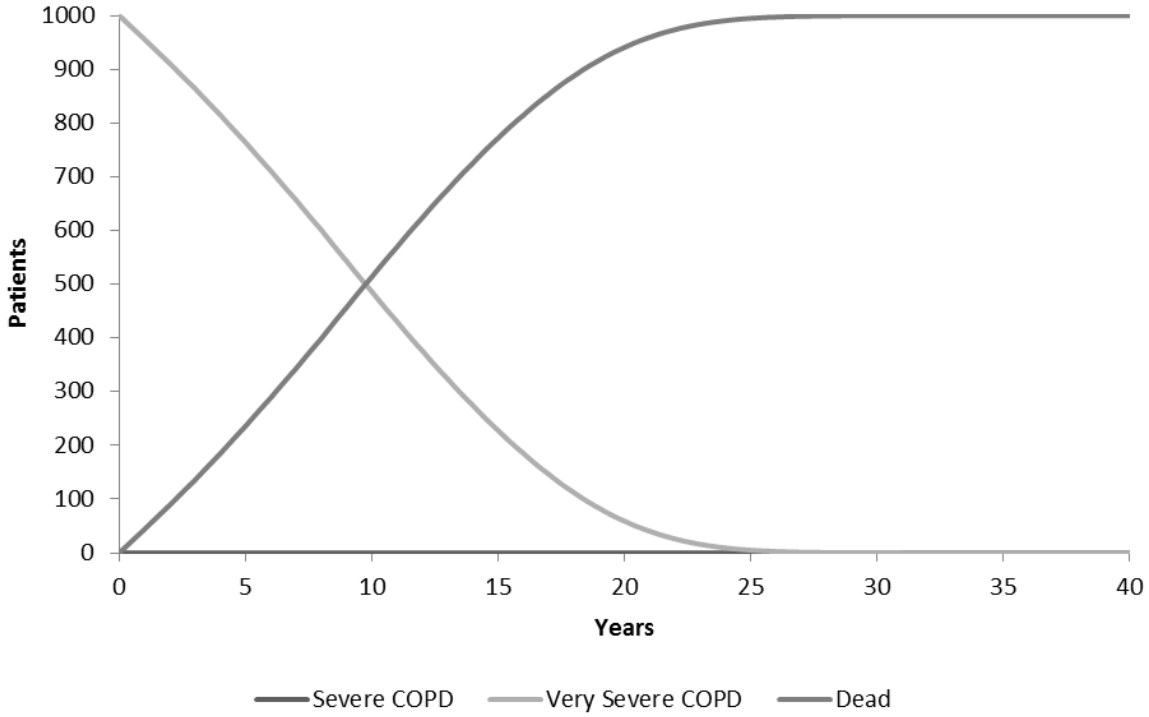


Figure 22: Very severe COPD scenario analysis – LABA / LAMA / ICS Markov trace

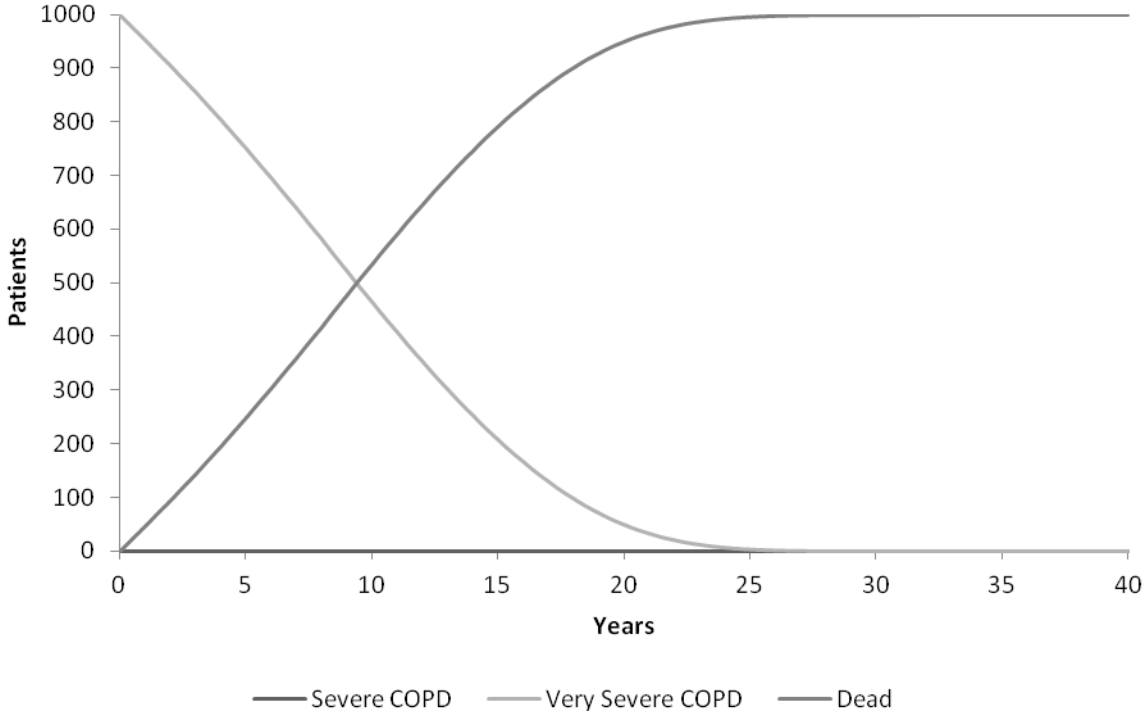


Figure 23: Very severe COPD scenario analysis – number of exacerbations per month

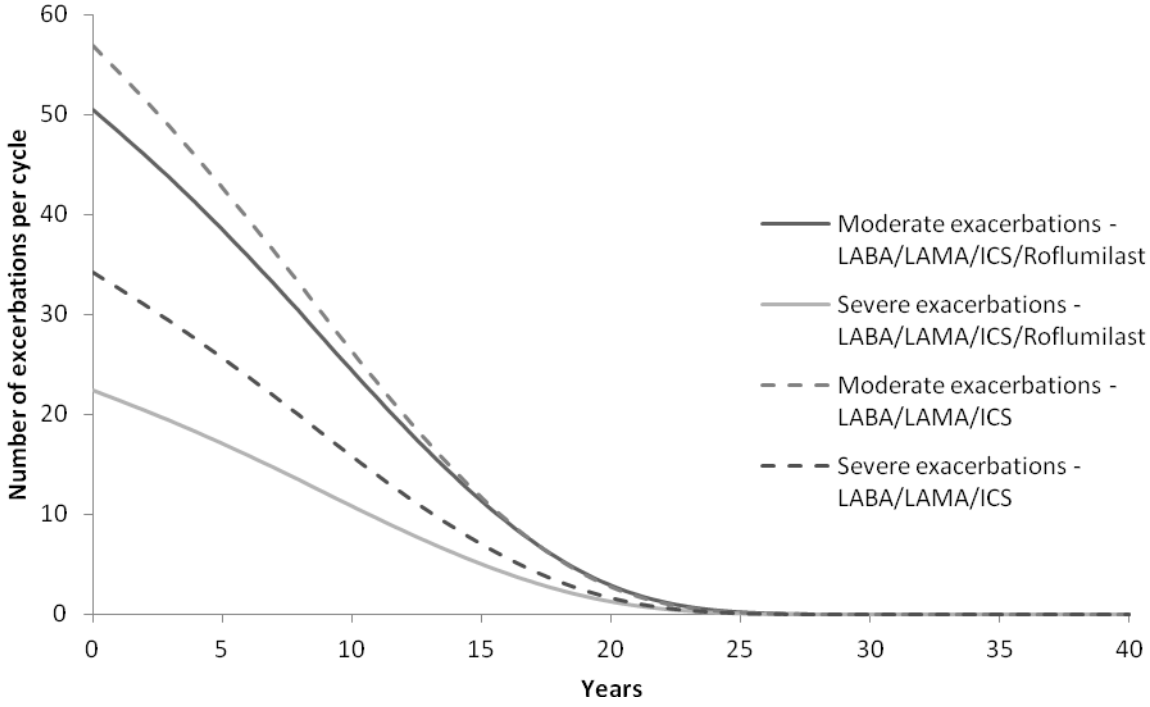
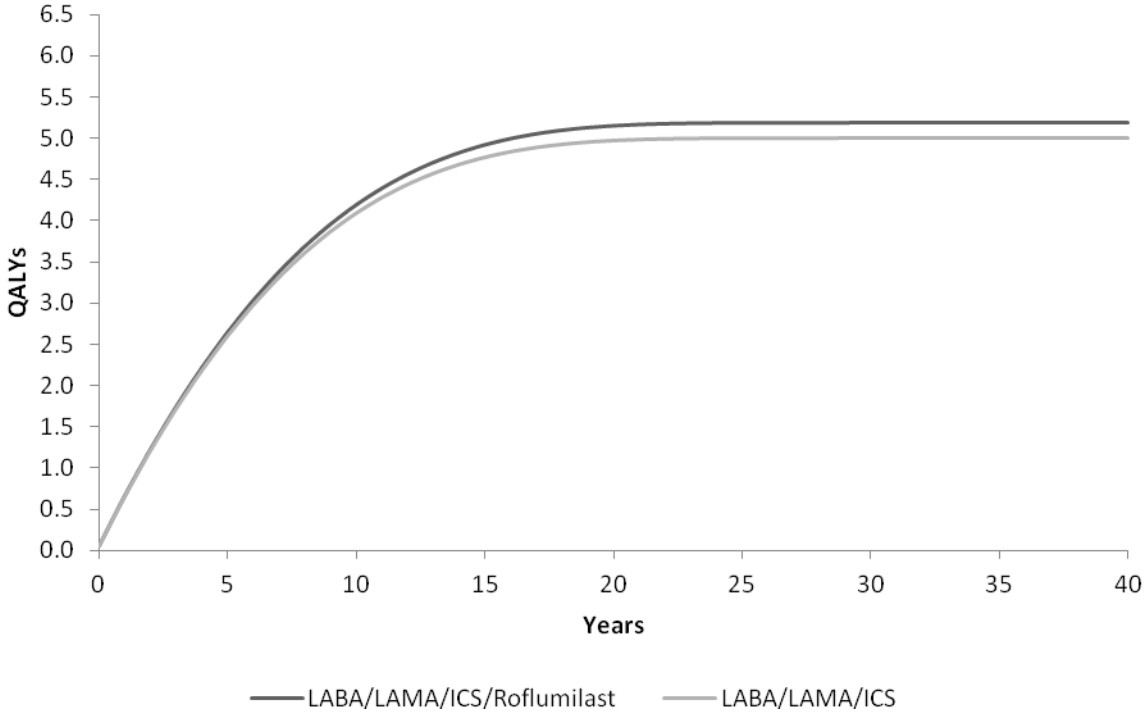


Figure 24 details how (discounted) QALYs accrue over the time horizon of the cost effectiveness model. The majority of QALYs are accrued over the first 15 years.

Figure 24: Very severe COPD scenario analysis – QALY accrual over time



Disaggregated results of the very severe COPD incremental cost effectiveness scenario analysis

Disaggregated results for QALYs by health state and costs by health state (including disaggregating treatment costs) are detailed in Table 58 and Table 59, respectively.

The conclusions drawn here are similar to the severe COPD population.

- LABA / LAMA / ICS / roflumilast accumulates more QALYs than LABA / LAMA / ICS due to fewer severe exacerbations and an increased life expectancy as fewer patients die due to severe exacerbations
- TEAEs have a negligible impact on both total QALYs and total costs.
- 31% of the absolute incremental difference in costs and 26% of the absolute incremental difference in QALYs is due to COPD exacerbations.

Table 58: Very severe COPD scenario analysis - Summary of QALY gain by health state

Health state	QALY intervention	QALY comparator	Increment	Absolute increment	% absolute increment
COPD Severity					
Severe COPD	0.000	0.000	0.000	0.000	0.00%
Very severe COPD	5.323	5.183	0.140	0.140	73.56%
Exacerbations					
Moderate exacerbations	-0.050	-0.055	0.005	0.005	2.58%
Severe exacerbations	-0.093	-0.138	0.045	0.045	23.73%
Adverse events					
TEAEs	-0.002	-0.001	0.000	0.000	0.14%
Total	5.178	4.988	0.190	0.190	100%

QALY, quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 59: Very severe COPD scenario analysis - Summary of costs by health state

Health state	Cost intervention	Cost comparator	Increment	Absolute increment	% absolute increment
Technology costs					
COPD treatments	£11028.38	£7,062.95	£3,965.43	£3,965.43	64.43%
COPD Severity					
Severe COPD	£0.00	£0.00	£0.00	£0.00	0.00%
Very severe COPD	£10,522.99	£10,275.29	£277.70	£277.70	4.51%
Exacerbations					
Moderate exacerbations	£518.84	£569.82	-£50.98	£50.98	0.83%
Severe exacerbations	£3827.70	£5682.53	-£1843.83	£1843.83	30.14%
Adverse events					
TEAEs	£85.83	£80.54	£5.28	£5.28	0.09%
Total	£26,013.73	£23,671.13	£2,342.60	£6,154.23	100%

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Very severe COPD scenario analysis - Probabilistic results

LABA / LAMA / ICS / roflumilast accumulates total (discounted) costs of £26,248 and 5.23 QALYs. LABA / LAMA / ICS alone accumulates total (discounted) costs of £23,869 and 5.03 QALYs. This equates to LABA / LAMA / ICS / roflumilast producing

an additional 0.20 QALYs at an incremental cost of £2,379 when compared to LABA / LAMA / ICS alone. This generates an ICER of £12,183.

These probabilistic results are highly comparable to the base case deterministic results demonstrating that the model is stable. Table 60 presents the probabilistic incremental cost effectiveness results in detail with the individual simulation scatter plot detailed in Figure 26: Very severe COPD scenario analysis – cost effectiveness acceptability curve. LABA / LAMA / ICS / roflumilast has 100% probability of being cost effective at £20,000 per QALY gained. The CEAC and CEAF are detailed in Figure 26 and Figure 27 respectively.

Table 60: Very severe COPD scenario analysis - Probabilistic results

Technologies	Total costs (£)	95% CI	Total QALYs	95% CI	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
LABA / LAMA / ICS / roflumilast	£26,248	£19,380 to £28,971	5.23	4.35 to 6.19	£2,379	0.20	£12,183
LABA / LAMA / ICS	£23,869	£21,395 to £31,706	5.03	4.21 to 5.93	-	-	-

Figure 25: Very severe COPD scenario analysis – incremental cost effectiveness scatter plot

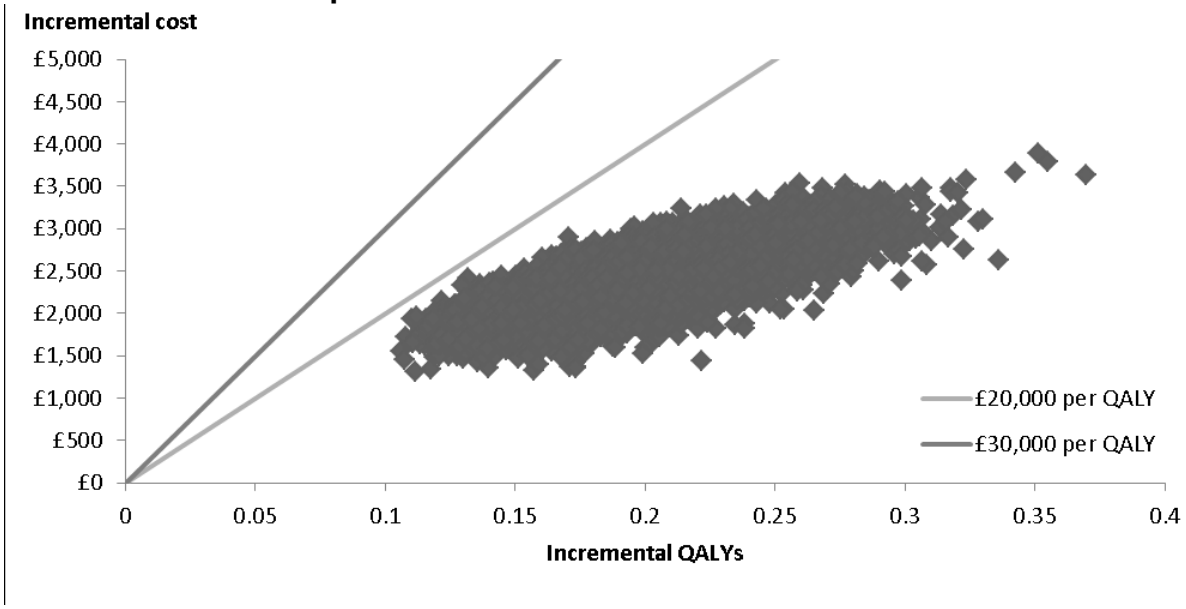


Figure 26: Very severe COPD scenario analysis – cost effectiveness acceptability curve

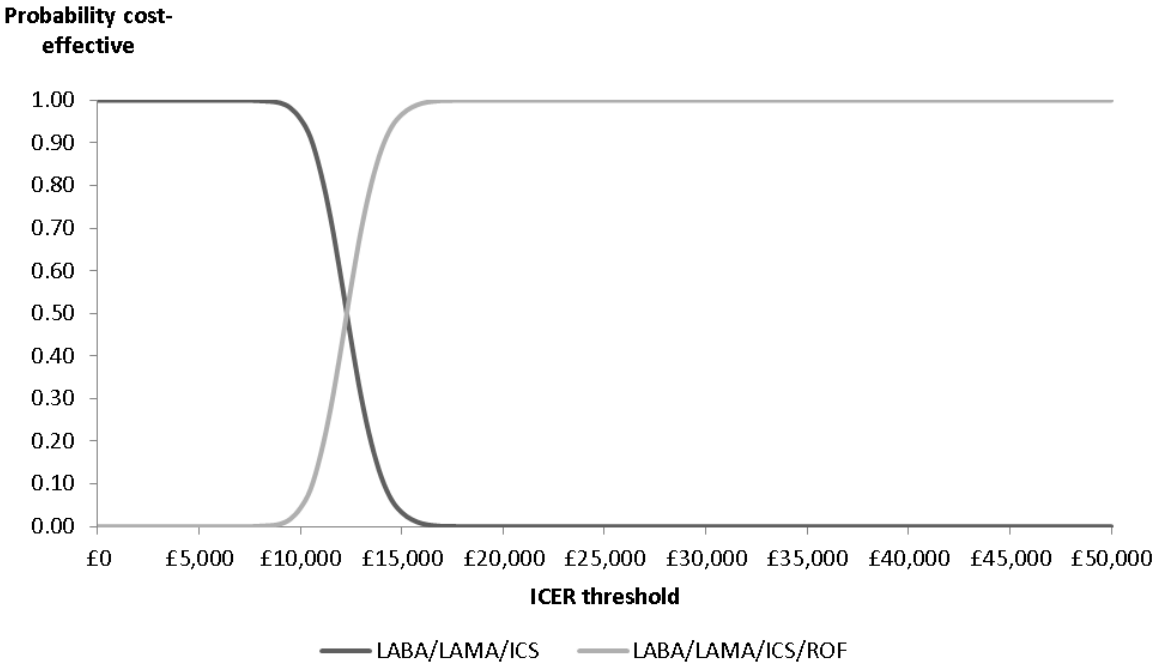
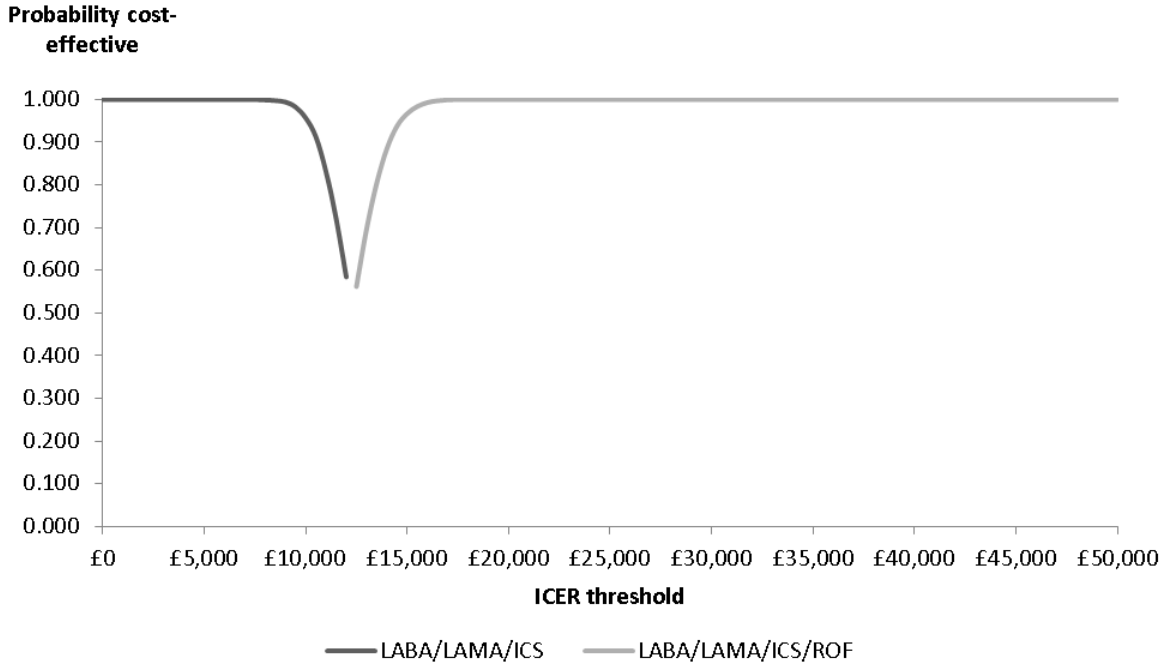


Figure 27: Very severe COPD scenario analysis – cost-effectiveness acceptability frontier

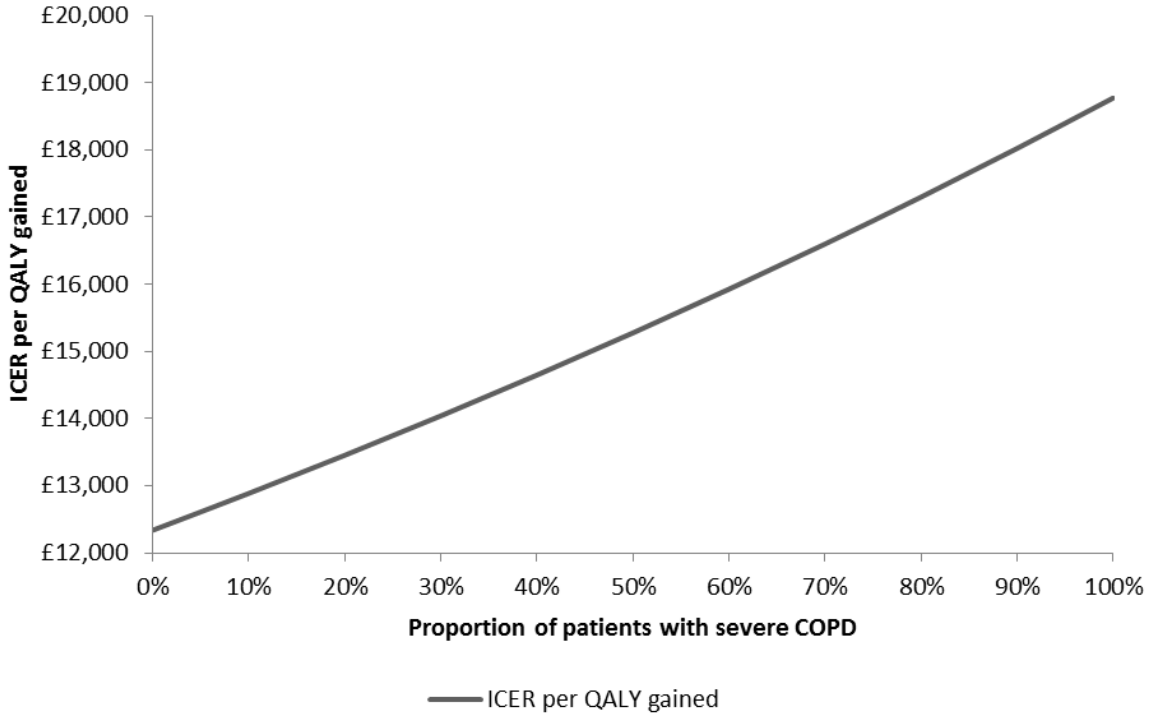


This demonstrates that roflumilast as add-on therapy to LABA / LAMA / ICS is cost effective in both patients with very severe COPD.

Mixed population of severe and very COPD patients – threshold analysis

The base case analysis and previous scenario analysis demonstrate that LABA / LAMA / ICS / roflumilast is cost effective in the severe and very severe COPD states. In reality, the population will contain a mix of severe and very severe COPD patients. In Figure 28, we present a threshold analysis demonstrating the ICER for various population compositions. This ranges between the ICER for the very severe COPD population of £12,337 and £18,774.

Figure 28: COPD severity mix threshold analysis



Mixed population of severe and very COPD patients as in REACT

The full deterministic and probabilistic analysis was undertaken on the population mix for the PP population who were on LAMA (68.81% severe COPD; 31.19% very severe COPD).

LABA / LAMA / ICS / roflumilast accumulates total (discounted) costs of £23,892 and 5.84 QALYs. LABA / LAMA / ICS alone accumulates total (discounted) costs of £21,099 and 5.67 QALYs. This equates to LABA / LAMA / ICS / roflumilast producing an additional 0.17 QALYs at an incremental cost of £2,792 when compared to LABA / LAMA / ICS alone. This generates a base-case ICER of £16,519. Table 61 below presents the base-case incremental cost effectiveness results in detail. This demonstrates that LABA / LAMA / ICS / roflumilast is cost effective at the £20,000 per QALY threshold.

Table 61: Mixed population scenario analysis – Deterministic results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
LABA / LAMA / ICS / roflumilast	£23,892	8.72	5.84	£2,792	0.19	0.17	£16,519
LABA / LAMA / ICS	£21,099	8.53	5.67	-	-	-	-

Proportion of the cohort in the health state over time (Markov trace)

Markov traces for the proportion of the cohort in each health state, for LABA / LAMA / ICS / roflumilast and LABA / LAMA / ICS are provided in Figures 29 and 30. As in the previous analyses, there are minor differences between the health states driven by a higher proportion of patients in the dead state for LABA / LAMA / ICS due to more deaths from a higher severe exacerbation rate. Differences in the number of moderate and severe exacerbations over time for the cohort of patients are provided in Figure 31. As expected, this is higher than in the severe COPD analysis but not as high as in the very severe COPD analysis.

Figure 29: Mixed population scenario analysis – LABA / LAMA / ICS / roflumilast Markov trace

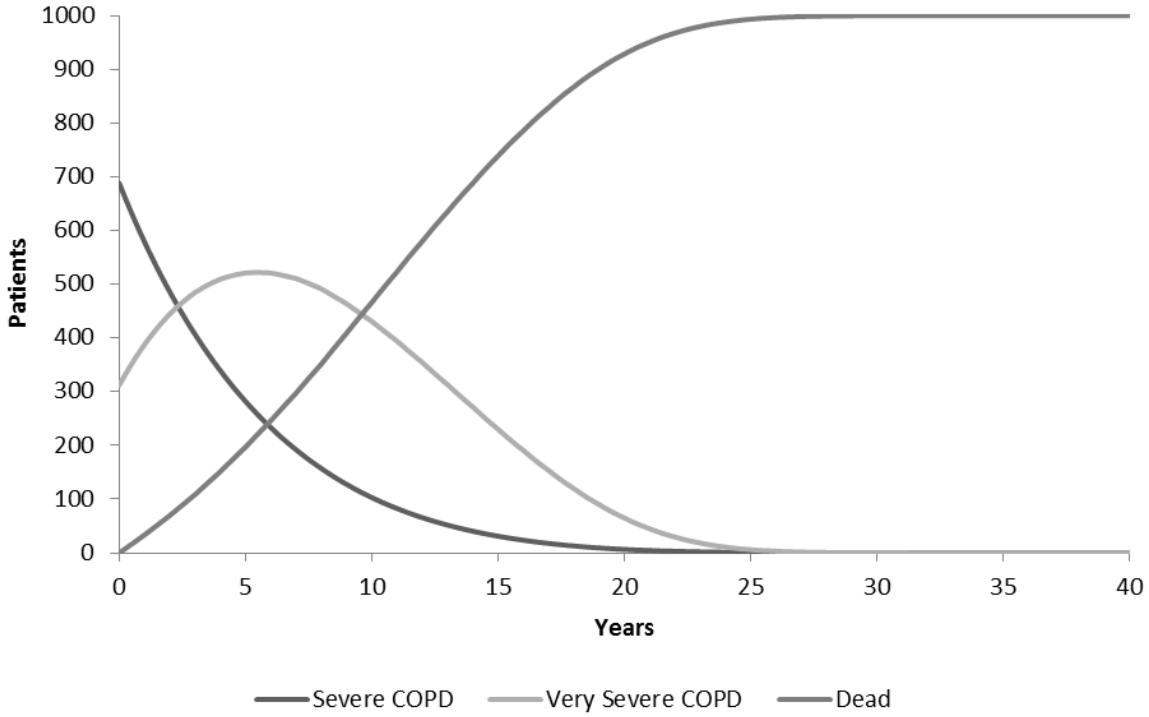


Figure 30: Mixed population scenario analysis – LABA / LAMA / ICS Markov trace

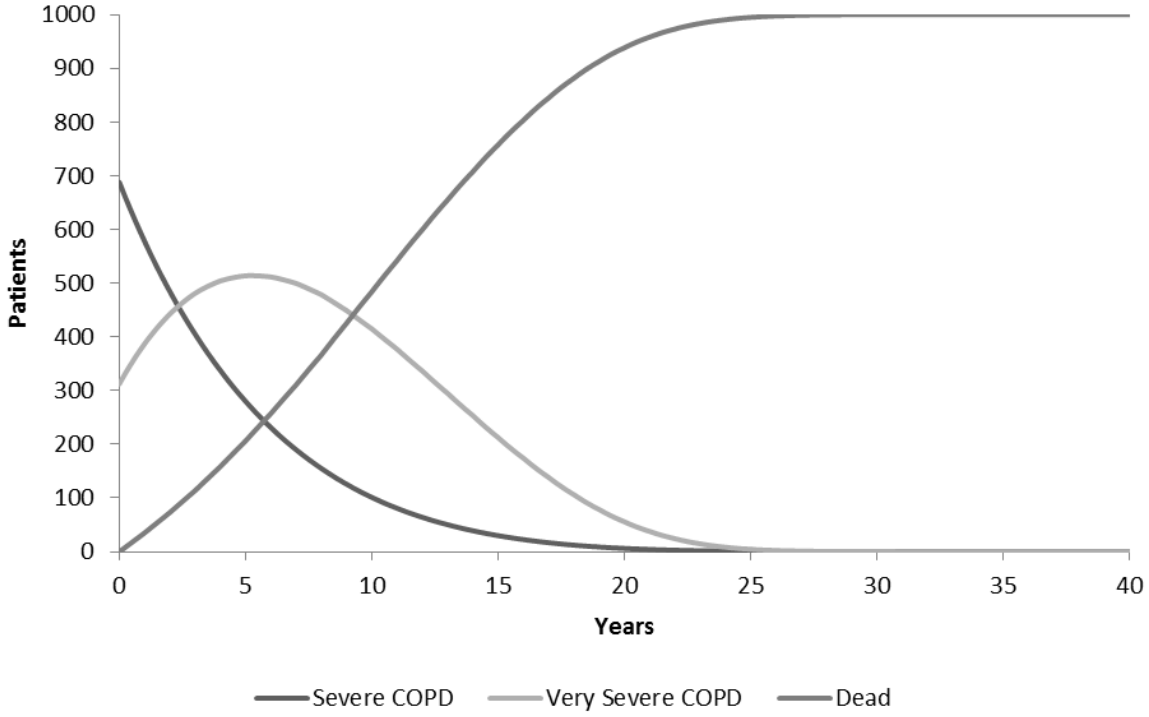


Figure 31: Mixed population scenario analysis – number of exacerbations per month

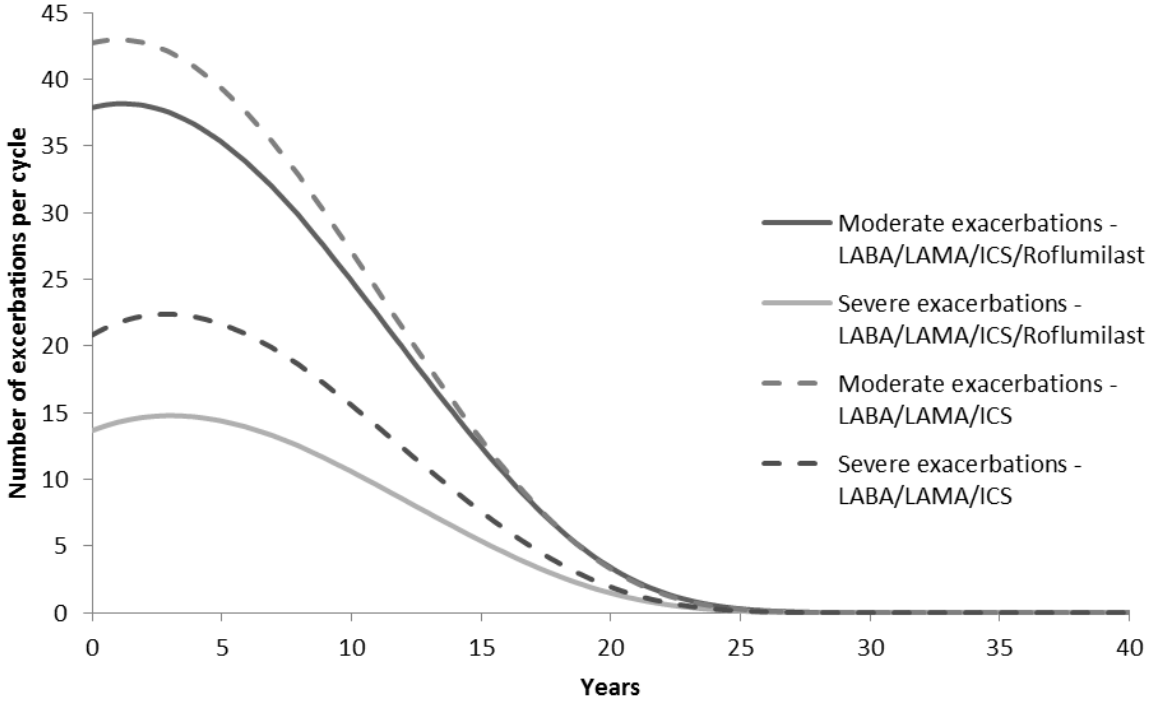
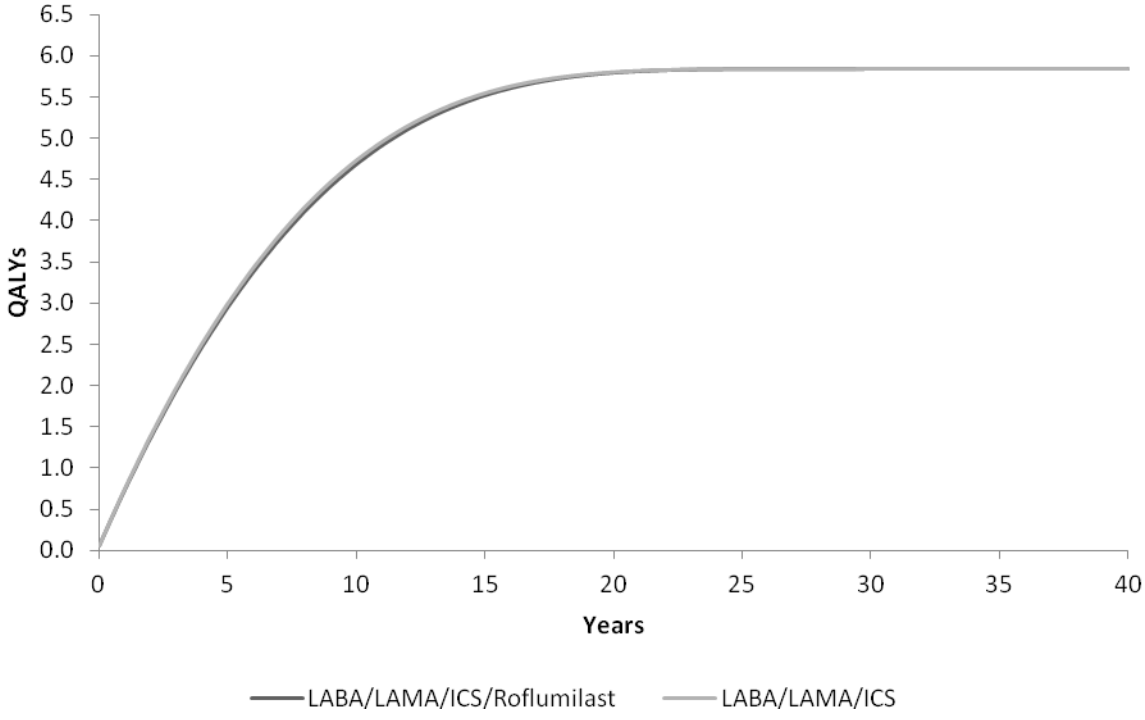


Figure 32 details how (discounted) QALYs accrue over the time horizon of the cost effectiveness model. The majority of QALYs are accrued over the first 15 years.

Figure 32: Mixed population scenario analysis – QALY accrual over time



Disaggregated results of the mixed population incremental cost effectiveness scenario analysis

Disaggregated results for QALYs by health state and costs by health state (including disaggregating treatment costs) are detailed in Table 62 and Table 63 respectively.

As in previous analyses:

- LABA / LAMA / ICS / roflumilast accumulates more QALYs than LABA / LAMA / ICS due to fewer severe exacerbations and an increased life expectancy as fewer patients die due to severe exacerbations
- TEAEs have a negligible impact on both total QALYs and total costs.
- 26% of the absolute incremental difference in costs and 27% of the absolute incremental difference in QALYS is due to COPD exacerbations.

Table 62: Mixed population scenario analysis – Summary of QALY gain by health state

Health state	QALY intervention	QALY comparator	Increment	Absolute increment	% absolute increment
COPD Severity					
Severe COPD	2.340	2.324	0.016	0.016	9.48%
Very severe COPD	3.626	3.515	0.111	0.111	65.17%
Exacerbations					
Moderate exacerbations	-0.046	-0.051	0.005	0.005	2.73%
Severe exacerbations	-0.079	-0.117	0.038	0.038	22.47%
Adverse events					
TEAEs	-0.002	-0.001	0.000	0.000	0.15%
Total	5.839	5.670	0.170	0.170	100%

QALY, quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 63: Mixed population scenario analysis – Summary of costs by health state

Health state	Cost intervention	Cost comparator	Increment	Absolute increment	% absolute increment
Technology costs					
COPD treatments	£11694.83	£7,522.68	£4172.15	£4172.15	69.34%
COPD Severity					
Severe COPD	£1219.07	£1210.70	£8.37	£8.37	0.14%
Very severe COPD	£7,189.07	£6969.96	£219.11	£219.11	3.64%
Exacerbations					
Moderate exacerbations	£477.97	£526.01	-£48.04	£48.04	0.80%
Severe exacerbations	£3224.72	£4789.10	-£1564.38	£1564.38	26.00%
Adverse events					
TEAEs	£85.90	£80.61	£5.29	£5.29	0.09%
Total	£23,891.55	£21099.06	£2,792.49	£6017.34	100%

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Mixed population scenario analysis - Probabilistic results

LABA / LAMA / ICS / roflumilast accumulates total (discounted) costs of £24,015 and 5.88 QALYs. LABA / LAMA / ICS alone accumulates total (discounted) costs of

£21,191 and 5.70 QALYs. This equates to LABA / LAMA / ICS / roflumilast producing an additional 0.17 QALYs at an incremental cost of £2,824 when compared to LABA / LAMA / ICS alone. This generates an ICER of £16,349.

These probabilistic results are highly comparable to the base case deterministic results demonstrating that the model is stable. Table 64 below presents the probabilistic incremental cost effectiveness results in detail with the individual simulation scatter plot detailed in Figure 34: Mixed population scenario analysis – cost effectiveness acceptability curve. LABA / LAMA / ICS / roflumilast has 96% probability of being cost effective at £20,000 per QALY gained increasing to 100% at £30,000 per QALY. The CEAC and CEAF are detailed in Figure 34 and Figure 35 respectively.

Table 64: Mixed population scenario analysis - Probabilistic results

Technologies	Total costs (£)	95% CI	Total QALYs	95% CI	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
LABA / LAMA / ICS / roflumilast	£24,015	£17,864 to £25,074	5.88	5.17 to 6.63	£2,824	0.17	£16,349
LABA / LAMA / ICS	£21,191	£20,461 to £28,181	5.70	5.03 to 6.41	-	-	-

Figure 33: Mixed population scenario analysis – incremental cost effectiveness scatter plot

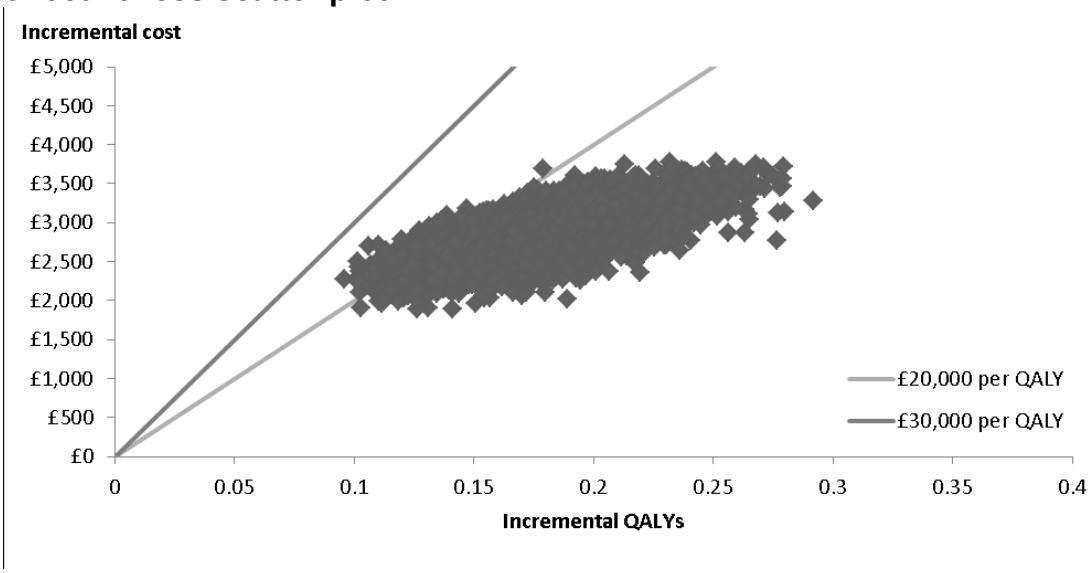


Figure 34: Mixed population scenario analysis – cost effectiveness acceptability curve

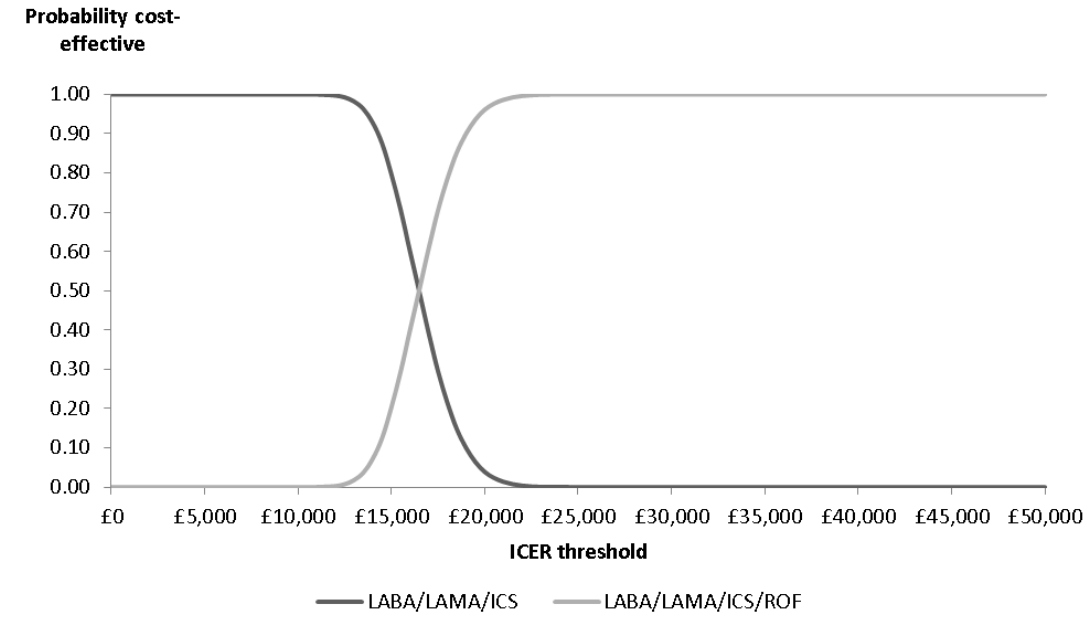
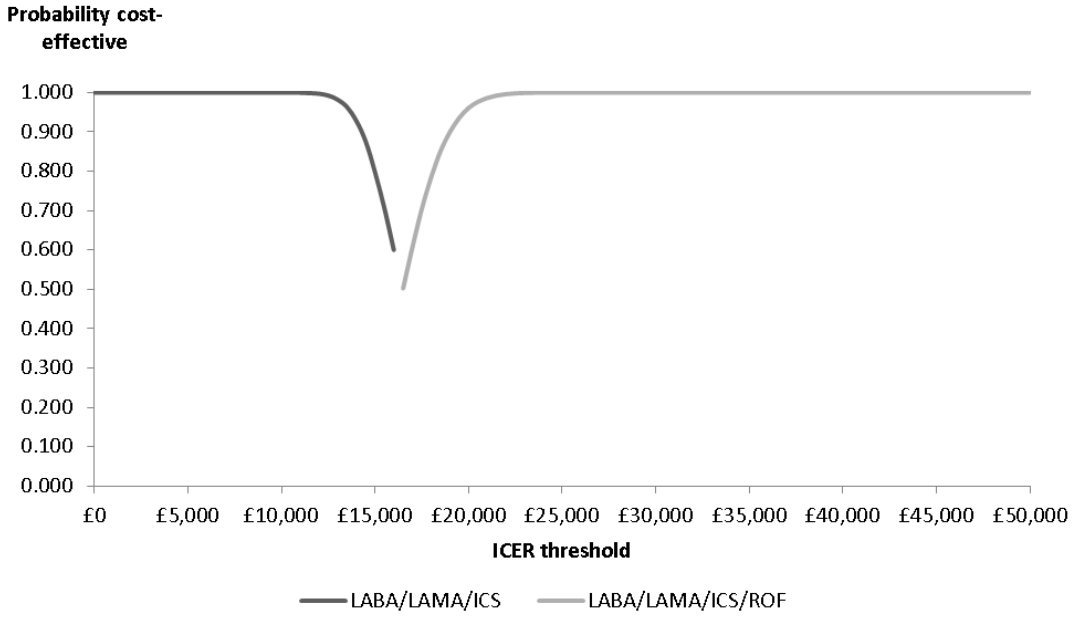


Figure 35: Mixed population scenario analysis – cost-effectiveness acceptability frontier



This demonstrates that roflumilast as add-on therapy to LABA / LAMA / ICS is cost effective in both patients with severe and very severe COPD

LAMA as covariate analysis

The second regression analysis, also using negative binomial regression, includes concomitant LAMA use as a covariate, whilst also controlling for COPD severity (GOLD stage – severe vs very severe), and treatment arm. Concomitant LAMA use was not found in the trial to impact on the relative effectiveness of roflumilast in terms of exacerbation reduction (hence no interaction term is included), and controlling for LAMA use allows differences in the underlying rate of exacerbations to differ by LAMA usage, without sacrifice of data.

When using this regression analysis, Table 65 details the incremental costs, incremental QALYs and ICER per QALY gained for each of the three populations. In this scenario, LABA / LAMA / ICS / roflumilast is cost effective at the £20,000 per QALY gained threshold.

Table 65: LAMA as covariate scenario analysis results

Population	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Severe	£2,859	0.18	£16,326
Very severe	£2,344	0.19	£12,385
Mixed	£2,698	0.18	£15,030

Unadjusted SMRs

In Samyshkin 2014,[18] SMRs of 3.1 for severe COPD and 5.0 for very severe COPD are adjusted to remove the severe exacerbation CFR. However, as the rates of exacerbations are lower in our analysis and the CFR lower there is the possibility that the SMR of 2.5 and 3.85 are underestimating the true SMR.

An analysis was undertaken where the unadjusted SMRs of 3.1 and 5.0 are used instead of the adjusted SMRs. Table 66 details the incremental costs, incremental QALYs and ICER per QALY gained for each of the three populations. In this scenario, LABA / LAMA / ICS / roflumilast is likely to be cost effective at the £20,000 per QALY gained threshold as this analysis is likely to include some double counting of mortality.

Table 66: Unadjusted SMR scenario analysis results

Population	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Severe	£2,964	0.13	£20,906
Very severe	£2,015	0.15	£13,186
Mixed	£2,482	0.14	£18,207

Including lung function benefit of roflumilast

One means of assessing the potential for lung function improvement to double-count the exacerbation effect is to contrast the model's base case exacerbation incidence with that resulting from the addition of the lung function effect. The exacerbation rates can then be adjusted in order to return to similar exacerbation incidence. Table 67 shows the adjusted exacerbation rate ratios when the ratios for moderate and severe exacerbations are

adjusted by a common factor. The adjustment is estimated based on exacerbations over both 1 and 5 year periods (under the assumption that lung function benefit persist for one year).

Table 67: Adjusted exacerbation rates (LAMA strata only)

Exacerbations	Adjustment	Rate ratio	Upper 95% CI	Lower 95% CI
1 year				
Moderate Exacerbations	1.0078	0.894	0.718	1.111
Severe Exacerbations		0.661	0.479	0.912
5 years				
Moderate Exacerbations	1.0080	0.894	0.719	1.111
Severe Exacerbations		0.661	0.479	0.913

The results using both 1 and 5 year adjustment ratios are detailed in Table 68.

Table 68: Lung function benefit inclusion scenario analysis results

Population	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
1 year adjustment			
Severe	£3,021	0.17	£18,159
Very severe	£2,454	0.17	£14,049
Mixed	£2,844	0.17	£16,834
5 year adjustment			
Severe	£3,021	0.17	£18,169
Very severe	£2,454	0.17	£14,060
Mixed	£2,844	0.17	£16,844

The inclusion of lung function improvement increases both incremental costs and incremental QALYs due to an increased life expectancy. As expected, the change in ICER is modest as improvements in lung function do not directly impact the rate of exacerbations.

Alternative sources of HRQoL

A number of analyses were undertaken to assess the impact of using different utilities and disutilities for the COPD health states and exacerbations including the addition of a further source for utilities and exacerbation disutilities. Solem

et al sampled 314 US patients (190 with severe COPD and 124 with very severe COPD) using the EQ-5D and the St George's Respiratory Questionnaire (SGRQ). Health state utilities and disutilities are detailed in Table 69. As the mean length of moderate and severe exacerbations was 10.7 days (± 8.4 days) and 9.7 days (± 5.8 days) respectively, it was assumed that this disutility is only applied for one month, i.e. the values reported are divided by 12. This provides a smaller disutility then those provided by Rutten van Molken 2009.

Table 69: Solem 2013 utility scores

Severity	Mean	SE	Upper 95% CI	Lower 95% CI
Severe COPD	0.707	0.013	0.682	0.732
Very severe COPD	0.623	0.021	0.582	0.664
Moderate exacerbations	-0.103	0.013	-0.077	-0.129
Severe exacerbations	-0.157	0.023	-0.111	-0.203

The results using various combinations of these utilities and disutilities are provided in Table 70. For this analysis, just the ICER per QALY gained is presented.

Table 70: Alternative sources of HRQoL scenario analysis results

Utilities	Rutten van-Molken 2006			Rutten van-Molken 2009			Solem 2013		
Disutilities	**Severe**	**Very severe**	**Mixed**	**Severe**	**Very severe**	**Mixed**	**Severe**	**Very severe**	**Mixed**
Rutten van-Molken 2009	£18,774	£12,337	£16,519	£21,464	£14,425	£19,034	£19,374	£12,684	£17,024
Solem 2013	£22,206	£14,818	£19,643	£26,069	£17,937	£23,305	£23,050	£15,332	£20,362

These results demonstrate the impact of differential health state utilities and exacerbation disutilities have on the result which ranges from an ICER of £18,774 to £26,069 per QALY gained. However, given that the utility values for Rutten van-Molken 2006 are the most appropriate given that they are based on UK general population weights, the ICER is likely to only range up to £22,206 when varying disutility values with considerable smaller disutilities for exacerbations. For the very severe COPD population the ICER ranged from £12,337 to £17,937 per QALY gained whilst in the mixed severity population the ICER ranged from £16,519 to £23,305 per QALY gained. All analyses are within the range considered cost effective by NICE.

Treatment emergent adverse events

In order to assess the impact of TEAEs on the model two analyses were undertaken. The two analyses below suggest that TEAEs have a negligible impact on both costs and QALYs.

Firstly, an analysis was undertaken where all grade TEAEs are included instead of TESAEs only. Table 71 details the incremental costs, incremental QALYs and ICER per QALY gained for each of the three populations. In this scenario, LABA / LAMA / ICS / roflumilast is likely to be cost effective at the £20,000 per QALY gained threshold.

Table 71: All grade TEAEs included scenario analysis results

Population	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Severe	£2,983	0.16	£19,498
Very severe	£2,329	0.18	£12,708
Mixed	£2,779	0.16	£17,109

Secondly, an analysis was undertaken where all TEAEs and TESAEs were removed from the model. Table 72 details the incremental costs, incremental QALYs and ICER per QALY gained for each of the three populations. In this scenario, LABA / LAMA / ICS / roflumilast is likely to be cost effective at the £20,000 per QALY gained threshold.

Table 72: All TEAEs and TESAEs removed scenario analysis results

Population	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Severe	£2,991	0.16	£18,711
Very severe	£2,337	0.19	£12,292
Mixed	£2,787	0.17	£16,462

5.9 Subgroup analysis

Not applicable

5.10 Validation

Validation of de novo cost effectiveness analysis

As well as a cell by cell verification, a range of test and checks were performed to identify errors that may have occurred in programming or during data incorporation into the model. These included:

- Set treatment exacerbations equal across treatment arms
    - As expected, both arms of the model produce the same clinical outcomes
- Set discount rate for costs to 0%
    - As expected, discounted costs equal undiscounted costs
- Set discount rate for QALYs to 0%
    - As expected, discounted QALYs equal undiscounted QALYs
- Set discount rate for QALYs to 0%, set all utilities to 1 and disutilities to 0
    - As expected, discounted QALYs, undiscounted QALYs, discounted life years and undiscounted life years are all equal.
- Set treatment costs to £0.
    - As expected, all treatment costs in the traces are equal to £0.
- Set all resource use costs to £0
    - As expected, all resource use costs in the traces are equal to £0.

5.11 Interpretation and conclusions of economic evidence

Comparison against previously published roflumilast models

Base case results from this analysis are compared against two previously published studies are presented in Table 73.

Table 73: Comparison of published roflumilast model results

Analysis	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Current	£2,996	0.16	£18,609
Hertel 2012	£414	0.03	£16,566
Samyshkin 2014	£3,197	0.16	£19,505

Incremental cost, QALYs and the ICER per QALY gained are similar in our analysis and Samyshkin 2014.[18]. Samyshkin compared LABA ± ICS with LABA ± ICS / roflumilast. Due to the omission of LAMA, this was not included in the systematic review of cost effectiveness studies. We have included this here for comparison as this study provides much of the basis for the current model. Hertel 2012[17] generates similar ICERs to both our analysis and Samyshkin but generate different estimates of incremental costs and QALYs. This is likely due to the use of a different model structure. Hertel uses a model structure that includes second-line treatment for patients who continue to exacerbate and without disaggregated costs, it is unable to undertake a direct comparison between these analyses. As the previous models generate similar ICER per QALY gained and Samyshkin generates similar incremental costs and QALYs the results generated by our model are likely to be robust.

Discussion

The economic model for this submission, compliant with the NICE reference case, has two key areas. Firstly the progression from severe to very severe COPD which is modelled using a standard approach among studies in COPD[17 18] Secondly, the model uses individual patient level data from 1122 patients within REACT to predict the rate of moderate and severe

exacerbations for patients treated with LABA / LAMA / ICS / roflumilast and LABA / LAMA / ICS alone.

Table 74 provides a summary of deterministic and probabilistic analyses results for the three key populations. This demonstrates that regardless of population chosen, the ICER per QALY gained is less than £20,000 per QALY gained.

Table 74: Summary of deterministic and probabilistic results

Population	Deterministic ICER per QALY gained	Probabilistic ICER per QALY gained
Severe	£18,774	£18,575
Very severe	£12,337	£12,183
Mixed	£16,519	£16,349

A comprehensive set of one-way sensitivity analyses and scenario analyses were undertaken. These analyses have demonstrated the relative stability of the results to different assumptions. The analyses that lead to the largest change in results is when different HRQoL utility values are used. For the severe COPD, very severe COPD and mixed severity population these analyses produce an ICER which ranges from £18,774 to £26,069, £12,337 to £17,937 and £16,519 to £23,305 per QALY gained respectively. All the analysis produces ICERs that are within the range considered cost effective by NICE when using substantially different utility and disutility values.

Conclusion

The analyses undertaken demonstrate that roflumilast in addition to LABA / LAMA / ICS is a cost effective use of NHS resources for patients with severe and very severe COPD or in a mixed severity COPD population.

6 Assessment of factors relevant to the NHS and other parties

6.1 Evaluation of the budget impact analysis

This budget impact analysis is concerned with the addition of roflumilast to triple therapy in patients with severe to very severe COPD (FEV_1% predicted < 50%) and ≥2 moderate or severe COPD exacerbations within the previous year.

6.2 State how many people are eligible for treatment in England

In England, 1,034,578 people have been diagnosed with COPD.[111] Of these, 13% have severe to very severe COPD (FEV_1% predicted < 50%) and ≥2 moderate or severe COPD exacerbations within the previous year.[12] Furthermore, 91% of this patient population are on triple therapy.[12] Therefore, 122,391 people are eligible for treatment with roflumilast. Data from the CPRD provides the split of patient with severe and very severe COPD, 82.11% and 17.89% respectively.[105] For this analysis, we have assumed this will remain constant over the next 5 years.

6.3 Explain any assumptions that were made about current treatment options and uptake of technologies

As roflumilast is an add-on to LABA / LAMA / ICS it is not anticipated to displace any other technologies.

6.4 When relevant, explain any assumptions that were made about market share in England

Table 75 shows the expected market share of roflumilast in England from 2016 to 2021.

Table 75: Current and future uptake of roflumilast

Market share	2017	2018	2019	2020	2021
Roflumilast	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.5 Other significant costs associated with treatment that may be of interest to commissioners

No significant costs associated to treatment with roflumilast are anticipated.

6.6 Unit costs used in the budget impact analysis

The unit costs applied in this budget impact analysis are the same as those in the cost effectiveness analysis.

6.7 Estimates of resource savings.

Resource use savings are due to arise through a reduction in the number of severe exacerbations. Each exacerbation avoided has a cost of £1,724. This is the same as that applied in the cost effectiveness analysis.

6.8 State the estimated annual budget impact on the NHS in England.

The estimated budget impact for the NHS in England rises from £40,385 in 2017 to £848,087 in 2021 (Table 76).

Roflumilast has a cost of £38.24 a month or £458.88 per annum. This is multiplied by the number of people treated with roflumilast in each year to calculate the total cost attributable to the technology. In order to calculate the number of severe exacerbations avoided for people with severe and very severe COPD, exacerbations rates as in the cost effectiveness analysis were applied to the proportion of people with severe and very severe COPD for both LABA / LAMA / ICS / roflumilast and LABA / LAMA / ICS with the incremental difference equivalent to the number of exacerbations avoided.

Table 76: Budget impact analysis

	2017	2018	2019	2020	2021
Market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients treated	122	979	2203	2325	2570
Cost of roflumilast	**£56,163**	**£449,301**	**£1,010,927**	**£1,067,089**	**£1,179,414**
Number of severe exacerbations avoided (severe COPD patients)	6	48	109	115	127
Number of severe exacerbations avoided (very severe COPD patients)	3	25	56	59	65
Total cost offset	**£15,777**	**£126,220**	**£283,995**	**£299,772**	**£331,327**
Net budget Impact	**£40,385**	**£323,081**	**£726,932**	**£767,317**	**£848,087**

6.9 Identify any other opportunities for resource savings or redirection of resources that it has not been possible to quantify.

All significant resource use savings have been captured in the analysis.

6.10 Highlight the main limitations within the budget impact analysis.

The main limitation of this analysis is that the percentage of people with severe to very severe COPD (FEV_1% predicted < 50%) and ≥2 moderate or severe COPD exacerbations within the previous year, and the percentage of people with COPD who are on triple therapy is taken from the Adelphi Respiratory Disease Specific Programme which are unpublished.

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8 Appendices

All appendices are provided as a separate document.

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Single technology appraisal

Roflumilast for treating chronic obstructive pulmonary disease (review of technology appraisal guidance 244) [ID984]

Dear [redacted],

The Evidence Review Group, Kleijnen Systematic Reviews, and the technical team at NICE have looked at the submission received on 22 April 2016 from AstraZeneca. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **4 November 2016**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals https://appraisals.nice.org.uk/request/20100

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact [redacted] Technical Lead
[redacted] Any procedural questions should be addressed to,
[redacted] Project Manager [redacted]

Yours sincerely

Janet Robertson
Associate Director – Appraisals

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Centre for Health Technology Evaluation

Encl. checklist for confidential information

Literature searching

1. Please provide details of the database service provider used to conduct the Embase, CENTRAL, NHS EED and EconLit searches so the ERG can reproduce the searches.

2. **Priority question:** Please clarify why conference abstracts were excluded from the search strategies for cost-effectiveness studies, cost and healthcare resource identification, measurement and valuation studies and health related quality of life studies?

3. **Priority question:** Please clarify why, in the clinical effectiveness searches, the Embase search was limited to remove conference abstracts (Appendix 4, page xvi, lines 122-124)? Why then was a separate conference search undertaken in Embase and limited to four conferences only? Is the Company confident that there are no other valid conference abstracts in Embase for clinical effectiveness?

4. Please confirm whether validated search filters were used in the clinical effectiveness searches to identify placebo, clinical trials and the severity of disease? If so, please provide references for these filters.

5. **Priority question:** Please clarify why the conference abstracts found in Embase and the American Thoracic Society have not been included in the PRISMA flow diagram in Appendix 4, page xxxvii? Please confirm whether or not conference abstracts for clinical effectiveness were assessed for inclusion and exclusion?

6. Please clarify why search terms for drugs that were not specified in the NICE scope for clinical effectiveness were included in the search strategy for clinical effectiveness (for example Azithromycn, Clarithromycin, Erythromycin Fidaxomicin, Telithromycin, Carbomycin, Josamycin, Kitasamycin, Midecamycin, Oleandomycin, Slithromycin, Spiramycin, Troleandomycin, Tylosin, Roxithromycin)?

7. **Priority question:** Please explain the rationale for limiting searches for cost-effectiveness studies, cost and healthcare resource identification, measurement and valuation and health related quality of life studies to English language publications only.

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8. Appendix 7 (page 57, line 38) states that the updated MEDLINE search for cost-effectiveness studies, cost and healthcare resource identification, measurement found 464 records, but Figure 6 of the Company Submission (page 94) reports that this was 563 records. Conversely, Appendix 7 (page 57, line 38) states that the updated Embase search found 563 records, but the PRISMA flow diagram in the company submission, (Figure 6, page 94) reports that 464 records were found. Please can you confirm that this is a transcription error and that the PRISMA diagram should read Embase (n=563), MEDLINE (n=464)?

9. **Priority question:** The update searches for cost-effectiveness studies, cost and healthcare resource identification, measurement and valuation and searches for health related quality of life studies have been limited to "yr="2015 –Current"". Please could you explain how records added to the databases in 2015, but which have a publication date before 2015 were identified.

10. Please clarify why the original searches for health related quality of life studies use a date limit of "2015 – Current" (Appendix 9, page 62, line 41, page 65, line 36)? Can you confirm that this is a transcription error?

11. **Priority question:** Please clarify why a separate search for adverse events was not carried out?

Section A: Clarification on effectiveness data

A1. **Priority question**: Please provide the full CSR for the REACT and RESPONSE trials.

A2. **Priority question**: Please provide separate analyses for current smokers and ex-smokers in the REACT trial. This is because the trial includes a relatively high number of current smokers (42-45%) which may differ from current demographics in the UK and affect the generalisability of the results. If there is no difference in effectiveness between current smokers and ex-smokers this might not be an issue. Please perform these analyses for the primary and key-secondary effectiveness outcomes and safety outcomes.

A3. Please provide the conference abstract by Sadigov and Huseynova from the 2015 American Thoracic Society International Conference (company submission, page 46).

A4. **Priority question**: Please explain why Zheng 2014[1] (ACROSS Trial) was not included.

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A5. **Priority question**: In Table 1 the company seems to have deviated from the population in the NICE scope by referring to the 'subgroup', which is described as '…the positioning of roflumilast as an add-on to triple therapy…'. If this is the case then the population might be described as 'patients eligible for triple therapy'. This subgroup can be defined according to current NICE guidelines (NICE, CG101):

> '1.2.2.8 Offer LAMA in addition to LABA+ICS to people with COPD who remain breathless or have exacerbations despite taking LABA+ICS, irrespective of their FEV1.'
> '1.2.2.9 Consider LABA+ICS in a combination inhaler in addition to LAMA for people with stable COPD who remain breathless or have exacerbations despite maintenance therapy with LAMA irrespective of their FEV1.'

Could the company please clarify whether the population in the company's decision problem for clinical and cost effectiveness should be:

- patients who remain breathless or have exacerbations despite maintenance therapy with either LAMA or LABA/ICS irrespective of their FEV1 **or**
- adults with severe COPD (FEV1 post-bronchodilator < 50% predicted) associated with chronic bronchitis and a history of frequent exacerbations (≥2 exacerbations in the prior 12 months) despite triple therapy with LABA / LAMA / ICS

A6. **Priority question**: Please provide results for the outcomes 'Moderate or severe exacerbations' and 'severe exacerbations' from the REACT trial, for roflumilast vs placebo separately for the following groups:

A. patients receiving LABA/ICS + LAMA, patients receiving LABA/ICS and All patients (with and without LAMA); using the ITT population and the Poisson regression model
B. patients receiving LABA/ICS + LAMA, patients receiving LABA/ICS and All patients; using the PP population and the Poisson regression model
C. patients receiving LABA/ICS + LAMA, patients receiving LABA/ICS and All patients; using the ITT population and the negative binomial regression model
D. patients receiving LABA/ICS + LAMA, patients receiving LABA/ICS and All patients; using the PP population and the negative binomial regression model

Please populate the tables below with these data. The data from Table A are taken from Table 4 of the supplementary appendix of Martinez et al. (Lancet, 2015)[2]

Please confirm that the regression analyses do not include any covariates (other than treatment). If they do, then please specify the covariates and provide an analysis with all covariates AND one without covariates for the tables below.

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Table A. Mean rate of COPD exacerbations per patient per year (subgroup: A- ITT population and Poisson regression)

	Roflumilast LAMA subgroup: N=677 No LAMA subgroup: N=292	**Placebo LAMA subgroup: N=669 No LAMA subgroup: N=297**	**Roflumilast vs placebo**
Moderate or severe exacerbations, ITT population based on a Poisson regression model Mean rate, per patient per year (95% CI):			
LAMA subgroup	0·901 (0·799–1·016); n=286	1·023 (0·918–1·141); n=320	RR 0·881 (0·749–1·036); p=0·1252
No LAMA subgroup	0·595 (0·478–0·742); n=94	0·716 (0·589–0·869); n=112	RR 0·832 (0·620–1·116); p=0·2186
All patients			
Severe exacerbations, ITT population based on a Poisson regression model Mean rate, per patient per year (95% CI):			
LAMA subgroup			
No LAMA subgroup			
All patients			

Table B. Mean rate of COPD exacerbations per patient per year (subgroup: B - PP population and Poisson regression)

	Roflumilast LAMA subgroup: N=677 No LAMA subgroup: N=292	**Placebo LAMA subgroup: N=669 No LAMA subgroup: N=297**	**Roflumilast vs placebo**
Moderate or severe exacerbations, PP population based on a Poisson regression model Mean rate, per patient per year (95% CI):			
LAMA subgroup			
No LAMA subgroup			
All patients			
Severe exacerbations, PP population based on a Poisson regression model Mean rate, per patient per year (95% CI):			
LAMA subgroup			
No LAMA subgroup			
All patients			

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Table C. Mean rate of COPD exacerbations per patient per year (subgroup: C - ITT population and negative binomial regression)

	Roflumilast LAMA subgroup: N=677 No LAMA subgroup: N=292	**Placebo LAMA subgroup: N=669 No LAMA subgroup: N=297**	**Roflumilast vs placebo**
Moderate or severe exacerbations, ITT population based on the negative binomial regression model Mean rate, per patient per year (95% CI):			
LAMA subgroup			
No LAMA subgroup			
All patients			
Severe exacerbations, ITT population based on the negative binomial regression model Mean rate, per patient per year (95% CI):			
LAMA subgroup			
No LAMA subgroup			
All patients			

Table D. Mean rate of COPD exacerbations per patient per year (subgroup: D - PP population and negative binomial regression)

	Roflumilast LAMA subgroup: N=677 No LAMA subgroup: N=292	**Placebo LAMA subgroup: N=669 No LAMA subgroup: N=297**	**Roflumilast vs placebo**
Moderate or severe exacerbations, PP population based on the negative binomial regression model Mean rate, per patient per year (95% CI):			
LAMA subgroup			
No LAMA subgroup			
All patients			
Severe exacerbations, PP population based on the negative binomial regression model Mean rate, per patient per year (95% CI):			
LAMA subgroup			
No LAMA subgroup			
All patients			

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A7. **Priority question**: Possible comparators mentioned in the scope are: LAMA+ LABA/ICS, LAMA+LABA, LAMA or LABA (with or without ICS) and theophylline. The submission explains why theophylline is not considered a relevant comparator. Table 1 in the company submission states that the reason for exclusion of LAMA+LABA and LAMA or LABA (with or without ICS) is that '…the scope of intervention is restricted to roflumilast in combination with LABA / LAMA / ICS,…' However, it is unclear what is meant by 'scope of intervention'. Does the company mean the subgroup referred to in question A5? The ERG would point out that this does not necessarily exclude non-triple therapy as a comparator, because some patients for whatever reason (related to patient or clinician choice) will continue to take non-triple therapy.

A. Please provide a clear explanation as to why these comparators were not included.

B. Looking at Table 19 (page 82 in the company submission), the FORWARD trial and/or the WISDOM trial can be used for an indirect comparison of roflumilast (in combination with LAMA+LABA/ICS) vs LAMA+LABA. Please either explain why this was not feasible, or perform the analysis.

C. Again looking at Table 19 (page 82 in the company submission), adding the FLAME, ILLUMINATE and/or LANTERN trials to the indirect analyses described in B allows an indirect comparison of roflumilast (in combination with LAMA+LABA/ICS) vs LAMA/ICS. Please either explain why this was not feasible, or perform the analysis.

D. Once more looking at Table 19 (company submission, page 82), adding the Cosio 2016 trial to the indirect analyses described in B and C allows an indirect comparison of roflumilast (in combination with LAMA+LABA/ICS) vs theophylline. Please either explain why this was not feasible, or perform the analysis.

See figure 1 below for a possible network.

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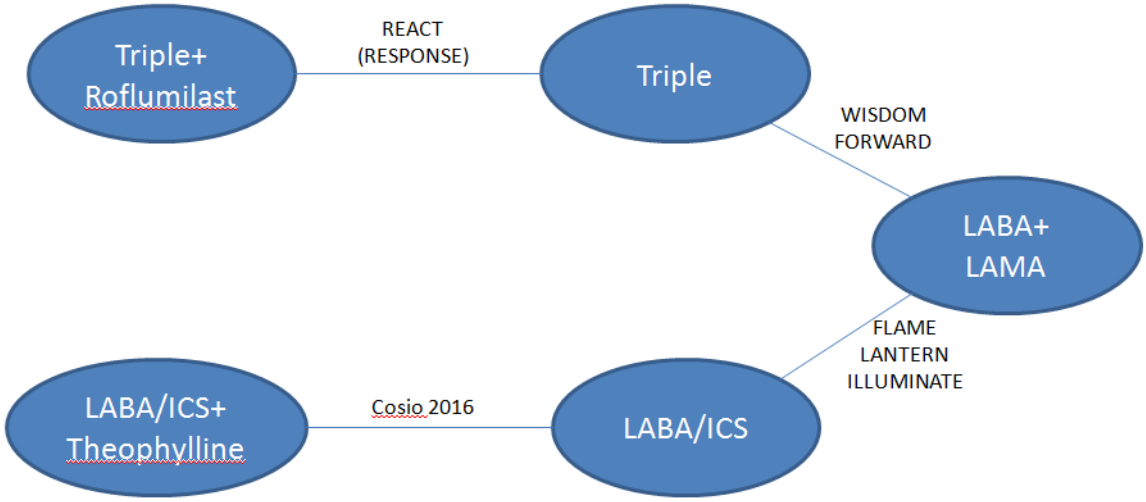
Figure 1. Possible network diagram



A8. **Priority question**: For the REACT trial please provide baseline characteristics (as in Table 13 and 14 of the company submission) for the concomitant LAMA subgroup (LABA / LAMA / ICS) ITT population.

A9. Please explain the number of major protocol violations in the REACT trial (Table 12, page 64 of the company submission). The numbers of patients with FEV_1 > 50 % of predicted at V0, not having used LABA/ICS for at least 12 months prior to the trial, and total cough and sputum count < 14 in the week before randomisation suggest that inclusion criteria have been reassessed at randomisation, but not used to exclude these patients from randomisation. If so, please explain why the PP population would be more relevant for the decision problem. In clinical practice, FEV_1 values and sputum counts will vary, and patients will forget medication changes.

A10. Please explain why differences in fluticasone dosage between the REACT and RE^{2}SPOND trials would lead to results not being applicable to the UK situation. For bronchodilators the current GOLD guideline states that dose-response relationships using FEV_1 as the outcome are relatively flat with all classes of bronchodilators (Gold 2016, page 21). For ICS GOLD 2016[3] states "The dose-response relationships …. of inhaled corticosteroids in COPD are not known".

A11. Please perform an additional analysis using pooled REACT/ RE^{2}SPOND results to populate the tables in question A6.

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Section B: Clarification on cost-effectiveness data

B1. Please explain why the SLR for cost and resource use and for HRQoL studies were restricted by geographical location. Please also provide the list of all excluded studies with the reasons of exclusion in the cost-effectiveness, HRQoL and cost and resource use searches as it was not clear to the ERG why some of the studies were not included. (E.g. Samyshkin et al (2014)[4] study was not identified in the company submission's cost effectiveness literature search).

B2. Please answer the questions below which are related to the base case population characteristics presented in Table 24 (page 98 in the company submission):

a. Are the characteristics of the base case population in Table 24 in line with those of the UK population for whom roflumilast is indicated (i.e. patients with severe to very severe COPD and ≥ 2 moderate or severe COPD exacerbations within the previous year)? Please provide a table that compares the base case characteristics in Table 24 with UK population characteristics derived from observational studies, including also % of smokers, BMI and comorbidity scores.

b. Are the characteristics in Table 24 related to the whole REACT trial population or to the concomitant LAMA subgroup (i.e. patients that received LABA/LAMA/ICS or LABA/LAMA/ICS /ROF in the REACT trial)? If it is not the latter one, please provide the characteristics of concomitant LAMA subgroup.

B3. The model structure excludes many important aspects of COPD progression as listed below. Please modify the model to include these issues, or alternatively justify the choice not to include them.

a. The health states in the model are only based on GOLD stages that were distinguished from each other by FEV1% predicted value thresholds only. However, in the literature it is mentioned that this classification might be insensitive to the heterogeneity of the patients (i.e. a severe patient with a FEV1% predicted value of 40% with symptoms might have a different prognosis compared to a patient with the same FEV1% predicted value without symptoms).[5]

b. In the model, it is assumed that there is no effect of exacerbations on FEV1, even though in the literature it was found that an exacerbation has an impact on the FEV1 value of a patient.[5]

c. In the model, it is assumed that there is no effect of previous exacerbation history on future exacerbation risk, even though in the literature it was

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demonstrated that previous exacerbation history is an important predictor of future exacerbation risk.[5]

d. In the model, baseline characteristics like race, smoking status, BMI and presence of other comorbidities have no effect on disease progression and exacerbation rates, even though it was shown that these characteristics impact the prognosis of COPD significantly.[5]

B4. **Priority question:** Please explain how the patients who discontinued the treatment were included in the calculation of the exacerbation rates.

B5. **Priority question**: Please incorporate the event that a patient may discontinue roflumilast and switch from LABA/LAMA/ICS/ROF to LABA/LAMA/ICS into the model. Switching may be due to any reason (for example side effects, serious adverse events, adherence and in case of lack of efficacy, i.e. if more than 2 exacerbations in the last year). Monthly discontinuation rates calculated from the REACT trial can be used to incorporate roflumilast discontinuation event to the model.

B6. **Priority question:** Please update the following model input data and re-conduct the health-economic analyses accordingly (one by one and all at once).

a. The reference equations used to transfer FEV1 to % FEV1 predicted (Crapo et al. 1981[6]) are from a study from 1981. Please use reference equations from a more recent study for this transformation (e.g. Hankinson et al.[7] from 1999, based on US population, by reweighting the races according to the UK population).

b. In the model, a 52 ml decline per year in FEV1 was assumed for all disease severity stages.

   i. Please explain how the literature was searched to find the estimate of yearly decline in FEV1.

   ii. Different studies suggest the FEV1 decline is not linear throughout the disease stages/age (e.g. Decramer and Cooper (2010)[8] estimated an annual decrease of 38 and 23 ml/ year for severe and very severe COPD patients from UPLIFT trial). Please incorporate these differential annual FEV1 decline rates (i.e. not the 52 ml used for all patients).

c. In the model, it is assumed that the average % FEV1 predicted value is 40% for severe COPD patients, which is the midpoint of 30% and 50% (range that defines severe COPD state). Please provide the actual average FEV1% predicted value of the severe COPD patients from the REACT trial (only

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consider the patients who received LAMA/LABA/ICS and LAMA/LABA/ICS/ROF, both for PP and ITT) and use the actual average FEV1% predicted value of the severe COPD patients from the REACT trial instead of the hypothetical value of 40%.

B7. Please provide the details of the conducted regression analyses for moderate/severe exacerbations for LAMA strata and LAMA as a covariate (input data for the statistical analysis, the output of the statistical regression, goodness of fit results as well as the script of the statistical software)

a. Please provide negative binomial regression results of moderate/severe exacerbations for ITT population
b. Please confirm that the Poisson regression models in the economic section included correction for overdispersion and please provide Poisson regression results of moderate/severe exacerbations for ITT and PP analysis
c. Please explain why treatment and the GOLD stage were chosen as the only covariates in the regression analyses for moderate/severe exacerbations. Please conduct a formal covariate selection procedure, from all possible covariates (besides treatment and GOLD stage; age, smoking, number of moderate/severe exacerbations last year before baseline and their interactions should also be taken into consideration)

B8. Please explain how the literature was searched to find the mortality estimates used in the model. Also, please recalculate the SMRs for background mortality by COPD severity stage, in the same way as explained in Samyshkin et al 2014, but use instead all the mortality inputs and the model provided in the submission.

B9. **Priority question**: Please provide the utility derived from the REACT trial based on CAT score by using the mapping algorithms in the literature (e.g. Hoyle et al 2016[9]).

B10. **Priority question**: Please incorporate the comparators in question A6 to the economic model and present the full incremental results (a separate analysis for part A, part B, part C and part D).

B11. In the calculation of the adverse events, the N from the ITT analysis was used (967 and 968), whereas in the calculation of the exacerbation rates, the N from the PP population was used. Please correct this inconsistency.

B12. Please provide the results of a scenario analysis in which treatment related adverse events could happen in all years, not only in the first year.

B13. In the OWSA and in the PSA, many important parameters were not taken into account (e.g. treatment effectiveness parameters not varied in OWSA, mortality inputs were not varied in PSA). At the same time, parameters such as time horizon

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and discount factors were varied where they should not. Please justify the inclusion criteria that were applied to the input parameters for OWSA and PSA.

B14. Please verify the programming error in the health economic model: In all of the following formulas in the "Treatment Effect" sheet, "probabilistic" should be replaced with "Probablistic": E22:E24; E30:E32; X22:X25 and X31:X34.

B15. The correlation between the coefficients of the exacerbation rate regression was not taken into consideration. Please re-conduct the PSA, in which all relevant correlations are correctly taken into account.

B16. Please provide trial and model exacerbation rate comparisons (of both treatment and control arms) in Table 53 in addition to rate ratio comparisons. Furthermore, please provide additional validation of the model, such as cross-validation, validation against external data, validation against internal data, clinical expert face validation.

REFERENCES

[1] Zheng J, Yang J, Zhou X, Zhao L, Hui F, Wang H, et al. Roflumilast for the treatment of COPD in an Asian population: a randomized, double-blind, parallel-group study. *Chest* 2014;145(1):44-52.

[2] Martinez FJ, Calverley PM, Goehring UM, Brose M, Fabbri LM, Rabe KF. Effect of roflumilast on exacerbations in patients with severe chronic obstructive pulmonary disease uncontrolled by combination therapy (REACT): a multicentre randomised controlled trial. *Lancet* 2015;385(9971):857-66.

[3] GOLD. *Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease*. Belgium: Global Initiative for Chronic Obstructive Lung Disease, 2016 Available from: http://goldcopd.org/

[4] 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;15(1):69-82.

[5] Briggs A, Baker T, Risebrough NA, Chambers M, Gonzalez-McQuire S, Ismaila AS, et al. Development of the Galaxy Chronic Obstructive Pulmonary Disease (COPD) Model using data from ECLIPSE: internal validation of a linked-equations cohort model. *Med Decis Making* 2016.

[6] Crapo RO, Morris AH, Gardner RM. Reference spirometric values using techniques and equipment that meet ATS recommendations. *Am Rev Respir Dis* 1981;123(6):659-64.

[7] Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;159(1):179-87.

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[8] Decramer M, Cooper CB. Treatment of COPD: the sooner the better? *Thorax* 2010;65(9):837-41.

[9] Hoyle CK, Tabberer M, Brooks J. Mapping the COPD Assessment Test onto EQ-5D. *Value Health* 2016;19(4):469-77.

Single technology appraisal: **Roflumilast for treating chronic obstructive pulmonary disease (review of technology appraisal guidance 244) [ID984]**

Clarification Questions: AstraZeneca

4th November 2016

On review of the clarification questions, we would like to clarify that AstraZeneca focused on the use of roflumilast in a subgroup of adult patients with severe chronic obstructive pulmonary disease (COPD) as part of maintenance treatment; as add-on to triple therapy (inhaled corticosteroids [ICS], long-acting beta2 agonist [LABA] and long-acting muscarinic antagonist [LAMA]) in patients with $FEV_1 < 50\%$ predicted, symptoms of chronic bronchitis and frequent exacerbations (≥ 2 / year). A recommendation in this specific subgroup is sought.

After incorporating the ERG's requested additional analyses into the economic model, the ICER changes very little and roflumilast remains a cost effective option for the treatment of severe COPD.

Literature searching

1. *Please provide details of the database service provider used to conduct the Embase, CENTRAL, NHS EED and EconLit searches so the ERG can reproduce the searches.*

OVID was used as the search provider for Embase and EconLit
CENTRAL was searched through the Cochrane library
NHSEED was searched through CRD

2. ***Priority question**: Please clarify why conference abstracts were excluded from the search strategies for cost-effectiveness studies, cost and healthcare resource identification, measurement and valuation studies and health related quality of life studies?*

The limited information available from conference abstracts were considered to be insufficient to fully inform model structure or parameters and hence these were excluded from the search strategies.

3. ***Priority question:** Please clarify why, in the clinical effectiveness searches, the Embase search was limited to remove conference abstracts (Appendix 4, page xvi, lines 122-124)? Why then was a separate conference search undertaken in Embase and limited to four conferences only? Is the Company confident that there are no other valid conference abstracts in Embase for clinical effectiveness?*

We believe the main relevant COPD conference abstracts, which had not yet been published as a full paper, would be available from the following five conferences; American College of Chest Physicians (CHEST) World congress 2014 and 2016, CHEST annual meeting 2014 and 2015,

American Thoracic Society (ATS) international conference 20145 and 2016, British Thoracic Society (BTS) winter meeting 2014 and 2015, and European Respiratory Society (ERS) annual congress 2014 and 2015. We consider these conferences to be the most relevant to COPD; and the most impactful congresses with regard to the latest clinical evidence about to be published in COPD.

4. *Please confirm whether validated search filters were used in the clinical effectiveness searches to identify placebo, clinical trials and the severity of disease? If so, please provide references for these filters.*

The trial filters are an adapted and updated version of the Cochrane Highly Sensitive Search Strategy for identification of RCTs first published in 1994 and updated in 2006. Below are the references to these publications:

(1) Glanville JM, Lefebvre C, Miles JN, Camosso-Stefinovic J. How to identify randomized controlled trials in MEDLINE: ten years on. J Med Libr Assoc 2006 Apr;94(2):130-6.

(2) Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. BMJ 1994 Nov 12;309(6964):1286-91.

(3) Lefebvre C, McDonald S. Development of a sensitive search strategy for reports of randomised controlled trials in EMBASE. Fourth International Cochrane Colloquium; 1996 Oct 20-24; Adelaide (Australia). 1996.

These searches have been updated to reflect changes in indexing.

The severity search filter was constructed de novo for this project in order to target the searches specifically at studies with a population of patients with severe and very severe disease.

5. ***Priority question:*** *Please clarify why the conference abstracts found in Embase and the American Thoracic Society have not been included in the PRISMA flow diagram in Appendix 4, page xxxvii? Please confirm whether or not conference abstracts for clinical effectiveness were assessed for inclusion and exclusion?*

Conference abstracts were screened for inclusion in the systematic review of efficacy and safety.

The number of conference abstracts included in the SLR is indicated in the flowchart in Appendix 4, page xxxvii (of our submission) as identified from other sources (n=1). The placing of the information here was based on our interpretation of this statement from the PRISMA explanation document.

“It is useful if authors delineate for readers the number of selected articles that were identified from the different sources so that they can see, for example, whether most articles were

identified through electronic bibliographic sources or from references or experts. Literature identified primarily from references or experts may be prone to citation or publication bias."

We did not record the primary reasons for exclusion after preliminary screening (e.g., screening of titles and abstracts); in our PRISMA flow diagram. Based on our interpretation of the explanation from PRISMA (see below), records refers to titles and abstracts whilst reports refers to the full publications. Therefore, in line with the PRISMA statement we only provide primary reasons for exclusion for reports.

"The flow diagram and text should describe clearly the process of report selection throughout the review. Authors should report: unique records identified in searches; records excluded after preliminary screening (e.g., screening of titles and abstracts); reports retrieved for detailed evaluation; potentially eligible reports that were not retrievable; retrieved reports that did not meet inclusion criteria and the primary reasons for exclusion; and the studies included in the review."

6. *Please clarify why search terms for drugs that were not specified in the NICE scope for clinical effectiveness were included in the search strategy for clinical effectiveness (for example Azithromycn, Clarithromycin, Erythromycin Fidaxomicin, Telithromycin, Carbomycin, Josamycin, Kitasamycin, Midecamycin, Oleandomycin, Slithromycin, Spiramycin, Troleandomycin, Tylosin, Roxithromycin)?*

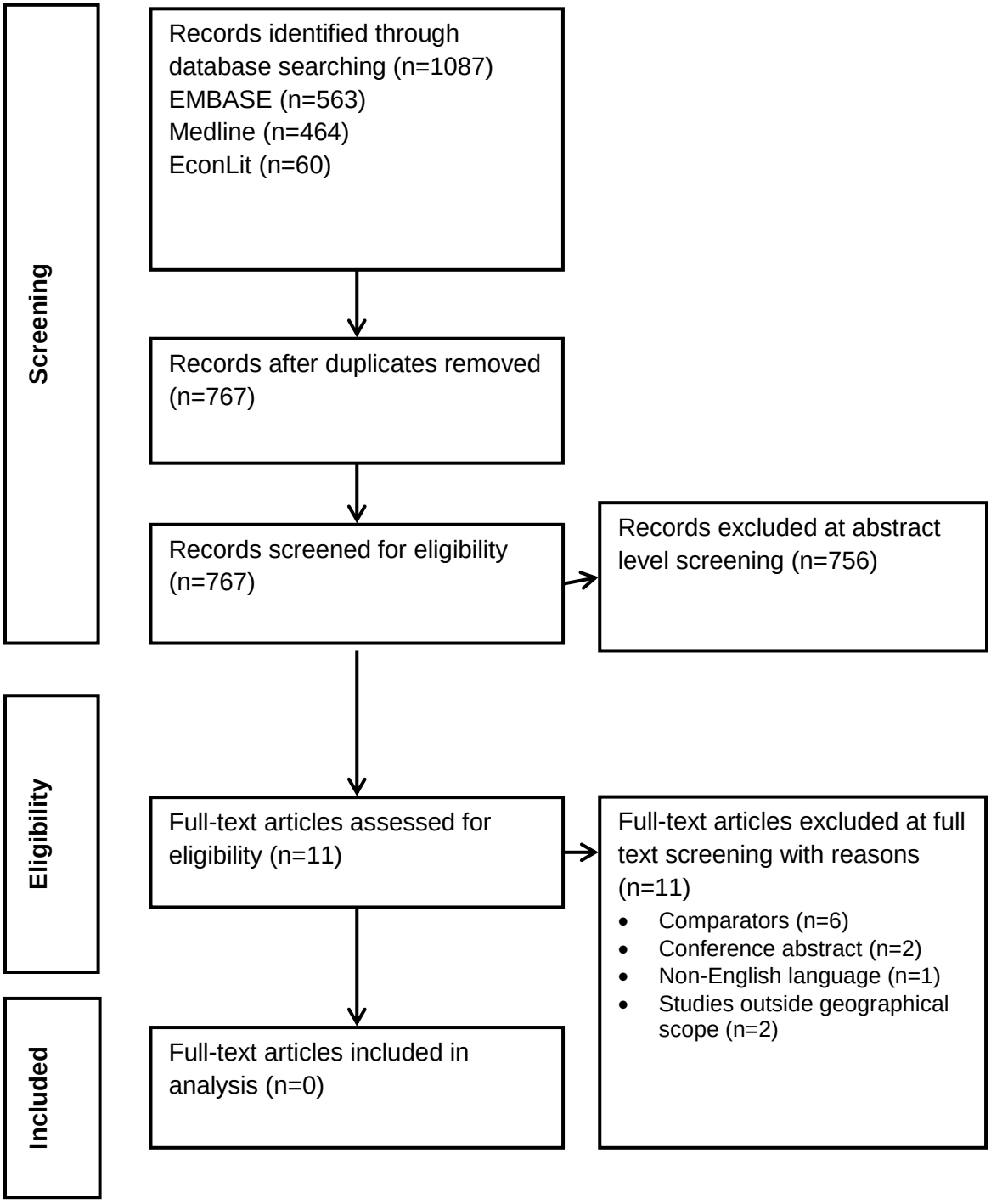
Searches were designed prior to release of the final NICE scope; and included antibiotics routinely used in the acute setting as add-on to existing therapy following an exacerbation. Antibiotics are used in this setting rather than as a maintenance therapy. Records for irrelevant comparators were subsequently excluded.

7. ***Priority question:*** *Please explain the rationale for limiting searches for cost-effectiveness studies, cost and healthcare resource identification, measurement and valuation and health related quality of life studies to English language publications only*.

As the remit of these searches is to inform a cost-effectiveness model for the NICE base case i.e. the population of England and Wales, non-English language publications are highly unlikely to be relevant to the decision problem, particularly when considering the wealth of English language publications available in the COPD literature.

8. *Appendix 7 (page 57, line 38) states that the updated MEDLINE search for cost-effectiveness studies, cost and healthcare resource identification, measurement found 464 records, but Figure 6 of the Company Submission (page 94) reports that this was 563 records. Conversely, Appendix 7 (page 57, line 38) states that the updated Embase search found 563 records, but the PRISMA flow diagram in the company submission, (Figure 6, page 94) reports that 464 records were found. Please can you confirm that this is a transcription error and that the PRISMA diagram should read Embase (n=563), MEDLINE (n=464)?*

Yes this is a transcription error. An updated PRISMA is provided below.



9. ***Priority question:*** *The update searches for cost-effectiveness studies, cost and healthcare resource identification, measurement and valuation and searches for health related quality of life studies have been limited to "yr="2015 –Current"". Please could you explain how records added to the databases in 2015, but which have a publication date before 2015 were identified.*

The original searches were run on 7th May 2015. It would be expected that all records with a publication date of 2014 or earlier would have been added to the databases before May 2015.

10. *Please clarify why the original searches for health related quality of life studies use a date limit of "2015 – Current" (Appendix 9, page 62, line 41, page 65, line 36)? Can you confirm that this is a transcription error?*

Yes this is a transcription error and should read 2004 – current.

11. ***Priority question:*** *Please clarify why a separate search for adverse events was not carried out?*

The search for RCTs was not limited by study outcomes; and therefore this search was used to identify efficacy and safety data from relevant studies.

Section A: Clarification on effectiveness data

A1. ***Priority question****: Please provide the full CSR for the REACT and RESPONSE trials.*

A copy of the CSR for REACT is provided.

REACT is the most relevant trial to the decision problem and as such is presented as the primary trial in our submission.

We have not provided the CSR for the RE^{2}SPOND trial as this is not, as stated in our submission document (Section 4.2, pages 48 and 49), considered appropriate for the assessment of roflumilast as add-on to triple therapy in UK patients with severe COPD, chronic bronchitis and frequent exacerbations. To reiterate:

- The patient profile of the RE^{2}SPOND population does not reflect accurately that of the target population in this decision problem (i.e. inclusion criteria prevented demonstration that patients were uncontrolled on ICS / LABA ± LAMA, proportion of patients on triple therapy was relatively low, a very small proportion of the study population were from Western Europe)

- The RE^{2}SPOND trial conditions do not reflect UK clinical practice (i.e. lower LABA / ICS dosing, different tablet formulation)

To conclude, REACT is the most relevant trial to the decision problem and as such is presented as the primary trial in this submission.

A2. ***Priority question****: Please provide separate analyses for current smokers and ex-smokers in the REACT trial. This is because the trial includes a relatively high number of current smokers (42-45%) which may differ from current demographics in the UK and affect the generalisability of the results. If there is no difference in effectiveness between current smokers and ex-smokers this might not be an issue. Please perform these analyses for the primary and key-secondary effectiveness outcomes and safety outcomes.*

In the REACT trial pre-specified subgroup analyses by smoking (current smoker vs. former smoker) status were performed. Analyses were performed for the primary endpoint (rate of moderate or severe exacerbations) and the key secondary endpoints (change in post-bronchodilator FEV1 and rate of severe exacerbations) based on the Poisson regression analysis, repeated measurements analysis, and negative binomial regression analysis, respectively. Only the results for the ITT population are available and these are provided below and indicate that smoking has no impact on efficacy. A difference between the ITT population and the PP population is not anticipated for these analyses; furthermore there would be no reason to expect a difference between all patients; the LAMA sub-group; and the no LAMA sub-group.

Mean rate of moderate or severe COPD exacerbations per patient per year: Poisson regression model (estimates of exacerbation rates (ITT)

			Ratio roflumilast/placebo				
	Roflumilast N, rate (n)	**Placebo N, rate (n)**	**Rate ratio**	**Change (%)**	**SE**	**95% CI**	**2 sided p value**
Current smoker	411, 0.750 (155)	432, 0.907 (179)	0.826	-17.4	0.0955	0.659,1.036	0.0989
Former smoker	558, 0.848 (225)	534, 0.944 (253)	0.899	-10.1	0.0843	0.748,1.081	0.2567

Source: REACT CSR Table 11.g

Changes from baseline to vend in post-bronchodilator FEV1 (L): (LS Means from ANCOVA including treatment-by-time interaction), repeated measurements analysis (ITT)

			Difference roflumilast - placebo		
	Roflumilast n	**Placebo n**	**LS Mean ± SE**	**95% CI**	**2 sided p value**

Current smoker	399	419	0.071±0.0143	0.043, 0.099	<0.0001
Former smoker	529	522	0.044±0.0113	0.022, 0.067	0.0001

Source: REACT CSR Table 11.i

Mean rate of severe COPD exacerbations per patient per year: Negative binomial regression model (estimates of exacerbation rates) (ITT)

			Ratio roflumilast/placebo				
	Roflumilast N, rate (n)	**Placebo N, rate (n)**	**Rate ratio**	**Change (%)**	**SE**	**95% CI**	**2 sided p value**
Current smoker	411, 0.223 (57)	432, 0.354 (0.88)	0.630	-37.0	0.1201	0.433,0.915	0.0153
Former smoker	558, 0.251 (94)	534, 0.281 (104)	0.893	-10.7	0.1307	0.670,1.189	0.4377

Source: REACT CSR Table 11.K

A3. *Please provide the conference abstract by Sadigov and Huseynova from the 2015 American Thoracic Society International Conference (company submission, page 46).*

A copy of the abstract is provided.

A4. ***Priority question**: Please explain why Zheng 2014[1] (ACROSS Trial) was not included*.

This trial gave patients roflumilast in combination with double-therapy (ICS / LABA) and is therefore not applicable to our submission.

A5. ***Priority question**: In Table 1 the company seems to have deviated from the population in the NICE scope by referring to the 'subgroup', which is described as '…the positioning of roflumilast as an add-on to triple therapy…'. If this is the case then the population might be described as 'patients eligible for triple therapy'. This subgroup can be defined according to current NICE guidelines (NICE, CG101):*

> *'1.2.2.8 Offer LAMA in addition to LABA+ICS to people with COPD who remain breathless or have exacerbations despite taking LABA+ICS, irrespective of their FEV1.'*
> *'1.2.2.9 Consider LABA+ICS in a combination inhaler in addition to LAMA for people with stable COPD who remain breathless or have exacerbations despite maintenance therapy with LAMA irrespective of their FEV1.'*

Could the company please clarify whether the population in the company's decision problem for clinical and cost effectiveness should be:

- *patients who remain breathless or have exacerbations despite maintenance therapy with either LAMA or LABA/ICS irrespective of their FEV1* ***or***

- *adults with severe COPD (FEV1 post-bronchodilator < 50% predicted) associated with chronic bronchitis and a history of frequent exacerbations (≥2 exacerbations in the prior 12 months) despite triple therapy with LABA / LAMA / ICS*

We can confirm that the population in the decision problem for clinical and cost effectiveness is:

- adults with severe COPD (FEV1 post-bronchodilator < 50% predicted) associated with chronic bronchitis and a history of frequent exacerbations (≥2 exacerbations in the prior 12 months) despite triple therapy with LABA / LAMA / ICS.

To clarify AstraZeneca is seeking a NICE recommendation for roflumilast as an **add-on** to triple therapy in this subgroup group of patients. Within the decision problem section of our submission (Table 1 on page 13) we have specified that while the scope included the full licensed population we have focused on the above subgroup which '*better reflects the recommendations for further research issued by NICE in their final guidance in 2012 and the unmet need for patients with severe COPD and chronic bronchitis with a history of frequent exacerbations'*
Treatment options for patients who continue to have exacerbations despite triple therapy (LABA / LAMA / ICS) are limited and guidance on how to best manage these patients is lacking. Roflumilast provides a further step in the treatment pathway post-triple therapy (LABA / LAMA / ICS) where currently there is no treatment available. Roflumilast will be added-on to triple therapy.

A6. ***Priority question****: Please provide results for the outcomes 'Moderate or severe exacerbations' and 'severe exacerbations' from the REACT trial, for roflumilast vs placebo separately for the following groups:*

A. patients receiving LABA/ICS + LAMA, patients receiving LABA/ICS and All patients (with and without LAMA); using the ITT population and the Poisson regression model

B. patients receiving LABA/ICS + LAMA, patients receiving LABA/ICS and All patients; using the PP population and the Poisson regression model

C. patients receiving LABA/ICS + LAMA, patients receiving LABA/ICS and All patients; using the ITT population and the negative binomial regression model

D. patients receiving LABA/ICS + LAMA, patients receiving LABA/ICS and All patients; using the PP population and the negative binomial regression model

Please populate the tables below with these data. The data from Table A are taken from Table 4 of the supplementary appendix of Martinez et al. (Lancet, 2015)[2]

Please confirm that the regression analyses do not include any covariates (other than treatment). If they do, then please specify the covariates and provide an analysis with all covariates AND one without covariates for the tables below.

Data for the LAMA subgroup, the only subgroup relevant to the decision problem, is provided in Tables A to D. AstraZeneca are, as stated above, seeking a NICE recommendation for the use of roflumilast as add-on therapy to LABA / LAMA/ ICS therefore the pre-specified concomitant therapy with the LAMA subgroup is the most relevant population with the clinical and economic sections of our submission focusing heavily on this group. We have also added and /or amended patient numbers in the header rows.

Table A. Mean rate of COPD exacerbations per patient per year (subgroup: A- ITT population and Poisson regression)

	Roflumilast N=969 LAMA subgroup: N=677 No LAMA subgroup: N=292	**Placebo N=966 LAMA subgroup: N=669 No LAMA subgroup: N=297**	**Roflumilast vs placebo**
Moderate or severe exacerbations, ITT population based on a Poisson regression model Mean rate, per patient per year (95% CI):			
LAMA subgroup	0·901 (0·799–1·016); n=286	1·023 (0·918–1·141); n=320	RR 0·881 (0·749–1·036); p=0·1252
No LAMA subgroup			
All patients			
Severe exacerbations, ITT population based on a Poisson regression model Mean rate, per patient per year (95% CI):			
LAMA subgroup	0.280 (0.226 - 0.347) n= 125	0.354 (0.295 - 0.425) n= 152	RR 0.791 (0.597 - 1.048) p= 0.1019
No LAMA subgroup			
All patients			

Table B. Mean rate of COPD exacerbations per patient per year (subgroup: B - PP population and Poisson regression)

	Roflumilast N=810 LAMA subgroup: N=~~677~~ 565 No LAMA subgroup: N=~~292~~ ~~245~~	**Placebo N=823 LAMA subgroup: N=~~669~~ 557 No LAMA subgroup: N=~~297~~266**	**Roflumilast vs placebo**
Moderate or severe exacerbations, PP population based on a Poisson regression model Mean rate, per patient per year (95% CI):			

LAMA subgroup	0.838 (0.732 - 0.960) n= 235	1.034 (0.920 - 1.164) n= 271	0.810 (0.677 - 0.969) p=0.0215
No LAMA subgroup			
All patients			
Severe exacerbations, PP population based on a Poisson regression model Mean rate, per patient per year (95% CI):			
LAMA subgroup	0.256 (0.200 - 0.327) n= 99	0.372 (0.305 - 0.452) n= 132	RR 0.688 (0.503 - 0.943) p=0.0200
No LAMA subgroup			
All patients			

Table C. Mean rate of COPD exacerbations per patient per year (subgroup: C - ITT population and negative binomial regression)

	Roflumilast N=969 LAMA subgroup: N=677 No LAMA subgroup: N=292	**Placebo N=966 LAMA subgroup: N=669 No LAMA subgroup: N=297**	**Roflumilast vs placebo**
Moderate or severe exacerbations, ITT population based on the negative binomial regression model Mean rate, per patient per year (95% CI):			
LAMA subgroup	0.924 (0.821 - 1.040) n= 286	1.061 (0.950 - 1.185) n= 320	RR 0.871 (0.741 - 1.024) p= 0.0944
No LAMA subgroup			
All patients			
Severe exacerbations, ITT population based on the negative binomial regression model Mean rate, per patient per year (95% CI):			
LAMA subgroup	0.287 (0.237 - 0.347) n= 125	0.374 (0.315 - 0.443) n= 152	RR 0.767 (0.595 - 0.989) p=0.0406
No LAMA subgroup			
All patients			

Table D. Mean rate of COPD exacerbations per patient per year (subgroup: D - PP population and negative binomial regression)

	Roflumilast N=810 LAMA subgroup: N=~~677~~ 565 No LAMA subgroup: N=~~292~~ 245	**Placebo N=823 LAMA subgroup: N=~~669~~ 557 No LAMA subgroup: N=~~297~~ 266**	**Roflumilast vs placebo**
Moderate or severe exacerbations, PP population based on the negative binomial regression model Mean rate, per patient per year (95% CI):			
LAMA subgroup	0.858 (0.754 - 0.978) n= 235	1.075 (0.954 - 1.211) n= 271	RR 0.799 (0.670 - 0.952) p=0.0122
No LAMA subgroup			
All patients			
Severe exacerbations, PP population based on the negative binomial regression model Mean rate, per patient per year (95% CI):			
LAMA subgroup	0.260 (0.210 - 0.322) n= 99	0.395 (0.329 - 0.475) n= 132	RR 0.659 (0.497 - 0.872) p=0.0035
No LAMA subgroup			
All patients			

A7. ***Priority question****: Possible comparators mentioned in the scope are: LAMA+ LABA/ICS, LAMA+LABA, LAMA or LABA (with or without ICS) and theophylline. The submission explains why theophylline is not considered a relevant comparator. Table 1 in the company submission states that the reason for exclusion of LAMA+LABA and LAMA or LABA (with or without ICS) is that '…the scope of intervention is restricted to roflumilast in combination with LABA / LAMA / ICS,…' However, it is unclear what is meant by 'scope of intervention'. Does the company mean the subgroup referred to in question A5? The ERG would point out that this does not necessarily exclude non-triple therapy as a comparator, because some patients for whatever reason (related to patient or clinician choice) will continue to take non-triple therapy.*

A. Please provide a clear explanation as to why these comparators were not included.

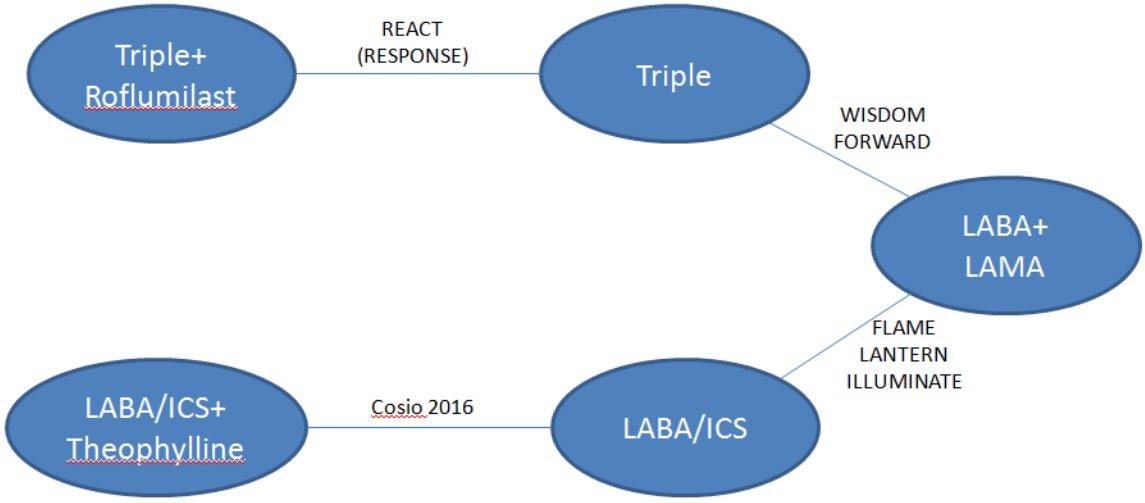
B. Looking at Table 19 (page 82 in the company submission), the FORWARD trial and/or the WISDOM trial can be used for an indirect comparison of roflumilast (in combination with LAMA+LABA/ICS) vs LAMA+LABA. Please either explain why this was not feasible, or perform the analysis.

C. Again looking at Table 19 (page 82 in the company submission), adding the FLAME, ILLUMINATE and/or LANTERN trials to the indirect analyses described in B allows an indirect comparison of roflumilast (in combination with LAMA+LABA/ICS) vs LAMA/ICS. Please either explain why this was not feasible, or perform the analysis.

D. Once more looking at Table 19 (company submission, page 82), adding the Cosio 2016 trial to the indirect analyses described in B and C allows an indirect comparison of roflumilast (in combination with LAMA+LABA/ICS) vs theophylline. Please either explain why this was not feasible, or perform the analysis.

See figure 1 below for a possible network.

Figure 1. Possible network diagram



Please note that within the above diagram we have assumed RESPONSE should be RE^{2}SPOND.

Response to 7A

As per our response to question A5, we are seeking a recommendation for the use of roflumilast as an add-on to triple therapy in adults with severe COPD (FEV1 post-bronchodilator < 50% predicted) associated with chronic bronchitis and a history of frequent exacerbations (≥2 exacerbations in the prior 12 months).

Since the submission is restricted to roflumilast in combination with LABA / LAMA / ICS (so as an add-on), mono- and dual therapy comparators are not considered relevant and are outside the decision problem specified in Table one of our submission. Only patients failing on triple therapy will be eligible for treatment.

Response to 7B and 7C

For the reasons stated above it is not appropriate to compare roflumilast as an add-on to triple therapy with dual therapy.

Response to 7D
Theophylline is not considered a relevant comparator owing to:
(i) its negligible use in UK clinical practice it does not represent standard practice in the UK. Of COPD patients experiencing frequent exacerbations (≥2 exacerbations in the prior 12 months) despite treatment with ICS / LABA / LAMA, only 4.6% are also prescribed theophylline. In addition theophylline is associated with serious treatment limiting side effects which do not favour chronic usage
(ii) lack of evidence demonstrating its effect on exacerbation rates as add-on to triple therapy in this patient group. There is no evidence on the use of theophylline as add-on to triple therapy and its impact on exacerbation rates in patients with severe COPD and frequent exacerbations.

The theophylline study most relevant to the decision problem, the Cosio 2016 trial, is a pilot clinical study, in which patients with severe COPD were treated with oral low-dose theophylline added to ICS+LABA. In this placebo-controlled study theophylline failed to prevent exacerbations. In fact, there was a trend (not statistically significant) of exacerbations being more frequent in the intervention group.

In light of the above, theophylline was excluded from the decision problem as a comparator to roflumilast. We would also like to highlight that the exclusion of theophylline was agreed as being appropriate at the Decision Problem Meeting.

Due to the above factors indirect comparison with theophylline is not appropriate.

A8. ***Priority question****: For the REACT trial please provide baseline characteristics (as in Table 13 and 14 of the company submission) for the concomitant LAMA subgroup (LABA / LAMA / ICS) ITT population.*

Available baseline characteristics for the concomitant LAMA subgroup (ITT population) are provided below.

Baseline characteristic	**Roflumilast**	**Placebo**
REACT (n=1,346)	N=677	N=669
Age, mean years n (%)		
<=65	353 (52.14)	364 (54.41)
>65	324 (47.86)	305 (45.59)
Male sex n (%)	506 (74.74)	499 (74.59)
Body-mass index, kg / m2, n (%)		
Underweight <18.5	33 (4.87)	32 (4.78)
Normal weight >18.5 to <25	266 (39.29)	238 (35.58)
Overweight >= 25 to <30	217 (32.05)	232 (34.68)
Obese <+ 30	161 (23.78)	167 (24.96)
Cigarette pack-years, n (%)		

Baseline characteristic	Roflumilast	Placebo
<40	263 (38.85)	258 (38.57)
>= 40	414 (61.15)	411 (61.43)
Smoking status, n (%)		
Current smoker	258 (38.11)	273 (40.81)
Former smoker	19 (61.89)	396 (59.19)
FEV1 reversibility increase n(%)		
<=12% and /or 200ml	575 (84.93)	570 (85.20)
>12% and > 200 ml	55 (8.120	56 (8.37)
COPD severity n (%)		
Mild	1 (0.15)	0 (0.00)
Moderate	13 (1.92)	11 (1.64)
Severe	437 (64.55)	455 (68.01)
Very severe	226 (33.38)	203 (30.34)
CAT score n (%)		
<10	45 (6.65)	41 (6.13)
>=10	630 (93.06)	626 (93.57)
MRC dyspnoea scale n (%)		
<2	149 (22.01)	164 (24.51)
>= 2	513 (75.78)	492 (73.54)
No. exacerbations in the prior year n (%)		
< 2	4 (0.59)	3 (0.45)
2	581 (85.82)	580 (86.70)
>2	88 (13.00)	84 (12.56)
History of cardiovascular disease n (%)		
Yes	304 (44.90)	309 (46.19)
No	373 (55.10)	360 (53.81)

A9. *Please explain the number of major protocol violations in the REACT trial (Table 12, page 64 of the company submission). The numbers of patients with FEV_1 > 50 % of predicted at V0, not having used LABA/ICS for at least 12 months prior to the trial, and total cough and sputum count < 14 in the week before randomisation suggest that inclusion criteria have been reassessed at randomisation, but not used to exclude these patients from randomisation. If so, please explain why the PP population would be more relevant for the decision problem. In clinical practice, FEV_1 values and sputum counts will vary, and patients will forget medication changes*.

NOTE: The following additional clarification was received from the ERG (via email):

We are concerned about the considerable number of patients with major protocol deviations (312 out of 1945 = 16.0 %). Table 12 in the CS shows that many of these protocol deviations were in randomised patients who appear to not fulfil the criteria, which they appear to have been fulfilled in order to be randomised in the first place. These include: postbronchodilator FEV1 > 50 % at V0 (105), not pretreated with LABA/ICS during 12 months previously (78 minus those who deviated in use during the trial), total cough or sputum score < 14 in the week before randomization (61), less than 2 documented moderate or severe COPD exacerbations within 1

year prior to V0 (19). We presume this must be due to patients being randomized based on fulfilment of inclusion criteria assessed prior to the baseline visit at V0 and non-compliance at V0. This leads to two questions for the company:

1) Are we correct in this presumption?

2)If so then why would the PP population (who met inclusion criteria both at randomisation and at V0) be more relevant for the decision problem than the ITT population? Or, alternatively phrased, does the company expect that practicing doctors will prescribe roflumilast only in patients who consistently have postbronchodilator FEV1 < 50% and sputum score >= 14?

In responding to the ERG points, we would highlight that they are not correct to presume that patients were randomised 'based on fulfilment of inclusion criteria assessed prior to the baseline visit at V0 and non-compliance at V0'.

Patients who met the inclusion criteria and exclusion criteria were eligible for trial participation. Prior to randomisation, eligibility had to be re-confirmed and randomisation criteria met. Patients had to meet all of the following randomisation criteria at V2 to be eligible for randomisation into the double-blind treatment period:

a. No moderate or severe COPD exacerbation and/or COPD exacerbation treated with antibiotics between visits V0 and V2.
b. Tablet compliance (placebo) ≥80% and ≤125%.
c. Total cough and sputum score ≥14 during the last week directly preceding the randomisation visit.
d. FEV1 (post-bronchodilator) ≤50% of predicted.

2,708 patients were enrolled into the trial and 1,945 patients were randomised. Of the 763 non-randomised patients:

- 311 violated the inclusion criteria,
- 116 met the exclusion criteria,
- 266 failed to meet the randomisation criteria and
- 763 discontinued during the baseline period due to other reasons

Please note there was a protocol change (Amendment 1) to the inclusion criteria to allow re-enrolment of patients not presenting with post-bronchodilator FEV1 ≤50% of predicted. Previously many patients screened for the trial met all inclusion and randomisation criteria with the exception of FEV1 % of predicted ≤50% at inclusion or randomisation; and so could not be included in the double-blind treatment period.

The PP population was selected over the ITT population for a range of reasons:

- The ITT population included randomised patients who took at least 1 dose of study drug following randomisation and incorporated all data until the patient discontinued (prematurely or as scheduled) the trial. The ITT population included a substantial proportion of patients with protocol violations which exclude these patients (16.0%) from

meeting either the licence criteria for roflumilast and / or the decision problem criteria for this technology appraisal.

- The PP population, however, included only those patients without major protocol violations (note: patients who discontinued treatment were included in the PP population provided there were no major protocol violations). The PP population was identified as being more appropriate (than the ITT population) as it more closely aligns with the patient subgroup defined in the decision problem.

A10. Please explain why differences in fluticasone dosage between the REACT and RE^{2}SPOND trials would lead to results not being applicable to the UK situation. For bronchodilators the current GOLD guideline states that dose-response relationships using FEV_1 as the outcome are relatively flat with all classes of bronchodilators (Gold 2016, page 21). For ICS GOLD 2016[3] states "The dose-response relationships …. of inhaled corticosteroids in COPD are not known".

The fluticasone/salmeterol dose used in RE^{2}SPOND was 250/50 µg (1 inhalation twice daily), a dose which is not licensed in the UK and Europe for the treatment of COPD and therefore any treatment results using this therapy as a background medication cannot be considered generalisable to UK clinical practice.

In REACT, the fluticasone/salmeterol 500/50 µg dose is reflective of clinical practice and prescribing guidelines in the UK.[1,2]

A11. Please perform an additional analysis using pooled REACT/ RE^{2}SPOND results to populate the tables in question A6.

As stated in our response to question A1, RE^{2}SPOND is not relevant to the decision problem; and hence a pooled analysis of REACT and RE^{2}SPOND will not inform the decision problem.

Section B: Clarification on cost-effectiveness data

B1. Please explain why the SLR for cost and resource use and for HRQoL studies were restricted by geographical location. Please also provide the list of all excluded studies with the reasons of exclusion in the cost-effectiveness, HRQoL and cost and resource use searches as it was not clear to the ERG why some of the studies were not included. (E.g. Samyshkin et al (2014)[4] study was not identified in the company submission's cost effectiveness literature search).

As the remit of these searches was to inform a cost-effectiveness model for the NICE base case i.e. the population of England and Wales, we aimed to capture UK data to populate the model. The search strategies were designed to capture data from eight countries: UK, US, Canada, Germany, France, Italy, Spain and Australia, but this was to be narrowed to UK specific data if it was available.

The lists of excluded studies have been added to Appendix 1.

Samyshkin 2014 was not included due to the study comparators. Within the AstraZeneca submission roflumilast is given as add-on to triple therapy while in Samyshkin 2014 roflumilast is given as add-on to double therapy.

B2. Please answer the questions below which are related to the base case population characteristics presented in Table 24 (page 98 in the company submission):

a. Are the characteristics of the base case population in Table 24 in line with those of the UK population for whom roflumilast is indicated (i.e. patients with severe to very severe COPD and ≥ 2 moderate or severe COPD exacerbations within the previous year)? Please provide a table that compares the base case characteristics in Table 24 with UK population characteristics derived from observational studies, including also % of smokers, BMI and comorbidity scores.

A comprehensive tabulation of UK observational studies would require a thorough literature search. Due to the timeframe allowed for response, it has not been possible to undertake this task for the specific sub-group population in question. The sub-group would need to also be aligned to the GOLD criteria as in the trial population. Furthermore, recent publications present patients with severe to very severe COPD or ≥ 2 moderate or severe COPD exacerbations within the previous year; hence we have not been able to locate data for the specific population defined by AstraZeneca in the decision problem. The data we have been able to source within the restricted timeframe is provided in the table below. The table only provides illustrative comparisons of baseline characteristics based on a small sample of studies.

Base-case population characteristics compared with UK population characteristics derived from observational studies

Baseline characteristic	Baseline value REACT	Punekar et al 2014[3] ≥ 2 moderate-severe exacerbations	McGarvey et al 2015[4] ≥ 2 moderate-severe exacerbations	J. Haughney et al, 2014[5] GOLD 2011 C+D
Age, (years)	64.70	69.44 (n= 13,351)	- (n=2,062)	70.2 (n=2820)
Male (%)	74.60%	48.83%	45.2%	53.2%
Current smokers (%)	43.6%	31.26%	38.4%	36.3%
Body mass index, kg/m^2	26.52	26.82	-	26.5
Charlson comorbidity index	-	2.58	-	-

b..Are the characteristics in Table 24 related to the whole REACT trial population or to the concomitant LAMA subgroup (i.e. patients that received LABA/LAMA/ICS or LABA/LAMA/ICS /ROF in the REACT trial)? If it is not the latter one, please provide the characteristics of concomitant LAMA subgroup.

Table 24 in our submission document is for the whole REACT trial population. A copy of Table 24 for the concomitant LAMA subgroup is provided below.

LAMA subgroup baseline characteristics

Baseline characteristic	Baseline value
Age (years)	65.0
Male (%)	74.5%
Mean height males (cm)	170.6
Mean height females (cm)	160.0

Including these minor changes to the baseline characteristics in the economic model has the effect of decreasing the ICER to £18,550 from the submitted base case of £18,774.

B3. The model structure excludes many important aspects of COPD progression as listed below. Please modify the model to include these issues, or alternatively justify the choice not to include them.

a. *The health states in the model are only based on GOLD stages that were distinguished from each other by FEV1% predicted value thresholds only. However, in the literature it is mentioned that this classification might be insensitive to the heterogeneity of the patients (i.e. a severe patient with a FEV1% predicted value of 40% with symptoms might have a different prognosis compared to a patient with the same FEV1% predicted value without symptoms).*[5]

The model structure used in the company submission which defines states based on FEV1% predicted normal values (spirometric classification), as defined by GOLD (2007) and GOLD (2011), is in keeping with previous COPD models in the area including Samyshkin (2014) as well as the NICE COPD Guidelines 2010. Although symptoms, in terms of CAT score, has been recently added to the GOLD categories there are no UK weighted utility studies based on these definitions, nor have any studies correlated CAT score with meaningful clinical outcomes, furthermore it is unlikely that these changes will have significant impact on this cost effectiveness analysis and therefore the pre 2013 definitions have been used in this instance to maintain consistency with previous economic assessments in this disease area. There will undoubtedly be heterogeneity in disease course that may be explained, as in the lagged equation disease model referred to, by inter related baseline patient characteristics and time varying disease attributes (FEV1, exacerbations, symptoms etc). This submission arguably addresses a less heterogeneous population in that patients are at severe disease with greater than or equal to two recent exacerbations.

b. *In the model, it is assumed that there is no effect of exacerbations on FEV1, even though in the literature it was found that an exacerbation has an impact on the FEV1 value of a patient.*[5]

AstraZeneca acknowledges that exacerbations have the potential to impact upon the FEV1 value of a patient, however, with the improvement in FEV1 in the roflumilast arm of 56ml seen in the REACT trial. AstraZeneca believes that there is the potential for double counting in this area and has therefore taken the conservative assumption that neither roflumilast nor exacerbations impact upon FEV1.

c. *In the model, it is assumed that there is no effect of previous exacerbation history on future exacerbation risk, even though in the literature it was demonstrated that previous exacerbation history is an important predictor of future exacerbation risk.*[5]

AstraZeneca acknowledges the literature which has demonstrated that previous exacerbation history is an important predictor of future exacerbation risk, however, COPD exacerbations are also environmentally triggered and therefore not solely explained by previous exacerbations. AstraZeneca notes that modifying the current model to accommodate tunnel states to attribute increased exacerbation risk in post exacerbation cycles (and therefore favour roflumilast) would not be feasible in the time available and has therefore made the conservative assumption that there is no relationship between past exacerbations and future exacerbations.

d. *In the model, baseline characteristics like race, smoking status, BMI and presence of other comorbidities have no effect on disease progression and exacerbation rates, even though it was shown that these characteristics impact the prognosis of COPD significantly.*[5]

AstraZeneca acknowledges the literature which has demonstrated that certain patient level characteristics impact the prognosis of COPD, however, with COPD and its accompanying exacerbations being environmentally (pollution, weather etc) impacted AstraZeneca believes that the model structure given in the submission is the most appropriate. Furthermore the historical precedence in economic modelling in this area has followed this same practice, for example the Samyshkin model (2014) and the NICE COPD Guideline model 2010. AstraZeneca therefore believes that the current model structure is best suited not only to the disease area but also to keeping consistency with previous models in this area.

The table below shows the rate of exacerbations in the placebo arm, stratified by patients smoking status. This is a proxy for the natural course of the disease in this patient group. The table shows that a patient's smoking status has no effect on the rate of exacerbations in these patients; and therefore cannot be considered as an important factor in determining disease prognosis.

Smoking Status	N	Number of exacerbations	Rate of exacerbations	95% CI
Current	231	106	1.105	0.908 – 1.346
Former	326	165	1.053	0.907 – 1.222

B4. ***Priority question:*** *Please explain how the patients who discontinued the treatment were included in the calculation of the exacerbation rates.*

The rate of COPD exacerbations was investigated using a Poisson regression model. The natural logarithm of the duration in terms of years in the trial was used as an offset variable. For each patient, the time in trial was calculated as follows: (date of end of treatment period – date of first intake of IMP + 1 day). This offset variable corrected for the time a patient was in the trial.

Data on moderate or severe exacerbations were collected by telephone contacts also for patients discontinuing the IMP prematurely to estimate the potential impact of missing data.

A sensitivity analysis was conducted including both (1) all moderate or severe exacerbations from the treatment period (defined as pre-discontinuation), (2) all post-discontinuation moderate

or severe exacerbations recorded via telephone contact for patients who discontinued prematurely (defined as post-discontinuation).

A post-discontinuation exacerbation was determined as moderate or severe from the Telephone Contact Premature Discontinuation page of the eCRF, where the moderate/severe COPD exacerbation box was ticked, or where the patient had died and the reason for death is COPD exacerbation.

For the analysis of moderate or severe exacerbations including pre- and post-discontinuation data a Poisson regression model in analogy to the primary model was applied. The dependent variable was the number of events of both (1) and (2) described above. For patients who discontinued IMP and for which post-discontinuation data regarding moderate or severe exacerbations were available the time in trial has to be recalculated as follows: date of telephone contact / date of death – date of first intake of double-blind IMP + 1 day, where the date of telephone contact was the latest date of contact for patients with more than one telephone contact. For all other patients the time in trial that was already calculated for the primary analysis will be used.

The frequency of moderate or severe exacerbations including pre- and post-discontinuation data was summarised by treatment.

B5. ***Priority question****: Please incorporate the event that a patient may discontinue roflumilast and switch from LABA/LAMA/ICS/ROF to LABA/LAMA/ICS into the model. Switching may be due to any reason (for example side effects, serious adverse events, adherence and in case of lack of efficacy, i.e. if more than 2 exacerbations in the last year). Monthly discontinuation rates calculated from the REACT trial can be used to incorporate roflumilast discontinuation event to the model.*

In the absence of monthly discontinuation rates, the overall discontinuation rate from the full ITT population has been used as a proxy. We assume that the majority of discontinuation of roflumilast will occur alongside AEs and therefore would occur early in the treatment course (in the first cycle of the model). Furthermore, given that patients who have discontinued roflumilast have also been included in the treatment effect calculation it is assumed that patients in the model maintain this treatment effect.

Incorporating discontinuation in this manner in the model produces an ICER of £16,869.

Taking the more conservative assumption that patients who discontinue roflumilast revert to the treatment effect of triple therapy yields an ICER of £18,917.

B6. ***Priority question:*** *Please update the following model input data and re-conduct the health-economic analyses accordingly (one by one and all at once).*

a. *The reference equations used to transfer FEV1 to % FEV1 predicted (Crapo et al. 1981[6]) are from a study from 1981. Please use reference equations from a more recent study for this transformation (e.g. Hankinson et al.[7] from 1999, based on US population, by reweighting the races according to the UK population).*

b. *In the model, a 52 ml decline per year in FEV1 was assumed for all disease severity stages.*

    i. *Please explain how the literature was searched to find the estimate of yearly decline in FEV1.*

    ii. *Different studies suggest the FEV1 decline is not linear throughout the disease stages/age (e.g. Decramer and Cooper (2010)[8] estimated an annual decrease of 38 and 23 ml/ year for severe and very severe COPD patients from UPLIFT trial). Please incorporate these differential annual FEV1 decline rates (i.e. not the 52 ml used for all patients).*

c. *In the model, it is assumed that the average % FEV1 predicted value is 40% for severe COPD patients, which is the midpoint of 30% and 50% (range that defines severe COPD state). Please provide the actual average FEV1% predicted value of the severe COPD patients from the REACT trial (only consider the patients who received LAMA/LABA/ICS and LAMA/LABA/ICS/ROF, both for PP and ITT) and use the actual average FEV1% predicted value of the severe COPD patients from the REACT trial instead of the hypothetical value of 40%.*

Alternative FEV1 reference equations.

At the ERG's request we performed an analysis based on the United States' third National Health and Nutrition Examination Survey (NHANES III), Hankinson et al (1999) in place of the reference equations of Crapo (1981). The base case predicted an average sojourn time in the severe state of 6.96 years. Using Hankinson et al the predicted sojourn time is 7.22 (Caucasian) and 5.72 (African American). The ICERs associated with these sojourn times are £18,922 and £17,989 respectively. If the analyses were weighted 95% to the Caucasian case (UK COPD audit), the ICER would be £18,875, as compared with the base case ICER of £18,774.

These analyses are based on sojourn times that satisfy for the base case; given the negligible impact on the ICER, and the added complexity of predicting sojourn times (due to the quadratic term in Hankinson et al), a general solution has not been implemented in the model.

Annual decline in FEV1

Our base case figure of 52 ml per annum is taken from the Lung Health Study (Scanlon et al, 2000)[6], as was the estimate applied by Samyshkin et al. A systematic review for this parameter estimate was not performed. The ERG suggests alternative estimates of 38 and 23 ml per annum for severe and very severe COPD patients from the UPLIFT trial. Though FEV1 decline

may indeed be non-linear through the disease stages, in the model FEV1 decline moderates sojourn time in the severe state (GOLD III) only – once patients transition to the very severe state (GOLD IV), the rate of decline has no further impact in the model. To address the ERG's request therefore we applied the estimate of 38 ml in place of the base case estimate from the Lung Health Study. In this case the ICER changes from a base of £18,774 to £20,281.

Starting FEV1% predicted

In the model base case, patients are assumed to be at the mid-point of the range for severe COPD (>30% to ≤50%). Lower staring FEV1% predicted values will have the effect of improving the ICER as sojourn times in the severe state are reduced, with higher exacerbation rates in the very severe state being applied sooner. For the range of 30.1% to 50% the ICERs range from £12,319 to £21,460.

B7. Please provide the details of the conducted regression analyses for moderate/severe exacerbations for LAMA strata and LAMA as a covariate (input data for the statistical analysis, the output of the statistical regression, goodness of fit results as well as the script of the statistical software)

Please note that the goodness of fit results are provided in four separate files (REACT tables 18 and 19).

a. Please provide negative binomial regression results of moderate/severe exacerbations for ITT population

As described in the submission, AstraZeneca believes that the most appropriate population for this decision problem is the per protocol (PP) population. This is because of the high proportion of major protocol violations which occurred in the ITT population with the most common being that patients; (i) had post-bronchodilator FEV1 ≥ 50%; (ii) had not been treated with ICS / LABA for the prior year; (iii) had a low cough and sputum score; and (iv) had fewer than 2 exacerbations in the prior year. All of these violations exclude these patients (16.0%) from meeting either the licence criteria for roflumilast and / or the decision problem criteria for this technology appraisal. Therefore AstraZeneca believes that the most appropriate population with which to address the decision problem is the PP.

b. Please confirm that the Poisson regression models in the economic section included correction for overdispersion and please provide Poisson regression results of moderate/severe exacerbations for ITT and PP analysis

In the economic section of the submission the Poisson regression model was not used in any of the analyses and therefore the models did not require the additional correction for overdispersion as this was handled within the Negative Binomial regression model itself

AstraZeneca maintains that the Negative Binomial regression model is the correct model to use for this dataset as Keene et al. (2007)[7] explain and Suissa et a. (2006)[8] illustrate. In the Poisson

regression model, estimates of treatment effect are unaffected by use of an over dispersion adjustment as only the estimates of standard error are increased. In contrast, the negative binomial model assumes that individuals' exacerbations follow a Poisson process with an underlying rate that is distributed as a gamma distribution. Therefore as Keene et al. (2007) conclude the negative binomial methodology is considered to give a more precise estimate of exacerbation rates.

c. *Please explain why treatment and the GOLD stage were chosen as the only covariates in the regression analyses for moderate/severe exacerbations. Please conduct a formal covariate selection procedure, from all possible covariates (besides treatment and GOLD stage; age, smoking, number of moderate/severe exacerbations last year before baseline and their interactions should also be taken into consideration)*

COPD GOLD stage was chosen as a covariate in the regression model as this corresponds to the COPD states in the model. Previous models have adopted this structure with estimates for exacerbation risk that vary by severity. Our analyses support this distinction between severe and very severe patients' exacerbation risks.

B8. Please explain how the literature was searched to find the mortality estimates used in the model. Also, please recalculate the SMRs for background mortality by COPD severity stage, in the same way as explained in Samyshkin et al 2014, but use instead all the mortality inputs and the model provided in the submission.

AstraZeneca maintain that the SMRs used in the economic model submission are suitable values to use – SMRs should be standardised, and independent of other model parameter estimates such as a lower case fatality rate for severe exacerbations.

B9. ***Priority question****: Please provide the utility derived from the REACT trial based on CAT score by using the mapping algorithms in the literature (e.g. Hoyle et al 2016[9]).*

AstraZeneca believes that although CAT score was a secondary endpoint in the REACT trial the study itself was not powered to detect significant differences between the two arms and therefore any interpretation of these values or attempted mapping of them to EQ-5D values would be flawed. In addition Hoyle (2016) conclude that the predictive performance of mapping algorithms is poor in populations with more severe COPD such as the one in REACT. Jones (2011) also show that CAT has only a weak, negative correlation with FEV1 % predicted (the key determinant of our model transitions) and therefore would provide a poor and potentially counterintuitive source of utility data.

B10. ***Priority question****: Please incorporate the comparators in question A6 to the economic model and present the full incremental results (a separate analysis for part A, part B, part C and part D).*

NOTE: Correspondence with NICE and the ERG confirmed that A7 should replace A6 in the above question

The comparators in question A7 are for the reasons stated in our response to A7 not relevant to the decision problem and on this basis the requested analyses are not presented.

B11. In the calculation of the adverse events, the N from the ITT analysis was used (967 and 968), whereas in the calculation of the exacerbation rates, the N from the PP population was used. Please correct this inconsistency.

The table below shows the incidence of AEs (grade 3 and above) from the PP population on LAMA:

Event	Roflumilast (n=565) N(%)	Placebo (n=557) N(%)	Total (n=1122) N(%)
Diarrhoea	1 (0.2)	0 (0)	1 (0.1)
Nausea	0 (0)	0 (0)	0 (0)
Weight Loss	1 (0.2)	0 (0)	1 (0.1)
Pneumonia	11 (1.9)	9 (1.6)	20 (1.8)

If these adverse event numbers are inputted into the model it has the effect of Increasing the ICER from a base case of £18,774 to £18,794

B12. Please provide the results of a scenario analysis in which treatment related adverse events could happen in all years, not only in the first year.

AstraZeneca believes that the current calculation of adverse events is a conservative estimate as we have not only applied a disutility associated with a severe (hospitalised) exacerbation for all adverse events but have also applied the full burden of these adverse events in the first cycle of the model meaning that they are not subject to any discounting. Furthermore, the Daxas SmPC states in clinical COPD studies the majority of these adverse reactions were mild or moderate. These adverse reactions mainly occurred within the first weeks of therapy and mostly resolved on continued treatment, suggesting that these adverse events would not continue into subsequent years.

B13. In the OWSA and in the PSA, many important parameters were not taken into account (e.g. treatment effectiveness parameters not varied in OWSA, mortality inputs were not varied in PSA). At the same time, parameters such as time horizon and discount factors were varied where they should not. Please justify the inclusion criteria that were applied to the input parameters for OWSA and PSA.

Responses to questions B13 and B14 are included with the response to B15.

B14. Please verify the programming error in the health economic model: In all of the following formulas in the "Treatment Effect" sheet, "probabilistic" should be replaced with "Probablistic": E22:E24; E30:E32; X22:X25 and X31:X34.

Responses to questions B13 and B14 are included with the response to B15.

B15. The correlation between the coefficients of the exacerbation rate regression was not taken into consideration. Please re-conduct the PSA, in which all relevant correlations are correctly taken into account.

Response for B13 to B15

We recognise the error regarding probabilistic analysis of the exacerbation rate treatment effect (point B14) and omission of associated covariance (B15). The error and omission have been corrected. The revised estimates for all three main scenarios (severe, very severe and the mixed cohort population are provided below)

For each of the probabilistic analyses below the results are in line with the deterministic analysis. The results are summarised in tables 1-3 below, with cost-utility plane scatterplots, CEACs, and CEAFs presented in figures 1-3, 4-6, and 7-9 for the severe, very severe, and mixed cohorts respectively.
For the severe cohort the probabilistic cost per QALY for roflumilast is £17,855, with probabilities of 0.70 and 0.98 of being cost effective at thresholds of 20,000 and 30,000 per QALY respectively.
For the very severe cohort the probabilistic cost per QALY for roflumilast is £12,206, with probability of 1.00 of being cost effective at a thresholds of 20,000 per QALY.
For the severe cohort the probabilistic cost per QALY for roflumilast is £15,964, with probabilities of 0.85 and 1.00 of being cost effective at thresholds of 20,000 and 30,000 per QALY respectively.

Table 1: LAMA strata severe cohort probabilistic results

Technologies	Total costs (£)	95% CI	Total QALYs	95% CI	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
LABA / LAMA / ICS / roflumilast	£23,129	£19,930 to £26,816	6.18	5.48 to 6.93	£2,996	0.17	£17,855
LABA / LAMA / ICS	£20,133	£17,055 to £23,717	6.01	5.33 to 6.74	-	-	-

Table 2: LAMA strata very severe cohort probabilistic results

Technologies	Total costs (£)	95% CI	Total QALYs	95% CI	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
LABA / LAMA / ICS / roflumilast	£26,228	£21,421 to £31,685	5.22	4.35 to 6.20	£2,376	0.19	£12,206
LABA / LAMA / ICS	£23,852	£19,402 to £28,947	5.02	4.20 to 5.94			

Table 3: LAMA strata mixed cohort probabilistic results

Technologies	Total costs (£)	95% CI	Total QALYs	95% CI	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
LABA / LAMA / ICS / roflumilast	£24,079	£20,570 to £28,230	5.88	5.17 to 6.66	£2,803	0.18	£15,964
LABA / LAMA / ICS	£21,276	£17,968 to £25,193	5.71	5.03 to 6.4			

Figure 1: LAMA strata severe cohort incremental cost effectiveness scatter plot

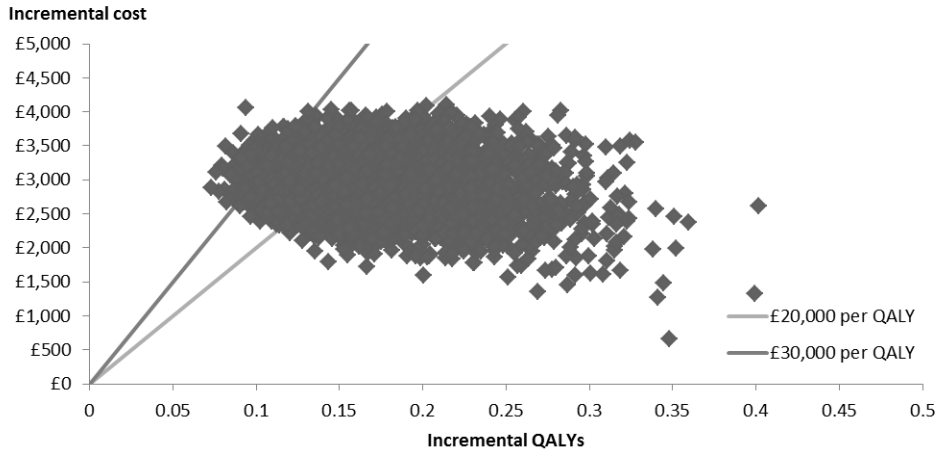


Figure 2: LAMA strata severe cohort cost effectiveness acceptability curve

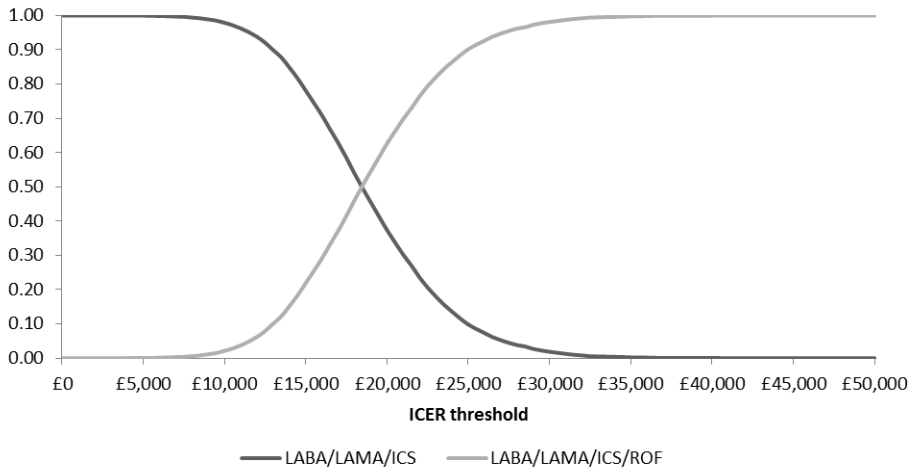


Figure 3: LAMA strata severe cohort cost effectiveness acceptability frontier

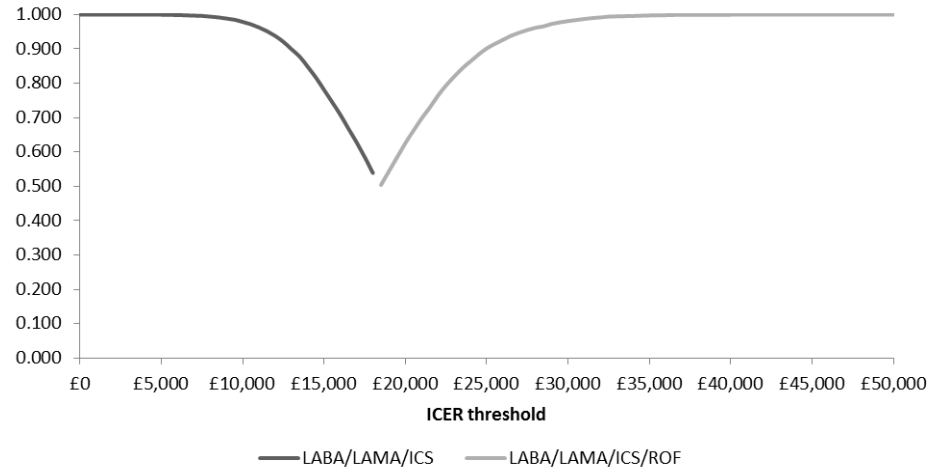


Figure 4: LAMA strata very severe cohort incremental cost effectiveness scatter plot

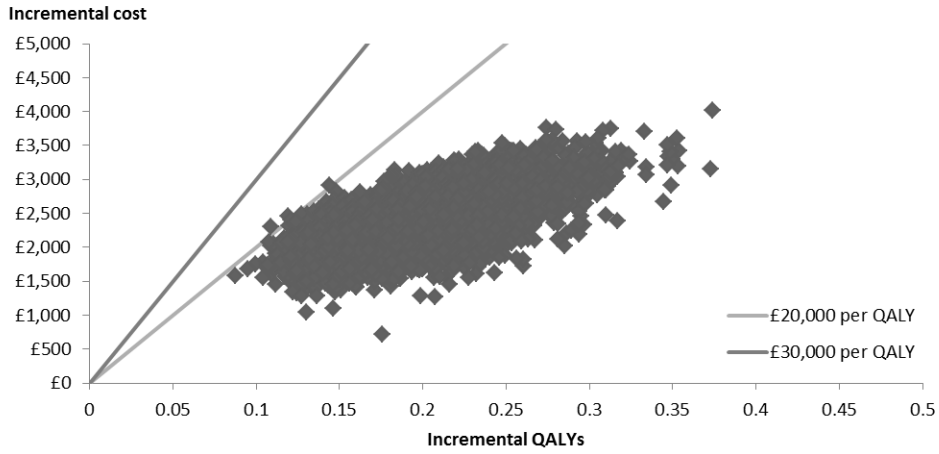


Figure 5: LAMA strata very severe cohort cost effectiveness acceptability curve

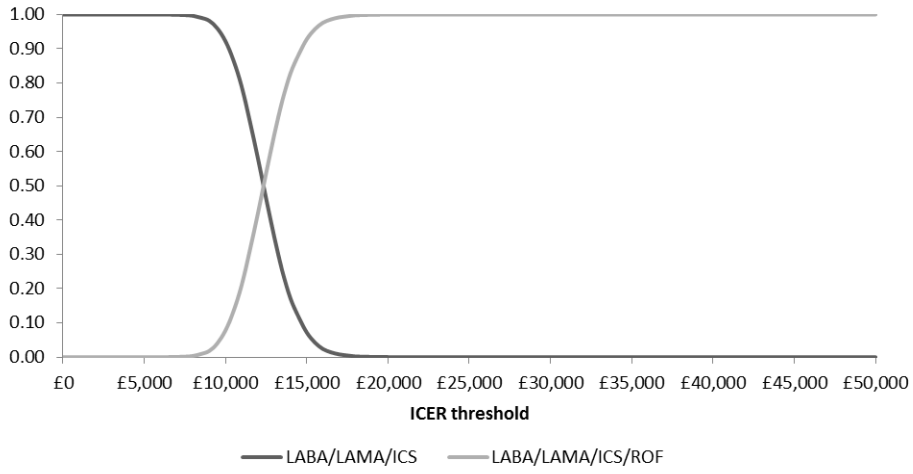


Figure 6: LAMA strata very severe cohort cost effectiveness acceptability frontier

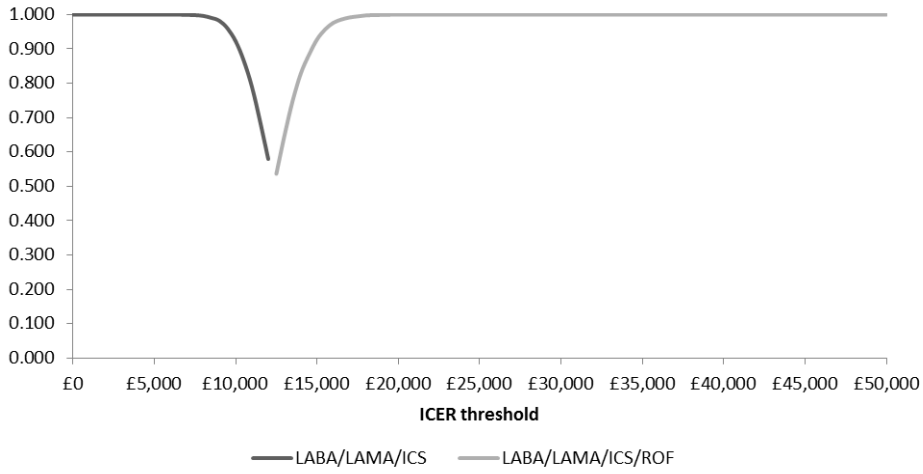


Figure 7: LAMA strata mixed cohort incremental cost effectiveness scatter plot

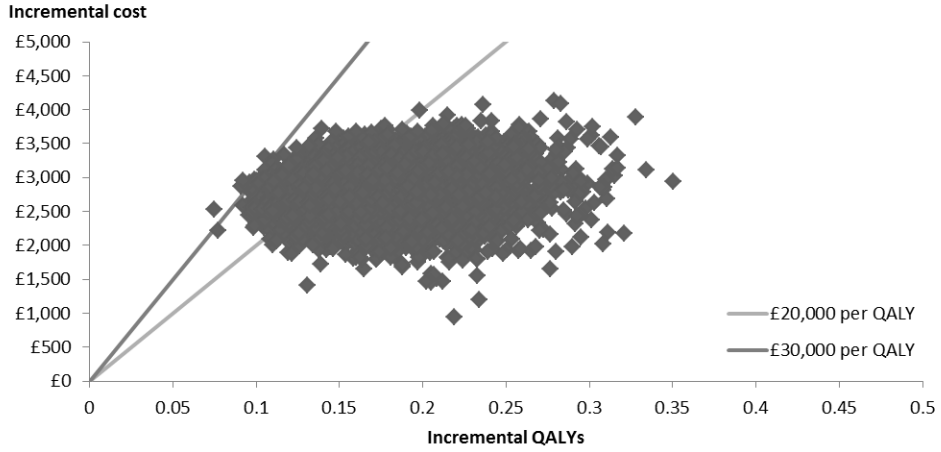


Figure 8: LAMA strata mixed cohort cost effectiveness acceptability curve

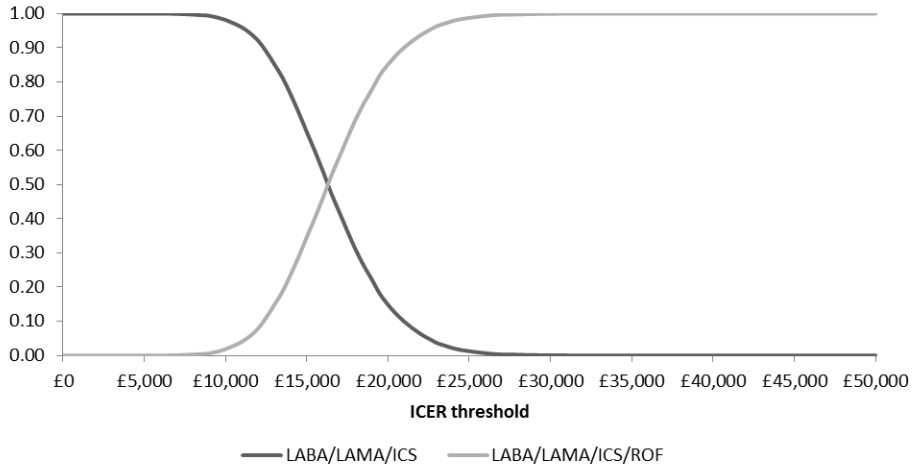
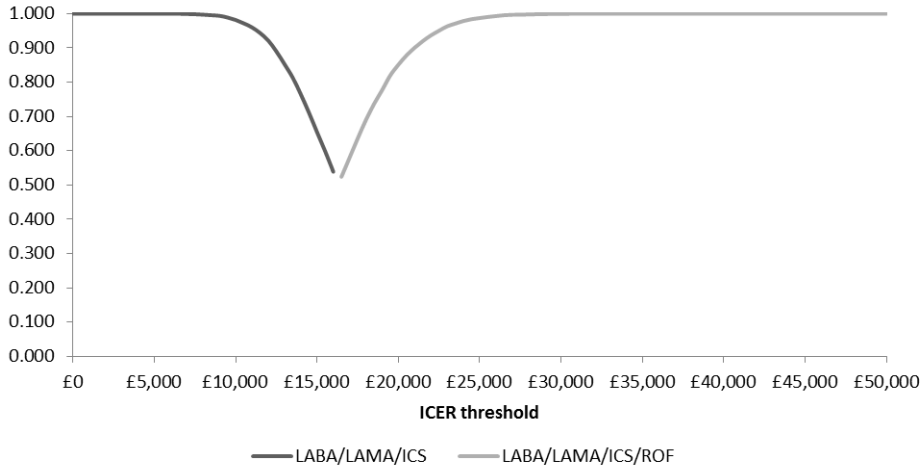


Figure 9: LAMA strata mixed cohort cost effectiveness acceptability frontier



We have some difficulty with the statement regarding mortality. Both the standardised mortality ratios applied to the severe and very severe states and the serious exacerbation case fatality rate are entered in the model as probability distributions. Population life table mortality is not treated probabilistically, however this is in keeping with degree of precision with which these population estimates are generated.

It is suggested that other 'important parameters' may also have been omitted from the probabilistic analysis, though no indication as to what these may be is provided. If there is a concern that the sojourn time calculations are not subject to probabilistic analysis we would point out that reference equations are deterministic, but that the annual decline is entered as a probability distribution.

Again, we have some difficulty with the comments around time horizon and discount rates, as neither is entered as a probability distribution.

B16. Please provide trial and model exacerbation rate comparisons (of both treatment and control arms) in Table 53 in addition to rate ratio comparisons. Furthermore, please provide additional validation of the model, such as cross-validation, validation against external data, validation against internal data, clinical expert face validation.

<u>Clinical outcomes</u>

The table below compares the regression based rates of exacerbations for the relevant trial data and the cost-effectiveness model's exacerbation output for one year.
The model applies estimates of mortality that are separate from the REACT trial and some divergence between the model and the trial might be expected as a result, even over a one year time horizon. No adjustments have been made in respect of the relevant model settings to enhance the comparability between the trial and the model (for example severe exacerbation case fatality is as applied in the base case model).
The table shows the comparison for a cohort entered in the model with severe COPD. Over one year approximately 140 of 1,000 patients transition to very severe COPD. Consequently the exacerbation rate for severe patients (as entered in the model on the basis of the regression) is exceeded in the model due to the transitions to the very sever state, in which the exacerbation rate is higher. However, if the very severe exacerbation rate is set equal to the severe rate (validation settings), the results as predicted in the cost-effectiveness model are more comparable with the model input rates based on the regression. Some minor difference between the modelled exacerbations and the input values may be attributable to additional mortality applied in the model by comparison with that observed in the short term of the trial.

Table 4: Comparison of model predicted versus observed exacerbations over 12 months – roflumilast arm

	Input	**Output (base settings)**	**Output (validation settings)**
Severe COPD			
Moderate exacerbations	0.384	0.395	0.379
Severe exacerbations	0.115	0.124	0.113
Very severe COPD			
Moderate	0.607	0.593	n/a
Severe	0.270	0.263	n/a

Historical validation

The model is based in large part on Samyshkin et al (2014). We therefore considered a validation in which parameter estimates in line with Samyshkin are applied, and the results of the two models compared. Summary results of this exercise are presented below.

Different methodologies were employed for the calculation of moderate and severe exacerbations between the two models. Samyshkin used the rate of total exacerbations (moderate and severe) and allocates a proportion as moderate and a proportion as severe. In the current version of the model, as rates of moderate and severe exacerbations were provided separately from the trial data the proportion input was not required. Minor edits to the model were required in order to use the data from Samyshkin 2014.

Other aspects of the model altered were:

- Costs for LAMA were removed
- Inclusion of an older version (2007-2009) of the UK general population life tables
- Changing the general population risk of death to age 73 in the ratio used to adjust the CFR to reflect an older source of the CFR calculations.

The table below compares the total costs, number of exacerbations, total LYs, total QALYs and the ICER per QALY gained generated from the base case analysis from the current version of the model (using the inputs and assumptions as in Samyshkin 2014) against those from Samyshkin 2014.

Table 5: Historical validation exercise

	Samyshkin 2014		Current model version	
Model outcomes	**LABA**	**LABA/Roflumilast**	**LABA**	**LABA/Roflumilast**
Total costs	£16,161	£19,358	£16,061	£19,223
% difference			-0.62%	-0.70%
Number of exacerbations	15.64	12.74	15.53	12.65
% difference			-0.70%	-0.71%
Total LYs	8.0	8.17	7.95	8.12
% difference			-0.62%	-0.61%
Total QALYs	5.451	5.615	5.415	5.578
% difference			-0.66%	-0.66%
ICER per QALY gained		£19,505		£19,392
% difference				-0.58%

The difference between the outputs from the current version of the model against those from Samyshkin 2014 is less than 1%.

Advisory board

At a recent advisory board, the model structure was presented to clinical experts for their opinion and validation of the structure was gained.[9]

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9. AstraZeneca Data on File created ROF-004-Oct16.

Appendix 1 – Excluded studies with reasons in the reviews

Table 6: Excluded studies in the original cost-effectiveness review

Author (Year)	Journal	Title	Reason for exclusion
Akazawa (2008)	Am J Manag Care	Economic assessment of initial maintenance therapy for chronic obstructive pulmonary disease	Study design
Akazawa (2008)	Health Services Res	Assessing treatment effects of inhaled corticosteroids on medical expenses and exacerbations among COPD patients: Longitudinal analysis of managed care claims	Comparators
Antoniu (2012)	J Comparative Effectiveness Res	Roflumilast as add-on therapy to conventional inhalers in COPD: a cost-effectiveness analysis	Study design
Braceras (2015)	Pharmacoecon Span Res Artic	[Cost minimization and budget impact analyses in the Basque Country for the treatment of moderate-to-severe chronic obstructive pulmonary disease using aclidinium bromide instead of tiotropium bromide] [Spanish]	Comparators
Briggs (2006)	Value Health	Estimating the cost-effectiveness of fluticasone propionate for treating chronic obstructive pulmonary disease in the presence of missing data	Comparators
Briggs (2010)	Eur Respir J	Is treatment with ICS and LABA cost-effective for COPD? Multinational economic analysis of the TORCH study	Comparators
Brosa-Riestra (2013)	Pharmacoecon Span Res Artic	[Cost-utility analysis of indacaterol versus tiotropium in the treatment of COPD in Spain] [Spanish]	Comparators
Chandra (2012)	Ont Health Technol Assess Ser	Cost-effectiveness of interventions for chronic obstructive pulmonary disease (COPD) using an Ontario policy model	Comparators
Chatterjee (2012)	Respir Res	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	Study design
Chuck (2008)	Can Respir J	Cost-effectiveness of combination therapy for chronic obstructive pulmonary disease	Comparators
Dal Negro (2007)	Int J Chron Obstruct Pulmon Dis	Cost-effectiveness and healthcare budget impact in Italy of inhaled corticosteroids and bronchodilators for severe and very severe COPD patients	Comparators
Dalal (2010)	Int J Chron Obstruct Pulmon Dis	Cost-effectiveness of combination fluticasone propionate-salmeterol 250/50 microg versus salmeterol in severe COPD patients	Study design
Dalal (2011)	Manag Care	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	Study design
Dalal (2012)	Int J Chron Obstruct Pulmon Dis	Clinical and economic outcomes for patients initiating fluticasone propionate/salmeterol combination therapy (250/50 mcg) versus anticholinergics in a comorbid COPD/depression population	Patient population
de Lucas (2004)	Pharmacoeconomics	Cost-effectiveness analysis of the use of tiotropium versus ipratropium for the treatment of chronic obstructive pulmonary disease	Comparators
Earnshaw	Respir Med	Cost-effectiveness of fluticasone propionate/salmeterol	Comparators

(2009)		(500/50 mug) in the treatment of COPD	
Gagnon (2005)	Respir Med	Economic evaluation of treating chronic obstructive pulmonary disease with inhaled corticosteroids and long-acting beta2-agonists in a health maintenance organisation	Comparators
Gani (2010)	Prim Care Respir J.	Economic analyses comparing tiotropium with ipratropium or salmeterol in UK patients with COPD	Comparators
Hettle (2012)	Respir Med	Cost-utility analysis of tiotropium versus usual care in patients with COPD in the UK and Belgium	Comparators
Hilleman (2009)	Chest	Pharmacoeconomic evaluation of COPD. 2000	Study design
Hoogendoorn (2013)	Eur Respir J	Cost-effectiveness of tiotropium versus salmeterol: The POET-COPD trial	Comparators
Iannazzo (2005)	Farmeconomia e Percorsi Terapeutici	Cost-effectiveness analysis of COPD therapy	Study design
Karabis (2014)	Clinicoecon Outcomes Res	Economic evaluation of aclidinium bromide in the management of moderate to severe COPD: An analysis over 5 years	Comparators
Lofdahl (2005)	Pharmacoeconomics	Cost effectiveness of budesonide/formoterol in a single inhaler for COPD compared with each monocomponent used alone	Country
Mittmann (2011)	Pharmacoeconom	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	Comparators
Naik (2010)	Clinicoecon Outcomes Res	Evaluating the cost-effectiveness of tiotropium versus salmeterol in the treatment of chronic obstructive pulmonary disease	Comparators
Najafzadeh (2008)	Thorax	Cost effectiveness of therapy with combinations of long acting bronchodilators and inhaled steroids for treatment of COPD	Comparators
Neyt (2010)	BMC Pulmon	Tiotropium's cost-effectiveness for the treatment of COPD: a cost-utility analysis under real-world conditions	Country
Neyt (2012)	Eur J Health Econ	The cost-effectiveness of tiotropium for the treatment of chronic obstructive pulmonary disease (COPD): the importance of the comparator	Study design
Oba (2007)	Mayo Clin Proc	Cost-effectiveness of long-acting bronchodilators for chronic obstructive pulmonary disease	Comparators
Oba (2009)	Am J Manag Care	Cost-effectiveness of salmeterol, fluticasone, and combination therapy for COPD	Comparators
Onukwugha(2008)	Value Health	Using cost-effectiveness analysis to sharpen formulary decision-making: The example of tiotropium at the veterans affairs health care system	Multiple publication
Oostenbrink (2005)	Value Health	Probabilistic Markov model to assess the cost-effectiveness of bronchodilator therapy in COPD patients in different countries	Comparators
Price (2011)	Appl Health Econ Health Policy	Cost-utility analysis of indacaterol in Germany: A once-daily maintenance bronchodilator for patients with COPD	Comparators
Price (2013)	Respir Med	A UK-based cost-utility analysis of indacaterol, a once-daily maintenance bronchodilator for patients with COPD,	Comparators

		using real world evidence on resource use	
Rutten-Van Molken (2007)	Pharmacoeconomics	A 1-year prospective cost-effectiveness analysis of roflumilast for the treatment of patients with severe chronic obstructive pulmonary disease	Comparators
Rutten-van Molken (2007)	Eur J Health Econ	Modelling the 5-year cost effectiveness of tiotropium, salmeterol and ipratropium for the treatment of chronic obstructive pulmonary disease in Spain	Comparators
Samyshkin (2014)	Eur J Health Econ	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	Multiple publication
Samyshkin (2014)	Eur J Health Econ	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	Comparators
Sin (2004)	Am J Med	Cost-effectiveness of inhaled corticosteroids for chronic obstructive pulmonary disease according to disease severity	Comparators
Spencer (2005)	Pharmacoeconomics	Development of an economic model to assess the cost effectiveness of treatment interventions for chronic obstructive pulmonary disease	Comparators
Sun (2011)	J Med Econ	Cost-effectiveness analysis of roflumilast/tiotropium therapy versus tiotropium monotherapy for treating severe-to-very severe COPD	Comparators
Van Der Palen (2006)	Thorax	Cost effectiveness of inhaled steroid withdrawal in outpatients with chronic obstructive pulmonary disease	Comparators
Yu (2014)	Thorax	Benefits and harms of roflumilast in moderate to severe COPD	Comparators
Zaniolo (2012)	Eur J Health Econ	Pharmacoeconomic evaluation of tiotropium bromide in the long-term treatment of chronic obstructive pulmonary disease (COPD) in Italy	Comparators

Table 7: Excluded studies in the update cost-effectiveness review

Author (Year)	Journal	Title	Reason for exclusion
Atsou (2016)	PLoS ONE	Simulation-Based Estimates of the Effectiveness and Cost-Effectiveness of Pulmonary Rehabilitation in Patients with Chronic Obstructive Pulmonary Disease in France	Comparators
Braceras (2015)	Pharmacoecon Span Res Artic	Cost minimization and budget impact analyses in the Basque Country for the treatment of moderate-to-severe chronic obstructive pulmonary disease using aclidinium bromide instead of tiotropium	Non-English Language
Dritsaki (2016)	Chronic Respiratory Disease	An economic evaluation of a self-management programme of activity, coping and education for patients with chronic obstructive pulmonary disease	Comparators
Eklund (2016)	Clinicoecon Outcomes Res	Cost-effectiveness of tiotropium versus glycopyrronium in moderate to very severe chronic obstructive pulmonary disease in Canada, Spain, Sweden, and the Uk	Comparators
Eklund (2015)	Value Health	Cost-Effectiveness Of Tiotropium Vs Glycopyrronium In Moderate To Very Severe Copd In Spain	Conference abstract

Miravitlles (2015)	Value Health	Cost-Effectiveness Of Umeclidinium/Vilanterol In Symptomatic Copd Spanish Patients	Conference abstract
Miravitlles (2016)	Int J Chron Obstruct Pulmon Dis	Cost-effectiveness of combination therapy umeclidinium/vilanterol versus tiotropium in symptomatic copd spanish patients	Comparators
Punekar (2015)	Cost Effectiveness and Resource Allocation	Cost-effectiveness of umeclidinium/vilanterol combination therapy compared to tiotropium monotherapy among symptomatic patients with chronic obstructive pulmonary disease in the UK	Comparators
Wright (2015)	Int J of Pharmacy Practice	An evaluation of a multi-site community pharmacy-based chronic obstructive pulmonary disease support service	Comparators
Zwerink (2016)	COPD: Journal of Chronic Obstructive Pulmonary Disease	Cost-effectiveness of a community-based exercise programme in COPD self-management	Country
Zwerink (2016)	Respirology	(Cost-)effectiveness of self-treatment of exacerbations in patients with COPD: 2 years follow-up of a RCT	Country

Table 8: Excluded studies in the original HRQoL review

Authors	**Journal**	**Title**	**Reasons for exclusion**
Andenaes (2006)	Quality of Life Research	Changes in health status, psychological distress, and quality of life in COPD patients after hospitalization	Country
Brown (2010)	North American Journal of Medical Sciences	Health-related quality of life and chronic obstructive pulmonary disease in North Carolina	Outcome
Carrasco (2006)	Health & Quality of Life Outcomes	Negative impact of chronic obstructive pulmonary disease on the health-related quality of life of patients. Results of the EPIDEPOC study	Multiple publication
Cleland (2007)	Family Practice	Associations of depression and anxiety with gender, age, health-related quality of life and symptoms in primary care COPD patients	Patient population
Corsonello (2007)	American Journal of Medicine	Functional status in chronic obstructive pulmonary disease	Study design
Dacosta (2012)	Copd: Journal of Chronic Obstructive Pulmonary Disease	The impact of COPD on quality of life, productivity loss, and resource use among the elderly united states workforce	Multiple publication
DiBonaventura (2012)	International Journal of Copd	The burden of chronic obstructive pulmonary disease among employed adults	Patient population
DiBonaventura (2012)	Copd: Journal of Chronic Obstructive Pulmonary Disease	The impact of COPD on quality of life, productivity loss, and resource use among the elderly United States workforce	Patient population
Divo (2013)	Copd: Journal of Chronic	COPD, co-morbidities and health-related quality of life (HRQOL): more is less	Study design

	Obstructive Pulmonary Disease		
Esteban (2006)	Respiratory Medicine	Use of medication and quality of life among patients with COPD	Patient population
Esteban (2009)	Respiratory Medicine	Impact of hospitalisations for exacerbations of COPD on health-related quality of life	Patient population
Garrido (2006)	Health and Quality of Life Outcomes	Negative impact of chronic obstructive pulmonary disease on the health-related quality of life of patients. Results of the EPIDEPOC study	Study design
Gowan (2008)	Australian Journal of Pharmacy	The chronic obstructive pulmonary disease burden	Study design
Halvani (2006)	Tanaffos	Quality of life and related factors in patients with chronic obstructive pulmonary disease	Country
Hesselink (2006)	Journal of Asthma	What predicts change in pulmonary function and quality of life in asthma or COPD?	Country
Holm (2009)	Copd: Journal of Chronic Obstructive Pulmonary Disease	Family relationship quality is associated with psychological distress, dyspnea, and quality of life in COPD	Patient population
Jenkins (2009)	European Respiratory Journal	Quality of life, stage severity and COPD	Study design
Jones (2012)	Primary Care Respiratory Journal	Patient-centred assessment of COPD in primary care: experience from a cross-sectional study of health-related quality of life in Europe	Outcome
Kapella (2006)	Nursing Research	Subjective fatigue, influencing variables, and consequences in chronic obstructive pulmonary disease	Outcome
Katsura (2007)	Respirology	Gender-associated differences in dyspnoea and health-related quality of life in patients with chronic obstructive pulmonary disease	Country
Kauppi (2011)	Journal of Asthma	Overlap syndrome of asthma and COPD predicts low quality of life	Country
Krishnan (2006)	BMC Pulmonary Medicine	Association between anemia and quality of life in a population sample of individuals with chronic obstructive pulmonary disease	Outcome
Loh (2012)	Chest	Racial differences influence health-related quality-of-life measurements	Study design
Merida (2010)	Journal of the American Geriatrics Society	Functional assessment of older adults with chronic obstructive pulmonary disease living at home	Outcome
Miravitlles (2004)	Thorax	Effect of exacerbations on quality of life in patients with chronic obstructive pulmonary disease: a 2 year follow up study	Outcome
Miravitlles (2005)	Respiratory Medicine	Characteristics of a population of COPD patients identified from a population-based study. Focus on previous diagnosis and never smokers	Patient population
Miravitlles (2006)	Quality of Life Research	Exacerbations, hospital admissions and impaired health status in chronic obstructive pulmonary disease	Outcome
Miravitlles (2007)	Therapeutic Advances in	Factors determining the quality of life of patients with COPD in primary care	Patient population

	Respiratory Disease		
Miravitlles (2011)	Respiration	Socioeconomic status and health-related quality of life of patients with chronic obstructive pulmonary disease	Patient population
Miravitlles (2014)	Respiratory Medicine	Factors associated with depression and severe depression in patients with COPD	Patient population
Miravitlles (2015)	International Journal of Copd	Clinical variables impacting on the estimation of utilities in chronic obstructive pulmonary disease	Study design
Naberan (2012)	Respiratory Medicine	Impairment of quality of life in women with chronic obstructive pulmonary disease	Patient population
Nishimura (2009)	Health & Quality of Life Outcomes	Effect of exacerbations on health status in subjects with chronic obstructive pulmonary disease	Country
Oga (2004)	Quality of Life Research	Longitudinal changes in health status using the chronic respiratory disease questionnaire and pulmonary function in patients with stable chronic obstructive pulmonary disease	Country
Orbon (2005)	International Archives of Occupational & Environmental Health	Employment status and quality of life in patients with chronic obstructive pulmonary disease	Country
Raherison (2014)	BMC Women's Health	Clinical characteristics and quality of life in women with COPD: an observational study	Patient population
Rodriguez-Gonzalez Moro (2009)	Respiratory Medicine	Health-related quality of life in outpatient women with COPD in daily practice: the MUVICE Spanish study	Patient population
Rodriguez-Pecci (2012)	Medicina (Argentina)	Chronic obstructive pulmonary disease: Differences between men and women	Patient population
Sanchez (2008)	Brazilian Journal of Medical & Biological Research	Relationship between disease severity and quality of life in patients with chronic obstructive pulmonary disease	Country
Scharloo (2007)	Journal of Asthma	Illness perceptions and quality of life in patients with chronic obstructive pulmonary disease	Country
Theander (2008)	International Journal of Nursing Practice	Severity of fatigue is related to functional limitation and health in patients with chronic obstructive pulmonary disease	Country
Wacker (2014)	BMC Pulmonary Medicine	Health-related quality of life and chronic obstructive pulmonary disease in early stages - longitudinal results from the population-based KORA cohort in a working age population	Patient population
Wang (2005)	Respirology	Outcomes and health-related quality of life following hospitalization for an acute exacerbation of COPD	Patient population
Zohal (2014)	Sleep Disorders Print	Sleep Quality and Quality of Life in COPD Patients with and without Suspected Obstructive Sleep Apnea	Country

Table 9: Excluded studies in the update HRQoL review

Authors	Journal	Title	Reason for exclusion
Calverley (2016)	International Journal of	Early response to inhaled bronchodilators and corticosteroids as a predictor of 12-month treatment	Study design

	COPD	responder status and COPD exacerbations	
Dhamane (2016)	Journal of Occupational and Environmental Medicine	Associations between COPD severity and work productivity, health-related quality of life, and health care resource use: A Cross-Sectional Analysis of National Survey Data	Patient population
Dodd (2015)	Annals of the American Thoracic Society	Executive function, survival, and hospitalization in chronic obstructive pulmonary disease: A longitudinal analysis of the national emphysema treatment trial (NETT)	Patient population
Donaldson (2015)	American Journal of Respiratory and Critical Care Medicine	Impact of prolonged exacerbation recovery in chronic obstructive pulmonary disease	Patient population
Ekici (2015)	Respiratory Care	Factors associated with quality of life in subjects with stable COPD	Patient population
Esposito (2016)	Pulmonary Pharmacology and Therapeutics	Effect of CArbocisteine in Prevention of exaceRbation of chronic obstructive pulmonary disease (CAPRI study): An observational study	Patient population
Garcia-Gutierrez (2016)	COPD: Journal of Chronic Obstructive Pulmonary Disease	Predictors of Change in Dyspnea Level in Acute Exacerbations of COPD	Outcomes
Garcia-Sidro (2015)	Respiratory Medicine	The CAT (COPD Assessment Test) questionnaire as a predictor of the evolution of severe COPD exacerbations	Patient population
Janssen (2016)	BMC Pulmonary Medicine	Prevalence of thoracic pain in patients with chronic obstructive pulmonary disease and relationship with patient characteristics: a cross-sectional observational study	Country
Javadzadeh (2016)	BMJ supportive & palliative care	Comparison of respiratory health-related quality of life in patients with intractable breathlessness due to advanced cancer or advanced COPD	Comparators
Kerstjens (2015)	Pulmonary Pharmacology and Therapeutics	The impact of treatment with indacaterol in patients with COPD: A post-hoc analysis according to GOLD 2011 categories A to D	Study design
Ketata (2015)	African Journal of Respiratory Medicine	Comparison of forced expiratory volume (FEV<inf>1</inf>) and BODE index in the assessment of health-related quality of life in patients with chronic pulmonary disorder	Country
Kim (2016)	Annals of the American Thoracic Society	Persistent and Newly Developed Chronic Bronchitis Are Associated with Worse Outcomes in Chronic Obstructive Pulmonary Disease	Patient population
Kurashima (2016)	International Journal of COPD	COPD assessment test and severity of airflow limitation in patients with asthma, COPD, and asthma-COPD overlap syndrome	Country
Lacasse	COPD: Journal	Utility Scores in Patients with Oxygen-Dependent	Patient population

(2015)	of Chronic Obstructive Pulmonary Disease	COPD: A Case-Control Study	
Mayoralas (2016)	Revista de Patologia Respiratoria	Clinical and sociodemographic characteristics of women diagnosed with chronic obstructive pulmonary disease (COPD) in Spain: ECME study	Non-English Language
Meek (2015)	Chest	Chronic Bronchitis Is Associated With Worse Symptoms and Quality of Life Than Chronic Airflow Obstruction	Patient population
Minov (2015)	Open Respiratory Medicine Journal	Course of copd assessment test (Cat) scores during bacterial exacerbations of chronic obstructive pulmonary disease treated in outpatient setting	Country
Miravitlles (2015)	International journal of chronic obstructive pulmonary disease	Clinical variables impacting on the estimation of utilities in chronic obstructive pulmonary disease	Mulitple publication
Mroczek (2015)	Advances in experimental medicine and biology	Socioeconomic Indicators Shaping Quality of Life and Illness Acceptance in Patients with Chronic Obstructive Pulmonary Disease	Country
Pasquale (2016)	International Journal of COPD	COPD exacerbations associated with the modified medical research council scale and COPD assessment test among humana medicare members	Patient population
Postolache (2015)	Revista medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi	Smoking cessation, pulmonary rehabilitation and quality of life at smokers with COPD	Country
Rubinsztajn (2016)	Advances in experimental medicine and biology	Exacerbations of Chronic Obstructive Pulmonary Disease and Quality of Life of Patients	Country
Siebeling (2015)	npj Primary Care Respiratory Medicine	Prediction of COPD-specific health-related quality of life in primary care COPD patients: A prospective cohort study	Country
Soler-Cataluna (2016)	Archivos de Bronconeumologia	Prevalence and Perception of 24-Hour Symptom Patterns in Patients With Stable Chronic Obstructive Pulmonary Disease in Spain	Patient population
Steer (2015)	BMJ open respiratory research	Longitudinal change in quality of life following hospitalisation for acute exacerbations of COPD	Patient population
Wacker (2016)	Respiratory Research	Relative impact of COPD and comorbidities on generic health-related quality of life: a pooled analysis of the COSYCONET patient cohort and control subjects from the KORA and SHIP studies	Mulitple publication
Wang (2016)	Value in Health Regional Issues	Quality of Life and Economic Burden of Respiratory Disease in Asia-Pacific-Asia-Pacific Burden of	Country

		Respiratory Diseases Study	
Waschki (2015)	American journal of respiratory and critical care medicine	Disease Progression and Changes in Physical Activity in Patients with Chronic Obstructive Pulmonary Disease	Patient population
Wilke (2015)	Thorax	One-year change in health status and subsequent outcomes in COPD	Patient population
Wilke (2015)	International Journal of Nursing Practice	Determinants of 1-year changes in disease-specific health status in patients with advanced chronic obstructive pulmonary disease: A 1-year observational study	Country
Worth (2016)	Respiratory Medicine	The 'real-life' COPD patient in Germany: The DACCORD study	Patient population
Xiong (2016)	International Journal of Experimental Pathology	A 12-month follow-up study on the preventive effect of oral lansoprazole on acute exacerbation of chronic obstructive pulmonary disease	Country

Table 10: Excluded studies in the original Cost and Resource use review

Author	Journal	Title	Reasons for exclusion
Abudagga (2013)	International Journal of COPD	Exacerbations among chronic bronchitis patients treated with maintenance medications from a US managed care population: an administrative claims data analysis	Patient population
Abudagga (2013)	Journal of Medical Economics	Healthcare utilization and costs among chronic bronchitis patients treated with maintenance medications from a US managed care population	Patient population
Allen (2012)	Journal of Occupational and Environmental Medicine	Managing the burden of chronic obstructive pulmonary disease on workforce health and productivity: Upping a leading employers game	Patient population
Anonymous (2014)	Managed Care	COPD costs to approach $50B per year in 2020	Patient population
Blanchette (2014)	American Health and Drug Benefits	Rising costs of COPD and the potential for maintenance therapy to slow the trend	Patient population
Blasi (2014)	PLoS ONE	The clinical and economic impact of exacerbations of chronic obstructive pulmonary disease: A cohort of hospitalized patients	Patient population
Dal Negro (2015)	Clinicoeconomics & Outcomes Research	Costs of illness analysis in Italian patients with chronic obstructive pulmonary disease (COPD): an update	Patient population
Darnell (2013)	Cost Effectiveness and Resource Allocation	Disproportionate utilization of healthcare resources among veterans with COPD: A retrospective analysis of factors associated with COPD healthcare cost	Patient population
De Miguel-Diez (2013)	Respiratory Medicine	Trends in hospital admissions for acute exacerbation of COPD in Spain from 2006 to 2010	Patient population

DiBonaventura (2012)	COPD: Journal of Chronic Obstructive Pulmonary Disease	The impact of COPD on quality of life, productivity loss, and resource use among the elderly United States workforce	Patient population
Dibonaventura (2012)	International Journal of COPD	The burden of chronic obstructive pulmonary disease among employed adults	Patient population
Doos (2014)	Journal of Public Health	Mosaic segmentation, COPD and CHF multimorbidity and hospital admission costs: a clinical linkage study	Patient population
D'souza (2014)	COPD: Journal of Chronic Obstructive Pulmonary Disease	Clinical and economic burden of COPD in a medicaid population	Patient population
Esquinas (2014)	Respiratory Medicine	Trends of hospital admissions for acute exacerbation of COPD in Spain: Are we needing a new of hospital and health system organization reappraisal?	Patient population
Ford (2015)	Chest	Total and state-specific medical and absenteeism costs of COPD among adults aged > 18 years in the United States for 2010 and projections through 2020	Patient population
Gershon (2013)	American Journal of Respiratory & Critical Care Medicine	Quantifying health services use for chronic obstructive pulmonary disease	Patient population
Guarascio (2013)	ClinicoEconomics and Outcomes Research	The clinical and economic burden of chronic obstructive pulmonary disease in the USA	Outcome
Herrick (2012)	Morbidity and Mortality Weekly Report	Chronic obstructive pulmonary disease and associated health-care resource use-North Carolina, 2007 and 2009	Patient population
Kuwornu (2013)	Health Services and Outcomes Research Methodology	A comparison of statistical models for analyzing episodes-of-care costs for chronic obstructive pulmonary disease exacerbations	Patient population
Lindenauer (2014)	JAMA Internal Medicine	Outcomes associated with invasive and noninvasive ventilation among patients hospitalized with exacerbations of chronic obstructive pulmonary disease	Patient population
Menn (2012)	Respiratory Medicine	Direct medical costs of COPD - An excess cost approach based on two population-based studies	Patient population
Miravitlles (2013)	Lung	Clinical outcomes and cost analysis of exacerbations in chronic obstructive pulmonary disease	Patient population
Nair (2012)	Population Health Management	Burden of illness for an employed population with chronic obstructive pulmonary disease	Patient population
Najafzadeh (2012)	PLoS ONE	Future Impact of Various Interventions on the Burden of COPD in Canada: A Dynamic Population Model	Patient population
Omachi (2013)	Medical Care	Risk adjustment for health care financing in chronic disease: What are we missing by failing to account for disease severity?	Outcome
Ornek (2012)	International Journal of	Clinical factors affecting the direct cost of patients hospitalized with acute exacerbation of chronic	Country

	Medical Sciences	obstructive pulmonary disease	
Pasquale (2012)	International Journal of COPD	Impact of exacerbations on health care cost and resource utilization in chronic obstructive pulmonary disease patients with chronic bronchitis from a predominantly Medicare population	Patient population
Perera (2012)	COPD: Journal of Chronic Obstructive Pulmonary Disease	Acute exacerbations of COPD in the United States: Inpatient burden and predictors of costs and mortality	Patient population

Table 11: Excluded studies in the update Cost and Resource use review

Author	Journal	Title	Reason for exclusion
Albrecht (2016)	International Journal of Geriatric Psychiatry	New episodes of depression among Medicare beneficiaries with chronic obstructive pulmonary disease	Patient population
Dal Negro (2016)	Multidisciplinary Respiratory Medicine	The BODECOST Index (BCI): a composite index for assessing the impact of COPD in real life	Outcomes
Dalal (2015)	Journal of managed care & specialty pharmacy	Impact of COPD Exacerbation Frequency on Costs for a Managed Care Population	Outcomes
Davis (2016)	Journal of Managed Care & Specialty Pharmacy	Health Care Utilization and Costs After Initiating Budesonide/Formoterol Combination or Fluticasone/Salmeterol Combination Among COPD Patients New to ICS/LABA Treatment	Outcomes
Dhamane (2015)	International Journal of COPD	COPD exacerbation frequency and its association with health care resource utilization and costs	Outcomes
Dhamane (2016)	Journal of Occupational and Environmental Medicine	Associations between COPD severity and work productivity, health-related quality of life, and health care resource use: A Cross-Sectional Analysis of National Survey Data	Patient population
Foo (2016)	PLoS ONE	Continuing to confront COPD international patient survey: Economic impact of COPD in 12 countries	Outcomes
Ford (2015)	Chest	Hospital discharges, readmissions, and ED visits for COPD or bronchiectasis among US adults: Findings from the Nationwide Inpatient Sample 2001-2012 and Nationwide Emergency Department Sample 2006-2011	Patient population
Ford (2015)	Chest	Total and state-specific medical and absenteeism costs of COPD among adults aged > 18 years in the United States for 2010 and projections through 2020	Outcomes
Garcia-Sidro (2015)	Respiratory Medicine	The CAT (COPD Assessment Test) questionnaire as a predictor of the evolution of severe COPD exacerbations	Outcomes
Gershon (2015)	European Respiratory Journal	Quantifying comorbidity in individuals with COPD: A population study	Patient population
Huckfeldt	Health Services	The Relative Importance of Post-Acute Care and	Outcomes

(2016)	Research	Readmissions for Post-Discharge Spending	
Hussain (2015)	Value in Health	Economic Analysis Of Cost Of Drug Treatment Involved In The Maintainance Therapy Of Copd	Conference abstract
Jain (2015)	Managed care (Langhorne, Pa.)	Roflumilast: Who Is Using It and How It Affects Health Care Resource Utilization and Costs	Outcomes
Khakban (2015)	Chest	Ten-Year Trends in Direct Costs of COPD: A Population-Based Study	Outcomes
Laverty (2015)	PLoS ONE	Impact of a COPD discharge care bundle on readmissions following admission with acute exacerbation: Interrupted time series analysis	Outcomes
Lee (2016)	American Health and Drug Benefits	Benefits of early roflumilast treatment after hospital or emergency department discharge for a COPD exacerbation	Outcomes
Lima (2015)	COPD: Journal of Chronic Obstructive Pulmonary Disease	Trends in in-hospital outcomes among adults hospitalized with exacerbation of chronic obstructive pulmonary disease	Outcomes
Lindenauer (2015)	Annals of the American Thoracic Society	Hospital patterns of mechanical ventilation for patients with exacerbations of COPD	Outcomes
Mannino (2015)	Chest	Economic Burden of COPD in the Presence of Comorbidities	Outcomes
Matsumura (2015)	Rehabilitation nursing : the official journal of the Association of Rehabilitation Nurses	Long-term Effect of Home Nursing Intervention on Cost and Healthcare Utilization for Patients with Chronic Obstructive Pulmonary Disease: A Retrospective Observational Study	Country
Merinopoulou (2015)	Value in Health	Resource Use And Exacerbations Of Chronic Obstructive Pulmonary Disease (Copd) By Gold Categories	Conference abstract
Milewska (2016)	Advances in Experimental Medicine and Biology	Costs of treatment of chronic obstructive pulmonary disease	Country
Miravitlles (2016)	Copd: Journal of Chronic Obstructive Pulmonary Disease	The Relationship Between 24-Hour Symptoms and COPD Exacerbations and Healthcare Resource Use: Results from an Observational Study (ASSESS)	Outcomes
Moll (2015)	International Journal of COPD	Impact of roflumilast on exacerbations of COPD, health care utilization, and costs in a predominantly elderly Medicare advantage population	Outcomes
Pasquale (2016)	International Journal of COPD	COPD exacerbations associated with the modified medical research council scale and COPD assessment test among humana medicare members	Outcomes
Pothirat (2015)	International Journal of Copd	Comparative study on health care utilization and hospital outcomes of severe acute exacerbation of chronic obstructive pulmonary disease managed by pulmonologists vs internists	Country
Roberts	ClinicoEconomics	The impact of chronic pain on direct medical utilization	Outcomes

(2015)	and Outcomes Research	and costs in chronic obstructive pulmonary disease	
Sadatsafavi (2016)	Annals of the American Thoracic Society	History of Asthma in Patients with Chronic Obstructive Pulmonary Disease. A Comparative Study of Economic Burden	Outcomes
Sakaan (2015)	Hospital Pharmacy	Inhaler use in hospitalized patients with chronic obstructive pulmonary disease or asthma: Assessment of wasted doses	Outcomes
Shiue (2016)	European Journal of Clinical Microbiology and Infectious Diseases	Increased health service use for asthma, but decreased for COPD: Northumbrian hospital episodes, 2013-2014	Outcomes
Simon-Tuval (2015)	Respirology	Tiotropium as part of inhaled polytherapy: Adherence and associated health-care utilization	Country
Singh (2016)	Respiratory Research	Utilization due to chronic obstructive pulmonary disease and its predictors: A study using the U.S. National Emergency Department Sample (NEDS)	Outcomes
Titova (2015)	Respiratory Research	Long term effects of an integrated care intervention on hospital utilization in patients with severe COPD: a single centre controlled study	Country
Trudo (2015)	International Journal of COPD	Comparative effectiveness of budesonide/formoterol combination and tiotropium bromide among COPD patients new to these controller treatments	Outcomes
Unni (2015)	International Journal of Pharmacy and Pharmaceutical Sciences	Drug utilization pattern in chronic obstructive pulmonary disease inpatients at a tertiary care hospital	Country
Wakeam (2015)	The Annals of thoracic surgery	Outcomes and Costs for Major Lung Resection in the United States: Which Patients Benefit Most From High-Volume Referral?	Comparators
Wan (2015)	International Journal of COPD	A longitudinal, retrospective cohort study on the impact of roflumilast on exacerbations and economic burden among chronic obstructive pulmonary disease patients in the real world	Outcomes
Wang (2016)	Value in Health Regional Issues	Quality of Life and Economic Burden of Respiratory Disease in Asia-Pacific-Asia-Pacific Burden of Respiratory Diseases Study	Country

Single technology appraisal: **Roflumilast for treating chronic obstructive pulmonary disease (review of technology appraisal guidance 244) [ID984]**

AstraZeneca Response to Further Clarification Question Regarding the RE^{2}SPOND trial (received 11th November – included below)

16th November 2016

Thank you for your request and the opportunity to respond. AstraZeneca would like to highlight that the RE^{2}SPOND trial is not a relevant source of evidence for the UK clinical setting; and therefore is not relevant to the decision problem of this appraisal. It is also not appropriate to pool the REACT and RE^{2}SPOND studies to inform this NICE appraisal since doing so would dilute the available evidence, which is applicable to the UK population (the REACT study).

Below we list the reasons why RE^{2}SPOND is not generalizable to the UK setting:

1. The RE^{2}SPOND trial required patients to be taking an ICS/LABA +/- LAMA for a minimum of 3 months prior to baseline. Given that the entry criteria required patients to have 2 or more exacerbations in the prior year, we cannot conclude that included patients were uncontrolled on ICS/LABA +/- LAMA therapy (i.e. patients may have had exacerbations on a previous treatment prior to progressing onto an ICS/LABA +/- LAMA and still have met the entry criteria). In contrast, in the REACT trial patients were required to have been on their ICS/LABA +/- LAMA for at least 1 year and have had 2 or more exacerbations in the year prior to trial entry.
   The expected clinical position for roflumilast in the UK is for COPD patients already receiving maximal inhaled therapy with ICS/LABA+ LAMA; and who are still experiencing two or more exacerbations per year. This group of patients would typically be receiving maximal inhaled therapy for at least a year before additional therapy is considered, as reflected in the inclusion criteria of the REACT trial. This was not the case in the RESPOND trial. (Data on File ROF-006-NOV2016).
2. The REACT trial included a greater proportion of patients matching the population for which AstraZeneca seeks a NICE recommendation (adults with severe COPD (FEV1 post-bronchodilator < 50% predicted) associated with chronic bronchitis and a history of frequent exacerbations (≥2 exacerbations in the prior 12 months) despite triple therapy with LABA / LAMA / ICS.) The REACT trial includes 70% of patients who were prescribed triple therapy (ICS/LABA/LAMA) at baseline compared with 47% of patients in the RE^{2}SPOND trial.
3. The RE^{2}SPOND trial includes patients, who were using the US licensed dose of fluticasone/salmeterol 250/50ug as background therapy. Conversely, the fluticasone/salmeterol dose used as background therapy in the REACT trial was the UK and EU licenced dose of 500/50ug. Therefore, the REACT trial is more applicable to the UK as it is reflective of the background therapy used in UK clinical practice.
4. Very few patients included in the RE^{2}SPOND trial are from Western Europe (1 from Italy and 12 from Spain) from a total of 2352 patients in the trial (0.5 %) vs 29.5% in the REACT trial.
5. Finally, the RE^{2}SPOND trial used a formulation of roflumilast which is not currently approved for use in the UK. The US FDA-approved uncoated formulation was used in the RE^{2}SPOND trial. The EMA-approved enteric film-coated formulation was used in the REACT trial.

Whilst RE^{2}SPOND is not applicable to the NICE decision problem, AstraZeneca recognise that the ERG will be interested in verifying the points above, and have provided the full CSR (including appendices); and the recent publication of this trial including supplementary appendices (Martinez et al, 2016) as part of this response.

We kindly ask that the ERG considers these points in their review of the data from both trials.

11/11/2016

NICE National Institute for Health and Care Excellence

Dear [redacted],

Thank you for providing responses to the clarification letter. The technical team at NICE and the ERG have noted that the company have not provided some of the information that was requested. Please could the company consider providing the full CSR for the RE^{2}SPOND trial (as requested in question A1 of the clarification letter) and a pooled analysis of REACT and RE^{2}SPOND (as requested in question A11 of the clarification letter). The ERG are particularly interested in the subgroup analyses from the RE^{2}SPOND trial for patients taking triple therapy with LAMA + LABA + ICS.

Please upload your documents to NICE docs by no later than **5pm, Tuesday 15 November**, using this link: https://appraisals.nice.org.uk/request/20100

Kind regards

[redacted]
Project Manager – Technology Appraisals – Committee A
Centre for Health Technology Evaluation
National Institute for Health and Care Excellence
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Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Roflumilast for treating chronic obstructive pulmonary disease (review of technology appraisal guidance TA244) [ID984]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: British Thoracic Society
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?xx
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Roflumilast for treating chronic obstructive pulmonary disease (review of technology appraisal guidance TA244) [ID984]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Roflumilast is an anti-inflammatory and bronchodilatory agent proposed for the treatment of severe COPD. The main issues have been whether it has any additional benefots when added to standard care for people with severe COPD and exacerbations (ie ICS, LABA, LAMA combinations). Additional concerns have been around side-effects (especially GI side effects including weight loss). An additional question is its efficacy relative to theophyllines as it has a similar mechanism of action.

The scope seems appropriate.

Only 20% of people with COPD have it as a single diagnosis so safety/efficacy in the context of multi-morbidity is important.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Roflumilast for treating chronic obstructive pulmonary disease (review of technology appraisal guidance TA244) [ID984]

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

When considering the REACT study it is important to note (1) the high rate of continued smoking 42-45% in the trial population – consider the relative efficacy of roflumilast and varenicline/counselling. (2) the higher drop out rate in the treatment arm.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from

registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Beyond cost pressure implementation would not be expected to be problematic or rasie equality issues.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed; - could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology; - could lead to recommendations that have any adverse impact on people with a particular disability or disabilities. Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Roflumilast for treating chronic obstructive pulmonary disease (review of technology appraisal guidance 244) [ID984

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation Royal Devon & Exeter Hospital

Are you (tick all that apply):

- ✓ a specialist in the treatment of people with the condition for which NICE is considering this technology?
- ✓ a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

None

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

COPD is treated according to NICE Clinical Guideline 101 but despite this patients continue to experience exacerbations. These exacerbations worsen patient health status, accelerate decline in lung function, result in hospitalisation and increase mortality. Exacerbations of COPD are one of the most common causes of hospital admission and the NICE guideline stated that exacerbations of COPD accounted for more than one million 'bed days' each year in hospitals in the UK.

The current NICE guidelines recommend using either an inhaled long-acting muscarinic antagonist alone, a fixed combination of an inhaled corticosteroid and long-acting β2 agonist, or these two treatments combined to reduce the risk of exacerbations, but despite this treatment many patients, particularly those with severe disease continue to experience several exacerbations each year (e.g. see Vestbo et al NEJM 2016; 375(13):1253-60)

Exacerbations are inflammatory events often triggered by infections. None of the currently prescribed therapies for COPD has significant anti-inflammatory actions. Roflimilast is a phospodiesterase 4 inhibitor and as such has a totally different mechanism of action to all other available therapies for COPD. It is not a bronchodilator and any effect on airway calibre is as a result of effects on inflammation rather than a direct effect on airway smooth muscle. It is most effective in patients with COPD who have symptoms of chronic bronchitis.

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In patients who continue to experience exacerbations despite optimal inhaled therapy the effects of several add on therapies have been investigated: long-term macrolide therapy, which is effective in ex-smokers but there are concerns about side-effects and the risk of developing antibiotic resistance; statins, which are ineffective; and theophylline and acetylcysteine, which have inconsistent effects in different studies.

A recent study has shown that roflumilast reduces exacerbations and hospital admissions in patients with severe chronic obstructive pulmonary disease and chronic bronchitis who are at risk of frequent and severe exacerbations despite inhaled corticosteroid, long-acting β2 agonist therapy and long acting anti-muscarinic therapy. A further study showed no statistically significant reduction in the rate of moderate and/or severe chronic obstructive pulmonary disease exacerbations in patients at risk for exacerbations despite treatment with inhaled corticosteroid/long-acting β2-agonist with or without a long-acting muscarinic antagonist. However there was a significant reduction in exacerbations in patients with frequent exacerbations (>3) and/or one or more hospitalization – the group in whom there is the greatest need for a new therapy. There were also some methodological differences between these trial which may explain the differences in the overall results.

The most frequently reported adverse events were diarrhoea (10% of roflumilast treated patients v 4% in placebo group) and weight loss (9% in roflumilast group v 3% in the placebo group). Patients who received roflumilast lost a mean of 2·65 kg, compared with 0·15 kg in the placebo group.

Roflumilast is recommended as an add on therapy for patients who continue to exacerbate despite treatment with inhaled corticosteroid/long-acting β2-agonist plus a long-acting muscarinic antagonist in the 2017 Global Obstructive Lung Disease (GOLD) Report.

To have roflumilast available as a treatment for patients who continue to exacerbate despite treatment in accordance with NICE CG 101 and particularly for those with frequent exacerbations or those who had been hospitalised would be a significant advance for the patients and for the NHS.

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The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

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Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

There are no equality or diversity issues related to this technology

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

I am not aware of any additional evidence

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Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

There are no major implementation issues. Clinicians would need to be educated about the recommendations made by the Appraisal Committee and the place of roflumilast in the therapy of COPD but as it is a tablet there would be no significant barriers to its inmplementation.

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Single Technology Appraisal (STA)

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Roflumilast for the management of chronic obstructive pulmonary disease

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors
Rob Riemsma acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Maiwenn Al acted as health economic project lead, contributed to the writing of the report and supervised the health economic part of the project. Nasuh Büyükkaramikli, Annemieke van Dongen-Leunis and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Piet Portegijs and Ching-Yun Wei acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Shelley de Kock critiqued the search methods in the submission and contributed to the writing of the report. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

ADL	Activities of daily living
AE	Adverse Events
AMP	Adenosine monophosphate
ATC	Anatomical Therapeutic Chemical
ATS	American thoracic society
BI	Budget impact
BIC	Bayesian information criterion
BSC	Best supportive care
BTS	British thoracic society
CADTH	Canadian Agency for Drugs and Technologies in Health
cAMP	Cyclic adenosine monophosphate
CAT	COPD Assessment Test
CE	Cost Effectiveness
CEA	Cost-effectiveness Analysis
CEAC	Cost effectiveness Acceptability Curve
CFR	Case fatality rate
CHEST	American College of Chest Physicians
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CSR	Clinical study report
CUA	Cost utility analysis
DoH	Department of Health
EMA	European Medicines Agency
EPAR	European public assessment report
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-3L	European Quality of Life-5 Dimensions, three-level scale
EQ-5D-5L	European Quality of Life-5 Dimensions, five-level scale
ERG	Evidence Review Group
ERS	European Respiratory Society
EUR	Erasmus University Rotterdam
FDA	Food and Drug Administration
FEF	Forced Expiratory Flow
FEV	Forced Expiratory Volume
FEV1	Forced Expiratory Volume in the first second
FEV6	Forced Expiratory Volume in the first 6 seconds
FVC	Forced Vital Capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HCP	Health Care Practitioner
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related Quality of Life
HTA	Health Technology Assessment
IC	Indirect Comparison
ICD	International Classification of Diseases
ICER	Incremental Cost-effectiveness Ratio
ICS	Inhaled corticosteroid
ICTRP	International Clinical Trials Registry Platform
IQR	Inter quartile range
ISPOR	International Society for Pharmacoecomics and Outcomes Research
ITT	Intention to Treat

IVRS	Interactive voice response system
KSR	Kleijnen Systematic Reviews
LABA	Long Acting Beta-Adrenoceptor Agonist
LABA / ICS	Long-acting beta2 agonist with an inhaled corticosteroid in a combination inhaler
LAMA	Long acting Muscarinic-receptor Antagonist
LY	Life year
LYG	Life years gained
LYS	Life Year Saved
MACE	Major adverse cardiovascular events
MCMC	Markov Chain Monte Carlo
MCS	Mental component summary
MeSH	Medical Subject Headings
MHRA	Medicines and Healthcare Products Regulatory Agency
mMRC	modified Medical Research Council dyspnoea scale
MTC	Mixed Treatment Comparison
NA	Not applicable
NHS	National Health Services
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NR	Not Reported
NYHA	New York Heart Association
OR	Odds ratio
OS	Overall survival
PCS	Physical component summary
PDE-4 inhibitor	Phosphodiesterase Type 4 Inhibitor
PICO	Population, Interventions, Comparators and Outcomes
PP	Per protocol
PRESS	Peer Review of Electronic Search Strategies
PRO	Patient-reported outcome
PS	Performance status
PSA	Probabilistic Sensitivity Analyses
PSS	Personal Social Services
QALY(s)	Quality-adjusted Life Year(s)
QoL	Quality of life
RCT	Randomised Controlled Trial
RE2SPOND	Roflumilast Effect on Exacerbations in Patients on Dual [LABA / ICS] Therapy
REACT	Roflumilast and Exacerbations in patients receiving Appropriate Combination Therapy
RMP	Risk management plan
RR	Relative Risk; Risk Ratio; Rate Ratio
SABA	Short Acting Beta-Adrenoceptor Agonist
SAE	Serious Adverse Events
SAMA	Short Acting Muscarinic -receptor Antagonist
ScHARR	School of Health and Related Research
SD	Standard deviation
SE	Standard error
SF-36	Short form 36
SGRQ	St. Georges Respiratory Questionnaire
SHTAC	Southampton Health Technology Assessments Centre
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics

SMR	Standardised mortality ratios
SOBQ	Shortness of Breath Questionnaire
STA	Single Technology Appraisal
TBC	To Be Confirmed
TDI	Transition Dyspnoea Index
TESAE	Treatment emergent serious adverse events
TEAE	Treatment emergent adverse events
TTO	Time Trade-Off
UK	United Kingdom
UMC	University Medical Centre
VAS	Visual analogue scale
WHO	World Health Organisation
WTP	Willingness to pay

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1. SUMMARY

1.1 Critique of the decision problem in the company's submission

The NICE scope describes the decision problem as roflumilast in combination with maintenance bronchodilator treatment (LABA, LABA / ICS, LAMA, LAMA plus LABA / ICS or LAMA plus LABA [if ICS not tolerated]) in adults with severe chronic obstructive pulmonary disease (FEV1 post bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations. The comparators are described as: LAMA / LABA / ICS, LAMA / LABA, LAMA or LABA (with or without ICS) and theophylline (in combination with inhaled maintenance bronchodilator treatment).

The company has restricted the population, intervention and comparators to roflumilast in combination with maintenance triple therapy (LABA / LAMA / ICS) in patients who have severe COPD despite triple therapy compared with triple therapy only. This means only patients who use triple therapy are considered in the company submission and interventions that do not include triple therapy are ignored. For the comparators, all alternatives mentioned in the scope are ignored, except triple therapy.

1.2 Summary of clinical effectiveness evidence submitted by the company

This submission relies on one clinical trial: the REACT trial comparing roflumilast as add-on to LABA / ICS with placebo plus LABA / ICS in patients with severe COPD; all patients were allowed to use LAMA. The company has restricted the population, intervention and comparators (contrary to the NICE scope) to "Roflumilast in combination with maintenance triple therapy, LABA / LAMA / ICS" in patients who have severe COPD despite triple therapy compared with triple therapy only. This means only a subgroup of patients in the REACT trial, those with concomitant LAMA therapy, (n=1,346 out of 1,935; i.e. 70%) are used for the submission. In addition the company uses the per protocol population, reducing the number of patients to 1,122 (58% of the total ITT population).

In the PP analysis (using negative binomial regression), the addition of roflumilast to LABA / LAMA / ICS significantly reduced the rate of moderate to severe exacerbations by 20.1% (roflumilast 0.858 vs placebo 1.075; rate ratio [RR] 0.799 [95% CI 0.670 to 0.952] p=0.0122) and by 34.1% (roflumilast 0.260 vs placebo 0.395; rate ratio [RR] 0.659 [95% CI 0.497 to 0.872] p=0.0035) for severe exacerbations.

The most common adverse events associated with roflumilast treatment reported in the REACT trial were diarrhoea (10% vs 4% in the placebo arm), weight decrease (9% vs 3% in the placebo arm) and nausea (6% vs 2% in the placebo arm).

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The clinical effectiveness literature searches reported in the CS were well documented and easily reproducible. A good range of databases were searched, and searches for conference proceedings were included. Searches were carried out in accordance with the NICE guide to the methods of technology appraisal. The CS and response to clarification provided sufficient details for the ERG to appraise the searches.

As reported above, the company has restricted the population, intervention and comparators. Regarding the comparators that were ignored in the submission, the company states "As the scope of intervention is restricted to roflumilast in combination with LABA / LAMA / ICS, mono- and dual therapy comparators are not considered relevant." If the committee agrees that the population can be restricted to adults with severe COPD associated with frequent exacerbations despite triple therapy, it might seem reasonable not to consider mono- and dual therapy comparators.

However, it is for the NICE appraisal committee to decide what the relevant population and relevant comparators are. There is evidence available to compare roflumilast in combination with LABA / ICS or in combination with triple therapy to most of the comparators listed in the scope. The company could have presented results for these comparisons. It is beyond the possibilities of the ERG to perform these analyses, as this involves full data extraction of these trials, a full network meta-analysis and inclusion of these comparators in the economic model. Therefore, the ERG suggests that the committee decides whether these analyses are relevant for the decision problem; and if they are, the committee can request the company to perform these analyses before the second committee meeting.

Regarding the results as presented in the CS, the company has chosen the populations and analyses that showed the most favourable effects for roflumilast. Therefore, the company base-case analysis may overestimate the effectiveness of roflumilast. As presented above the company uses a rate ratio of moderate to severe exacerbations of 0.799 (95% CI 0.670 to 0.952) for roflumilast versus placebo, based on the concomitant LAMA population from the REACT trial only, the per-protocol population, and the negative binomial model. The ERG prefers an analysis based on the concomitant LAMA ITT populations from the REACT and RE2SPOND trials combined, using the negative binomial model. This results in a rate ratio of moderate to severe exacerbations of 0.90 (95% CI 0.80 to 1.02).

Similarly, the company uses a rate ratio for severe exacerbations of 0.659 (95% CI 0.497 to 0.872) p=0.0035). The ERG prefers an analysis based on the concomitant LAMA ITT populations from the REACT and RE2SPOND trials combined, using the negative binomial model. However, it is not possible for the ERG to calculate the rate ratio because we do not have these data from the RE2SPOND trial.

Table 1.1: Key finding from company and ERG analyses (Mean rate (95% CI) of COPD exacerbations per patient per year)

	Roflumilast vs placebo
Company preferred analyses	
Moderate to severe exacerbation*	RR 0.799 (95% CI: 0.670 to 0.952)
Severe exacerbation*	RR 0.659 (95% CI: 0.497 to 0.872)
ERG preferred analyses	
Moderate to severe exacerbation**	RR 0.90 (95% CI 0.80 to 1.02)
Severe exacerbation***	RR 0.85 (95% CI 0.68 to 1.06)
* Based on PP population from the REACT trial, using the negative binomial regression model and the concomitant LAMA subgroup; ** Based on ITT populations from the REACT and RE2SPOND trials, using the negative binomial regression model and the concomitant LAMA subgroup; *** Based on ITT populations from the REACT and RE2SPOND trials, using the negative binomial regression model (data for the concomitant LAMA subgroup were not available).	

Adverse events were reported by 67% of the roflumilast group and 59% of the placebo group, with serious adverse events reported by 26% and 30% respectively. More people withdrew because of adverse events in the roflumilast group (11% compared with 5%). The most frequently reported adverse events were COPD exacerbations (15% with roflumilast compared with 19% with placebo), diarrhoea (10% compared with 4% respectively), weight loss (9% compared with 3% respectively) and nausea (6% compared with 2% respectively). Mortality rates were the same in both groups (2%); as were major adverse cardiovascular events (2% in both groups). There was no increase in the incidence of pneumonia with roflumilast.

1.4 Summary of cost effectiveness submitted evidence by the company

The company developed a decision model to assess the cost effectiveness of roflumilast as an add-on to triple therapy (roflumilast/ LAMA / LABA / ICS) in patients with (very) severe COPD (FEV1 ≤50% FEV1 predicted) associated with chronic bronchitis and a history of frequent exacerbations (≥ 2 moderate or severe COPD exacerbations within the previous year) despite triple therapy with LAMA / LABA / ICS. The continuation of triple therapy without any additional medication is the only comparator in the submission.

The model was a cohort state transition (Markov) model with monthly cycles and a lifetime horizon. The model consisted of three health states: severe COPD, very severe COPD and death. These COPD states are based on the severity classification defined by the GOLD lung function criteria. Severe COPD patients have FEV1 values between 30 and 50% of FEV1 predicted according to general population values, whereas very severe COPD patients have FEV1 values below 30% FEV1 predicted. Due to the progressive nature of COPD, patients can only progress to a more severe health state or death; patients cannot reverse this transition back to a less severe health state. In both COPD states, patients are at risk of moderate or severe exacerbations. These risks were estimated from the per protocol population of the REACT trial (excluding patients with at least one major protocol violation). The exacerbation risks differ by health state, treatment, and exacerbation severity. Exacerbations lead to additional costs, a temporary decrease in quality of life and additional mortality (only for severe exacerbations). Additionally, serious adverse events were included in the model, also leading to extra costs and the temporary decrease in quality of life.

The company assumed that all patients enter the model in the severe COPD health state with on average FEV1 values of 40% FEV1 predicted. The transition probability from severe to very severe COPD is determined by the average time it takes until patients reach the threshold of 30% FEV1 predicted, while taking into account the annual decline in FEV1 values for COPD patients. This transition probability does not differ between the intervention and the comparator. The monthly mortality rate is a combination of case fatality due to severe exacerbations and COPD associated background mortality non-related to exacerbations. The monthly mortality rate differs between COPD health states and treatments.

Quality of life data included health state utilities, disutilities due to exacerbations and those due to adverse events. Health state utilities were derived from a large multinational study and were measured with the EQ-5D and the UK tariff. Disutilities due to exacerbations were taken from another study in which the Dutch general public valued COPD-specific health state descriptions with the Time-Trade Off. Furthermore, it was assumed that all serious adverse events had a disutility similar to severe exacerbations.

Cost categories included in the model were: medication costs, maintenance costs for severe and very severe COPD, costs of moderate and severe exacerbations and costs of treating adverse events. For all these categories, except medication costs, resource use was derived from previous published studies and multiplied with UK-specific unit costs.

The addition of roflumilast to triple therapy (LAMA / LABA / ICS) was more costly (incremental costs £2,996), but also yields more QALYs (incremental QALYs: 0.16) than triple therapy only, resulting in an ICER of £18,774. The incremental QALY gains were mostly due to the fewer exacerbations, and increased life expectancy (due to fewer exacerbation related deaths). The increase in costs is mainly due to higher treatment costs.

The probabilistic sensitivity analysis showed that the probability that roflumilast/ LAMA / LABA / ICS is cost effective compared to LAMA / LABA / ICS is approximately 70% at a £20,000 per QALY

gained threshold. Within the deterministic sensitivity analysis, the company varied some of the input parameters to its upper and lower limits. This analysis showed that the most influential parameters were the transition probability from 'severe' to 'very severe' COPD state for both arms, discount rates for both costs and health outcomes, and cohort starting age.

The company performed several scenario analyses including varying the severity of COPD of the baseline cohort. If all patients have very severe COPD at the start of roflumilast treatment, the ICER decreases to £12,337. For a mixed population of severe and very severe COPD at baseline, the ICER lies between £12,337 and £18,774 (base-case ICER: all severe COPD). Furthermore, scenarios on changes in the use of standardised mortality ratios and quality of life utilities seem to have an important effect on ICERs, whereas assumptions on adverse events have a limited impact on the ICER.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The major concern of the ERG with respect the company submission was the source for the exacerbations rates. The company used the exacerbation rates of the per protocol study population in the REACT trial while pooled estimates from the REACT and RE2SPOND trial might provide more robust treatment effectiveness estimates. Furthermore, the ERG considers the intention-to-treat population more in line with UK clinical practice than the per protocol population because it is likely that in clinical practice patients who do not strictly fulfil the inclusion criteria of REACT will receive treatment with roflumilast. Unfortunately, the ERG could not completely assess the impact of the company's choices on the ICER, because not all relevant data were available despite requests in the clarification letter. Nevertheless, the ERG conducted several exploratory analyses in which treatment effectiveness was based on the ITT population.

Other concerns of the ERG were related to the generalisability to UK clinical practice, estimation of transition probabilities and costs and utility inputs and the model structure. The ERG considers the economic model described in the CS a simplistic representation of COPD progression, which does not take patient heterogeneity, as well as the impact of exacerbation on disease progression, into account. Even though estimating the direction of bias without a formal analysis would be speculative, the ERG thinks that not incorporating some of these modelling aspects, for instance the impact of previous exacerbation history on future exacerbations, might have resulted in a more conservative estimate of the ICER. Finally, some of the model inputs used for deriving transition probabilities (e.g. FEV1 decline rate), costs (e.g. ambulance transport costs or resource use for severe COPD state) and utilities (e.g. exacerbation utility decrements) were critiqued by the ERG, and more plausible alternatives were used in the exploratory analyses performed by the ERG.

According to the evidence in the company submission, the ERG could not judge whether the population in the REACT trial was representative for UK clinical practice. From additional information in the clarification response, it can be seen that the average age of patients from the REACT trail was slightly lower than those from other, observational, studies. Also, there were more male patients and slightly more smokers in the REACT trial. Furthermore, within the company's base-case, the patient characteristics were not taken from the subpopulation for whom the addition of roflumilast was intended (patients already receiving LAMA / LABA / ICS). The ERG used the patient characteristics from this subgroup in the ERG base-case analysis.

The transition from severe to very severe COPD depended on annual decline in FEV1 for COPD patients. The ERG was concerned about the validity of the assumption that FEV1 declines with 52 ml per year irrespective of the severity of COPD. First, this information is derived from a relatively old study (dating back to 1981) and secondly, it can be questioned whether FEV1 deteriorates linearly. A more recent study showed an annual decrease of 38 and 23 ml for severe and very severe COPD patients,

respectively. The ERG considers these data more plausible and therefore used an annual decline of 38 ml for severe COPD patients in the ERG base-case analysis.

The ERG agrees with the distinction between age-adjusted case-fatality rates and background mortality in the mortality rates. Nevertheless, the ERG questions whether the effect of age on case-fatality rates is exactly the same as the effect of age on all cause mortalities. In addition, the ERG could not adequately trace the method used to estimate standardised mortality ratios. Therefore, the ERG performed a scenario analysis where non-adjusted case-fatality rates were used and one where standardised mortality rates were derived from another source.

All relevant cost and quality of life parameters were included in the company's submission. The ERG only disagrees with the values of some of these parameters. First, the disutilities of exacerbations were not derived from patient-reported EQ-5D, but from general public time-trade-off valuations of COPD health profiles. As these valuations are not preferred in the NICE reference case, the ERG used EQ-5D specific disutilities in the ERG base-case analysis. Second, the additional GP visits due to exacerbations were overestimated by the company as they did not take into account that patients could have more than one exacerbation a year. Third, some of the costs parameters were incorrectly estimated and were corrected by the ERG.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

Searches were carried out in line with the NICE guide to the methods of technology appraisal. The CS and response to clarification provided sufficient details for the ERG to appraise the searches. A good range of databases were searched for clinical effectiveness; cost effectiveness; and cost and healthcare resource identification, measurement and valuation studies; and health related quality of life studies. An appropriate combination of index terms, free text and synonyms for the interventions and comparators was used. Clinical effectiveness searches were not limited by language, country or year and a supplementary search for unpublished conference proceedings was also undertaken in the American Thoracic Society Conference 2016.

The main strength of the clinical effectiveness section of the company submission is the fact that the submission is supported by two large randomised controlled trials comparing roflumilast as an add-on to triple therapy to triple therapy alone in patients with COPD. Unfortunately, the company decided to use only one of these trials (REACT).

The main strength of the cost effectiveness section of the company submission relates to the transparency with which the cost effectiveness analysis has been reported. Additionally, a well-known and often used model structure was used and where input was sourced from literature, often well-known studies were selected. However, the model structure would have gained strength if it had incorporated the impact of exacerbations on the decline of lung function.

1.6.2 Weaknesses and areas of uncertainty

The ERG was concerned about the language bias of restricting searches to English language in MEDLINE and EMBASE searches for cost effectiveness studies; cost and healthcare resource identification, measurement and valuation studies; and health related quality of life studies as this is not in line with current best practice. In addition, searches for adverse events were based on the clinical effectiveness search strategies which included study design filters and it is possible that relevant evidence may have been missed as a consequence of this. Apart from a search of the American Thoracic Society Conference 2016, no additional efforts were made to find unpublished or supplementary information.

The main weakness of the clinical effectiveness section of the company submission is the fact that the company decided to use only the per-protocol population of one of the two trials that were relevant for the decision problem. Instead the company could have used pooled results from the ITT populations in both trials. Therefore, the company base-case analysis may overestimate the effectiveness of roflumilast. In addition, the company ignored most of the interventions and comparators in the scope. There is evidence available to compare roflumilast in combination with LABA / ICS or in combination with triple therapy to most of the comparators listed in the scope. The company could have presented results for these comparisons.

In line with the clinical effectiveness section, the main weakness of the cost effectiveness section of the company submission is the source for the exacerbations rates used in the model. The company used the exacerbation rates of the concomitant LAMA subgroup of the per protocol study population in the REACT trial while pooled estimates from the concomitant LAMA subgroup from the ITT populations of REACT and RE2SPOND trial might provide more robust treatment effectiveness estimates.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG has incorporated various adjustments to the company base-case. Ideally, the adjustments would have included using exacerbation rate ratios based on the pooled ITT estimates from the REACT and RE2SPOND trial. However, the RE2SPOND trial did not report severe exacerbation rates specific to the LAMA subpopulation. Whilst speculative assumptions could be made, it was decided to leave those for a scenario analysis, and base the ERG base case on ITT data from the REACT trial only.

The ERG base-case resulted in an ICER of £35,821 per QALY gained. The most influential adjustments/corrections made by the ERG were 1) using exacerbation rate ratios obtained from the negative binomial regressions performed on the ITT population from REACT trial patients who received concomitant LAMA treatment; 2) using severe COPD specific FEV1 decline rates from Decramer and Cooper 2010 and; 3) using exacerbation related utility decrements from Hoogendoorn et al. 2011. From the PSA results, the probability that roflumilast plus triple therapy is cost effective compared to triple therapy alone is approximately 3% at a £20,000 per QALY gained threshold and 28% at a £30,000 per QALY gained threshold. The key findings from company and ERG preferred analyses are given in Table 1.2

Table 1.2: Key finding from company and ERG analyses

Scenarios	roflumilast plus triple therapy		triple therapy		Incr. costs	Incr. QALYs	ICER
	Total costs	Total QALYs	Total costs	Total QALYs			
CS base-case	£22,930	6.14	£19,933	5.98	£2,996	0.16	£18,774
ERG preferred base-case	£21,384	6.10	£17,895	6.01	£3,489	0.10	£35,821

CS = company submission; ERG = expert review group; ICER = incremental cost effectiveness ratio; QALYs = quality adjusted life years.

The ERG conducted some additional scenario analyses on the preferred base-case to assess structural uncertainty.

One of the scenarios used different exacerbation rate ratios than the ERG preferred base-case (which assumes the same roflumilast vs. placebo rate ratios for severe and very severe COPD patients), instead

using mean exacerbation rates separately derived from the severe and very severe COPD patients in the ITT concomitant LAMA treatment subpopulation. These rates were derived from the Poisson regression analyses for moderate or severe exacerbations and negative binomial regression analyses for severe exacerbations, which were provided in the CSR of the REACT trial. Assuming that negative binomial and Poisson regression estimates would give similar results, the moderate exacerbation rate estimates were calculated from the difference between the moderate or severe exacerbation rate and the severe exacerbation rate. This scenario resulted in an ICER of £21,187 per QALY gained.

In another scenario, we multiply the exacerbation rate ratios used in the ERG preferred base-case by a factor of (0.9/0.871), which is the ratio of moderate or severe RR from the ITT population, concomitant LAMA subgroup of REACT and RE2SPOND trials with the same RR from REACT trial only. In this scenario, it was assumed that incorporating RE2SPOND trial would change the severe and moderate exacerbation rate ratios uniformly. This scenario resulted in an ICER of £41,592 per QALY gained.

From the results of these two scenarios, it is obvious that the assumptions on exacerbation rates have a considerable impact on the ICER. Specifically, incorporating the pooled results from REACT and RE2SPOND trials increased the ICER, whereas using exacerbation rates derived separately for severe and very severe COPD patients decreased the ICER. However, both of these scenario implementations were based on assumptions, therefore the results of Scenario 1a and 1b should be interpreted with caution.

The ERG thinks that the most robust exacerbation rate would be the moderate and severe exacerbation rates derived separately for severe and very severe COPD patients from the negative binomial regression analyses performed on the pooled ITT population subgroup of LAMA concomitant patients from both REACT and RE2SPOND trials. And as these data are readily available to the company, the current uncertainty around the ICER stemming from uncertainty about the exacerbation rates can easily be resolved.

Whilst the source for estimation of exacerbation rates has a considerable impact on the ICER, the scenario analyses made it clear that how these exacerbations are translated to mortality is very important for the cost effectiveness results as well. Applying standardised mortality ratios (SMRs) that included exacerbation related deaths and therefore not using exacerbation case fatality rates (CFRs) as explained in scenario 4b in Section 5.3.1 increased the ICER to £149,564 per QALY gained.

From the additional scenarios, it can be also seen that utility estimates, baseline population COPD states and adverse events also have an impact on ICER. The ICER range from the scenario analyses are between £21,000 and £150,000.

In conclusion, based on the ERG base-case analysis, the ICER is estimated to be around £35,000 per QALY gained. This ICER value is larger than the £20,000 per QALY threshold. In addition, due to several assumptions regarding the exacerbation rates, and translation of exacerbations to mortality, the ERG deems that the uncertainty around the cost effectiveness of roflumilast is substantial.

2. BACKGROUND

This chapter provides a review of the evidence submitted by AstraZeneca in support of roflumilast (trade name Daxas®) for the maintenance treatment of severe chronic obstructive pulmonary disease (COPD) (FEV1 post-bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add-on to bronchodilator treatment.[1] The background section of the report by the Evidence Review Group (ERG) outlines and critiques the company's description of the underlying health problem and the overview of current service provision. The information is taken from Chapter 3 of the company submission (CS) with sections referenced as appropriate.

2.1 Critique of company's description of underlying health problem.

The underlying health problem of this appraisal is COPD described in the CS Section 3.1 as "a common preventable and treatable disease, is characterised by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases".[1] COPD must be distinguished from chronic bronchitis, but for the purpose of this review, there is a large overlap. Clinical manifestations of COPD range from chronic bronchitis, with predominantly structural changes and narrowing of the small airways, to emphysema, with predominantly destruction of lung parenchyma. As patients with chronic bronchitis have more frequent exacerbations than other COPD patients, COPD with ≥ 2 exacerbations in the previous year defines a predominantly chronic bronchitis group.

Central in the pathogenesis of COPD are abnormal inflammatory responses in the small airways. They are caused by long-term exposure to noxious particles and gases: smoking and/or outdoor, occupational, or indoor air pollution. COPD is a progressive disease. Superimposed on a gradual decline in lung function each exacerbation will lead to further loss. Risk of exacerbation increases with disease severity, which completes the vicious circle. Exacerbations can be triggered by bacterial or viral infection, environmental pollutants or unknown factors, which makes prevention through removal of these triggers difficult.

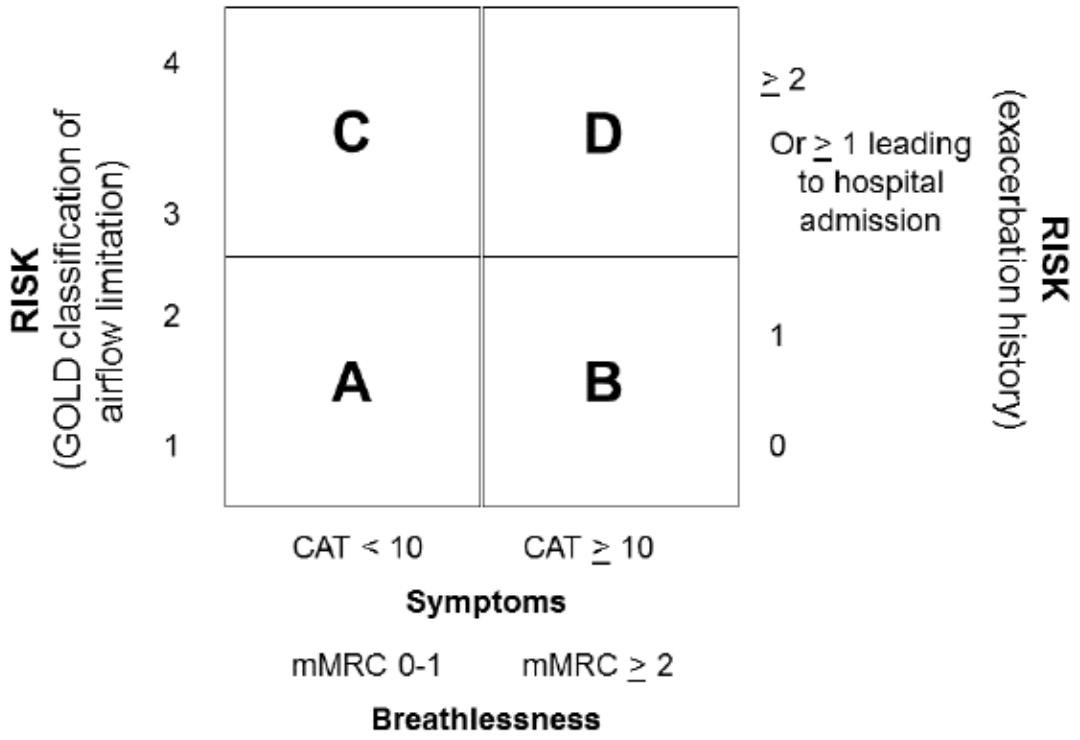
COPD is mostly diagnosed in people aged ≥40 years. Cigarette smoking is the most commonly encountered risk factor for COPD. In recent years, its prevalence is more equally distributed between men and women due to a more equal distribution of smoking, as well as outdoor and indoor air pollution. Characteristic symptoms of COPD include breathlessness, excessive sputum production, and chronic cough that can be variable from day-to-day.[2] Exacerbations are common for many patients with COPD and contribute greatly to an increase in morbidity, frequent emergency department visits, hospital admissions, and increased healthcare costs.[3-5] Comorbidities including cardiovascular disease, stroke and diabetes mellitus occur frequently in COPD patients.[2, 6] Exacerbations and comorbidities contribute to the impact of COPD on patients' quality of life. Therefore, the management of exacerbations and comorbidities is key in the treatment of COPD to prevent further progression.[2]

In the UK, the diagnosis of COPD in the primary care setting is made on the basis of symptoms and signs supported by spirometry according to NICE guideline CG101.[7] Severity is graded according to the new Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2016 guideline and based on two main criteria:

- Symptoms of breathlessness using either the modified Medical Research Council (mMRC) dyspnoea grade or current health status assessed by the COPD Assessment Test (CAT) and
- Future risk based on either severity of airflow limitation or exacerbation history.

The severity of COPD has been classified as GOLD A to D. GOLD A is the least severe stage, and GOLD D is the most severe stage of COPD with the worst lung function, highest exacerbation risk and most symptoms. This approach to combined assessment is illustrated in Figure 2.1.[2]

Figure 2.1: The GOLD model of symptom / risk evaluation of COPD showing the criteria for patient classification in groups A–D



Source: CS, Figure 2, page 28[1]
CAT = COPD Assessment Test; mMRC = modified Medical Research Council dyspnoea scale

The process of applying the two main criteria is explained in the guideline and involves assessing symptoms first in order to place in either left (A or C) or right side of the box (B or D).[2] Risk is then assessed by one of three methods: GOLD classification of airflow limitation, number of exacerbations of any kind or number of exacerbations leading to hospitalisation) in order to place the patient in the top or bottom of the table.

The GOLD classification of airflow limitation in COPD is based on the post-bronchodilator forced expiratory volume in 1 second (FEV1), as shown in Table 2.1 below:

Table 2.1: Classification of Severity of Airflow Limitations in COPD (In patients with FEV1/FVC <0.7)

GOLD classification	Disease severity	FEV1 predicted
GOLD 1	Mild	FEV1 ≥ 80% of predicted
GOLD 2	Moderate	50% ≤ FEV1 < 80% of predicted
GOLD 3	Severe	30% ≤ FEV1 < 50% of predicted
GOLD 4	Very severe	FEV1 < 30% of predicted
Source: CS, Table 4, page 291 FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; Predicted: reference value given gender, body height and mass, age and ethnicity		

As estimated by the British Lung Foundation, 1.2 million people in the UK have been diagnosed with COPD. The proportion of people living with COPD increases markedly with advancing age.[8] In the context of UK's aging population, these numbers are expected to increase. A recent UK study, which characterised a prevalent 2013 COPD cohort of 49,286 patients (≥ 40 years), reported that the overall prevalence of COPD was 33.3 per 1,000 persons; 66.4% were classified as GOLD A/B and 33.6% as C/D.[9]

ERG comment: In the NICE scope, it defined the population as "Adults with severe COPD (FEV_1 post-bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations." However, the ERG notices that the company restricts the submission to "Adult with severe COPD (FEV_1 post-bronchodilator < 50% predicted) associated with chronic bronchitis and a history of frequent exacerbations (≥2 exacerbations in the prior 12 months) despite triple therapy with long-acting muscarinic antagonists (LAMA) plus long-acting beta2 agonists (LABA) plus inhaled corticosteroids (ICS)", stating that this subgroup better reflects the recommendations for further research issued by NICE and the unmet need for patients with severe COPD and chronic bronchitis with a history of frequent exacerbations.

Overall, the description of the disease is in line with the relevant clinical guidance by NICE (NICE CG101)[7] and a more recent guideline, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2016.[2] Therefore, the ERG considers the company's description of the disease to be appropriate.

2.2 Critique of company's overview of current service provision

The company refer to the GOLD 2016 guideline[2] for the assessment and management of COPD. International guidelines distinguish between steps to minimise risk of disease progression (smoking cessation, vaccination, physical activity and rehabilitation) and pharmacological treatment aimed at reducing COPD symptoms, frequency and severity of exacerbations and improving health status and exercise tolerance.

Pharmacologic therapy in COPD is used to reduce symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance. The detail of proposed pharmacological management of COPD is presented in Table 2.2. In general, the GOLD guideline recommends use of a short-acting bronchodilator for GOLD A, a LABA or LAMA for GOLD B, ICS / LABA or LAMA for GOLD C and ICS / LABA with or without LAMA for GOLD D as first line choice. In patients with GOLD severity D, a combination of all three classes of drugs (LABA / LAMA / ICS) is recommended as a second choice. A PDE4 inhibitor (i.e. roflumilast) in combination with other therapies is recommended as an alternative treatment choice in patients with GOLD severity C and D. Other possible treatment options used as either monotherapy or as add-on to first line or alternative treatment options for the management of patients with GOLD stage C and D, include mucolytic (GOLD D only), short-acting bronchodilators or theophylline, if long-acting bronchodilators are unavailable or unaffordable.[2]

The CS suggests that although exact figures of patients who fall into the defined population are not known, according to a UK cohort study (including 49,286 patients), the majority of prevalent patients with COPD (55.9%) were prescribed combination therapy. The most frequent combination therapy was LABA / LAMA / ICS, prescribed for 28.6% of patients.[9] The CS also suggests that the treatment options for patients who continue to have exacerbations despite triple therapy with LABA / LAMA / ICS are limited and guidance on how to best manage these patients is lacking. Therefore, the company proposed that roflumilast is used as a treatment option for add-on to triple therapy with LABA / LAMA / ICS in those patients with FEV1 < 50% predicted and chronic bronchitis who continue to have frequent exacerbations (≥ 2 / year).[1]

Table 2.2: GOLD 2016 guideline on initial pharmacologic management of COPD

Patient group (GOLD category)	Recommended First choice*	Alternative choice*	Other possible treatments* (used alone or in combinations with other options in recommended first choice and alternative choice columns)
A	SABA as required or SAMA as required	LABA or LAMA or SABA + SAMA	Theophylline†
B	LABA or LAMA	LAMA / LABA	SABA and / or SAMA as required Theophylline†
C	ICS / LABA or LAMA	LABA / LAMA or LABA / PDE4 inhibitor or LAMA / PDE4 inhibitor	SABA and / or SAMA as required Theophylline†
D	ICS / LABA and / or LAMA	ICS / LABA / LAMA or ICS / LABA / PDE4 inhibitor or LABA / LAMA or LAMA / PDE4 inhibitor	Carbocysteine N-acetycysteine SABA and / or SAMA as required Theophylline†

Source: CS, Table 6, page 42[1]

ICS = inhaled corticosteroid; LAMA = long-acting muscarinic antagonist; LABA = long-acting beta2-agonist; PDE = phosphodiesterase; SAMA = short-acting muscarinic antagonist; SABA = short-acting beta2-agonist

*Medications are listed in alphabetical order, and therefore not necessarily in order of preference.

†GOLD guidelines state theophylline can be used if long-acting inhaled bronchodilators are unavailable or unaffordable.

Note: actual guidelines use the terminology 'anticholinergic' in place of 'muscarinic antagonists'.

ERG comment: The ERG broadly agrees with the company's description of the current state of service provision for COPD based on the updated GOLD guideline. However, it should be noted that the populations in this submission is more restricted than the NICE scope and roflumilast is limited to use as an add-on to LABA / LAMA / ICS triple therapy.

There is an inconsistency in the CS that is inevitable given the scope, and that the ERG cannot resolve. The aim of the proposed treatment is to minimise progression of disease, as measured with frequency of exacerbations (primary outcome of the REACT and RE2SPOND trials), lung function (FEV1) and mortality. Smoking cessation is the intervention with the greatest capacity to influence the natural history of COPD. Limiting the comparator(s) to pharmacotherapy in the scope makes the decision problem relatively straightforward, but it precludes considering other options that might be more effective investments of NHS money: pharmacological support or counselling for smoking cessation, vaccinations, physical activity and rehabilitation.[2] If roflumilast treatment would influence in any way patient motivation to stop smoking, or success of attempts to stop, this might well be more important than its effect on exacerbation frequency or FEV1 in the controlled environment of an RCT.

3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 3.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
Population(s)	Adults with severe COPD (FEV1 post-bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations	Adult with severe COPD (FEV1 post-bronchodilator < 50% predicted) associated with chronic bronchitis and a history of frequent exacerbations (≥2 exacerbations in the prior 12 months) despite triple therapy with LABA / LAMA / ICS	In line with current clinical evidence from the REACT trial, the positioning of roflumilast as add-on to triple therapy in patients with severe COPD and chronic bronchitis with a history of frequent exacerbations represents a subgroup of the current scope issued by NICE AstraZeneca believe this subgroup better reflects the recommendations for further research issued by NICE in their final guidance in 2012 and the unmet need for patients with severe COPD and chronic bronchitis with a history of frequent exacerbations.	The company has defined the population as "Adults with severe COPD (FEV1 post-bronchodilator < 50% predicted) associated with chronic bronchitis and a history of frequent exacerbations (≥2 exacerbations in the prior 12 months) despite triple therapy with LABA / LAMA / ICS". This is more restricted than the NICE scope.
Intervention	Roflumilast in combination with maintenance bronchodilator treatment (LABA, LABA / ICS, LAMA, LAMA plus LABA / ICS or LAMA plus LABA [if ICS not tolerated])	Roflumilast in combination with maintenance triple therapy, LABA / LAMA / ICS	Roflumilast will be positioned throughout the UK and Europe as add-on to triple therapy in patients with chronic bronchitis and a history of frequent exacerbations. AstraZeneca are seeking a recommendation for this subgroup only	The following interventions were specified in the scope, but ignored in the submission: • Roflumilast / LABA, • Roflumilast / LABA / ICS, • Roflumilast / LAMA, • Roflumilast / LAMA / LABA / ICS, • Roflumilast / LAMA / LABA (if ICS not tolerated)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
Comparator (s)	• LAMA in combination with LABA and ICS • LAMA in combination with LABA • LAMA or LABA (with or without ICS) • Theophylline (in combination with inhaled maintenance bronchodilator treatment)	• LAMA in combination with LABA and ICS (LABA / LAMA / ICS)	As the scope of intervention is restricted to roflumilast in combination with LABA / LAMA / ICS, mono- and dual therapy comparators are not considered relevant. Theophylline is not considered as an appropriate comparator as it does not represent standard practice in the UK. Of COPD patients experiencing frequent exacerbations (≥2 exacerbations in the prior 12 months) despite treatment with ICS / LABA / LAMA, only 4.6% are also prescribed theophylline. In addition theophylline is associated with serious treatment limiting side effects which do not favour chronic usage	The following comparators were specified in the scope, but ignored in the submission: • LAMA / LABA • LAMA / ICS • LABA / ICS • LAMA • LABA • Theophylline (in combination with inhaled maintenance bronchodilator treatment)
Outcomes	The outcome measures to be considered include: • lung function • incidence and severity of acute exacerbations, including hospitalisation • symptom control (e.g. shortness of breath) • mortality • adverse effects of treatment • health-related quality of life	The key outcome measures presented in the submission include: • rate of moderate to severe exacerbations (including hospitalisation) • rate of severe exacerbations (requiring hospitalisation) • lung function as measured by FEV1 • mortality	N / A	Most outcome measures were reported in the REACT trial and therefore in the CS. However, symptom control (e.g. shortness of breath) was not reported. In addition health related quality of life is not reported in the clinical effectiveness section of the CS.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
		• health related quality of life • Adverse effects of treatment		
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs will be considered from an NHS and Personal Social Services perspective.	As per the scope of the decision problem		In line with the scope of the decision problem.
Subgroups to be considered	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be	The intervention and target population are in accordance with the marketing authorisation	No further subgroup analysis is provided. The target population is itself a subgroup of the licensed population and RE2SPOND trial.	No subgroup analyses are reported in the CS.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
	issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator			
Special considerations including issues related to equity or equality				Not reported

COPD = Chronic obstructive pulmonary disease; CS = Company submission; FEV1 = Forced Expiratory Volume in the first second; GOLD = Global initiative for chronic obstructive lung disease; ICS = Inhaled corticosteroid; LABA = Long-acting beta2 agonist; LAMA = Long-acting muscarinic antagonist; RCT = randomised controlled trial.

3.1 Population

The company has defined the population as "Adults with severe COPD (FEV1 post-bronchodilator < 50% predicted) associated with chronic bronchitis and a history of frequent exacerbations (≥2 exacerbations in the prior 12 months) despite triple therapy with LABA / LAMA / ICS".

This is more restricted than the NICE scope which defined the population as "Adults with severe COPD (FEV1 post-bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations."

3.2 Intervention

The company has restricted the intervention to "Roflumilast in combination with maintenance triple therapy, LABA / LAMA / ICS". This means that the following interventions that were specified in the scope were ignored in the submission:

- Roflumilast / LABA,
- Roflumilast / LABA / ICS,
- Roflumilast / LAMA,
- Roflumilast / LAMA / LABA / ICS,
- Roflumilast / LAMA / LABA (if ICS not tolerated)

In addition the company has not provided evidence for comparisons with these interventions. Thus making it very difficult for NICE to issue guidance for any treatment involving roflumilast, other than roflumilast in combination with LABA / LAMA / ICS.

The restriction to the intervention follows from the restriction in the population. If the population is restricted to adults who have severe COPD despite triple therapy, it seems reasonable that the intervention is roflumilast in addition to triple therapy.

3.3 Comparators

The company has restricted the comparators to "LAMA in combination with LABA and ICS (LABA / LAMA / ICS)". This means that the following interventions that were specified in the scope were ignored in the submission:

- LAMA / LABA,
- LAMA / ICS,
- LABA / ICS,
- LAMA,
- LABA,
- Theophylline (in combination with inhaled maintenance bronchodilator treatment)

Regarding theophylline the company states that "Theophylline is not considered as an appropriate comparator as it does not represent standard practice in the UK. Of COPD patients experiencing frequent exacerbations (≥2 exacerbations in the prior 12 months) despite treatment with ICS / LABA / LAMA, only 4.6% are also prescribed theophylline. In addition theophylline is associated with serious treatment limiting side effects which do not favour chronic usage." The ERG does not agree with this justification, theophylline was clearly specified by NICE in the scope as a relevant comparator. In addition, the company provided evidence for a possible indirect comparison of theophylline with roflumilast – this will be discussed in Section 4.5 of this report.

Regarding the other comparators that were ignored in the submission, the company states "As the scope of intervention is restricted to roflumilast in combination with LABA / LAMA / ICS, mono- and dual

therapy comparators are not considered relevant." If the committee agrees that the population can be restricted to adults with severe COPD associated with frequent exacerbations despite triple therapy, it might seem reasonable not to consider mono- and dual therapy comparators. Nevertheless, trials have been performed in patients with severe COPD comparing triple therapy with dual therapy (e.g. FORWARD[10] and WISDOM[11]). Therefore, the company could have presented evidence showing the comparative effectiveness of roflumilast versus dual therapy using indirect comparisons. This will be discussed in Section 4.5 of this report.

3.4 Outcomes

Most outcome measures were reported in the REACT trial and therefore in the CS. However, symptom control (e.g. shortness of breath) was not reported in the CS. COPD Symptom Scores were reported in the CSR (Tables 14.2.3.5 to 14.2.3.7), but the relevant tables with results were missing from the stripped version of the CSR that was send to the ERG as part of the clarification response. After a second request the company finally did send the full CSR of the REACT trial.

In addition health related quality of life is not reported in the clinical effectiveness section of the CS. Quality of Life (COPD Assessment Test) data were presented in the CSR (Tables 14.2.7.1 to 14.2.7.5 and Listing 16.2.6.25). This is reported in Section 4.2.5 of this report.

3.5 Other relevant factors

Special considerations including issues related to equity or equality are not reported in the CS. There is no patient access scheme for roflumilast (CS, Section 2.3, page 25).

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence based checklist for the Peer Review of Electronic Search Strategies, was used to inform this critique.[12] The submission was checked against the Single Technology Appraisal (STA) specification for company/sponsor submission of evidence.[13] The ERG has presented only the major limitations of each search strategy in the main report.

Clinical effectiveness

The CS states in Section 4.1 that a systematic review was carried out to identify RCTs of roflumilast as an add-on to triple therapy (LABA / LAMA / ICS) in patients with severe or very severe COPD as defined in the pre-2013 GOLD report as stages 3 and 4.

Searches were reported for MEDLINE, MEDLINE Epub ahead of print and In-Process, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL). Searches were conducted on 18 July 2016. Search strategies combined free text and controlled vocabulary terms (Medical Subject Headings [MeSH] in MEDLINE and CENTRAL, and EMTREE in EMBASE).

To identify conference abstracts, a search was undertaken in EMBASE limiting to American College of Chest Physicians (CHEST) World congress 2014 and 2016, CHEST annual meeting 2014 and 2015, British Thoracic Society (BTS) winter meeting 2014 and 2015 and European Respiratory Society (ERS) annual congress 2014 and 2015. A supplementary search of American Thoracic Society (ATS) international conference 2016 was undertaken also. The company states that these five conferences were considered the most relevant and impactful on the latest clinical evidence for COPD.[14]

Search strategies for the database searches were provided in Appendix 4 of the Appendices[15] and were well reported and reproducible.

These meet the requirements detailed in the NICE guide to the methods of technology appraisal.[16]

Database searches were clearly structured and divided into population and intervention facets. Strategies used a combination of index terms appropriate to the resource, free text and synonyms for the condition, intervention and comparators. The host provider was Ovid for EMBASE and MEDLINE databases and the Cochrane Library for CENTRAL. To identify RCTs and patients with severe and very severe COPD, study design filters were applied to the search strategies. The company confirmed in the clarification letter to the ERG that filters for RCTs were based on Glanville 2006,[17] Dickersin 1994[18] and Lefebvre 1996[19] and that the severity search filter was constructed de novo to identify patients with severe and very severe COPD.[14]

A search of trials registers, such as ClinicalTrials.gov and WHO International Clinical Trials Registry Platform (ICTRP), for unpublished and ongoing trials would have been a useful addition to the clinical effectiveness searches.

Indirect and mixed treatment comparisons

The clinical effectiveness searches presented in Appendix 4 were used to identify all RCTs of roflumilast as an add-on to triple therapy. However, in Section 4.10,[1] the CS states: “none of the trials identified in the review were considered relevant to the roflumilast indication. Therefore an indirect comparison was not carried out.”

Non-randomised and non-controlled evidence
Non-randomised and non-controlled evidence was not considered applicable for this review.

Adverse events
Separate adverse events searches were not performed. When the ERG queried this omission, the clarification response[14] stated that the "search for RCTs was not limited by study outcomes; and therefore this search was used to identify efficacy and safety data from relevant studies." However, the clinical effectiveness searches incorporated a methodological filter intended to limit the search to RCTs. Guidance by the Centre for Reviews and Dissemination (CRD)[20] recommends that if searches have been limited by a study design filter, additional searches should be undertaken to ensure that adverse events that are long-term, rare or unanticipated are not missed. The ERG considered that it was possible that some relevant evidence may not have been identified as a consequence of the study design limits used. Unfortunately, the ERG was unable to undertake independent adverse events searches and review the results with the STA timeline, as this would be outside of the ERG remit.

4.1.2 Inclusion criteria

The eligibility criteria used in the search strategy for randomised controlled trials (RCTs) is presented in Table 4.1 (see CS Table 7, page 46 and Table 18, page 80).

Table 4.1: Eligibility criteria used in search strategy for RCT evidence

Inclusion criteria	
Population	Patients with severe / very severe COPD (defined as FEV_1 <50% predicted level, corresponding to pre-2013 GOLD report stages III and IV) (Include patients with emphysema or bronchitis. Exclude asthma patients)
Comparators / Interventions	Roflumilast given as add-on to triple therapy LABA / LAMA LABA / ICS LABA / LAMA / ICS LABA / ICS / Methylxanthines LABA / LAMA / Methylxanthines LABA / ICS / LAMA / Methylxanthines
Outcomes	Annual rate of exacerbations Patients with ≥1 moderate / severe exacerbations Number of exacerbations requiring corticosteroids Time to first exacerbation Pre-bronchodilator FEV_1 mean change from baseline Post-bronchodilator FEV_1 mean change from baseline Mortality Quality of life Adverse events, and safety endpoints
Study design	RCTs [of at least 24 weeks (6 months) duration] (Pooled study designs to be included) Separate searches were conducted for RCTs and non-RCTs
Language	No language limit To reduce number of hits and to identify studies in patient populations relevant to the UK setting

Inclusion criteria
Source: Tables 7 and 18 of the CS COPD = Chronic obstructive pulmonary disease; FEV1 = Forced Expiratory Volume in the first second; GOLD = Global initiative for chronic obstructive lung disease; ICS = Inhaled corticosteroid; LABA = Long-acting beta2 agonist; LAMA = Long-acting muscarinic antagonist; RCT = randomised controlled trial.

ERG comment: These inclusion criteria broadly match the decision problem set out within the final NICE scope[21] in terms of the population and the intervention. Although, roflumilast in combination with LABA, LABA / ICS, LAMA, or LAMA plus LABA are not included as interventions. This is already discussed in Section 3.2.

In addition, monotherapy (LAMA or LABA) and LAMA + ICS are not included as possible comparators. However, it is unlikely that relevant studies will have been missed as a result of this omission.

4.1.3 Critique of data extraction

For cost effectiveness studies, HRQoL and cost and healthcare resources studies data were extracted by a single reviewer for the full text article that met the inclusion criteria and were validated by a second reviewer (CS, Section 5.1, page 91; Section 5.4, page 110 and Section 5.5, page 124). For effectiveness studies it is not stated how many reviewers were involved in the data extraction process.

4.1.4 Quality assessment

Table 15 in Section 4.6 of the CS[1] provided an overview of the risk of bias assessment of the REACT trial (see Table 4.2 below).

Table 4.2: Risk of bias assessment REACT trial by the company and ERG

Question	Yes / No / Not clear How is the question addressed in the study?	ERG Comment
Was randomisation carried out appropriately?	Yes. Randomisation was carried out by an IVRS web response system using computerised central randomisation system	Yes
Risk	Low	Low
Was the concealment of treatment allocation adequate?	Yes. All parties masked to treatment assignment. Interactive voice response system-interactive web response system used and patients received identical tablets in both treatment and control group	Yes
Risk	Low	Low
Were the groups similar at the outset of the study in terms of prognostic factors e.g. severity of disease?	Yes. No imbalances in baseline characteristics	Unclear In the concomitant LAMA subgroup (LABA / LAMA / ICS) small, but possibly relevant differences between the two groups were: the roflumilast arm has slightly more young patients, slightly

Question	Yes / No / Not clear How is the question addressed in the study?	ERG Comment
		fewer current smokers, and slightly more very severe patients.
Risk	Low	Low
Blinding of care providers, participants and outcome assessors to treatment allocation?	Yes. Participants and care-givers blinded. Patients received identical pills	Yes
Risk	Low	Low
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No. No large imbalances in patients lost to follow up	No
Risk	Low	Low
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. No evidence to suggest more outcomes measured than reported	No
Risk	Low	Low
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data	Not clear. An ITT analysis was conducted but no information is given on accounting for missing data	Yes for ITT-analysis. No for PP analysis.
Risk	Unclear	High for PP analysis
Source: Table 15, page 71 of the CS ITT = Intention to treat ; IVRS = Interactive voice response system		

ERG comment: In the concomitant LAMA subgroup (LABA / LAMA / ICS) there were small, but possibly relevant differences between the two groups (the roflumilast arm has slightly more young patients, slightly fewer current smokers, and slightly more very severe patients). In addition, a relative large number of patients were excluded from the PP population due to protocol violations (312 out of 1,945 = 16.0 %). It is unclear to the ERG how patients could have fulfilled inclusion criteria at time of randomisation, yet still be excluded later because of protocol violations; including 105 patients not fulfilling the inclusion criterion: 'postbronchodilator FEV1 > 50 % at V0' (V0 is two weeks before randomisation) (see also Section 4.2.3 of this report).

4.1.5 Evidence synthesis

The company presented the results of a systematic review to identify RCTs of roflumilast or relevant comparators in combination with triple therapy in patients with severe or very severe COPD. A PRISMA flow diagram detailing the numbers of studies excluded at each stage of the review, is provided in Appendix 4 (page 38) of the CS.[15]

Ten full text articles and one conference abstract were included based on this review. The conference abstract presented by Sadigov and Huseynova[22] at the 2015 American Thoracic Society International Conference did not contain sufficient information to determine inclusion according to the company (CS,

Section 4.10, page 83). The company contacted the trial authors to obtain further information but no response was received and therefore this trial is not discussed further. The ERG agrees that the conference abstract as such has not sufficient details to warrant inclusion.

Table 4.3: Trials identified by the systematic review

Study ID	Population FEV1 % predicted	Treatments	Treatment type summary	Primary reference
Altaf 2016	<50%	Salmeterol / fluticasone	LABA / ICS	Altaf 2016[23]
		Formoterol / budesonide	LABA / ICS	
		Formoterol / fluticasone	LABA / ICS	
Calverley 2010	30%≤FEV1 <50%	Beclomethasone / formoterol	LABA / ICS	Calverley 2010[24]
		Budesonide / formoterol	LABA / ICS	
Cosio 2016	<50%	Salmeterol / fluticasone propionate / theophylline	LABA / ICS / methylxanthines	Cosio 2016[25]
		Salmeterol / fluticasone propionate	LABA / ICS	
FLAME	25%≤FEV1 <60%	Indacaterol / glycopyrronium	LABA / LAMA	Wedzicha 2016[26]
		Salmeterol / fluticasone	LABA / ICS	
FORWARD	30%≤FEV1 <50%	Formoterol / tiotropium / beclomethasone	LABA / LAMA / ICS	Wedzicha 2014[10]
		Formoterol / tiotropium	LABA / LAMA	
ILLUMINATE	40-80%	Indacaterol / glycopyrronium	LABA / LAMA	Vogelmeier 2013[27]
		Salmeterol / fluticasone	LABA / ICS	
LANTERN	30%≤FEV1 <80%	Indacaterol / glycopyrronium	LABA / LAMA	Zhong 2015[28]
		Salmeterol / fluticasone	LABA / ICS	
REACT	≤50%	Roflumilast / LABA / LAMA / ICS	LABA / LAMA / ICS / roflumilast	Martinez 2015[29]
		LABA / LAMA / ICS	LABA / LAMA / ICS	
RE2SPOND	≤50%	LABA / LAMA / ICS / roflumilast	LABA / LAMA / ICS / roflumilast	Martinez 2016[30]
		LABA / LAMA / ICS	LABA / LAMA / ICS	
WISDOM	<50%	Salmeterol / tiotropium / fluticasone propionate	LABA / LAMA / ICS	Magnussen 2014[11]
		Salmeterol / tiotropium	LABA / LAMA	

Source: Table 19, page 82 of the CS
FEV1 = Forced Expiratory Volume in the first second; ICS = Inhaled corticosteroid; LABA = Long-acting beta2 agonist; LAMA = Long-acting muscarinic antagonist.

An overview of the trials identified by the systematic review is presented in Table 4.3 (CS, Table 19, page 82). Two of these studies (REACT and RE2SPOND) included roflumilast. The company concluded that RE2SPOND was not appropriate for the decision problem because of the following reasons:

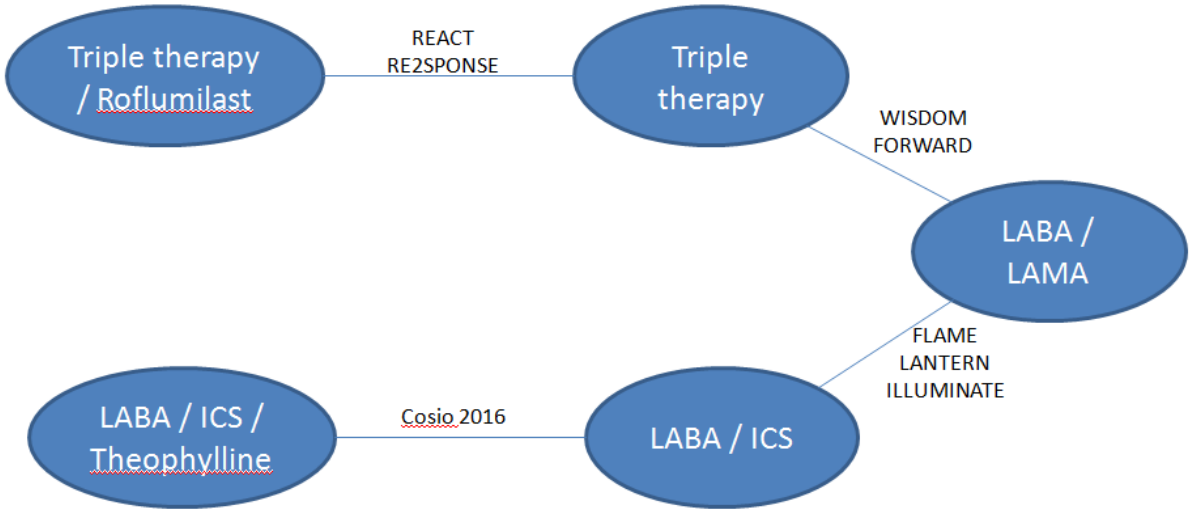
- The LABA/ICS dose in the RE2SPOND trial was lower than the maximum UK-approved dose.
- A low proportion of patients were on triple therapy (47%).
- RE2SPOND inclusion criteria specified dual ICS / LABA therapy for a minimum of 3 months prior to inclusion into the trial (compared with 12 months for REACT).
- Low proportion of Western European patients (one patient from Italy and 12 from Spain; no patients from the UK or other Western European countries).
- The RE2SPOND trial used a US FDA-approved non-film coated tablet whereas the REACT trial used the EMA-approved enteric film coated tablet. The formulation used in RE2SPOND is not approved for use in the UK.

We do not agree that the RE2SPOND trial is not relevant to the decision problem. We think the REACT trial and the RE2SPOND trial are similar enough to provide a pooled analyses of both trials. In fact the RE2SPOND authors themselves state that "both studies share similar methodologies and generally similar baseline patient characteristics, potentially allowing these data sets to be pooled for more robust analyses."[31] Unfortunately the company refused to send us the CSR of the RE2SPOND trial as part of the clarification response, and the company declined to perform a pooled analysis using data from both trials (Clarification letter, Questions A1 and A11). When the CSR of the RE2SPOND trial finally arrived (10 days before our deadline) the relevant data for the LAMA subgroup could not be found. Therefore, we can only report limited results from the RE2SPOND trial for the triple therapy population.

The remaining eight trials were excluded because they do not include a comparison of roflumilast plus triple therapy with triple therapy. Therefore, the only evidence presented in the CS for this appraisal is the REACT trial. The ERG does not agree with this. It is for the NICE appraisal committee to decide what the relevant population and relevant comparators are. There is evidence available to compare roflumilast in combination with LABA / ICS or in combination with triple therapy to most of the comparators listed in the scope. The company could have presented results for these comparisons.

Figure 4.1 shows a possible network of studies that would allow a comparison of roflumilast in combination with triple therapy to triple therapy, LABA / LAMA, LABA / ICS and LABA / ICS in combination with theophylline. In a similar way, results from the REACT trial can be used to compare roflumilast in combination with LABA / ICS with LABA / ICS, LABA / LAMA, and LABA / ICS in combination with theophylline.

Figure 4.1: Possible network for indirect comparisons



It is beyond the possibilities of the ERG to perform these analyses, as this involves full data extraction of these trials, a full network meta-analysis and inclusion of these comparators in the economic model. Therefore, the ERG suggests that the committee decides whether these analyses are relevant for the decision problem; and if they are, the committee can request the company to perform these analyses before the second committee meeting.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The CS focuses on part of one trial, the REACT trial, comparing roflumilast plus triple therapy with triple therapy. In the REACT trial, patients were randomised to receive either roflumilast or placebo as add-on to LABA / ICS ± LAMA; 70% and 69% of patients in each treatment arm received concomitant LAMA, respectively. In addition, out of the 1945 randomised patients, 163 in the roflumilast group and 149 in the placebo group had one or more major protocol deviations and were excluded from the PP analysis set. In the economic model, the company uses the 70% of patients that received LAMA and minus those with one or more major protocol deviations.

One other trial was identified through the searches, the RE2SPOND trial, but this was considered not relevant for the decision problem (see Section 4.1.5 of this report).

4.2.1 The REACT trial – trial design

REACT (NCT01329029) was a one year double-blind, placebo controlled, parallel group phase 3/4 trial conducted in the EU (including the UK (n=51, i.e. 2.6%)), Australia, Brazil, Canada, Israel, Republic of Korea, South Africa and Turkey. Patients (n=1,945) with severe COPD (FEV1 < 50% predicted) with symptoms of chronic bronchitis and ≥ 2 exacerbations in the previous year were randomly assigned in a 1:1 ratio to either roflumilast or placebo. Study drug was added to a background of LABA / ICS fixed combination; tiotropium (LAMA) was also permitted.

An overview of the REACT trial design is presented in Table 4.4. Note that the start of the single-blind baseline period was referred to as V0 (See footnote to Table 12 in CS) and that the time of randomisation was referred to as V2 (See Table 9 in the CS).

Table 4.4: Overview of the REACT trial design

Trial number (acronym)	REACT (NCT01329029)
Location	Australia Austria, Belgium, Brazil, Canada, Denmark, France, Germany, Greece, Hungary, Israel, Italy, Republic of Korea, Netherlands, Poland, Russia, Slovak Republic, South Africa, Spain, Turkey, and the UK
Trial design	1-year double-blind, placebo controlled, parallel group phase 3-4 trial, comprising a 4-week baseline period, 52-week double-blind treatment period, and a 12-week follow-up period.
Eligibility criteria for participants	Key inclusion criteria were: • history of COPD associated with symptoms of chronic bronchitis • post-bronchodilator FEV1 / FVC ratio < 0·70 • post-bronchodilator FEV1 of ≤ 50% predicted • age ≥ 40 years • smoking history ≥ 20 pack-years • 2 moderate or severe exacerbations (separated by at least 10 days) in the previous year • pre-treatment with inhaled ICS and LABA combination for at least 12 months before baseline; and at a fixed dose for 3 months prior to baseline
Settings and locations where the data were collected	The trial was carried out in 21 countries, including the UK. 105 patients were recruited in the UK, of which 55 were randomised
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) Intervention(s) Permitted and disallowed concomitant medication	Trial drugs were roflumilast (500 μg) or placebo, taken orally, once daily. Roflumilast n=969; placebo n=966 Permitted concomitant medication included LAMA. In addition, 40 mg prednisolone / day and antibiotic therapy were permitted to manage exacerbations and purulent sputum / suspected bacterial infection, respectively Disallowed concomitant medications included oral and parenteral glucocorticosteroids (except to treat acute exacerbations), LABA or ICS monotherapy, short-acting muscarinic antagonists, and any SABA (with the exception of salbutamol) or oral β2 agonists
Primary outcomes (including scoring methods and timings of assessments)	The primary endpoint was the rate of moderate or severe COPD exacerbations per patient per year. (Moderate exacerbations were defined as requiring oral or parenteral glucocorticosteroids and severe exacerbations as requiring hospitalisations and / or leading to death)
Secondary outcomes (including scoring methods and timings of assessments)	Key secondary endpoints were change in post-bronchodilator FEV1 over the 52-week treatment period and the rate of severe COPD exacerbations per patient per year Other secondary endpoints included rate and time to exacerbations, post-bronchodilator lung function endpoints, COPD assessment test (specifically over the 52-week treatment period), mortality, major adverse

Trial number (acronym)	REACT (NCT01329029)
	cardiovascular events, time to withdrawal, and pharmacokinetics / pharmacodynamics. Safety endpoints included adverse events, changes in vital signs, changes in physical examination, changes in bodyweight and body mass index
Pre-planned subgroups	There were 21 pre-planned subgroups, of which concomitant treatment with LAMA is considered to be relevant to this decision problem
Source: Table 10, page 56 of the CS COPD = chronic obstructive pulmonary disease; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; ICS = inhaled corticosteroid; LABA = long-acting beta2 agonist; LAMA = long-acting muscarinic antagonist; SABA = short-acting beta2 agonist	

4.2.2 The REACT trial – statistical tests

The primary analysis of the REACT study looked at the impact of roflumilast on LABA / ICS ± LAMA background therapy. However, as the company submission seeks recommendation for the use of roflumilast in combination with LABA / ICS / LAMA triple therapy, the CS focuses on the LABA / ICS/ LAMA subgroup.

ERG comment: Subgroup analyses should be pre-specified in the statistical analysis plan. The full CSR of the REACT trial does mention a statistical analysis plan in Appendix 16.1.9, but this Appendix was missing from both versions (stripped and 'full' CSR) we received from the company. Therefore, we cannot assess whether this subgroup analysis was pre-specified. Section 9.8.2 of the CSR lists post-hoc analyses one of which is "by concomitant treatment with LAMA". This suggests that this analysis was not pre-specified in the analysis plan. As the number of subgroup analyses increases and hence the number of statistical comparisons performed then the chance of finding a false positive result increases. Subgroup results should be based on a test of interaction between the randomised treatment and the subgroup, which have not been reported in the company submission or the CSR. The company submission states that concomitant treatment with LAMA was one of 12 subgroup analyses pre-specified in the statistical analysis plan, but the ERG could not verify this. An additional concern when using subgroup results is that unless the subgroup was included as a randomisation stratification factor the treatment groups will not be randomly allocated within the subgroup. This could lead to an imbalance between the treatment groups in one or more baseline characteristics. However, the baseline data by treatment group is reported in Table 14 in the company submission which indicates that the treatment groups within the concomitant LAMA subgroup appear to be well-balanced for those variables which have been reported but there may be other unknown imbalances in other factors due to the lack of randomisation within this subgroup.

The primary endpoint was analysed using a Poisson regression model, with an accompanying negative binomial analysis as a planned sensitivity analysis. This modelled the rate of moderate to severe exacerbations as the outcome, with an offset variable of the natural logarithm of duration in the study to correct for the time each patient spent in the trial. Treatment was included as an independent variable. The Poisson model assumes events are independent of each other. Therefore, a Pearson Chi-Square correction was applied in order to account for potential over dispersion resulting from lack of independence of the events and/or zero inflation. An alternative negative binomial model which relaxes the assumption required by the Poisson model that the expected value (mean) of the outcome is equal to its variance, was performed as a sensitivity analysis.

In the company submission they state that "However, as Keene et al. (2007)[32] explain and Suissa et al. (2006)[33] illustrate, in the Poisson regression model, estimates of treatment effect are unaffected by use of an over dispersion adjustment as only the estimates of standard error are increased. In contrast, the pre-specified negative binomial model assumes that individuals' exacerbations follow a Poisson process with an underlying rate that is distributed as a gamma distribution." The company submission states that due to a lower event rate than anticipated (0.927 moderate to severe exacerbations per patient per year for placebo compared to the 1.25 assumed in the sample size calculation) the Poisson regression model may not have been the optimal model for the REACT population. Therefore the negative binomial model, which uses a less simplistic assumption of variability and allows a different exacerbation rate for each patient, was considered to be the more appropriate model for the analysis of exacerbation rates. The negative binomial model has been used to analyse exacerbation rates in other studies, including TORCH, WISDOM and RE2SPOND. Secondary endpoints were analysed using the Poisson regression model and/or negative binomial regression model.

ERG comment: The pre-specified primary analysis of the primary endpoint (moderate to severe exacerbations) was a Poisson regression model with a negative binomial regression model as a sensitivity analysis. The company submission presents the results of the negative binomial model as well as those from the Poisson model and states that they considered the negative binomial model to be the most appropriate model for exacerbation data. As the ERG did not have access to the individual patient data we were unable to check the amount of over dispersion in the data, or the fit of both models to ascertain which was the better fitting model. As the negative binomial model is essentially a modification to a Poisson model with an extra parameter to model the over dispersion it is a more flexible model and if there is only a small amount over dispersion the results will approach those of the Poisson model. Therefore it is quite likely that it was the more appropriate and better fitting model but the ERG were not able to verify this decision. It is important to note, that the choice of model has only a marginal impact on the clinical effectiveness results.

The primary analysis for the primary outcome (and subgroup analyses) used the ITT analysis and a Poisson regression model. The ITT analysis assigned patients to the treatment group based on the study drug to which they were randomised and includes all:

- randomised patients who took at least one dose of study drug following randomisation
- data until a patient discontinued (prematurely or as scheduled) the trial.

A PP analysis of the primary endpoint was also pre-specified to assess the robustness of the results. This analysis included all patients without any major protocol deviations (Table 4.5) including patients terminating early (provided there were no major protocol violations).

ERG comment: The primary analysis of a superiority RCT should always be an intention to treat analysis which should include all randomised participants in their randomised groups. Excluding any patients from the analysis is a potential source of bias and means the originally randomised groups are no longer being compared. The per-protocol population presented in the company submission excluded patients with major protocol violations and was stated to be the population which more closely aligns with the target population in the decision problem. In total 312 out of 1,945 randomised patients (16%) were excluded from the REACT trial (See Table 4.5). The ERG thinks that the company submission did not fully explain the rationale for using the PP population and did not acknowledge the potential bias of this choice compared to using the ITT population. Any per-protocol analysis is likely to be biased as it is no longer based on the randomised allocation and the reasons that patients may not comply with the treatment protocol could be related to their allocated treatment (see Section 4.2.3). The ERG

considers the appropriate population for the economic base case analysis to be the ITT subgroup of triple therapy using the results from the negative binomial model.

Table 4.5: Major protocol deviations (all randomised patients)

	Roflumilast (N=973) n (%)	**Placebo (N=972) n (%)**	**Total (N=1945) n (%)**
Number of patients with ≥ 1 major protocol deviation	163 (16.8)	149 (15.3)	312 (16.0)
Total number of major protocol deviations	203	188	391
Protocol deviation breakdown			
Postbronchodilator FEV_1 % predicted >50% at V0	57 (5.9)	48 (4.9)	105 (5.4)
Not pre-treated with LABA / ICS for at least 12 months prior to V0, or did not use a fixed combination of LABA / ICS on a constant daily dose throughout the trial	41 (4.2)	37 (3.8)	78 (4.0)
Total cough and sputum score < 14 during the last week prior to randomisation	30 (3.1)	31 (3.2)	61 (3.1)
Use of prohibited medication during the trial	21 (2.2)	15 (1.5)	36 (1.9)
Non-compliance during baseline period	8 (0.8)	16 (1.6)	24 (1.2)
Less than 2 documented moderate or severe COPD exacerbations within 1 year prior to V0	11 (1.1)	8 (0.8)	19 (1.0)
Issues with site noncompliance	8 (0.8)	9 (0.9)	17 (0.9)
Postbronchodilator FEV1 / FVC > 70% at V0	7 (0.7)	3 (0.3)	10 (0.5)
Randomised but not treated	4 (0.4)	6 (0.6)	10 (0.5)
Premature unblinding	4 (0.4)	5 (0.5)	9 (0.5)
Misallocation resulting in at > 1 dose of incorrect treatment	4 (0.4)	0	0 4 (0.2)
Medical history of asthma and / or other relevant lung disease, or lower respiratory tract infection unresolved 4 weeks prior to V0	2 (0.2)	2 (0.2)	4 (0.2)
Smoking history < 20 pack years	2 (0.2)	2 (0.2)	4 (0.2)
Current participation in a pulmonary rehabilitation program or completion of a pulmonary rehabilitation program within 3 months preceding the baseline visit V0	2 (0.2)	1 (0.1)	3 (0.2)
Moderate or severe COPD exacerbation and / or a COPD exacerbation treated with antibiotics between visits V0 and V2	0	0 3 (0.3)	3 (0.2)
History of COPD less than 12 months	2 (0.2)	0	0 2 (0.1)
Randomised to placebo but received commercial DAXAS▼ during trial period	0	2 (0.2)	2 (0.1)

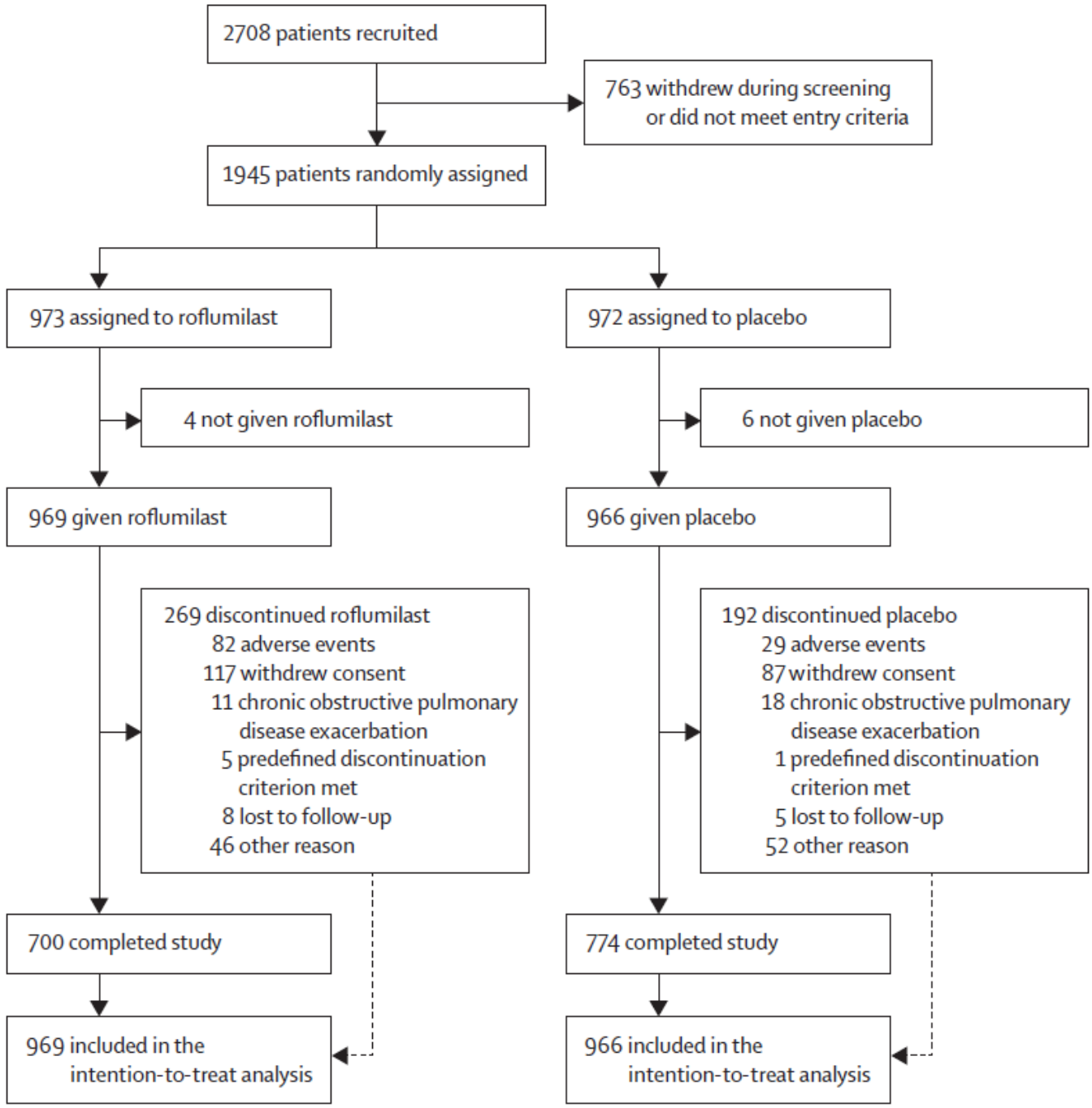
Source: Table 12, page 64 of the CS

COPD = chronic obstructive pulmonary disease; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; ICS = inhaled corticosteroid; LABA = long-acting beta2 agonist

4.2.3 The REACT trial – participant flow

In the REACT trial a total of 2,712 patients were screened of these 2,708 were enrolled in the trial and 1,945 were randomised (973 to the roflumilast treatment arm and 972 to placebo). Patient disposition is summarised in Figure 4.2. Reasons for non-randomisation included violation of inclusion criteria, met exclusion criteria, failure to meet randomisation criteria, or discontinuation during the baseline period for other reasons. Of those patients who were randomised, 969 received at least 1 dose of roflumilast and 966 received at least 1 dose of placebo; these patients comprised the ITT study population.

Figure 4.2: Patient disposition of the REACT trial



ERG comment: The ERG questions the use of the PP population for two main reasons, one being that the ITT population i.e. all those randomised is most likely to provide an unbiased estimation of the treatment effect. The other reason pertains to the way in which the PP population was constituted, which is summarised in Table 4.5 above. In the clarification letter, the ERG requested that the company explain the number of major protocol violations in the REACT trial. In particular, it was put to the company that the numbers of patients with FEV1 > 50 % of predicted at V0, not having used LABA/ICS for at least 12 months prior to the trial, and total cough and sputum count < 14 in the week before randomisation suggest that inclusion criteria have been reassessed at randomisation, but not used to exclude these patients from randomisation. On the basis of the ERG's understanding that this must be due to variation in the health status of the patients, the company were then asked to explain why the PP population would be more relevant for the decision problem given that in clinical practice, FEV1 values and sputum counts will vary, and patients will forget medication changes. The company requested help to understand the question and the ERG responded that there were 312 out of 1,945 randomised patients who had major protocol deviations. The ERG suggested that for some of these patients, such as the 105 patients reported in Table 4.5 to have had postbronchodilator FEV1 > 50 % at V0, which is two weeks before randomisation (V2), in order to be randomised, they must have fulfilled the inclusion criteria for the trial at V0 and yet they were deemed to be non-compliant at the same time. In other words, the problem with Table 12 (CS, page 64 and Table 4.5 in this report) was less that patients might have been excluded because of variation in health status and more a question of inconsistency, namely how could patients get to be randomised if they had not fulfilled the inclusion criteria for entry to the trial in the first place. The company responded by stating that it the ERG were not correct in this presumption:

"In responding to the ERG points, we would highlight that they are not correct to presume that patients were randomised 'based on fulfilment of inclusion criteria assessed prior to the baseline visit at V0 and non-compliance at V0'."

They reiterated the point that patients had to meet all of the inclusion criteria at V0 and then, prior to randomisation (V2), eligibility had to be re-confirmed. The company did state that there had been a protocol change to allow patients to enter with FEV1 > 50%. However, they did not make it clear that these were the 105 referred to in Table 12, nor did they explain the other major protocol deviations that involved lack of compliance with inclusion criteria at V0, such as less than two documented moderate or severe COPD exacerbations within one year prior to V0.

In conclusion, the ERG consider that the company have not provided adequate justification for the major protocol amendments and thus the production of the PP population and so continue to believe that the ITT population is superior to the PP population.

4.2.4 The REACT trial – patient characteristics

Baseline characteristics of participants in the REACT study (ITT population) are provided in the CS together with baseline characteristics of the PP population of the LABA / LAMA / ICS subgroup (CS, Tables 13 and 14, pages 66-67). However, baseline characteristics for the concomitant LAMA subgroup (ITT population) were not provided in the CS. Therefore, the ERG requested this information in the Clarification letter (Clarification letter, Question A8). Available baseline characteristics for the concomitant LAMA subgroup (ITT population) are provided in Table 4.6 below.

Table 4.6: Baseline characteristics of participants in the REACT study in the concomitant LAMA subgroup (LABA / LAMA / ICS) ITT population

Baseline characteristic	Roflumilast	Placebo
REACT (n=1,346)	**N=677**	**N=669**
Age, mean years n (%)		
<=65	353 (52.14)	364 (54.41)
>65	324 (47.86)	305 (45.59)
Male sex n (%)	506 (74.74)	499 (74.59)
Body-mass index, kg / m2, n (%)		
Underweight <18.5	33 (4.87)	32 (4.78)
Normal weight >18.5 to <25	266 (39.29)	238 (35.58)
Overweight >= 25 to <30	217 (32.05)	232 (34.68)
Obese <+ 30	161 (23.78)	167 (24.96)
Cigarette pack-years, n (%)		
<40	263 (38.85)	258 (38.57)
>= 40	414 (61.15)	411 (61.43)
Smoking status, n (%)		
Current smoker	258 (38.11)	273 (40.81)
Former smoker	419 (61.89)	396 (59.19)
FEV1 reversibility increase n(%)		
<=12% and /or 200ml	575 (84.93)	570 (85.20)
>12% and > 200 ml	55 (8.12)	56 (8.37)
COPD severity n (%)		
Mild	1 (0.15)	0 (0.00)
Moderate	13 (1.92)	11 (1.64)
Severe	437 (64.55)	455 (68.01)
Very severe	226 (33.38)	203 (30.34)
CAT score n (%)		
<10	45 (6.65)	41 (6.13)
>=10	630 (93.06)	626 (93.57)
MRC dyspnoea scale n (%)		
<2	149 (22.01)	164 (24.51)
>= 2	513 (75.78)	492 (73.54)
No. exacerbations in the prior year n (%)		
< 2	4 (0.59)	3 (0.45)
2	581 (85.82)	580 (86.70)
>2	88 (13.00)	84 (12.56)
History of cardiovascular disease n (%)		
Yes	304 (44.90)	309 (46.19)
No	373 (55.10)	360 (53.81)

Source: Response to the Clarification letter, Question A8.
COPD = chronic obstructive pulmonary disease; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; LAMA = long-acting muscarinic antagonist; CAT = Chronic Obstructive Pulmonary Disease Assessment Test; MRC = Medical Research Council.

ERG comment: Small, but possibly relevant differences between the two groups are as follows: the roflumilast arm has slightly more young patients, slightly fewer current smokers, and slightly more very severe patients. The same differences were shown in the concomitant LAMA subgroup (LABA / LAMA / ICS) PP population (CS, Table 14, page 67).

4.2.5 The REACT trial – results

The CS explains that the pre-specified primary analysis of the REACT trial used the ITT population and a Poisson regression model to determine exacerbation rates in patients receiving roflumilast vs

placebo as add-on to LABA / ICS ± LAMA. However, the company prefers to present results for the PP population, using the negative binomial model for patients treated with LABA / ICS + LAMA only (CS, Section 4.7, page 72).

Regarding the treatment population (LABA / ICS ± LAMA or LABA / ICS + LAMA), this is for the committee to decide. As explained in Section 3.1 to 3.3 of this report, the population, intervention and comparators used in the CS are not in line with the scope provided by NICE. Nevertheless, restrictions to the population, intervention and comparators may be regarded reasonable by the committee.

Regarding the use of the PP population instead of the ITT population, the ERG strongly believes that the ITT population should be the preferred population for all analyses. The company states that "The ITT population does not accurately reflect the target population in the decision problem – the PP population is more appropriate". However, the ERG believes that the ITT population provides the most reliable and unbiased estimate of the treatment effect and the ERG has concerns about the large number of protocol violations at the time of randomisation (16% of randomised patients were excluded). The ITT analysis results should be considered as the primary result as the PP results are no longer based on the randomised treatment allocation, exclude 16% of the randomised participants, and is subject to selection bias.

Primary endpoint: moderate to severe exacerbations

In the primary ITT analysis LABA / ICS ± LAMA, using the Poisson model, the frequency of moderate to severe exacerbations was 13.2% lower in the roflumilast group compared with placebo (0.805 [95% CI: 0.724–0.895] vs 0.927 [95% CI: 0.843–1.020], RR 0.868 [95% CI: 0.753–1.002]) on a background of LABA / ICS ± LAMA. This difference was not statistical significant (p=0.0529). The ITT analysis using a negative binomial regression model revealed a statistically and clinically significant reduction of 14.2% in the rate of moderate to severe COPD exacerbations in patients treated with roflumilast vs placebo (0.823 [95% CI: 0.738–0.915] vs 0.959 [95% CI: 0.867–1.061]; RR 0.858 [95% CI; 0.740–0.995], p=0.0424.

In the pre-specified PP analysis, a 19.4% statistically significant reduction was observed in moderate to severe exacerbation event rates, favouring roflumilast vs placebo as add-on to LABA / ICS ± LAMA (0.742 [95% CI: 0.659–0.836] vs 0.921 [95% CI: 0.831–1.021], RR 0.806 [95% CI: 0.688–0.943], p=0.0070, Poisson regression model) (Table 4.7).

Secondary endpoints

Severe exacerbations were defined as exacerbations that required hospitalisation and/or lead to death. Due to the low event rate (and as per the statistical plan), this endpoint was analysed by negative binomial regression. In the ITT analysis, the rate of severe exacerbations was significantly reduced by 24.3% in the roflumilast group compared with the placebo group on a background of LABA / ICS ± LAMA (Table 4.7).

Treatment with roflumilast was also associated with a significant improvement in post-bronchodilator FEV1 and FVC (Table 4.7).

Results for other secondary endpoints are summarised in Table 4.8. The company added: "Although not all secondary endpoints achieved statistical significance, there was a consistent trend that roflumilast reduced exacerbation rates and time to second and third moderate to severe exacerbations." (CS, Section 4.7, page 77). Health related quality of life was assessed using the COPD Assessment Test (CAT), the mean change in CAT total score showed no significant difference between groups. Specific results for the CAT scores are reported in Table 4.9. Overall, most items on the CAT score and the overall CAT

score showed no significant differences between groups. Two specific items did show significant differences between groups: ‘Breathlessness’ favoured roflumilast and ‘Sound sleep’ favoured placebo.

The developers of the CAT score “believe that a difference or change of 2 or more suggests a clinically significant difference or change in health status”.[34] That means, none of the changes in CAT scores are clinically significant.

Table 4.7: REACT: Primary and secondary endpoint data

Analysis	Roflumilast (ITT n=969, PP n=810)	Placebo (ITT n=966, PP n=823)	Roflumilast vs placebo
Primary endpoint: Moderate to severe COPD exacerbation rate (mean per patient year (95% CI); number of patients with ≥1 exacerbation			
Primary analysis: Poisson regression, ITT*	0.805 (0.724–0.895); n=380	0.927 (0.843–1.020); n=432	RR 0.868 (0.753–1.002), p=0.0529
Pre-specified analysis Poisson regression, PP* Negative binomial regression, ITT†	0.742 (0.659–0.836); n=310 0.823 (0.738–0917); n=380	0.921 (0.831–1.021); n=369 0.959 (0.867–1.061); n=432	RR 0.806 (0.688–0.943); p=0.0070 RR 0.858 (0.740–0.995) p=0.0424
Secondary endpoint: severe COPD exacerbation rate (mean rate per patient year (95% CI); number of patients with ≥1 severe exacerbation.			
Negative binomial regression, ITT†	0.239 (0.201–0.283); n=151	0.315 (0.270–0.368); n=192	RR 0.757 (0.601–0.952) p=0.0175
Negative binomial regression, PP†	0.218 (0.180–0.264); n=120	0.326 (0.277–0.385); n=167	RR 0.668 (0.518–0.861) p=0.0018
Secondary endpoint: Lung function, mean change from baseline to week 52; no. patients with data available			
Post-bronchodilator FEV1, ITT, mL	52 (6.4); n=928	–4 (6.2); n=941	Difference 56 (38–73); p<0.0001
Post-bronchodilator FVC, ITT, mL	36 (11.4); n=928	–57 (11.1); n=941	Difference 92 (61–124); p<0.0001
Secondary endpoint: exacerbation rate mean rate per patient year (95% CI); number of patients with at least one exacerbation			
Leading to hospital admission Negative binomial regression, ITT†	0.238 (0.200–0.283); n=150	0.313 (0.268–0.365); n=190	RR 0.761 (0.604–0.960); p=0.0209

Source: Table 16, page 76 of the CS

PP = per protocol; RR = rate ratio; HR = hazard ratio; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; ITT = intention to treat.

Data in second and third columns are mean rate per patient per year (95% CI), median (IQR), or mean change (SE); data in final column are RR (95% CI), or mean difference (95% CI) and p values.

*Estimated exacerbation rates based on a Poisson regression model including a correction for over dispersion

†Estimated exacerbation rates based on a negative binomial regression model excluding correction for over dispersion

Table 4.8: REACT; secondary endpoints (Martinez 2015)

Analysis	Roflumilast (ITT n = 969, PP n = 810)	Placebo (ITT n = 966, PP n = 823)	Roflumilast vs placebo
Other secondary exacerbation rate endpoints: exacerbation rate mean rate per patient year (95% CI); number of patients with at least one exacerbation			
Moderate Poisson regression, ITT†	0.574 (0.508 – 0.648); n = 287	0.627 (0.561 – 0.702); n = 333	RR 0.914 (0.775 – 1.078); p = 0.2875
Moderate or treated with antibiotics Poisson regression, ITT†	0.794 (0.716 – 0.881); n = 370	0.929 (0.847 – 1.019); n = 433	RR 0.854 (0.744 – 0.982); p = 0.0262
Moderate or severe or treated with antibiotics Poisson regression, ITT†	1.012 (0.922 – 1.110); n = 448	1.210 (1.115 – 1.313); n = 513	RR 0.837 (0.739 – 0.947); p = 0.0047
Secondary time to exacerbation endpoints: median time (days) to exacerbation (IQR); number of patients with at least one exacerbation			
Time to first moderate to severe exacerbation	103.5 (45.5 – 195.5); n= 380	111.5 (46.5 – 191.0); n = 432	HR 0.918 (0.800 – 1.054); p = 0.2245
Time to second moderate to severe exacerbation	197.0 (135.0 - 281.0); n = 153	190.0 (128.0 – 271.0); n = 206	HR 0.790 (0.641 – 0.974); p= 0.0272
Time to third moderate to severe exacerbation	248.0 (185.0 – 321.0) n = 65	242.0 (174.0 – 280.0); n = 93	HR 0.749 (0.545- 1.028); p= 0.0735
Other outcomes; CAT score, mean change (SE); number of patients with data available			
Change in CAT total score	-1.270 (0.1556); n = 924	-0.985 (0.1518); n = 940	Difference -0.285 (-0.711 to 0.142); p = 0.1909

Source: Table 7, Appendix 6, pages 43-46 of the CS; Martinez 2015[29]

Data in second and third columns are mean rate per patient per year (95% CI), median (IQR), or mean change (SE); data in final column are RR or HR (95% CI), or mean difference (95% CI) and p values.

ITT = intention to treat. PP = per protocol. RR = rate ratio. HR = hazard ratio. FEV1 =forced expiratory volume in 1 s. FVC = forced vital capacity. CAT = Chronic Obstructive Pulmonary Disease Assessment Test.

*Estimated exacerbation rates based on a Poisson regression model.

†Estimated exacerbation rates based on a negative binomial regression

Table 4.9: CAT scores, mean change (SE); number of patients with data available (ITT analysis)

	Roflumilast (n = 924)	Placebo (n = 940)	Difference (95% CI)
CAT total score	-1.270 (0.1556)	-0.985 (0.1518)	-0.285 (-0.711 to 0.142); p = 0.1909
Cough	-0.284 (0.0261)	-0.242 (0.0254)	-0.042 (-0.113 to 0.029); p = 0.2496
Phlegm/mucus	-0.248 0.0268	-0.244 0.0261	-0.003 (-0.077 to 0.070); p = 0.9270
Tightness of chest	-0.169 0.0289	-0.161 0.0282	-0.008 (-0.087 to 0.071); p = 0.8431
Breathlessness	-0.338 0.0283	-0.230 0.0276	-0.108 (-0.186 to -0.031); p = 0.0062
Activities limitations	-0.199 0.0300	-0.139 0.0292	-0.059 (-0.141 to 0.023); p = 0.1564
Confidence to leave home	0.018 0.0324	0.052 0.0316	-0.034 (-0.123 to 0.055); p = 0.4514
Sound sleep	0.033 0.0293	-0.082 0.0285	0.114 (0.034 to 0.194); p = 0.0052
Energy	-0.037 0.0270	-0.028 0.0263	-0.010 (-0.084 to 0.064); p = 0.7951

Source: CSR of REACT, Table 14.2.7.3
ITT = intention to treat. CAT = Chronic Obstructive Pulmonary Disease Assessment Test.

Subgroup analysis

The company states that the "submission is seeking a recommendation for the use of roflumilast in combination with LABA / LAMA / ICS". Consequently, the submission focuses on the 'concomitant treatment with LAMA' subgroup in the REACT trial, which provides data on the impact of roflumilast as add-on to LABA / LAMA / ICS. It is for the NICE Appraisal Committee to decide whether this restriction of the population, intervention and comparators is acceptable, as this is not according to the NICE final scope.

Over two-thirds of the REACT study population received concomitant treatment with LAMA in addition to LABA / ICS (677 / 969 [70%] in the roflumilast group and 669 / 966 [69%] in the placebo group). Analyses of the LABA / LAMA / ICS subgroup are summarised in Table 4.10.

As discussed before, the company prefers to use data from the PP population, but the ERG disagrees and we will use data from the ITT population instead (see Section 4.2.2 of this report).

In the ITT analysis (using the negative binomial regression model), compared with placebo, roflumilast as add-on to LABA / LAMA / ICS reduced the rate of:

- moderate to severe exacerbations by 13.7% (roflumilast 0.924 vs placebo 1.061; RR 0.871 [95% CI: 0.741 to 1.024]; p=0.0944).
- severe exacerbations by 8.7% (roflumilast 0.287 vs placebo 0.374; RR 0.767 [95% CI: 0.595 to 0.989]; p=0.0406).

ERG comment: As reported in Section 4.2.2 of this report, we believe that the analysis using the ITT population is the most reliable analyses. Table 4.10 shows that there is a considerable difference in effectiveness outcomes between the ITT analyses and the PP analyses. Not only do the analyses based on the ITT population no longer show statistically significant differences between groups; the economic analysis also shows a considerably less favourable cost effectiveness ratio as shown in the ERG preferred base-case results in Section 5.3.2 of this report.

Table 4.10: Mean rate (95% CI) of COPD exacerbations per patient per year with concomitant LAMA treatment

	Roflumilast ITT: LABA / LAMA / ICS N=677; PP: LABA / LAMA / ICS N=565	**Placebo ITT: LABA / LAMA / ICS N=669; PP: LABA / LAMA / ICS N=557**	**Roflumilast vs placebo**
Moderate to severe exacerbation			
ITT population, Poisson regression model	0.901 (0.799–1.016); n=286	1.023 (0.918–1.141); n=320	RR 0.881 (0.749–1.036); p=0.1252
ITT population, Negative binomial regression model	0.924 (0.821–1.040); n=286	1.061 (0.950–1.185); n=320	RR 0.871 (0.741–1.024); p=0.0944
PP population, Poisson regression model	0.838 (0.732–0.960), n=235	1.034 (0.920–1.164) n= 271	RR 0.810 (0.677–0.969); p=0.0215
PP population, Negative binomial regression model	0.858 (0.754–0.978), n=235	1.075 (0.954–1.211) n= 271	RR 0.799 (0.670–0.952); p=0.0122
Severe exacerbation			
ITT population, Poisson regression model	0.280 (0.226–0.347); n=125	0.354 (0.295–0.425); n=152	RR 0.791 (0.597–1.048); p=0.1019
ITT population, Negative binomial regression model	0.287 (0.237–0.347); n=125	0.374 (0.315–0.443); n=152	RR 0.767 (0.595–0.989); p=0.0406
PP population, Poisson regression model	0.256 (0.200–0.327); n=99	0.372 (0.305–0.452); n =132	RR 0.688 (0.503–0.943); p=0.0200
PP population, Negative binomial regression model	0.260 (0.210–0.322); n=99	0.395 (0.329–0.475); n =132	RR 0.659 (0.497–0.872); p=0.0035
Moderate exacerbation			
ITT population, Negative binomial regression model	0.631 (0.550–0.725); n=212	0.676 (0.564–0.770); n=242	RR 0.934 (0.773–1.128); p=0.4775
PP population, Negative binomial regression model	0.593 (0.511–0.689); n= 177	0.669 (0.582–0.769); n= 204	RR 0.886 (0.722–1.087); p=0.2457

Source: Table 17, page 79 of the CS and Response to Clarification letter, Question A6
ITT = intention to treat. PP = per protocol. RR = rate ratio.

Adverse effects of treatment

Adverse events were reported by 648 (67%) of 968 patients receiving roflumilast and by 572 (59%) of 967 patients in the placebo group (Table 4.11); serious adverse events were reported by 249 (26%) patients in the roflumilast group and 285 (30%) in the placebo group. The most frequently reported adverse events were COPD exacerbations, diarrhoea, and weight loss. Patient withdrawals associated with adverse events were more common in patients who were given roflumilast (104 [11%]) than in those receiving placebo (52 [5%]).

Mortality was a secondary efficacy endpoint in the study. During double-blind treatment, 17 (2%) deaths occurred in the roflumilast group and 18 (2%) in the placebo group (Table 4.12). Additionally, the number of major adverse cardiovascular events did not differ between the two groups (Table 4.12). No increase in the incidence of pneumonia occurred during treatment with roflumilast (Table 4.13). Weight loss was self-reported as an adverse event by 88 (9%) of 968 patients who received roflumilast compared with 27 (3%) of 967 in the placebo group. Patients who received roflumilast lost a mean of 2.65 kg (SD 4.37), compared with 0.15 kg (SD 3.69) in the placebo group (Table 4.12).

During market authorisation, the CHMP flagged psychiatric disorders as a potential safety concern. In the REACT study depression was reported by 2% (19/968) of patients in the roflumilast group and 1.1% (11/967) in the placebo group.[29] Roflumilast is not recommended in patients with a history of depression associated with suicidal ideation or behaviour. In addition, risk minimisation materials (HCP and patient education) have been put in place to further address this risk.

Table 4.11: Adverse events occurring in at least 2·5% of patients in either treatment group

	Roflumilast group (n=968)	Placebo group (n=967)	Difference between groups (95% CI)
COPD exacerbation	145 (15%)	185 (19%)	–4.2% (–5.08 to –3.23)
Diarrhoea	99 (10%)	35 (4%)	6.6% (5.50 to 7.71)
Weight decrease	88 (9%)	27 (3%)	6.3% (5.22 to 7.38)
Nausea	55 (6%)	15 (2%)	4.1% (3.24 to 5.02)
Nasopharyngitis	52 (5%)	52 (5%)	0% (–0.04 to 0.03)
Headache	40 (4%)	21 (2%)	2.0% (1.34 to 2.58)
Pneumonia	39 (4%)	45 (5%)	–0.6% (–0.98 to –0.27)
Decreased appetite	36 (4%)	5 (1%)	3.2% (2.42 to 3.99)
Insomnia	29 (3%)	15 (2%)	1.4% (0.91 to 1.98)
Back pain	27 (3%)	14 (1%)	1.3% (0.83 to 1.85)
Upper abdominal pain	25 (3%)	10 (1%)	1.5% (1.00 to 2.10)
Hypertension	24 (3%)	27 (3%)	–0.3% (–0.56 to –0.06)

Source: Martinez 2015[29]
Data are n (%), unless otherwise indicated. Adverse events were reported independently of the investigator causality assessments. Patients might have had more than one adverse event. One patient assigned to roflumilast accidentally received placebo for the entire duration of the study and was therefore included in the placebo group for the safety analysis.

Table 4.12: Key safety outcomes

	Roflumilast group	Placebo group
Mortality (n=969 in roflumilast group; n=966 in placebo group)		
Deaths*	17 (2%)	18 (2%)
Primary cause of death*		
COPD exacerbation	7 (1%)	7 (1%)
Adverse event	10 (1%)	11 (1%)
Major adverse cardiovascular events (n=969 in roflumilast group; n=966 in placebo group)		
Composite major adverse cardiovascular events	16 (2%)	16 (2%)
Major adverse cardiovascular event due to cardiovascular death (including death from undetermined cause)	9 (1%)	7 (1%)
Major adverse cardiovascular event due to non-fatal myocardial infarction	3 (<1%)	6 (1%)
Major adverse cardiovascular event due to non-fatal stroke	4 (<1%)	3 (<1%)
Bodyweight changes (n=968 in roflumilast group; n=967 in placebo group)		
Change in bodyweight (kg) during double-blind treatment	–2.65 (4.37); n=938†	–0.15 (3.69); n=944†
Change in bodyweight (kg) post-randomisation to end of follow-up‡		
Roflumilast in post-treatment period	0.28 (1.58); n=36†	–1.62 (2.49); n=48†
No roflumilast in post-treatment period	1.10 (2.61); n=612†	0.11 (2.60); n=679†

Source: Martinez 2015[29]
Data are n (%) or mean (SD). One patient assigned to roflumilast received placebo for the entire study and was therefore included in the placebo group for the safety analysis. The total numbers of patients for the mortality and major adverse cardiovascular event analyses are based on the full analysis population of patients, whereas bodyweight is based on the safety population.
* Analysis includes deaths during the double-blind treatment period only.
†The number of patients with bodyweight measurements available.
‡Analysis includes data from the entire observation period.

Table 4.13: Frequency of pneumonia events (safety set)

Adverse event category (MedDRA Preferred term)	Roflumilast N=968 n (%)	Placebo N=967 n (%)
Pneumonia	45 (4.6)	47 (4.9)
Pneumonia	39 (4.0)	45 (4.7)
Bronchopneumonia	2 (0.2)	1 (0.1)
Atypical pneumonia	1 (0.1)	2 (0.2)
Lobar pneumonia	1 (0.1)	
Pneumonia moraxella	1 (0.1)	
Pneumonia pseudomonas aeruginosa	1 (0.1)	

Source: Martinez 2015 (appendix page 19)[29]

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Only one trial is included in the CS: the REACT trial. No indirect comparisons and/or multiple treatment comparisons were performed.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

Only one trial is included in the CS: the REACT trial. No indirect comparisons and/or multiple treatment comparisons were performed.

4.5 Additional work on clinical effectiveness undertaken by the ERG

The company has stated in their submission (CS, Section 4.2, pages 48 and 49), that the RE2SPOND trial is not considered appropriate for the assessment of roflumilast as add-on to triple therapy in UK patients with severe COPD, chronic bronchitis and frequent exacerbations for the following reasons (see Response to the Clarification letter, Question A1):

- The patient profile of the RE2SPOND population does not reflect accurately that of the target population in this decision problem (i.e. inclusion criteria prevented demonstration that patients were uncontrolled on ICS / LABA ± LAMA, proportion of patients on triple therapy was relatively low, a very small proportion of the study population were from Western Europe)
- The RE2SPOND trial conditions do not reflect UK clinical practice (i.e. lower LABA / ICS dosing, different tablet formulation)

As reported in Section 4.1.5, we do not agree that the RE2SPOND trial is not relevant to the decision problem. We think the REACT trial and the RE2SPOND trial are similar enough to provide a pooled analyses of both trials. Unfortunately the company refused to send us the CSR of the RE2SPOND trial as part of the clarification response, and the company declined to perform a pooled analysis using data from both trials (Clarification letter, Questions A1 and A11). When the CSR of the RE2SPOND trial finally arrived (10 days before our deadline) the relevant data for the LAMA subgroup could not be found. Therefore, we can only report limited results from the RE2SPOND trial for the triple therapy population.

The RE2SPOND trial is a 52-week, phase 4, double-blind, placebo controlled trial including participants aged 40 years or older with severe/very severe chronic obstructive pulmonary disease, chronic bronchitis, two or more exacerbations and/or hospitalizations in the previous year, and receiving inhaled corticosteroid/long-acting b2-agonist with or without LAMA daily for three or more months. Participants were equally randomised to once-daily roflumilast, 500 mg (n = 1,178), or placebo (n = 1,176). Stratification was based on LAMA use and 47% of the population was on additional LAMA therapy. The results showed that the addition of roflumilast produced an 8.5% reduction in moderate or severe exacerbations but the between group difference was not statistically significant. The time to the first exacerbation event was also not different between the two groups. In conclusion, the authors state that "Roflumilast failed to statistically significantly reduce moderate and/or severe exacerbations in the overall population. Roflumilast improved lung function and reduced exacerbations in participants with frequent exacerbations and/or hospitalization history. The safety profile of roflumilast was consistent with that of previous studies."[30]

Specific results of the RE2SPOND trial compared to the REACT trial are presented in Tables 4.14 to 4.18 below.

ERG comment: As can be seen in Tables 4.14 to 4.18, the two trials are generally comparable. In fact the RE2SPOND authors themselves state that "both studies share similar methodologies and generally similar baseline patient characteristics, potentially allowing these data sets to be pooled for more robust analyses."[31] Results show that they are mostly the same; although all results seem slightly more favourable for roflumilast in the REACT trial.

Table 4.14: Differences between the REACT and RE2SPOND trials

Study design	REACT[29, 35]	RE2SPOND[30]
Participant recruitment beginning and study ending dates	April 3, 2011–May 27, 2014	September 30, 2011–January 8, 2016
Treatment	500 µg roflumilast or placebo + FDC ICS/LABA[a] (no limit to the % of participants allowed LAMA[b] treatment)	500 µg roflumilast or placebo + FDC ICS/LABA[c] (+ up to 60% of participants allowed LAMA treatment)
Fluticasone/salmeterol dose	fluticasone/salmeterol 500/50 µg or 250/50 µg (1 inhalation twice daily)	fluticasone/salmeterol 250/50 µg (1 inhalation twice daily)
Roflumilast formulation	Film-coated tablets	Uncoated tablets
Baseline exacerbation data capture	Chart documentation of moderate or severe COPD exacerbations. • Moderate exacerbations were defined as those requiring oral or parenteral corticosteroids • Severe exacerbations were defined as those requiring hospitalisation or leading to death.	One or more of the following (all requiring confirmation of COPD exacerbation diagnosis and oral or parenteral corticosteroid treatment [with or without hospitalisation or other medications]): • Note on official letterhead from primary/referring physician • Outpatient or hospital records • Investigator contact with treating physician • Pharmacy records
Treatment period exacerbation data capture	• Daily symptom diary/rescue medication logs • Participant report	• Daily EXACT-PRO/rescue medication logs • Participant report • Monthly phone calls made to each participant • OR a combination of these
Definition of the primary outcome (moderate to severe exacerbations)	• Moderate: required oral/parenteral corticosteroid treatment • Severe: resulting in hospitalisation and/or leading to death • Exacerbations occurring within 10 days were counted as one exacerbation	• Moderate: required oral/parenteral corticosteroid treatment • Severe: resulting in hospitalisation and/or leading to death • Exacerbations occurring within 10 days were counted as one exacerbation

Source: Martinez 2016 (Supplementary files)[30]

a Participants were allowed to use any commercially available fixed ICS/LABA combination at the maximum dosage approved in each country (not sponsor provided).

b Participants were classified as receiving concomitant treatment with a LAMA if they used this therapy during baseline and at least 80% of the duration of the treatment period.

c Sponsor provided fluticasone 250 µg/salmeterol 50 µg (1 inhalation twice daily) or budesonide 160 µg/formoterol 4.5 µg (2 inhalations twice daily).

d Intent-to-treat population.

COPD = chronic obstructive pulmonary disease; EXACT-PRO = EXAcerbations of Chronic Pulmonary Disease Tool – Patient-Reported Outcomes; FDC = fixed-dose combination; ICS = inhaled corticosteroid; LABA = long-acting β2-agonist; LAMA = long-acting muscarinic antagonist.

Table 4.15: Clinical characteristics for patients in the REACT and RE2SPOND trials

Study design	REACT[29, 35]		RE2SPOND[30]	
	Roflumilast (n=969)[d]	Placebo (n=966)[d]	Roflumilast (n=1178)[e]	Placebo (n=1174)[e]
Age, mean (SD), y	65 (8.4)	65 (8.4)	64.4 (8.8)	64.5 (8.4)
Male, n (%)	718 (74)	725 (75)	821 (70)	794 (68)
Smoking status, n (%)[f]				
Current	411 (42)	432 (45)	462 (39)	464 (40)
Former	558 (58)	534 (55)	716 (61)	710 (60)
COPD severity, n (%)				
Moderate	18 (2)	16 (2)	1 (<1)	0
Severe	658 (68)	677 (70)	697 (59)	720 (61)
Very Severe	291 (30)	273 (28)	474 (40)	446 (38)
% predicted pre-bronchodilator FEV1, mean (SD), L	33.3 (9.08)	33.6 (9.00)	29.87 (8.93)	29.96 (8.87)
% predicted post-bronchodi-lator FEV1, mean (SD), L	35.4 (9.25)	35.5 (8.76)	33.00 (9.04)	32.97 (8.88)
CAT total score, mean (SD)	20.4 (7.2)	19.8 (6.9)	18.0 (7.1)	18.1 (6.8)
LAMA use, n (%)	677 (70)	669 (69)	548 (47)	546 (47)
ICS/LABA therapy, n (%)				
Fluticasone propionate/salmeterol FDC	--	--	768 (65)	766 (65)
Budesonide/formoterol FDC	--	--	410 (35)	408 (35)
Moderate or severe exacerbations in previous year, n (%)				
<2	6 (<1)	4 (<1)	--	--
2	855 (88)	859 (89)	874 (74)	876 (75)
>2	103 (11)	100 (10)	291 (25)	288 (25)
3	--	--	179 (15)	180 (15)
>3	--	--	112 (10)	108 (9)
Prior hospitalization, n (%) (reference 8 for REACT)				
0	647 (67)	647 (67)	789 (67)	805 (68)
≥1	322 (33)	319 (33)	381 (32)	364 (31)

Source: Martinez 2016 (Supplementary files)[30]

--, not applicable.

[d] Intent-to-treat population.

[e] Safety population.

[f] Current smoker=the date of last cigarette smoked is ≤1 year prior to the screen visit date; former smoker=the date of last cigarette smoked is >1 year prior to the screen visit date.

CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; FDC = fixed-dose combination; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; ICS = inhaled cortico-steroid; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; SD = Standard deviation.

Table 4.16: Efficacy Results from the REACT and RE2SPOND trials

	REACT[29, 35]			RE2SPOND[30]		
	Roflumilast (n=969)	Placebo (n=966)	Roflumilast vs placebo	Roflumilast (n=1178)	Placebo (n=1174)	Roflumilast vs placebo
Moderate to severe exacerbations per participant per year (primary endpoint), rate 95% CI	0.81, 0.72-0.90	0.93, 0.84-1.02	RR, 95% CI: 0.87, 0.75-1.00 (*P*=0.0529)h	1.17, 1.06-1.28	1.27, 1.17-1.39	RR, 95% CI: 0.92, 0.81-1.04 (*P*=0.163)i
Moderate to severe exacerbations per participant per year (sensitivity analysis), rate 95% CI	0.82, 0.74-0.92	0.96, 0.87-1.06	RR, 95% CI: 0.86, 0.74-0.995 (*P*=0.0424)i	--	--	--
Severe exacerbations per participant per year, rate 95% CI	0.24, 0.20-0.28	0.32, 0.27-0.37	RR, 95% CI: 0.76, 0.60-0.95 (*P*=0.018)i	0.28, 0.23-0.33	0.29, 0.25-0.34	RR, 95% CI: 0.95, 0.75-1.19 (*P*=0.635)i
Moderate or severe or antibiotic-treated exacerbations per participant per year, rate 95% CI	1.01, 0.92-1.11	1.21, 1.12-1.31	RR, 95% CI: 0.84, 0.74-0.95 (*P*=0.005)h	1.31, 1.20-1.43	1.45, 1.34-1.57	RR, 95% CI: 0.90, 0.80-1.02 (*P*=0.088)i
Moderate or severe exacerbations in participants with a prior history of severe exacerbation/ hospitalisation, rate 95% CI	--	--	--	1.23, 1.04-1.44	1.63, 1.41-1.90	RR, 95% CI: 0.75; 0.60-0.93 (*P*=0.010)i
Severe exacerbations in participants with a prior history of hospitalisation, rate 95% CI (reference 8 for REACT)	0.39	0.60	RR, 95% CI: 0.65, 0.48-0.89 (P<0.01)i	0.47, 0.36-0.60	0.59, 0.47-0.75	RR, 95% CI: 0.79; 0.56-1.10 (P=0.1652)i
	REACT			RE2SPOND		
Time to first moderate to severe exacerbation, HR, 95% CI	0.9, 0.8-1.1 (*P*=0.22)			0.9, 0.8-1.1 (*P*=0.323)		
Change from baseline to Week 52 in postdose or predose FEV1, mean difference, 95% CIj	0.056 L, 0.038-0.073 (*P*<0.0001)			0.053 L, 0.040-0.066 (*P*<0.0001)k		
Change from baseline to Week 52 in FVC, mean difference, 95% CI	0.092 L, 0.061-0.124 (*P*<0.0001)			0.083 L, 0.055-0.111 (*P*<0.0001)k		
Change from baseline in CAT total score, mean difference, 95% CI	–0.29, –0.71 to 0.14 (*P*=0.191)			0.06, -0.29 to 0.41 (*P*=0.754)k		

Source: Martinez 2016 (Supplementary files)[30]
--, not applicable.
h Analysed using a Poisson regression model (ITT population).
i Analysed using a negative binomial regression model (ITT population).
j REACT measured postdose FEV1 and RE2SPOND measured predose FEV1.
k Least squares mean difference.
CAT = COPD Assessment Test; CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HR = hazard ratio; RR = rate ratio.

Table 4.17: Safety Results from the REACT and RE2SPOND trials

	REACT[29, 35]		RE2SPOND[30]	
	Roflumilast (n=969)[d]	**Placebo (n=966)[d]**	**Roflumilast (n=1178)[e]**	**Placebo (n=1174)[e]**
Participants discontinuing, n (%)[e]	269 (28)	192 (20)	337 (29)	254 (22)
Participants discontinuing due to AEs, n (%)[e]	82 (8)	29 (3)	138 (12)	64 (5)
Participants with TEAEs, n (%)[e]	648 (67)	572 (59)	804 (68)	758 (65)
Participants with SAEs, n (%)[e]	249 (26)	285 (30)	180 (15)	162 (14)
Deaths, n (%)[e]	17 (2)	18 (2)	30 (3)[g]	25 (2)

Source: Martinez 2016 (Supplementary files)[30]
[d] Intent-to-treat population.
[e] Safety population.
AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Table 4.18: Rate of moderate or severe exacerbations per participant per year by participant subgroup (RE2SPOND ITT population)

Subgroup	n	Roflumilast	n	Placebo	Rate Ratio (SE)	95% CI	*P value*
LAMA use							
Yes	548	1.36 (1.20, 1.53)	546	1.45 (1.29, 1.62)	0.94 (0.085)	0.79, 1.11	0.444
No	630	1.00 (0.87, 1.14)	628	1.12 (0.99, 1.27)	0.89 (0.094)	0.74, 1.07	0.221

Source: Martinez 2016 (Supplementary files)[30]
CI = confidence interval; ITT = intent-to-treat; LAMA = long-acting muscarinic antagonist; SE = standard error.

4.6 Conclusions of the clinical effectiveness section

This submission relies on one clinical trial: the REACT trial comparing roflumilast as add-on to LABA / ICS with placebo plus LABA / ICS in patients with severe COPD, all patients were allowed to use LAMA. The company has restricted the population, intervention and comparators (contrary to the NICE scope) to "Roflumilast in combination with maintenance triple therapy, LABA / LAMA / ICS" in patients who have severe COPD despite triple therapy compared with triple therapy only. This means only a subgroup of patients in the REACT trial (n=1,346 out of 1,935; i.e. 70%) are used for the submission. In addition the company uses the per protocol population, reducing the number of patients further to 1,122 (58% of the total ITT population).

As reported in Section 4.1.5 of this report, there is evidence available to compare roflumilast in combination with LABA / ICS or in combination with triple therapy to most of the comparators listed in the scope. The company could have presented results for these comparisons. It is beyond the possibilities of the ERG to perform these analyses, as this involves full data extraction of these trials, a full network meta-analysis and inclusion of these comparators in the economic model. Therefore, the ERG suggests that the committee decides whether these analyses are relevant for the decision problem; and if they are, the committee can request the company to perform these analyses before the second committee meeting.

There is also a second roflumilast trial, the RE2SPOND trial with comparable methodology and patient populations. The company considered the RE2SPOND trial not to be representative of clinical practice in the UK and therefore excluded the trial. The ERG disagrees, and believes the two trials are similar enough to provide a pooled analysis.

Results based on the REACT trial show that roflumilast has effects on moderate to severe exacerbations and severe exacerbations. However, the size of the effect depends on whether:

- the analysis is based on data from REACT trial only, or the REACT trial combined with RE2SPOND trial
- The whole population (with or without concomitant LAMA therapy) or only those on concomitant LAMA therapy.
- the ITT population is used or the per-protocol (PP) population
- the analysis uses the Poisson model or the negative binomial model.

There are pros and cons for each choice, but the company's preferred analysis (REACT only, PP and concomitant LAMA only and the negative binomial model), seems to favour roflumilast disproportionally. The ERG disagrees with two of the company's choices (REACT only and PP population instead of ITT). Regarding the concomitant LAMA subgroup, we are not certain. As explained in Section 3.1 and 3.2 of this report, the population and intervention used in the CS are not in line with the scope provided by NICE. Nevertheless, these restrictions may be regarded reasonable by the committee. Regarding the negative binomial model versus the Poisson model, the ERG accepts the company's arguments that the negative binomial regression model is considered to be more appropriate than the Poisson regression model for the analysis of REACT (see also Section 4.2.2 of this report).

Regarding the results as presented in the CS, the company has chosen for the populations and analyses that showed most favourable effects for roflumilast. Therefore, the company base-case analysis may overestimate the effectiveness of roflumilast. As presented above the company uses a rate ratio of moderate to severe exacerbations of 0.799 (95% CI 0.670 to 0.952) for roflumilast versus placebo, based on the concomitant LAMA population from the REACT trial only, the per-protocol population, and the negative binomial model. Using ITT data instead of PP data from the REACT trial results in a rate ratio for moderate to severe exacerbations of 0.871 (95% CI: 0.741 to 1.024). Alternatively, the company could have used data from the total ITT populations from the REACT and RE2SPOND trials, based on the negative binomial model analyses. This would have resulted in a rate ratio of moderate to severe exacerbations of 0.90 (95% CI 0.82 to 0.99). The ERG prefers an analysis based on the concomitant LAMA ITT populations from the REACT and RE2SPOND trials combined, using the negative binomial model. This results in a rate ratio of moderate to severe exacerbations of 0.90 (95% CI 0.80 to 1.02).

Similarly, the company uses a rate ratio for severe exacerbations of 0.659 (95% CI 0.497 to 0.872) p=0.0035). Using ITT data instead of PP data from the REACT trial results in a rate ratio for severe exacerbations of 0.767 (95% CI: 0.595 to 0.989). An alternative analysis using data from the total ITT populations from the REACT and RE2SPOND trials, based on the negative binomial model analyses would have resulted in a rate ratio of 0.85 (95% CI 0.68 to 1.06). The ERG prefers an analysis based on the concomitant LAMA ITT populations from the REACT and RE2SPOND trials combined, using the negative binomial model. However, it is not possible for the ERG to calculate the rate ratio because we do not have these data from the RE2SPOND trial.

Adverse events were reported by 67% of the roflumilast group and 59% of the placebo group, with serious adverse events reported by 26% and 30% respectively. More people withdrew because of adverse events in the roflumilast group (11% compared with 5%). The most frequently reported adverse events were COPD exacerbations (15% with roflumilast compared with 19% with placebo), diarrhoea (10% compared with 4% respectively), weight loss (9% compared with 3% respectively) and nausea (6% compared with 2% respectively). Mortality rates were the same in both groups (2%); as were major adverse cardiovascular events (2% in both groups). There was no increase in the incidence of pneumonia with roflumilast.

5. COST EFFECTIVENESS

5.1 ERG comment on company's review of cost effectiveness evidence

This section pertains mainly to the review of cost effectiveness analysis studies. However, the search section (Section 5.1.1) also contains summaries and critiques of other searches related to cost effectiveness presented in the company submission. Therefore, Section 5.1.1 includes searches for the cost effectiveness analysis review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation. The summary and critique for the review of the latter two parts will be elaborated on in the next subsections.

The objective of the cost effectiveness review in the CS was to identify and review evidence from economic analyses relating to the use of roflumilast as an add-on treatment to triple therapy and/or other relevant comparator therapies for the treatment of adults with severe and very severe COPD (FEV1 post-bronchodilator ≤ 50% FEV1 predicted) associated with chronic bronchitis and a history of frequent exacerbations (≥2 exacerbations in the prior 12 months) despite triple therapy with LAMA / LABA / ICS.

5.1.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness presented in the company submission.

Searches for cost effectiveness analysis review

A systematic review was undertaken on 7 May 2015 and updated on 15 July 2016 to identify and summarise all studies that reported cost effectiveness of roflumilast as an add-on to triple therapy. In the original review, searches were carried out in EMBASE, MEDLINE, MEDLINE Epub ahead of print and In-Process, Econlit and NHS EED. In the update search, NHS EED was not searched as the updating of this database had ceased. EMBASE, EconLit and MEDLINE databases were searched via the Ovid platform and NHS EED was searched from the Centre for Reviews and Dissemination website. Searches were limited to English language only in EMBASE and MEDLINE databases.

ERG comment: Search strategies for the database searches were provided in Appendix 7 of the Appendices[15] and were well reported. These meet the requirements detailed in the NICE guide to the methods of technology appraisal.[16]

For the most part, database searches were clearly structured and used a combination of index terms, free text and synonyms appropriate to the resource searched. A study design filter was applied but it was not clear whether this was a validated study design filter as it was not referenced. However, the ERG felt that an appropriate combination of controlled vocabulary terms, free text and synonyms had been used to identify cost effectiveness studies.

The ERG was concerned about the language bias of restricting searches to English language only as this is not in line with current best practice.[36-40] The company's response was that an English language limit had been applied as the remit was to inform a cost effectiveness model for the population of England and Wales and therefore "non-English language publications are highly unlikely to be relevant to the decision problem, particularly when considering the wealth of English language publications available in the COPD literature."[14] However, this appears to be contrary to the CS which specifically states in Section 5.1 that "search strategies were designed to capture data from eight countries: UK, US, Canada, Germany, France, Italy, Spain and Australia."[1] The ERG also believes that using a limit because there is a "wealth" of information is not acceptable systematic review practice which seeks "to collate all evidence that fits pre-specified eligibility criteria in order to address a specific research question."[36]

Measurement and valuation of health effects
A systematic review was undertaken in May 2015 and updated in July 2016 to identify the humanistic burden of disease in severe and very severe COPD patients. Searches were carried out in EMBASE, MEDLINE and MEDLINE Epub ahead of print and In-Process. These were reported in Section 5.4 and Appendix 9 of the CS.[1, 15]

For the most part, database searches were clearly structured and used a combination of index terms, free text and synonyms appropriate to the resource searched. A study design filter was applied but it was not clear whether this was a validated study design filter as it was not referenced. However, the ERG felt that an appropriate combination of controlled vocabulary terms, free text and synonyms had been used to identify health related quality of life studies. However, the same restrictions to the use of an English language limit also apply here.

Cost and healthcare resource identification, measurement and valuation
The cost effectiveness searches reported in Section 5.1 and Appendix 7 of the CS were used to inform this section.[1, 15]

ERG comment: The study design filters were not referenced and did not appear to be published objectively derived filters. However, the filters contained a combination of controlled vocabulary terms and free text terms to capture literature referring to costs, economics and utilisation which the ERG felt was appropriate. The same restrictions to the use of an English language restriction also apply here.

5.1.2 Inclusion/exclusion criteria used in the study selection

Table 5.1 presents an overview of inclusion criteria used for the review.

Table 5.1: Inclusion and exclusion criteria used for the cost effectiveness review

Criteria	Inclusion
Patients	Severe or very severe COPD (defined as FEV1 ≤ 50% FEV1 predicted level, corresponding to pre-2013 GOLD report stages III and IV)
Interventions	Roflumilast given as add-on to triple therapy
Comparators	• LAMA / LABA • LABA / ICS • LABA / ICS / LAMA • LABA / ICS / Methylxanthines • LABA / LAMA / Methylxanthines • LABA / ICS / LAMA / Methylxanthines • LABA / ICS / placebo • LAMA / LABA/ ICS / placebo
Outcomes	• Cost utility analyses, • Cost effectiveness analyses, • Cost benefit analyses or • Cost minimisation analyses
Geography	United Kingdom, United States, Canada, Germany, France, Italy, Spain and Australia
Language	English Only
Date restriction	2004 and onwards

Source: Based on Table 22 of the CS[1]
CS = company submission; COPD = chronic obstructive pulmonary disease; FEV1 = forced expiratory volume in 1 second; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroid; LABA = Long acting beta-adrenoceptor agonist; LAMA = Long acting muscarinic receptor antagonist.

ERG comment: In this submission, stricter inclusion criteria were applied compared to the previous company submission of roflumilast (TA244), in the sense that the intervention of this submission was limited to the "*roflumilast as an add-on to triple therapy*" and the list of comparators was limited to the treatments that were used for severe and very severe COPD patients. The ERG thinks that some relevant studies might have been missed, which might have provided useful information on the modelling methodology, inputs and cost effectiveness results.

In a similar manner, the ERG has the opinion that some of the relevant utility or resource use studies might have been missed because of the applied restrictions in terms of geography. Particularly, the ERG could not understand the reason behind the restriction of non-native English spoken countries to the following four: France, Germany, Italy and Spain. Due to this restriction, relevant studies from other countries (e.g. Netherlands, Sweden, etc.), which might have provided valuable insights in terms of cost effectiveness analysis, might have been missed.

The ERG identified some reporting errors, namely in the PRISMA diagram (Figure 6, p94 in CS) and in the date limits for the HRQoL search strategy (Appendix 9 in CS, p62). At the request of the ERG, the company corrected these errors in their response to the clarification letter.[14]

5.1.3 Included/excluded studies in the cost effectiveness review

In the CS[1], it was mentioned that only one study was identified that met the inclusion criteria. In Hertel et al. 2012[41], a Markov model was developed to estimate the cost effectiveness of various combinations of LAMA / LABA / ICS and roflumilast in two fully incremental analyses that were conducted separately for ICS tolerant and ICS intolerant patients with severe COPD in the UK.

The model included five Markov states: severe COPD, first-line regimen; severe COPD, second-line regimen; very severe COPD, first-line regimen; very severe COPD, second-line regimen; and death. The severe and very severe health states were defined according to the GOLD criteria (severe COPD state when 30% FEV1 predicted < FEV1 ≤ 50% FEV1 predicted and very severe COPD when FEV1 ≤ 30% FEV1 predicted). The average age of patients in the cohort at the start of the model was 64 years. The baseline characteristics of the modelled cohort were obtained from the pooled analysis of the M2–124 and M2–125 clinical trials of roflumilast.[42]

For the ICS tolerant patients, roflumilast as an add-on to the triple therapy (roflumilast / LAMA / LABA / ICS) resulted in 5.51 total QALYs and £23,230 total costs, whereas the triple therapy only (LAMA / LABA / ICS) resulted in 5.48 total QALYs and £22,816 total costs. The ICER (roflumilast / LAMA / LABA / ICS vs LAMA / LABA / ICS) according to these figures was £16,566 per QALY gained.

For the ICS intolerant patients, roflumilast as an add-on to the LAMA / LABA combination therapy (roflumilast / LAMA / LABA) resulted in 5.22 total QALYs and £22,222 total costs, whereas the LAMA / LABA combination therapy only (LAMA / LABA) resulted in 5.19 total QALYs and £21,814 total costs. The ICER (roflumilast / LAMA / LABA vs LAMA / LABA) according to these figures was £13,764 per QALY gained.

A quality assessment of Hertel et al. 2012[41] was performed using Drummond and Jefferson (1996) checklist[43] and provided in Appendix 8 of the CS[15]. In the CS, it was deemed that the model was clear and transparent in terms of study design. The company considered that the research question, perspective taken, comparators chosen and the form of the economic evaluation chosen were clearly stated and justified and the details relating to data (primary outcomes, resources and costs) used in the model, the model choice and key parameters used for the model were clearly explained. Even though the analysis and interpretation of the results were considered as appropriate, the company thought the details of the statistical tests and confidence intervals for stochastic data (e.g. type of distributions

assigned to key model parameters) could have been clearer. Overall, the model was deemed as reliable but lacking transparency in the presentation of some analyses and results.

ERG comment: The ERG noted that the list of excluded studies was missing in the CS, however at the request of the ERG, it was provided in the Appendix of the response to the clarification letter.[14]

5.1.4 Conclusions of the cost effectiveness review

Besides the summary and the quality assessment of the Hertel et al. 2012[41] study, no specific conclusions from the economic review were provided in the CS.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

Table 5.2 presents a summary of the de novo economic model developed by the company.

Table 5.2: Summary of the company submission economic evaluation

	Approach	Source/Justification	Signpost (location in CS)
Model	A cohort Markov (state transition) model was developed with monthly cycles. Time horizon in the base-case was lifetime. The average age of the cohort was 64.7 years. Patients entering the model were considered to be severe COPD patients suffering from at least 2 moderate to severe exacerbations last year. Baseline patient characteristics were taken from the REACT trial.[29]		Section 5.2. (p. 98)
States and events	Three health states were defined: severe COPD, very severe COPD and death. Severe COPD is defined as having a post-bronchodilator FEV1 between 30% and 50% FEV1 predicted, and very severe COPD as below 30% FEV1 predicted. Patients in severe COPD can either stay in the severe COPD state, or can progress to very severe COPD or can die in the next cycle. Patients in very severe COPD can either stay in very severe COPD or can die in the next cycle. Death is an absorbing state. In the base-case, all patients entered the model in the severe COPD state. Patients in both severe and very severe COPD states are at risk of moderate and severe exacerbations. Exacerbations lead to additional costs, decrease in utilities and additional mortality	In the CS it was stated that the model structure and the health states in this submission were considered similar to the previous submission (NICE TA 244)[44], Samyshkin et al. 2014[45] and NICE COPD clinical guideline[7] .	Section 5.2 (p. 98)
Comparators	LAMA / LABA / ICS	Even though there are more comparators in the NICE scope[21], the company positioned the use of roflumilast only as an add-on to the triple therapy (LAMA / LABA / ICS), and hence only the triple therapy (LAMA / LABA / ICS) was considered as a comparator	Section 5.2 (p. 100)
Natural History	COPD is a progressive disease and a patient in the severe COPD state is at risk of progression to very severe COPD state. This transition probability was calculated based on the ratio of cohort's FEV1 to the predicted FEV1 value of the general population and estimated FEV1 decline in COPD patients		Section 5.3 (p. 101)

	Approach	Source/Justification	Signpost (location in CS)
Treatment effectiveness	Treatment influences the moderate and severe exacerbation rates. Through the differences in moderate and severe exacerbation rates, the utilities, costs and mortality differ between the treatment (Roflumilast / LAMA / LABA / ICS) and control (LAMA / LABA / ICS) arms.	The moderate and severe exacerbation rates were predicted based on regression analyses with only treatment and COPD severity as factors, performed on data from the REACT trial	Section 5.3 (p. 103)
Adverse events	The model includes pneumonia (the most common serious adverse event) and three most common adverse events of any grade (diarrhoea, weight decrease and nausea) observed in the REACT trial. The cost and disutility effects of these adverse events were incorporated in the first cycle.		Section 5.4 (p. 119)
Health related QoL	The model uses COPD health state utilities from Rutten-van Mölken et al. 2006[46] and temporary disutilities due to moderate and severe exacerbations from Rutten-van Mölken et al. 2009[47]. All adverse event disutilites were considered to be the same as the disutility of a severe exacerbation.	In the CS, it was mentioned that the health state utility estimates from Rutten-van Mölken et al. 2006[46] were considered the most appropriate because they were derived from United Kingdom general population preference weights. For exacerbations, values from Rutten-van Mölken et al. 2009[47] were used.	Section 5.4 (p. 120)
Resource utilisation and costs	Treatment cost (e.g. technology acquisition costs of LAMA / LABA / ICS and Roflumilast), COPD maintenance costs for severe and very severe COPD health states, COPD moderate/severe exacerbation costs and unit costs for adverse events.	Based on literature and United Kingdom reference costs.	Section 5.5 (p. 122)
Discount rates	A 3.5% discount rate was used for both costs and effects.	According to NICE reference case	Section 5.3 (p. 99)
Sensitivity analysis	One-way deterministic sensitivity analysis, scenario analyses and probabilistic sensitivity analysis	Ranges/scenarios based on observed confidence intervals and different assumptions.	Section 5.8 (p. 152)

COPD = chronic obstructive pulmonary disease; FEV1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; LABA = Long acting beta-adrenoceptor agonist; LAMA = Long acting muscarinic receptor antagonist; NICE = The National Institute for Health and Care Excellence; TA = Technology Appraisal.

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.3: Comparison of the CS model with the NICE reference case

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether de novo evaluation meets requirements of NICE reference case
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	Partly	Only LAMA / LABA / ICS was considered as a comparator. The company positioned the use of roflumilast only as an add-on treatment to LAMA / LABA / ICS. In the scope, other comparators were listed.
Type of economic evaluation	Cost effectiveness analysis	Yes	
Perspective on costs	NHS and PSS	Yes	
Perspective on outcomes	All health effects on individuals	Yes	
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	Time horizon is considered to be lifetime.
Synthesis of evidence in outcomes	Systematic review	Yes	Meta-analysis was not used, all effectiveness data used in the model were based on single (REACT) trial.
Measure of health effects	QALYs Life-years	Yes	
Source of data for measurement HRQOL	Reported directly by patients and/or carers.	Yes/partly	Health state utility data was based on a sample of 1235 patients, using EQ-5D questionnaire across 13 countries. The decrement due to exacerbations were based on valuations of COPD-specific health profiles by a sample of the Dutch general public (N=239).
Source of preference data for valuation of changes in HRQOL	Sample of public	Yes/partly	For health states: UK tariff was applied to the EQ5D data obtained from sampled 1235 patients across 13 countries. For exacerbations: Dutch time trade off tariff was applied.
Discount rate	Annual rate of 3.5% on costs and health effects	Yes	
Equity weighting	No special weighting	Yes	
Sensitivity analysis	Probabilistic sensitivity analysis	Yes	In addition, univariate sensitivity and scenario analyses were performed.

COPD = chronic obstructive pulmonary disease; EQ-5D = European Quality of Life-5 Dimensions; FEV1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; LABA = Long acting beta-adrenoceptor agonist; LAMA = Long acting muscarinic receptor antagonist; NICE = The National Institute for Health and Care Excellence; QALYs = Quality adjusted life years.

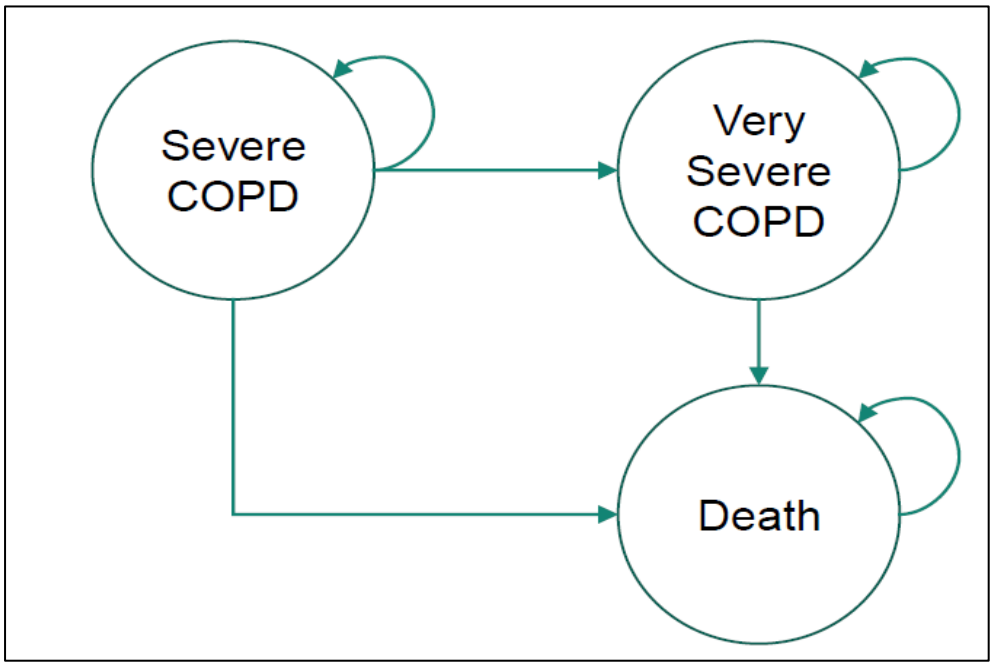
5.2.2 Model structure

In this submission, a cohort state transition (Markov) model with monthly cycles was developed. The model comprises three health states: severe COPD, very severe COPD and death.

The COPD states in the model were based on the severity classifications defined by the GOLD lung function criteria using the ratio of post-bronchodilator FEV1 to the FEV1 predicted value based on general population (age, gender and height specific). Severe COPD patients are those whose FEV1 was between 50% and 30% FEV1 predicted, whereas very severe COPD patients are those whose value was below 30% FEV1 predicted.[48]

The model structure is given in Figure 5.1 below. Patients in the severe COPD state can either stay in that state, or progress to the very severe state or die in the next cycle. Patients in the very severe COPD state can either stay in that state or die in the next cycle. Death is an absorbing state. In the base-case, all patients enter the model in the severe COPD state. Patients in both severe and very severe COPD states are at risk of moderate exacerbations (i.e. can be treated with systemic glucocorticosteroids without hospitalisation) and severe exacerbations (i.e. lead to hospitalisation/death). The exacerbation risks differ by health state, by treatment and by exacerbation severity. Exacerbations lead to additional costs, a temporary decrease in quality of life and additional mortality (if severe).

Figure 5.1: Model diagram



Source: Based on Figure 7 in the CS[1].

ERG comment: The model structure in the CS excluded many important aspects of COPD progression as listed below.

Firstly, the health states in the model were only based on GOLD stages that were distinguished from each other by FEV1 percentage predicted value thresholds only. However, this classification is insensitive to the heterogeneity of the patients (i.e. a severe patient with a FEV1 percentage predicted value of 40% with symptoms might have a different prognosis compared to a patient with the same FEV1 percentage predicted value without symptoms) as reflected by the GOLD 2011 classification.[49]

Secondly, in the model it was assumed that there was no effect of exacerbations on FEV1, no effect of previous exacerbation history on future exacerbation risk, and no effect of baseline characteristics like

race, smoking status, BMI and presence of other comorbidities on disease progression and exacerbation rates. However, in the literature it was found that an exacerbation has an impact on the FEV1 value of the patient, that previous exacerbation history is an important predictor of future exacerbation risk and that the baseline characteristics impact the prognosis of COPD significantly.[50]

In the response to the clarification letter document, the company acknowledged that these assumptions might conflict with the literature on COPD prognosis, however they were not incorporated into the model due to the lack of time. Even though estimating the direction of bias without a formal analysis would be speculative, the ERG does not think that not incorporating these assumptions into the model would be in favour of the intervention arm.

As a final point, in the model, discontinuing roflumilast was not allowed. However, in clinical practice, a patient may discontinue roflumilast due to several reasons (adverse events or lack of efficacy). In the clarification letter, the ERG asked the company to incorporate the discontinuation events in the model. In their response to the clarification letter[14], the company mentioned that they conducted two additional analyses regarding roflumilast discontinuation. In both of these analyses, it was mentioned that the overall rate of discontinuation from the full ITT population was used as a proxy and it was assumed that all roflumilast discontinuation took place in the first cycle. According to the company's response, the first analysis incorporated only the cost consequences of roflumilast discontinuation (i.e. after roflumilast discontinuation no drug costs for roflumilast was incurred but roflumilast add-on treatment effect remained unchanged), and therefore resulted in a lower ICER compared to the base-case (£16,869 per QALY gained compared to the £18,774 per QALY gained in the base-case). In the second analysis, both cost and effect consequences of roflumilast discontinuation were incorporated (i.e. after roflumilast discontinuation, no drug costs for roflumilast was incurred and the roflumilast add-on treatment effect was changed to the placebo add-on treatment effect), leading to a slight increase in ICER compared to the base-case (£18,917 per QALY gained compared to the £18,774 per QALY gained in the base-case). In the response to the clarification letter,[14] the details of the model input data used were missing and the ERG could not trace these calculations in the resubmitted electronic model. Therefore, the ERG cannot comment on the reliability of the results of these additional analyses.

5.2.3 Population

The cost effectiveness analysis is concerned with adult patients with (very) severe COPD (FEV1 ≤50% FEV1 predicted) associated with chronic bronchitis and a history of frequent exacerbations (≥ 2 moderate or severe COPD exacerbations within the previous year) despite triple therapy with LAMA / LABA / ICS. The analysis used the data from the REACT trial as the main source of evidence. In the REACT trial, roflumilast / LABA / ICS ± LAMA was compared with LABA / ICS ± LAMA. In the model, only the patients who received concomitant LAMA were considered (roflumilast / LAMA / LABA / ICS vs LAMA / LABA / ICS) in line with the decision problem as defined by the company. This concomitant LAMA subpopulation approximately comprised 69% of the REACT trial participants (ITT: 677/969 patients in the roflumilast arm and 669/966 patients in the comparator arm; PP: 565/810 patients in the roflumilast arm and 557/823 patients in the comparator arm).

The analyses for the model input in the cost effectiveness part were based on the PP population. In the CS, it was mentioned that a total of 312 patients were excluded from the ITT population because of at least one major protocol deviation (e.g. post-bronchodilator FEV1 > 50% FEV1 predicted at visit zero, not pre-treated with LABA / ICS for at least 12 months, less than two documented moderate or severe exacerbations within one year prior to visit zero, total cough and sputum score < 14 during the last week prior to randomisation). The base-case population characteristics used in the electronic model are given in Table 5.4 below (based on patients who received either roflumilast or placebo treatment at least once in the ITT population).

Table 5.4: Baseline characteristics

Patient characteristic	Baseline value	Source
Age (years)	64.7	REACT trial[29]
Proportion male	74.60%	REACT trial[29]
Mean height (cm, males)	172.74	REACT trial (Data on file)
Mean height (cm, females)	161.67	REACT trial (Data on file)
Source: Based on Figure 7 in the CS[1]		

ERG comment: In the CS, there was no information on whether the baseline characteristics of the patient population in the REACT trial were reflective of patients in UK clinical practice, for whom roflumilast was indicated (i.e. patients with severe to very severe COPD and with two or more moderate or severe COPD exacerbations within the previous year). Therefore, in the clarification letter[14], the ERG asked for a comparison of baseline characteristics of the REACT trial with those of the relevant UK population in clinical practice. In their response to the clarification letter[14], the company provided a comparison of the baseline characteristics from the REACT trial with those from three recently published observational studies, namely Punekar et al. 2014[51], McGarvey et al. 2015[52] and Haughney et al. 2014[53], given in Table 5.5 below.

Table 5.5: Baseline characteristics of the REACT trial and three observational studies

Baseline characteristic	Baseline value from REACT	Punekar et al 2014[51]	McGarvey et al 2015[52]	Haughney et al, 2014[53]
COPD severity and exacerbation frequency	Severe COPD patients; ≥ 2 moderate-severe exacerbations	≥ 2 moderate-severe exacerbations	≥ 2 moderate-severe exacerbations	GOLD staged C or D (based on 2011 criteria)
Age, (years)	64.70	69.44 (n= 13,351)	NA (n=2,062)	70.2 (n=2820)
Male (%)	74.60%	48.83%	45.2%	53.2%
Current smokers (%)	43.6%	31.26%	38.4%	36.3%
Body mass index, kg/m2	26.52	26.82	NA	26.5
Charlson comorbidity index	NA	2.58	NA	NA
Source: Based on response to the clarification letter document[14], p18. COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; NA = Not available				

As it can be seen in Table 5.5, the average age of the patients from the REACT trial was slightly lower than those from the observational studies. Also, there were more male patients and slightly more smokers in the REACT trial compared to the observational studies.

Furthermore, in the CS, the baseline characteristics used in the base-case analysis belonged to the full ITT population of the REACT trial, including patients with and without concomitant LAMA treatment. This is inconsistent with the exacerbation rates used in the base-case analysis, as they were based on

the subgroup of patients who had received concomitant LAMA treatment in the REACT trial. Therefore, the ERG asked the company the baseline characteristics of the concomitant LAMA subgroup of the REACT trial, which was provided by the company as in Table 5.6 below.

Table 5.6: Baseline characteristics of the concomitant LAMA subgroup

Patient characteristic	Baseline value
Age (years)	65.0
Proportion male	74.50%
Mean height (cm, males)	170.6
Mean height (cm, females)	160
Source: Based on response to the clarification letter document[14], p18.	

The ERG will use the baseline characteristics provided in Table 5.6 in the exploratory analyses conducted in Section 5.3.

5.2.4 Interventions and comparators

In the European Medicines Agency (EMA) summary of product characteristics, roflumilast is indicated for "maintenance treatment of severe chronic obstructive pulmonary disease (COPD) (FEV1 post-bronchodilator less than 50% FEV1 predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add-on to bronchodilator treatment".[54] Roflumilast is administered orally at a recommended dose of 500 micrograms (one tablet) once daily.

The company positioned roflumilast only as an add-on to triple therapy (roflumilast / LAMA / LABA / ICS) in severe and very severe COPD patients and therefore it is compared only against triple therapy (LAMA / LABA / ICS). Other comparators as listed in the NICE scope are not included to the cost effectiveness analysis.

ERG comment: Similar to the comparators in the clinical effectiveness section, the company considered only the triple therapy as a comparator and all the other comparators mentioned in the scope were considered irrelevant. In line with the critique in Section 3.3, the ERG does not agree with the company on the exclusion of theophylline as a comparator in the cost effectiveness analysis and holds the opinion that the exclusion of other comparators should be considered based on the committee's judgement on the restriction of the indicated population of roflumilast for adults with severe COPD associated with frequent exacerbations despite triple therapy.

5.2.5 Perspective, time horizon and discounting

In the cost effectiveness analysis, a lifetime horizon was used. The analysis adopted the perspective of the NHS/PPS and a discount rate of 3.5% was applied for both costs and effects.

ERG comment: The ERG has no specific comments on these choices for perspective, time horizon and the discount rates. In the electronic model, half cycle corrections were not applied, arguing short cycle length. The ERG considers that half cycle corrections still should have been applied, therefore half cycle correction will be incorporated in the ERG exploratory analyses in Section 5.3.

5.2.6 Treatment effectiveness and extrapolation

Disease progression

COPD is a progressive disease. Hence, once a patient is in a more severe state, there is no possibility that the patient can reverse this transition back to a less severe health state.

As explained in Section 5.2.3, the population of interest for roflumilast as an add-on therapy is severe (30% FEV1 predicted < FEV1 ≤ 50% FEV1 predicted) and very severe (FEV1 ≤ 30% FEV1 predicted) COPD patients. Severe and very severe COPD states were assumed to differ in terms of resource use, utility and mortality risks. The patients who are in the severe health state can progress to the very severe health state at any cycle. This progression probability is calculated from the predicted FEV1 values for the general population and the estimated FEV1 decline in COPD patients.

Predicted FEV1 values for the general population

The ratio of a patient's FEV1 value to the corresponding FEV1 predicted value (based on general population) is used in COPD health state categorisations. The general population FEV1 predicted values are calculated from the two reference equations below, taken from (Crapo et al. 1981[55]), which was a study of 251 healthy non-smoking males and females.

$$\text{FEV1(males, in litres)} = (0.0414 \times \text{height}) - (0.0244 \times \text{age}) - 2.190 \quad (1)$$

$$\text{FEV1(females, in litres)} = (0.0342 \times \text{height}) - (0.0255 \times \text{age}) - 1.578 \quad (2)$$

In the CS, it was mentioned that at baseline, FEV1 predicted values for males and females were 3.38 and 2.3 litres, respectively, derived from the base-case population characteristics in Table 5.4.

Transition probability from the severe COPD state to the very severe COPD state

For the calculation of the transition probability from 'severe' to 'very severe', first, it was assumed that the FEV1 of a patient with COPD declines at a rate of 52 ml per year. This value was taken from the Lung Health Study[56], in which the lung functioning of mild to moderate COPD patients (50% FEV1 predicted < FEV1 < 90% FEV1 predicted) were followed up for five years. Secondly, in the base-case, it was assumed that at baseline, the FEV1 of a severe COPD patient was always 40% FEV1 predicted (i.e. midpoint of the upper and lower percentage FEV1 predicted thresholds that define the severe COPD state).

Based on these assumptions above and the base-case population characteristics in Table 5.4, the average time (y_M) it takes until a male patient, who is in the 'severe' state at base line, enters to the 'very severe' state, or in other words, reaches the threshold 30% FEV1 predicted value, can be found from the solution of the linear equation (3) below:

- For Males: $((0.0414 \times \text{height\_males}) - (0.0244 \times (\text{age\_males} + y\_M)) - 2.190) \times 0.3 = ((0.0414 \times \text{height\_males}) - (0.0244 \times \text{age\_males}) - 2.190) \times 0.4 - 0.052 \times y\_M$ (3)

Similarly, the average time (y_F) it takes until a female patient enters the 'very severe' state can be found from the solution of the linear equation (4) below:

- For Females: ((0.0342 × height_females) – (0.0255 × (age_females + y_F)) – 1.578) × 0.3 = ((0.0342 × height_females) – (0.0255 × age_females) – 1.578) × 0.4 – 0.052 × y_F (4)

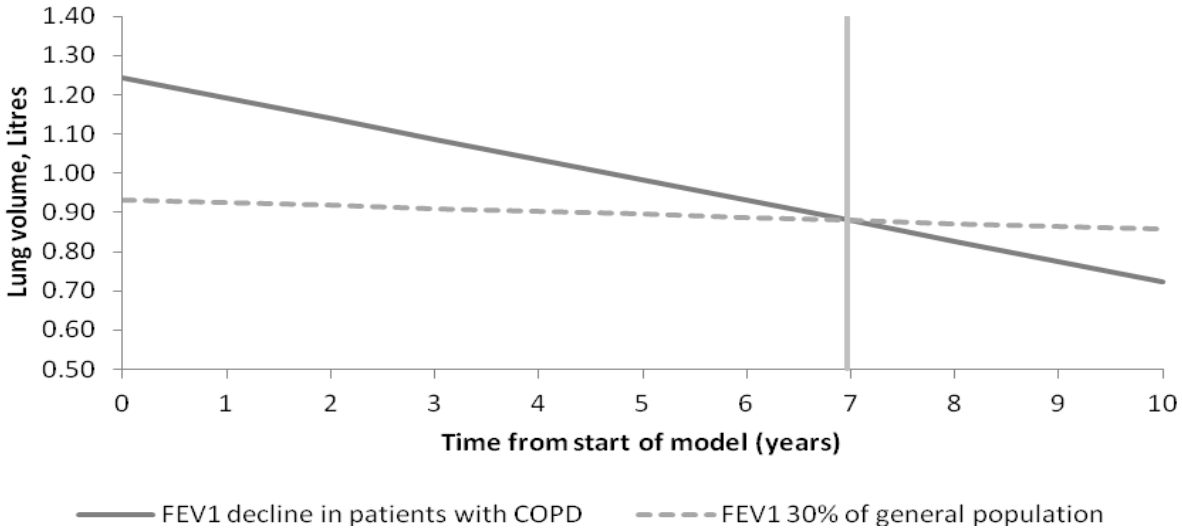
In each of the equation 3 and equation 4 above, the left-hand side represents the 30% of the FEV1 predicted value of a non-COPD cohort with baseline height values as in the Table 5.4, at the age of "64.7+ y_M" for males and at the age of "64.7+y_F" for females, calculated from equations (1) and (2) respectively. On the contrary, the right-hand side represents the FEV1 value of a severe COPD patient after y_M or y_F years, whose FEV1 percentage predicted value was 40% at baseline, for male or female patients, respectively.

Solving the equations given in (3) and (4), when height_males=172.74, height_females=161.67 and age_males = age_females = 64.7, yields the average time to 'very severe' for males, y_M=90.85 months, and for females, y_F=62.27 months.

After y_M and y_F are calculated, in the electronic model, the average time to the very severe COPD state for all patients can be found by taking the weighted average of y_M and y_F, according to the male proportion percentage (74.6%) from the REACT trial, as given in Table 5.4. Finally, the monthly transition probability from 'severe' to 'very severe' is derived by taking the reciprocal of this weighted average time, assuming an underlying geometric distribution, yielding a monthly transition probability of 1.196%.

In Figure 5.2, the mechanism behind the calculation of the average time to very severe COPD state is depicted. The dashed line corresponds to the left-hand side (30% of the FEV1 predicted value of general population) and the solid line represents the right-hand side (FEV1 value decline of a severe COPD patient) in the equations (3) and (4). The year in which the dashed and the solid lines intersect is the average time to the very severe COPD state.

Figure 5.2: Calculation of the average time to very severe COPD state.



Source: Based on Figure 8 in the CS[1].

ERG comment: In the base-case, reference equations used to translate the FEV1 value of a patient to that patients' percentage FEV1 predicted value dates back to 1981.[55] The ERG suggested replacing these equations with equations from a more recent study (e.g. Hankinson et al. 1999[57]). In their response

to the clarification letter[14], the company stated that they performed an analysis based on the reference equations in Hankinson et al. 1999[57], assuming a population consisting of 95% Caucasians and 5% African Americans. According to the company, the analysis resulted in a very similar ICER of £18,875 per QALY gained compared to the base-case ICER of £18,774, however the details of the analysis (e.g. assumptions around the sojourn times) lacked clarity and the calculations could not be traced in the electronic model. Therefore, the ERG cannot comment on the reliability of the results of these additional analyses.

In addition, in the CS, the annual FEV1 decline for COPD patients was assumed to be 52 ml per year, which was taken from the Lung Health Study.[56] However, different studies in the literature (e.g. Decramer and Cooper, 2010[58]) suggested a piecewise linear deterioration of FEV1 instead of a linear deterioration and estimated an annual decrease of 38 and 23 ml per year for severe and very severe COPD patients from UPLIFT trial. The ERG considers these COPD state specific estimates to be more plausible than the annual decline used in the base-case, which was the same for all COPD states, therefore the 38 ml decline for severe COPD patients from Decramer and Cooper, 2010[58] will be used in the ERG exploratory analyses in Section 5.3.

In the model, it was assumed that the starting value of all patients' percentage FEV1 predicted value was 40%, which is the midpoint of 30% and 50%. The ERG holds the opinion that the company should have used the average percentage FEV1 predicted value of the severe COPD patients from the REACT trial. Therefore, the ERG requested to provide this average value from the company, however this value was not provided in the company's response to the clarification letter.[14]

Lung function improvement (only in selected scenario analyses)
In the CS[1], it was mentioned that roflumilast / LAMA / LABA / ICS treatment resulted in a 56ml (95% CI: 38-73) improvement in post-bronchodilator FEV1 over 52 weeks compared to the patients treated with LAMA / LABA / ICS. In the base-case analysis, this improvement was not taken into account, however in some of the scenario analyses, this lung function improvement was incorporated and the transition probability from the severe COPD state to the very severe COPD state was derived accordingly.

Exacerbations
In the model, in each cycle, patients can experience moderate or severe exacerbations. Moderate exacerbations are defined as those that require treatment with oral or parenteral corticosteroids whilst severe exacerbations are defined as those that cause hospital admission or lead to death. Different rates for moderate and severe exacerbations are applied dependent on patients' COPD health state and treatment (roflumilast / LAMA / LABA / ICS or LAMA / LABA / ICS).

Prediction of exacerbation rates
For the model, the moderate and severe exacerbation rates were estimated separately using negative binomial regression analyses conducted on data from the REACT study. Data from the PP population was used. Two approaches were considered in the estimation of exacerbation rates.

The first approach, used in the base-case, controlled for COPD severity and treatment arm and focused on patients with concomitant LAMA use only (roflumilast / LAMA / LABA / ICS or LAMA / LABA / ICS). The RRs, coefficients and 95% CIs for all covariates included in this analysis for both moderate and severe exacerbations are detailed in Table 5.7 below:

Table 5.7: Moderate and severe exacerbation negative binomial risk models (concomitant LAMA use only)

Moderate Exacerbations	Rate ratio*	Coefficient	Lower 95% CI	Upper 95% CI
Intercept	-	-0.836	-1.309	-0.362
Roflumilast use	0.887	-0.120	-0.324	0.083
Very severe COPD	1.579	0.457	-0.018	0.933
Severe Exacerbations	**Rate ratio***	**Coefficient**	**Lower 95% CI**	**Upper 95% CI**
Intercept	-	-1.743	-2.476	-1.011
Roflumilast use	0.656	-0.422	-0.702	-0.142
Very severe COPD	2.351	0.855	0.116	1.594

Source: Based on Table 27 and Table 28 in the CS[1]
*Rate ratio = exp(coefficient); rate ratio < 1 represents a favourable outcome for reference category.

In the second approach, all patients in the PP population (including triple therapy, roflumilast plus triple therapy, LABA / ICS and roflumilast / LABA / ICS) are included and the use of concomitant LAMA is adjusted for though a covariate, along with the severity of the COPD and the treatment. The RRs, coefficients and 95% CIs for all covariates included in this analysis for both moderate and severe exacerbations are detailed in Table 5.8 below:

Table 5.8: Moderate and severe exacerbation negative binomial risk models (LAMA use as a covariate)

Moderate Exacerbations	Rate ratio*	Coefficient	Lower 95% CI	Upper 95% CI
Intercept	-	-1.098	-1.540	-0.656
Roflumilast use	0.861	-0.150	-0.326	0.027
Very severe COPD	1.519	0.418	-0.002	0.838
LAMA use	1.369	0.314	0.100	0.510
Severe Exacerbations	**Rate ratio***	**Coefficient**	**Lower 95% CI**	**Upper 95% CI**
Intercept	-	-2.210	-2.859	-1.561
Roflumilast use	0.657	-0.420	-0.672	-0.168
Very severe COPD	1.726	0.546	-0.066	1.159
LAMA use	2.151	0.766	0.466	1.065

Source: Based on Table 29 and Table 30 in the CS[1]
*Rate ratio = exp(coefficient); rate ratio < 1 represents a favourable outcome for reference category.
COPD = chronic obstructive pulmonary disease; LAMA = Long acting muscarinic receptor antagonist.

In all analyses, roflumilast use is associated with a decrease in both moderate and severe exacerbation rates, and being in the very severe COPD state is associated with a higher exacerbation risk.

ERG comment: The exacerbation rate estimates of roflumilast rely on a single trial: REACT. The company restricted the population, to patients who have severe COPD despite triple therapy. Thus, only a subgroup of patients in the REACT trial were used (concomitant LAMA patients) in the submission.

As mentioned in Section 4.1.5 of this report, the company might have incorporated the results from the RE2SPOND trial, which had a comparable methodology and similar patient population with REACT

trial. The ERG considers the pooled results from REACT and RE2SPOND might provide robust treatment effectiveness estimates.

In the clarification letter, the ERG questioned why the treatment and the GOLD stage were selected as the only covariates for the regression analyses performed for the exacerbations, and suggested a formal covariate selection procedure from all possible covariates instead. In the response to the clarification letter[14], the company did not provide this required analysis and did not provide a convincing argument besides that these covariates were in line with the model structure used in the submission, and that the model structure used in the submission was adopted in previous model structures. If other covariates than GOLD stage and treatment were selected, it might have been possible to estimate the exacerbation rates based on these covariates and incorporate them into the model structure.

The company had a strong preference to use the results from the concomitant LAMA subgroup in the per protocol population, due to the high proportion of protocol violations occurred in the ITT population. However, the ERG thinks these violations would take place in real clinical practice as well, and also using per protocol population would break the randomisation as discussed in Section 4.2.5. Therefore, the ERG asked the COPD state specific ITT results for the concomitant LAMA subgroup in the clarification letter, but these results were not provided by the company. In Section 5.3, the ERG will conduct a number of analyses, in which the treatment effectiveness is based on ITT population.

As discussed in Sections 4.2 and 4.6, the ERG finds the justifications provided by the company for the use of negative binomial regression plausible (e.g. as discussed in Keene et al. 2007[32] and Suissa et al. 2006[33]). However, in the clarification letter, asked the company to provide the details (input data, statistical analysis outputs and goodness of fit) of all the regression analyses (negative binomial and Poisson) conducted for the LAMA concomitant subpopulation, full ITT population and PP population. In their response to the clarification letter, the company provided only the goodness of fit tables, without sufficient explanations. From those tables, without any explanations, it was not possible for the ERG to comment on which regression provided the best statistical model according to the goodness of fit and other information criteria. Nevertheless, the ERG will base the exploratory analyses in Section 5.3 mainly on negative binomial regression results.

Another unclear issue for the ERG was how the patients who discontinued the treatment were included in the calculation of the exacerbation rates. Therefore, the ERG asked the company to provide additional clarification on this issue. In their response to the clarification letter[14], the company mentioned that in their primary analyses, time until the end of treatment was used, and therefore exacerbations that took place after treatment discontinuation were not included. However, the company mentioned that in sensitivity analyses, they analysed exacerbation during both pre- and post-discontinuation periods and using different data imputation methods. In the post-discontinuation period, data was still collected via telephone contacts to estimate the potential impact of missing data. However, the results from these sensitivity analyses were not provided in the response to the clarification letter. Therefore, the ERG exploratory analyses will be based on company's primary analyses, which include only pre-discontinuation exacerbations.

Mortality

In the economic model, the mortality is incorporated via two ways: first, via the case fatality due to severe exacerbations and second, via COPD associated background mortality non-related to exacerbations.

The case fatality rate (CFR) due to severe exacerbations

The CFR for severe exacerbations (4.3%, S.E:0.18%) was obtained from the 2014 UK National COPD Audit[59]. In the audit, it was reported that 576 of the 13,414 patients died during admission to a hospital

due to severe exacerbation. The company stated that the average age of the patients in the 2014 audit was 72 years, which was higher than the average age at baseline in the economic model (64.7). Therefore, the company applied an age specific adjustment to the CFR, arguing unadjusted CFRs would be an overestimation of exacerbation related mortality for patients younger than 72. The adjustment ratio of a certain age was derived by dividing that age's risk of death by the risk of death at age 72, both could be found from UK life tables. These adjustment ratios and associated adjusted CFRs are illustrated in Table 5.9. Note that CFR adjustments are applied not only for the depicted ages in Table 5.9 but for all ages in the model.

Table 5.9: Age-adjusted severe exacerbation CFR

Age, years	64	70	72	75	80	85
Adjustment ratio	0.48	0.78	1	1.33	2.29	4.13
Hospital CFR	2.1%	3.4%	4.3%	5.7%	9.8%	17.8%

Source: Based on Table 31 in the CS[1]
CFR = Case fatality rate

COPD associated mortality (not related to exacerbations)

For the calculation of the background mortality that is not related to exacerbations in the severe and very severe COPD states, UK life tables and standardised mortality ratios (SMRs) from the literature were used. In Eckberg-Aronsson et al. 2005[60], all-cause mortality SMRs for the patients in severe and very severe COPD states were calculated as 3.1 and 5, respectively. However, these SMRs included deaths that were related to exacerbations as well. Therefore, in Samyshkin et al. 2014[45], background COPD SMRs for severe and very severe COPD states ('severe':2.5 and 'very severe':3.85) were calculated by deducting the severe exacerbation related deaths from the all-cause deaths obtained from the SMRs of Eckberg-Aronsson et al. 2005[60] in the model. In the CS base-case, SMRs from Samyshkin et al. 2014[45] were used, however in a scenario analysis, the cost effectiveness implications of using the SMRs from Eckberg-Aronsson et al. 2005[60] were explored.

ERG comment: In the age adjustment for the severe exacerbation CFRs, it was assumed that the effect of age on CFR would be exactly the same as the effect of age on all cause mortalities as seen in the life tables. However, there can be other factors which would create a non-linear relation between age and severe exacerbation CFRs. The ERG considers that it would have been better if this assumption was substantiated with findings from the literature. In Section 5.3, the ERG will explore a scenario where non-adjusted CFRs were used.

In addition, it was unclear how the company calculated the SMRs for background mortality, as these rates were found in Samyshkin et al. 2014[45], using the model developed in that paper. As these calculations could not be traced back in the model, the ERG requested further details from the company and asked the company to calculate these SMRs using the submission model in the clarification letter[14]. However the company declined and reiterated that these SMRs were suitable.

Due to the ambiguity of the mortality calculations in the CS, as a scenario, in Section 5.3, SMRs from Eckberg-Aronsson et al. 2005[60] (which included all COPD related deaths) were implemented without incorporating severe exacerbation CFRs.

5.2.7 Adverse events

In the economic model, pneumonia (the most common serious adverse event) and the three most common adverse events of any grade (diarrhoea, weight decrease, nausea) observed in the REACT trial were included.

The rates of treatment emergent serious adverse events (TESAEs) and treatment emergent adverse events (TEAEs) are provided in Table 5.10 and Table 5.11 below.

Table 5.10: Occurrence rate of the TESAEs

TESAEs	Roflumilast arm (mean, SE)	Comparator arm (mean, SE)
Diarrhoea	0.21% (0.15%)	0.21% (0.15%)
Weight loss	0.41% (0.21%)	0.00% (0.00%)
Nausea*	0.00% (0.00%)	0.00% (0.00%)
Pneumonia	3.41% (0.58%)	3.21% (0.57%)
Source: Based on Table 36 in the CS[1] *Serious nausea did not occur in ≥2 patients and therefore not reported. Assumed to be zero.		

Table 5.11: Occurrence rate of the TEAEs

TEAEs	Roflumilast arm (mean, SE)	Comparator arm (mean, SE)
Diarrhoea	10.23% (0.97%);	3.62% (0.60%)
Weight loss	9.09% (0.92%)	2.79% (0.53%)
Nausea	5.68% (0.74%);	1.55% (0.40%)
Pneumonia	4.03% (0.63%)	4.65% (0.68%)
Source: Based on Table 37 in the CS[1]		

In the base-case analysis, only the serious AE rates were used in the economic model. Different scenario analyses explored the impact of incorporating all AE rates instead of serious AE rates or the impact of not incorporating any adverse events at all. The adverse events were assumed to emerge during the first treatment cycle (i.e. rates were applied only in the first cycle) and discontinuation of roflumilast due to adverse events (or due to any other cause) was not considered.

ERG comment: The ERG considers using all treatment emergent adverse events to be more plausible than using only the serious adverse events, as the company's selection of the three adverse events to incorporate to the model was based on the frequencies of all adverse events, not on the frequencies of the serious adverse events.

The adverse event calculations were based on ITT full population whereas the exacerbation rates were based on PP population in the CS base-case. In the ERG analysis, this inconsistency was removed by basing all estimations of input parameters for the model on the ITT, concomitant LAMA patient subpopulation, as already discussed in Section 5.2.6. The emergent (severe) adverse event rates used in the model based on ITT concomitant LAMA patient subpopulation are given in Table 5.12 below:

Table 5.12: Occurrence rate of the TEAEs and TEASEs based on ITT concomitant LAMA subpopulation

TEAEs	Roflumilast arm (mean, SE)	Comparator arm (mean, SE)
Diarrhoea	11.23% (1.21%);	4.04% (0.76%)
Weight loss	10.64% (1.18%)	3.44% (0.70%)
Nausea	6.06% (0.92%);	1.79% (0.51%)
Pneumonia	3.69% (0.72%)	3.89% (0.75%)
TESAEs	**Roflumilast arm (mean, SE)**	**Comparator arm (mean, SE)**
Diarrhoea	0.15% (0.15%)	0.30% (0.21%)
Weight loss	0.44% (0.26%)	0.00% (0.00%)
Nausea*	0.00% (0.00%)	0.00% (0.00%)
Pneumonia	2.95% (0.65%)	3.44% (0.70%)
Source: Based on Table 14.3.1.17 and Table 14.3.2.4 from CSR of REACT *Serious nausea did not occur in ≥2 patients and therefore not reported. Assumed to be zero.		

In addition, in the model it was assumed that the adverse events took place only in the first month. However, the ERG finds this approach too simplistic, since it is clear from Table 12.f of the CSR of the REACT trial that most of the adverse events took place after the first month. Therefore, the ERG requested that the company conduct an analysis where adverse events could take place in all years and not only the first month. The company argued that the application of adverse events in the first month was a conservative one, as the costs and disutilities due to adverse events were not subject to discounting. As the percentage of patients with adverse events is limited, and the costs and disutility associated with the AEs are relatively low, the ERG expects that the overall impact of this simplification on the ICER is small.

5.2.8 Health related quality of life

Within the REACT trial, HRQoL was measured with the COPD Assessment Test (CAT). For both treatment arms (triple therapy + placebo and triple therapy + roflumilast) a significant decrease in CAT score was found between baseline and end of treatment, indicating an improvement in HRQoL. However, no difference was found between the two treatment arms. The company stated that an algorithm to estimate EQ-5D utilities from the CAT was not sufficiently valid to use in the submission. In the mapping study[61], utilities were underestimated for both poor HRQoL (utility <0.5) and at near full health (utility ≥ 0.9). Therefore, the company decided to not use evidence from the REACT trial for HRQoL estimates in the cost effectiveness model but instead perform a systematic literature review to identify utility values.

Fifteen studies fulfilled the in- and exclusion criteria. The studies reported HRQoL with the EQ-5D (N=8), SF-6D (N=1), SF-12 (N=4), St. George Respiratory Questionnaire (SGRQ) (N=6) and CAT (N=2). Six studies included more than one questionnaire. None of the studies were exclusively performed in the UK, but five studies were multinational studies including the UK. Moreover, only two studies used the UK tariff to estimate utilities from the EQ-5D.

Health state utilities

The utility values in the base-case analysis were derived from the study of Rutten-van Mölken et al. 2006[46] in which utility values were estimated for both severe and very severe COPD. The study was performed in 13 countries (N=1,235) and utilities were estimated from the EQ-5D-3L using the UK tariff. These values were therefore most in line with NICE clinical guidelines. In a scenario analysis, the company used two alternative sources of health care utilities (valuations of health profiles[47] and EQ-

5D US tariff [62]). One scenario includes a larger difference in utility value between severe and very severe COPD, while the other scenario includes smaller difference in utility between these health states. All utility values are shown in Table 5.13.

Table 5.13: Health state utilities in the base-case and scenario analyses

Severity	Mean	SE	Upper 95% CI	Lower 95% CI	Source
Base-case analysis					
Severe COPD	0.750	0.009	0.768	0.731	Rutten-van Mölken et al. 2006[46]
Very Severe COPD	0.647	0.025	0.695	0.598	Rutten-van Mölken et al. 2006[46]
Scenario analysis 1					
Severe COPD	0.717	0.0008	0.733	0.701	Rutten-van Mölken et al. 2009[47]
Very Severe COPD	0.512	0.0008	0.538	0.506	Rutten-van Mölken et al. 2009[47]
Scenario analysis 2					
Severe COPD	0.707	0.013	0.682	0.732	Solem et al. 2013[62]
Very Severe COPD	0.632	0.021	0.582	0.664	Solem et al. 2013[62]
Source: Based on Table 38, Table 39 and Table 69 in the CS[1]					

Exacerbations

Decrements in health-related quality of life due to exacerbations were derived from another study of Rutten-van Mölken et al. 2009[47]. These decrements were derived from a study in which the Dutch general public was asked to value several COPD health states, (presented as vignettes) through Time Trade Off (TTO), including health states with moderate and severe exacerbations. Within one scenario analysis, the disutility of exacerbations was changed towards those reported by Solem et al. 2013[62]. In that study, patients were asked to report the EQ-5D for their current health and for their health at the time of the last exacerbations. The disutility due to exacerbations was the difference between these two estimates. The disutilities of exacerbation in the base-case and scenario analysis are reported in Table 5.14.

Table 5.14: Disutilities of exacerbations in the base-case and scenario analysis

Severity	Mean	SE	Upper 95% CI	Lower 95% CI	Source
Base-case analysis					
Moderate exacerbations	-0.010[1]	0.007	0.004	-0.024	Rutten-van Mölken et al. 2009[47]
Severe exacerbations	-0.042[1]	0.009	-0.024	-0.060	Rutten-van Mölken et al. 2009[47]
Scenario analysis					
Moderate exacerbations	-0.103[2]	0.013	-0.077	-0.129	Solem et al. 2013[62]
Severe exacerbations	-0.157	0.023	-0.111	-0.203	Solem et al. 2013[62]
Source: Based on Table 39 and Table 69 in the CS[1]					

1. These disutilities represent the annual disutility for patients with one moderate or severe exacerbations per year. Since an exacerbation only occurs during a specific period, the disutility at time of the exacerbations is larger. However, since the company did not adjust the disutility according to the cycle length in the Markov trace, it was accurately implemented in the model.
2. These disutilities reflect the utility at the time of the exacerbations. Within the model, this disutility is divided by twelve to accurately reflect the disutility within on model cycle (1 month). Consequently, these disutilities are 0.009 and 0.013 per month for moderate and severe exacerbations, respectively.

Adverse events

It was assumed that each TEAE had a disutility of 0.042. This is equal to that of severe exacerbations. The company did not provide any argumentation for this assumption.

ERG comment: The ERG agrees with the company that the HRQoL utilities used in the base-case analysis were valid and reliable for this analysis. The utility values from Rutten-van Mölken et al. 2006[46] were derived from a substantial number of patients, including patients from the UK, and were estimated with the UK tariff. Furthermore, other utility values in the literature are more or less similar to these utility values (Einarson et al. 2015[63]).

The ERG considers the source for disutilities of the exacerbations as less appropriate., The disutilities reported by Rutten-van Mölken et al. 2009[47] were not derived from the EQ-5D but from valuations (through TTO) of COPD health profiles by the Dutch general public. Furthermore, the utility for severe exacerbations appear to be higher than used in other studies (Menn et al. 2010[64], Hoogendoorn et al. 2011[65], Hettle et al. 2012[66], Oostenbrink et al. 2005[67]). The ERG considers the use of the disutility reported by Hoogendoorn et al. 2011[65] more valid to the UK setting since utilities were derived from patient-reported EQ-5D and valued with the UK-tariff (severe exacerbations) or US tariff (moderate exacerbations). Hoogendoorn et al. 2011[65] reports the relative reduction in utility due to an exacerbation in one year (Table 5.15). Within the ERG base-case, the ERG applied these disutilities as a relative decline instead of an absolute utility (see Section 5.3). Consequently, the absolute decline in utility due to exacerbations is larger for patients with severe COPD. This is also supported by evidence from Menn et al. 2010[64] with an absolute annual decline in utility due to severe exacerbations of 0.26 for patients with severe COPD compared to 0.17 for patients with very severe COPD. The utility values used in the ERG base-case are shown in Table 5.15.

Table 5.15: Relative disutility due to exacerbations in the ERG base-case

Severity	Mean	Upper 95% CI	Lower 95% CI	Source
Moderate exacerbations	-0.0166	0.0123	-0.0209	Hoogendoorn et al. 2011[65]
Severe exacerbations	-0.0482	-0.0311	-0.0653	Hoogendoorn et al. 2011[65]

The ERG considers the assumption of the company that the disutility of adverse events is similar to the disutility of severe exacerbations to be conservative. Patients receiving triple therapy plus roflumilast experience more adverse events than patients receiving triple therapy alone, and the disutility of adverse events is quite large and is expected to overestimate the actual disutility, especially for nausea, weight loss and diarrhoea.

5.2.9 Resources and costs

The company performed a literature search to identify resource utilisation and direct and indirect costs in patients with (very) severe COPD (FEV1 ≤ 50% predicted level). This search was not restricted to specific interventions. Five studies fulfilled the in- and exclusion criteria of which three were conducted

in the UK. However, most of the cost and resource inputs in the company's submission were not derived from any of these studies.

Health state costs

The health state costs consist of medication and maintenance costs. Relevant medication costs are the costs of LABA, LAMA, ICS and roflumilast. For each of these drugs, the drug costs, dose requirements and days of treatment were derived from the British National Formulary.[68] The drug unit costs are shown in Table 5.16. This table also included the costs of prednisolone which is administered to patients with moderate exacerbations.

Table 5.16: Drug costs per dose

Drug	Pack size	Pack cost	Cost per dose
Roflumilast			
Roflumilast 500 µg	30	£37.71	£1.26
Roflumilast 500 µg	90	£113.14	£1.26
Average cost			£1.26
LAMA			
Spiriva® 18 µg	30	£33.50	£1.12
LABA/ICS			
Symbicort (200/6) (x2)	120	£38.00	£0.63
Symbicort (400/12)	60	£38.00	£0.63
Seretide 500	60	£40.92	£0.68
Average cost (x2)			£1.30
Prednisolone*			
Prednisolone 5 mg	28	£1.24	£0.04
Prednisolone 25 mg	56	£75.00	£1.34
Combined dose (30 mg dose)			£1.38

* lowest pill burden for patients via this combination
Source: Based on Table 45 in the CS[1]
ICS = inhaled corticosteroid; LABA = Long acting beta-adrenoceptor agonist; LAMA = Long acting muscarinic receptor antagonist.

The BMJ Best Practice states that COPD patients should be assessed at six month intervals.[69] The company therefore assumes that patients in both severe and very severe COPD state visit a GP twice a year as part of the maintenance treatment. Other maintenance costs were assumed the same as in Samyshkin et al. 2014.[45] These resource use estimates were derived from Oostenbrink et al. 2005.[67] The costs per health state are shown in Table 5.18.

Exacerbation costs

The treatment of moderate exacerbation consists of 30 mg prednisolone daily for 7-14 days and additional primary care visits. The treatment of severe exacerbations consists of additional primary care consultations and a non-elective hospital admission. Furthermore, the company assumes that an ambulance transports 90% of all patients to the hospital in case of severe exacerbations.

The company assumed that 50% of the patients with moderate exacerbations receive prednisolone for seven days and the other 50% receive prednisolone for 14 days. The costs of a hospital admission is the weighted average of costs of HRG Code DZ65 "Chronic Obstructive Pulmonary Disease or Bronchitis"

non-elective short stay and non-elective long stay. The costs of ambulance transport is the costs of the HRG code ASS02 "See and treat and convey".

The number of additional primary care visits in case of exacerbations was derived from Thomas et al. 2014.[70] This study reported the median number of primary care visits by exacerbation frequency (none, infrequent and frequent). Since the number of primary care visits for patients without exacerbations in that study was smaller than recommended in BMJ Best Practice, the company considered the absolute number of visits inappropriate to use. Instead, the company estimated the relative increase in primary care visits of infrequent and frequent exacerbations compared to no exacerbations. Subsequently, the two maintenance visits as recommended by BMJ Best Practice were multiplied with these ratios to estimate the number of primary care visits in case of moderate and severe exacerbations. The primary care visits due to exacerbations is defined as the difference in GP visits between moderate or severe exacerbations and none exacerbations (Table 5.17). The total costs of moderate and severe exacerbations are given in Table 5.18.

Table 5.17: Estimation of additional GP visits in the company submission

	No exacerbation	**Infrequent exacerbations**	**Frequent exacerbations**
Median number of primary care contacts per year[69]	1.33	2.67	6.67
Ratio compared to no exacerbations	1.00	2.01	5.02
	No exacerbation	**Moderate exacerbations**	**Severe exacerbations**
Number of primary care contacts per year	2.00	4.03	10.03
"Excess" number of primary care contacts per year applied in model (mean, SE)	0.00	2.03 (0.61)	8.03 (2.42)
Source: Based on Table 48 in the CS[1]			

Adverse event costs

The costs of diarrhoea, nausea and weight loss were assumed to be equivalent to that of a GP consultation. The unit costs of pneumonia was the weighted average of HRG DZ11 "Lobar, Atypical or Viral Pneumonia", non-elective inpatient short and non-elective inpatient long stay. The costs of adverse events assumed in the company submission are also shown in Table 5.18.

Table 5.18: Cost estimates in the company submission

	% of patients	Resource use	Unit costs	Total costs (per cycle/ exacerbation or adverse event)	Cost reference	Resource use reference
Health state costs						
Medication costs						
Roflumilast	100%	30.42*	£1.26	£38.24	BNF (see Table 5.16)	BNF
LAMA	100%	30.42	£1.12	£33.97	BNF (see Table 5.16)	BNF
LABA / ICS	100%	30.42	£1.30	£39.51	BNF (see Table 5.16)	BNF
Total medication costs roflumilast + triple therapy				*£111.72*		
Total medication costs triple therapy				*£73.48*		
Maintenance costs severe COPD						
GP consultation	100%	0.167	£44.00	£7.33	PSSRU 2015	BMJ Best Practice
Spirometry	100%	0.167	£50.05	£8.34	Samyshkin 2014 [45]	Oostenbrink et al. 2005[67]
Influenza vaccination	75%	0.083	£6.29	£0.39	BNF July 2016	Oostenbrink 2005[67]
Oxygen therapy	100%	1.22	£13.56	£16.50	Oostenbrink 2005 [67]	Oostenbrink 2005[67]
Total maintenance costs severe COPD per cycle				*£32.57*		
Maintenance costs very severe COPD						
GP consultation	100%	0.167	£44.00	£7.33	PSSRU 2015	BMJ Best Practice
Spirometry	100%	0.333	£50.05	£16.68	Samyshkin 2014 [45]	Oostenbrink et al. 2005[67]
Influenza vaccination	75%	0.083	£6.29	£0.39	BNF July 2016	Oostenbrink et al. 2005[67]
Oxygen therapy	100%	6.08	£13.56	£82.44	Oostenbrink 2005 [67]	Oostenbrink et al. 2005[67]
Total maintenance costs very severe COPD per cycle				*£106.90*		

Exacerbations costs						
Moderate exacerbations						
Excess GP consultations (per year)	100%	2.03	£44.00	£89.32	PSSRU 2015	Derived from Thomas et al. 2014[70](see Table 5.19).
Prednisolone 30 mg/day	50%	7	£1.38	£4.84	BNF (see Table 5.16)	Assumption
Prednisolone 30 mg/day	50%	14	£1.38	£9.69	BNF (see Table 5.16)	Assumption
Total costs per moderate exacerbation				*£103.85*		
Severe exacerbations						
Excess GP consultations (per year)	100%	8.03	£44.00	£353.32	PSSRU 2015	Derived from Thomas et al. 2014[70] (see Table 5.19).
Hospital admission	100%	1	£1,183.06	£1.183.06	NHS Ref Costs (DZ65)	By definition
Ambulance transport	90%	1	£223.02	£209.72	NHS Ref Costs (ASS02)	Assumption
Total costs per severe exacerbation				*£1,724.43*		
Adverse events costs						
Diarrhoea, weight loss and nausea	Table 5.10 and Table 5.11	1	£44.00		Assumed to be equivalent to GP consultation	
Pneumonia	Table 5.10 and Table 5.11	1	£2,518.00		NHS Ref Costs (DZ11)	

* days per month (365/12)
Source: Based on Table 45, Table 46, Table 47, Table 48, Table 49 and Table 50 in the CS[1]
BMJ = British Medical Journal; BNF = British National Formulary; GP = general practitioner; ICS = inhaled corticosteroid; LABA = Long acting beta-adrenoceptor agonist; LAMA = Long acting muscarinic receptor antagonist; NHS = The National Health Service; PSSRU = Personal Social Services Unit.

ERG comment: The company did not identify all relevant articles with resource use and/or costs in the UK. A recent literature review[71] regarding cost effectiveness of maintenance treatment in COPD patients identified five UK studies of which the company only included one (Punekar et al. 2014[51]) in their review. Furthermore, it was not always clear how the company selected the resource use and unit costs for the economic analysis because the different studies reported different values.

The ERG is especially concerned about the resource use of exacerbations. The company assumed that exacerbations are accompanied by additional GP visits, based upon Thomas et al. 2014[70]. However, Thomas et al. 2014[70] reports the number of GP visits according to the frequency of exacerbations in one year instead of the severity of exacerbations. The assumption of the company that the frequency of exacerbations in one year reflects the severity of exacerbations is incorrect. First, all patients within the model should be classified in the frequent exacerbation group since they need to have at least two exacerbations within the previous year to be eligible for roflumilast. Secondly, the classification of (in)frequent exacerbations implies that patients could have more than one exacerbation per year. However, the company assumes that all additional GP visits observed in Thomas et al. (2014)[70] should be assigned to one exacerbation, with a risk of double counting for patients with more than one exacerbation per year. In most other studies it is assumed that patients visit the GP one additional time in case of a moderate exacerbation.[41] Patients with a severe exacerbation have no additional GP visits, because these patients are hospitalised as a consequence of their exacerbation. Hence, the ERG will use this approach for the estimation of exacerbation costs (Table 5.19) in the ERG base-case (see Section 5.3).

The ERG also adjusted the costs of maintenance treatment for patients with very severe COPD and hospitalisation costs for treatment of severe exacerbations or pneumonia in the ERG base-case. The ERG increased the number of GP visits during maintenance treatment for patients with very severe COPD to four instead of two visits per year according to Oostenbrink et al. 2005.[67] Within the company submission, the hospitalisation costs were calculated as the weighted average of long- and short-term non-elective stay excluding costs of excess bed days. However, the costs of excess bed days are part of the total hospitalisation costs. Therefore, the ERG incorporated these in the total hospitalisation costs in the ERG base-case. In addition, the ERG was unable to reproduce the company reported hospitalisation costs of pneumonia from the weighted average of HRG DZ11. Therefore, the ERG estimated this weighted average, including the excess bed days.

Finally, the ERG found some small errors in the estimation or reporting of the ambulance costs and the costs of LABA / ICS. These errors were corrected in the ERG base-case (Section 5.3). All adjustments in cost parameters for the ERG base-case are reported in Table 5.19.

Table 5.19: ERG adjustment in cost parameters

Cost parameter	Value in company submission	Value in ERG Base-case
Very severe COPD	£106.90	£114.23
Moderate exacerbation	£103.85	£58.49
Severe exacerbation	£1,724.43	£1,455,17
Pneumonia	£2,518.00	£1,924.72
Costs of LABA/ICS	£1.30	£1.32

COPD = chronic obstructive progressive disease; ICS = inhaled corticosteroid; LABA = Long acting beta-adrenoceptor agonist.

5.2.10 Cost effectiveness results

Base-case incremental cost effectiveness analysis results

In the base-case analysis, roflumilast plus triple therapy resulted in a total (discounted) costs of £22,930 and QALYs of 6.14. On the other hand, triple therapy alone resulted in a total (discounted) costs of £19,933 and QALYs of 5.98. Based on these results, roflumilast plus triple therapy produced an additional 0.16 QALYs at an incremental cost of £2,996 when compared to triple therapy alone, leading to an ICER of £18,774. The base-case incremental cost effectiveness results are shown in Table 5.20 below.

Table 5.20: Base-case results

Technologies	Total costs	Total LYG	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER
Roflumilast plus triple therapy	£22,930	8.95	6.14	£2,996	0.18	0.16	£18,774
Triple therapy alone	£19,933	8.77	5.98	-	-	-	-

Source: Based on Table 52 in the CS[1]
ICER = incremental cost effectiveness ratio; LYG= life years gained; QALYs = quality adjusted life years.

From the Markov traces provided in the CS[1], a similar trend could be observed in both arms. The percentage of the patients in severe COPD state decreased in time, whereas the percentage of the patients in very severe COPD state first increased and declined afterwards. The percentage of dead patients increased over time though slower for the roflumilast plus triple therapy arm.

Disaggregated results of the base-case incremental cost effectiveness analysis

Disaggregated results for QALYs and costs by health state are given in Table 5.21 and Table 5.22, below.

Table 5.21: Disaggregated QALY gained results from the base-case analysis

Health state / events	QALY roflumilast	QALY comparator	Increment	Absolute increment	% of total abs. incr.
COPD Severity					
Severe COPD	3.400	3.377	0.023	0.023	14.58%
Very severe COPD	2.857	2.760	0.097	0.097	60.65%
Exacerbations					
Moderate exacerbations	-0.044	-0.049	0.004	0.004	2.81%
Severe exacerbations	-0.072	-0.107	0.035	0.035	21.79%
Adverse events					
TEAEs	-0.002	-0.001	0.000	0.000	0.16%
Total	6.139	5.980	0.160	0.160	100%

Source: Based on Table 54 in the CS[1]
COPD = chronic obstructive progressive disease; QALY= quality adjusted life years; TEAE = treatment emergent adverse event

Table 5.22: Disaggregated cost results from the base-case analysis

Health state / events	Cost roflumilast	Cost comparator	Increment	Absolute increment	% of total abs. incr.
Technology costs					
COPD treatments	£11,996.91	£7,731.07	£4,265.84	£4,265.84	71.63%
COPD Severity					
Severe COPD	£1,771.64	£1,759.48	£12.17	£12.17	0.20%
Very severe COPD	£5,664.28	£5,471.73	£192.55	£192.55	3.23%
Exacerbations					
Moderate exacerbations	£459.45	£506.16	-£46.71	£46.71	0.78%
Severe exacerbations	£2951.40	£4384.13	-£1432.73	£1432.73	24.06%
Adverse events					
TEAEs	£85.93	£80.64	£5.29	£5.29	0.09%
Total	£22,929.61	£19,933.19	£2,996.42	£5955.29	100%

Source: Based on Table 55 in the CS[1]
COPD = chronic obstructive progressive disease; TEAE = treatment emergent adverse event

Based on the results above, the company concluded that the incremental QALYs gained for triple therapy plus roflumilast were mostly due to the fewer exacerbations, and increased life expectancy (due to fewer exacerbation related deaths). It was further mentioned that around 25% of the absolute incremental difference in costs and QALYs were due to the COPD exacerbations and TEAEs had a negligible impact on costs and QALYs.

5.2.11 Sensitivity analyses

Probabilistic sensitivity analysis

The probabilistic sensitivity analyses (PSA) were conducted for the base-case scenario. The uncertainty of the following parameters was incorporated using the corresponding distributions in the parenthesis.

- FEV1 decline per annum (Gamma)
- Exacerbation regression equations (Normal)
- TEAE and TSEAE rates (Beta)
- Resource use (Beta or Gamma)
    - except for prednisolone use, hospital admission and ambulance transport
- Unit costs (Gamma)
    - expect spirometry, influenza vaccination and oxygen therapy
- COPD health state utilities (Beta)
- COPD exacerbation disutilities (Beta)
- Standardised mortality ratios (Gamma)
- Severe exacerbation case fatality rate (Beta).

The summary results of the PSA (10,000 iterations), which includes the mean and the 95 % CI of the costs, QALYs and resultant ICERs for the PSA are presented below (See Table 5.23) with corresponding scatterplots (See Figure 5.3) and CEACs (See Figure 5.4). Note that these results pertain

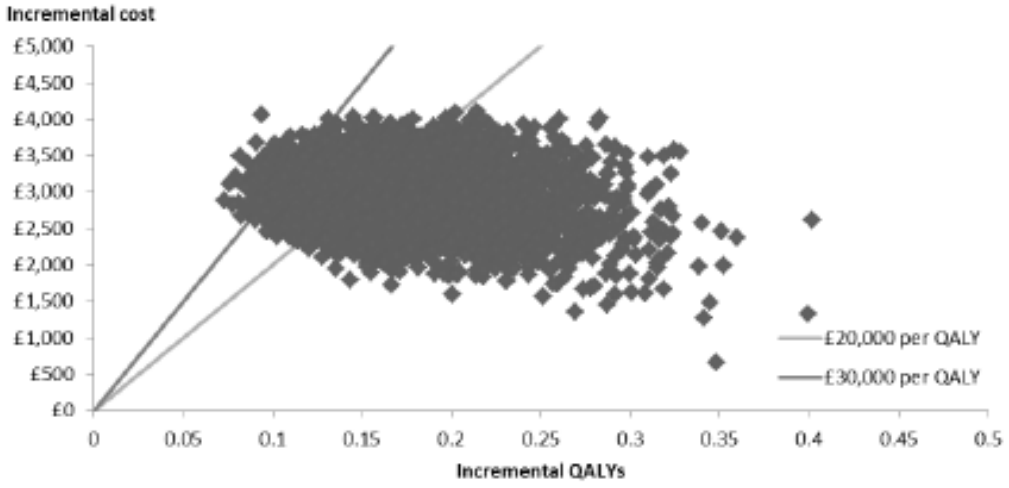
to the updated PSA results that were provided in the response to the clarification letter[14], which included the correction of the programming error that the ERG identified and inclusion of the correlation of the regression coefficients.

In the CS, it was mentioned that the PSA results (incremental costs: £3,033, incremental QALYS: 0.16 and ICER: £18,425 per QALY gained) were highly comparable to the deterministic base-case results. From the CEAC and scatterplots it can be seen that the probability that roflumilast plus triple therapy is cost effective compared to triple therapy alone is approximately 70% at a £20,000 per QALY gained threshold.

Table 5.23: PSA results of the base-case

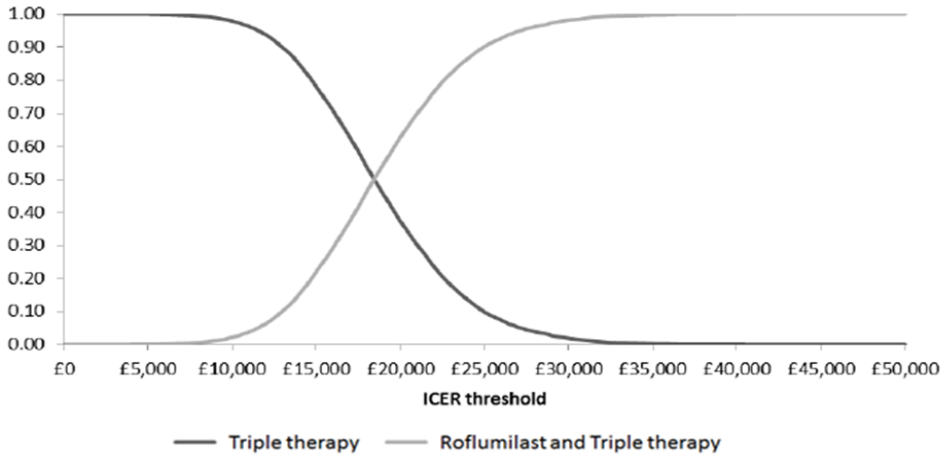
Technologies	Total costs	95% CI	Total QALYs	95% CI	Incr. costs	Incr. QALYs	ICER
roflumilast plus triple therapy	£23,129	£19,930 to £26,816	6.18	5.48 to 6.93	£2,996	0.17	£17,855
triple therapy alone	£20,133	£17,055 to £23,717	6.01	5.33 to 6.74	-	-	-
Source: Based on Table 1 in the response to the clarification letter[14] CI= confidence interval; ICER = incremental cost effectiveness ratio; LYG= life years gained; QALYs = quality adjusted life years.							

Figure 5.3: Incremental cost effectiveness scatterplot of the base-case analysis



Source: Based on Figure 1 in the response to the clarification letter[14]

Figure 5.4: Cost effectiveness acceptability curve



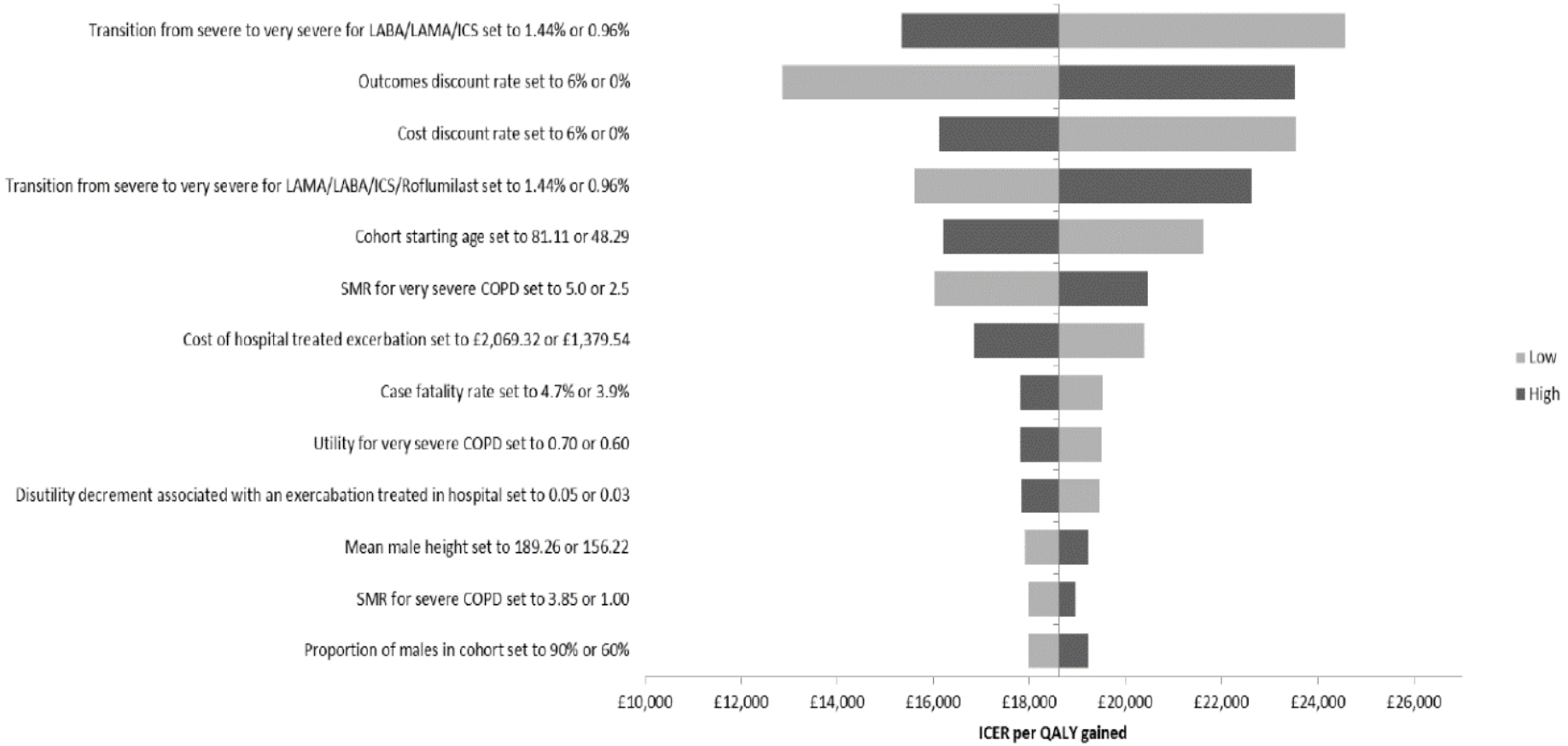
Source: Based on Figure 2 in the response to the clarification letter[14]

Deterministic sensitivity analysis

The company conducted deterministic sensitivity analyses (DSA) by varying some of the parameters used in the model to its upper and lower limits, while holding all other parameters constant, to identify the relative importance of each parameter in terms of its impact on the ICER.

If a 95% confidence interval for a parameter was available, then the lower and upper limit of the interval were used as lower and upper limit in the DSA. If a confidence interval was not available, the lower and upper limit were defined as 80% and 120% of the mean value of that parameter; in some instances other lower and upper limits (e.g. 0% and 6% for discount rates for costs and effects) were used. The DSA results are presented in Figure 5.5 below.

Figure 5.5: Tornado diagram



Source: Based on Figure 20 in the CS[1]

From the DSA in the CS[1], it was observed that the most influential parameters were the transition probability from 'severe' to 'very severe' COPD state for both arms, discount rates for both costs and health outcomes and cohort starting age.

Exploratory analyses (severity of COPD of the baseline cohort)

In the company base-case, it was assumed that all patients entered the model in the severe COPD state. In the CS[1], two exploratory analyses were conducted around the impact of this assumption. For this purpose, in the first analysis, it was assumed that all patients entered the model in the very severe COPD state, whereas in the second analysis, it was assumed that at the baseline, a mixed population consisting of both severe and very severe COPD patients entered in the model (as in the REACT trial).

Patients starting the model with very severe COPD

In this exploratory analysis, all patients started the model in the very severe COPD state. Roflumilast plus triple therapy resulted in a total (discounted) costs of £26,014 and QALYs of 5.18. On the other hand, triple therapy alone resulted in a total (discounted) costs of £23,671 and QALYs of 4.99, yielding an additional 0.19 QALYs at an incremental cost of £2,343 for roflumilast plus triple therapy compared to triple therapy, and thus an ICER of £12,337. The incremental cost effectiveness results of this exploratory analysis are shown in Table 5.24 below.

Table 5.24: Incremental cost effectiveness results of the exploratory analysis where patients started the model in the very severe COPD state.

Technologies	Total costs	Total LYG	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER
roflumilast plus triple therapy	£26,014	8.23	5.18	£2,343	0.22	0.19	£12,337
triple therapy alone	£23,671	8.01	4.99	-	-	-	-

Source: Based on Table 57 in the CS[1]
ICER = incremental cost effectiveness ratio; LYG= life years gained; QALYs = quality adjusted life years.

Mixed population of severe and very severe COPD patients at the baseline

In this exploratory analysis, it is assumed that the patients at the baseline which enter the model is a mixed population of both severe and very severe COPD patients reflecting the REACT trial's PP population (68.81% severe COPD and 31.19% very severe COPD). In this analysis, roflumilast plus triple therapy resulted in a total (discounted) costs of £23,892 and QALYs of 5.84 and triple therapy resulted in a total (discounted) costs of £21,099 and QALYs of 5.67. Based on these results, roflumilast plus triple therapy produced an additional 0.17 QALYs at an incremental cost of £2,792 compared to triple therapy, leading to an ICER of £16,519. The incremental cost effectiveness results of this exploratory analysis are shown in Table 5.25 below.

Table 5.25: Incremental cost effectiveness results of the exploratory analysis where mixed population of severe and very severe COPD patients entered in the model.

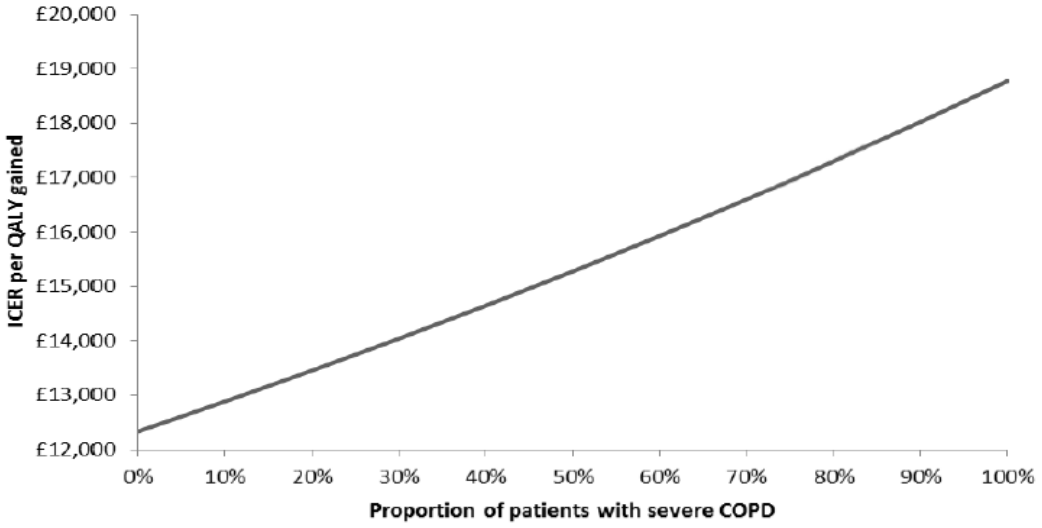
Technologies	Total costs	Total LYG	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER
roflumilast plus triple therapy	£23,892	8.72	5.84	£2,792	0.19	0.17	£16,519
triple therapy alone	£21,099	8.53	5.67	-	-	-	-

Source: Based on Table 58 in the CS[1]
ICER = incremental cost effectiveness ratio; LYG= life years gained; QALYs = quality adjusted life years.

For both of these analyses above, besides incremental cost effectiveness results various other outputs were provided: detailed clinical outcomes (CS Figures 21-24 for very severe COPD population and Figures 29-32 for the mixed COPD population); disaggregated cost and QALY results (CS Tables 58-59 for very severe COPD population and Tables 62-63 for the mixed COPD population); and probabilistic sensitivity analysis results (CS Table 60 and Figures 25-27 for very severe COPD population and Table 64 and CS Figures 33-35 for the mixed COPD population). These results lead to conclusions that are similar to the conclusions drawn from the results in the base case.

Finally, a threshold analysis was conducted, where the ICERs for different severe or very severe COPD state compositions at baseline were demonstrated.

Figure 5.6: Threshold analysis with different COPD severity (severe and very severe) mix



As can be seen from Figure 5.6, the ICER ranges from £12,337 (all very severe COPD) to £18,774 (all severe COPD) per QALY gained for different severe and very severe COPD patient mix compositions.

Scenario analyses

Several scenario analyses were conducted to explore the structural uncertainties in the economic evaluation. Each scenario was conducted for 100% severe patients, 100% very severe patients and the mixed severity population (based on REACT trial) at baseline. The scenario analyses considered are listed as below:

Scenario analysis 1 – LAMA as a covariate

In this scenario, the exacerbation rates from Table 5.8 were used, which were derived from the negative binomial analysis that included concomitant LAMA use as an additional covariate. In the base-case, the exacerbation rates in Table 5.7, derived from only the concomitant LAMA population were used.

Scenario analysis 2 – Unadjusted SMRs

In this scenario, the unadjusted SMRs from Eckberg-Aronsson et al 2005[60] were used (3.1 for severe COPD and 5.0 for very severe COPD), which included exacerbation related mortality, as well. In the base-case, adjusted SMRs calculated in Samyshkin et al. 2014[45] were used (2.5 for severe COPD and 3.85 for very severe COPD) from which the exacerbation related deaths were deducted.

Scenario analysis 3 – Lung function benefit scenario

In this scenario, the lung function benefit observed in the REACT trial (as explained in Section 5.2.6 above) was reflected in the model, assuming a lung function benefit observed after one year for the

patients who received roflumilast. The exacerbation rates were then adjusted in the model to return the similar (without lung function benefit) exacerbation incidences. The adjustments were based on one year and five year periods and these adjustment factors were applied as a common factor. These adjustment factors and exacerbation rates are given in Table 5.26. In the base-case no lung function benefit was assumed.

Table 5.26: Adjusted exacerbation rates with lung function benefit

Exacerbations	Adjustment	Rate ratio	95% Confidence intervals
1 year			
Moderate Exacerbations	1.0078	0.894	(0.718, 1.111)
Severe Exacerbations		0.661	(0.479, 0.912)
5 years			
Moderate Exacerbations	1.0080	0.894	(0.719, 1.111)
Severe Exacerbations		0.661	(0.479, 0.913)
Source: Based on Table 67 in the CS[1]			

Scenario analysis 4 – Alternative sources for HRQoL

In this scenario, different HRQoL estimates for the COPD health states and exacerbations from Solem et al. 2013[62] and COPD health state utility from Rutten-van Mölken et al. 2009[47] were used. In the base-case, COPD health state utility estimates were from Rutten-van Mölken et al. 2006[46].

Table 5.27: Solem et al. 2013 utility scores

Severity	Mean	Standard error	Upper 95% CI	Lower 95% CI
Severe COPD	0.707	0.013	0.682	0.732
Very severe COPD	0.623	0.021	0.582	0.664
Moderate exacerbations	-0.103	0.013	-0.077	-0.129
Severe exacerbations	-0.157	0.023	-0.111	-0.203
Source: Based on Table 69 in the CS[1]; Solem et al. 2013[62] CI = confidence interval.				

Table 5.28: Rutten-van Mölken et al. 2009 utility scores for health states

Severity	Mean	Standard error
Severe COPD	0.72	0.08
Very severe COPD	0.52	0.08
Source: Based on Table 39 in the CS[1]; Rutten-van Mölken et al. 2009[47]		

The results using various combinations of these utilities and disutilities are provided in Table 5.29. As can be seen from Table 5.29, the scenario with the minimum ICER for the severe COPD population is £18,774 per QALY gained, used in the base-case of the company, which used health state utilities from Rutten Mölken et al. 2006[46] and exacerbation related disutilities from Rutten Mölken et al. 2009[47]. The scenario with the highest ICER was the scenario which used health state utilities from Rutten Mölken

et al. 2009[47] and exacerbation related disutilities from Solem et al 2013[62], which resulted in an ICER of £26,069 per QALY gained.

Scenario analysis 5 – Alternative assumptions around treatment emerged adverse events
In order to assess the impact of TEAEs on the model two analyses were undertaken. Firstly, an analysis was undertaken where all grade TEAEs are included instead of TESAEs only as in the base-case. Secondly, an analysis was undertaken where all TEAEs and TESAEs were removed from the model.

Results of all the scenario analyses for all three populations at the baseline (severe COPD only, very severe COPD only and mixed population) are given in Table 5.30 below. Scenarios on SMRs, and utilities seem to have important effect on ICERs, whereas assumptions on TEAES do not seem to affect ICERs that much.

Table 5.29: ICER results resulting from different HRQoL sources (Scenario 4)

State utilities ►	Rutten van-Mölken 2006			Rutten van-Mölken 2009			Solem 2013		
Disutilities ▼	**Severe**	**Very severe**	**Mixed**	**Severe**	**Very severe**	**Mixed**	**Severe**	**Very severe**	**Mixed**
Rutten van-Mölken 2009	£18,774	£12,337	£16,519	£21,464	£14,425	£19,034	£19,374	£12,684	£17,024
Solem 2013	£22,206	£14,818	£19,643	£26,069	£17,937	£23,305	£23,050	£15,332	£20,362

Source: Based on Table 70 in the CS[1]; Solem et al. 2013[62]; Rutten-van Mölken et al. 2009[47]

Table 5.30: Incremental cost effectiveness results of the scenario analyses

Scenario no	Severe only patients			Very severe patients			Mixed population		
	Incremental Costs	**Incremental QALYs**	**ICER**	**Incremental Costs**	**Incremental QALYs**	**ICER**	**Incremental Costs**	**Incremental QALYs**	**ICER**
Base-case	£2,996	0.16	£18,774	£2,343	0.19	£12,337	£2,792	0.17	£16,519
Scenario 1 LAMA as a covariate	£2,859	0.18	£16,326	£2,344	0.19	£12,385	£2,698	0.18	£15,030
Scenario 2 Unadjusted SMRs	£2,964	0.13	£20,906	£2,015	0.15	£13,186	£2,482	0.14	£18,207
Scenario 3a Lung benefit 1-year adjustment	£3,021	0.17	£18,159	£2,454	0.17	£14,049	£2,844	0.17	£16,834
Scenario 3b Lung benefit 5-year adjustment	£3,021	0.17	£18,169	£2,454	0.17	£14,060	£2,844	0.17	£16,844
Scenario 5a All grade TEAEs	£2,983	0.16	£19,498	£2,329	0.18	£12,708	£2,779	0.16	£17,109
Scenario 5b No AEs	£2,991	0.16	£18,711	£2,337	0.19	£12,292	£2,787	0.17	£16,462

Source: Based on Table 65, Table 66, Table 68, Table 71 and Table 72 in the CS[1]
ICER = incremental cost effectiveness ratio; QALYs = quality adjusted life years

ERG comment: The ERG identified a programming error in the implementation of the probabilistic sensitivity analysis which resulted in not incorporating the parameter uncertainty pertaining to the treatment effects. Furthermore, the ERG noticed that the correlations between the coefficients of the exacerbation rate regression were not taken into consideration. In the clarification letter[14], the ERG asked the company to correct the programming error and incorporate the correlation between the exacerbation rate regression coefficients. The company provided a new corrected model and its PSA results with correlation calculations. The results presented in this report were based on this corrected model.

Considering the deterministic sensitivity analysis, the ERG noticed that some of the parameters were not included into the deterministic sensitivity analysis, such as the treatment effect parameters. The justification for the parameter inclusion criteria used by the company for deterministic sensitivity analysis is not clear to the ERG. The ERG conducted several scenarios exploring the treatment effectiveness in Section 5.3.

In scenario analyses, in Scenario no 3, where the lung function benefit of roflumilast was explored, it was not clear to the ERG how the adjustment ratios for one and five years were derived. Considering that these adjustment factors are almost identical, the ERG considers whether both one year and five year scenarios were necessary. The ERG noted that the majority of the scenario analyses resulted in more favourable ICER results for roflumilast, and deemed that more scenarios exploring the uncertainty on treatment effectiveness and mortality assumptions were necessary. Therefore, in Section 5.3, the ERG performed additional scenarios on these areas of structural uncertainty.

5.2.12 Model validation and face validity check

The company performed a range of checks to identify programming errors or other errors in data incorporation into the model. In the CS, it was mentioned that all model checks resulted in model outcomes as expected.

As an additional validation exercise, the rate ratios observed in the trial (median exposure to treatment was 364 days for both arms of REACT) and those generated by the model (in the first year) were compared in the CS. As REACT contained both severe and very severe COPD patients, a mixed population was assumed. These rate ratios are given in Table 5.31.

Table 5.31: Exacerbation rate ratios from the trial and from the model.

Exacerbations	Trial	Model	Difference (%)
Moderate or Severe	0.810	0.810	0.01%
Moderate	0.879	0.887	0.87%
Severe	0.688	0.656	4.66%
Source: Based on Table 53 in the CS[1]			

In the CS, the figures in Table 5.31 were interpreted as the model's high predictive ability and the minor differences between the trial and model outcomes were considered to originate from other facets of the model such as the transition probability from severe to very severe COPD.

ERG comment: The ERG found the list of programming error checks useful, however considered that the reporting of these error checks did not provide sufficient information. While reporting verification efforts, in addition to the qualitative description, technical description of each effort (e.g. which cell or programming lines were modified and from which cells/output lines the model outcome could be assessed) should be also reported to facilitate reproducibility of verification test results.

The ERG conducted some of the steps of an in-house technical verification checklist (TECH-VER checklist) to verify whether the model was correctly implemented and whether the report (description of the model as well as the results) and the model (calculations and results) were consistent or not. The protocol and cell by cell checking of the model helped ERG identifying a number of programming errors, which will be corrected in ERG exploratory analyses

In addition to the rate ratio comparisons, as provided in Table 5.31, between trial and model outcomes in the CS, the ERG also requested the exacerbation rate comparisons from the company. In the response to the clarification letter[14], the company provided exacerbation rate comparisons between trial and model outcomes. The company explored two different settings for this validation exercise: base-case setting and validation setting. In the first setting, the exacerbation outputs in one year from the model in the base-case were compared with the annual exacerbation rates from the REACT trial. In this setting, it was observed that the model slightly overestimated the exacerbation rates for patients in severe COPD state, since some of the severe COPD state patients in the model progressed to very severe COPD state, where they were at higher risk for exacerbations. Therefore, for the patients in the severe COPD state, a validation setting was explored. In that setting, for the very severe COPD patients, exacerbation risk was assumed to be the same as the risk of severe COPD patients. From Table 5.32, it can be seen that the results from the validation setting were closer to the trial results. In the response to the clarification letter[14], the minor differences between the trial and model outputs were attributed to the additional mortality applied in the model.

Table 5.32: Roflumilast exacerbation rates from the trial and from the model.

COPD state	Exacerbations	Trial	Output (base-case settings)	Output (validation settings)
Severe	Moderate	0.384	0.395	0.379
	Severe	0.115	0.124	0.113
Very severe	Moderate	0.607	0.593	-
	Severe	0.270	0.263	-
Source: Based on Table 4 in the response to the clarification letter[14] COPD = chronic obstructive progressive disease				

In addition to this validation exercise, the company also provided a comparison between the results from the model used in Samyshkin et al. 2014[45] and the modified CS model, in which the drug costs (removal of the LAMA costs), baseline age (older version of UK life table used from 2007-2009) and exacerbation CFR model inputs (older source for CFR calculations) were adjusted to be more in line with Samyshkin et al. 2014[45]. In the response to the clarification document[14], the company demonstrated that the outputs (Costs, life years, QALYs, ICER and number of exacerbations) from the Samyshkin et al. 2014[45] model and from the adjusted CS model were very similar, and that the absolute difference between two model results was always less than 1% for each output.

Finally, in the response to the clarification letter[14], the company stated that the model structure was presented to clinical experts in an advisory board for the purpose of face validation, however the details of the advisory board and face validation efforts were not provided.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

Based on all considerations from Section 5.2, the ERG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the CS. Some of the adjustments considered in Section 5.2 were already incorporated in the model file provided by the company in response to clarification, thus provided an updated CS base-case.[14] Therefore, the ERG will use the updated CS

base-case as a starting point for its analysis. These adjustments made by the ERG/provided in the updated company base-case form the ERG base-case and were subdivided into three categories (derived from Kaltenthaler 2016[72]):

- Fixing errors (correcting the model were the company's submitted model was unequivocally wrong)
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (amending the model were the ERG considers that reasonable alternative assumptions are preferred)

After the ERG base-case analysis, additional scenario analyses were performed by the ERG in order to examine the potential impact of alternative assumptions on the cost effectiveness estimates.

5.3.1. Explanation of the ERG adjustments

Fixing errors

1. Fixing errors consisted of:
   a. Changing the cost of moderate exacerbations: the ERG considers the method to estimate the number of additional GP visits during exacerbations wrong, because moderate and severe exacerbations are not the same as infrequent and frequent exacerbations. The company overestimates the number of GP visit per exacerbations (2.03) as they did not take into account that patients may experience more than one exacerbation a year. To correct for this, the ERG applied one additional GP visits for patients with moderate exacerbations.
   b. Adjusting the number of GP visits for severe exacerbations: The ERG also deems that the additional number of GP visits for severe exacerbations are overestimated (8.03). In line with Oostenbrink et al. 2005[67], the ERG considers that patients do not visit the GP as they are all hospitalised for the severe exacerbation (0).
   c. Adjusting the unit cost for hospitalisation related to severe exacerbation: the ERG added the costs for excess bed days to the weighted average of short- and long-term non-elective hospital stay for COPD (£1,183.06 without excess bed days £1245.45 with excess bed days).
   d. Correcting the cost related to pneumonia costs: the ERG could not replicate the weighted average of the costs of short- and long-term non-elective hospital stay for pneumonia (£2518). Therefore, the ERG used their own calculated weighted average, whilst also including the excess bed days (£1,924.72).
   e. Correcting the drug costs for LABA / ICS: The ERG identified a minor error in the estimation of the total drug costs of this combination treatment. Although LABA can be administered in two different ways (either 1x 400/12 or 2x 200/6), the unit costs of these combinations are identical. Therefore, the ERG opted to simply add the costs of LABA (£0.63) to the costs of ICS (£0.68). This results in daily costs of £1.32 instead of £1.30.

Fixing violations

2. Changing the cost of ambulance transport according to the most recent available costs: the ERG used £233.02 from HRG code ASS02 "See and treat and convey" instead of £208.95 from Samyshkin et al. 2014[45] used in the model.

The ERG incorporated this change to the model to be in line with good modelling practice to use the most recently published cost and resource use data.

3. Changing the utility decrements due to moderate and severe exacerbations: the ERG uses 0.0166 and 0.0482 from Hoogendoorn et al. 2011[65] instead of 0.01 and 0.042 from Rutten-van Mölken et al. 2009[47] for disutilities associated with moderate and severe exacerbations, respectively.

The ERG incorporated this change to the model, because the current estimates from Rutten-van Mölken et al. 2009[47] were not derived from the EQ-5D but from TTO valuations of COPD health profiles by the Dutch general public. Therefore, to be more in line with NICE reference case, the estimates from Hoogendoorn et al. 2011[65] were used for moderate and severe exacerbations, since they were derived from patient-reported EQ-5D and valued with the UK-tariff.

4. Implementing half cycle correction

The ERG implemented a half cycle correction in the model. Even though the impact was expected to be small, it is more in line with good modelling practices.

5. Using the baseline population characteristics and adverse event rates from the ITT LAMA concomitant subpopulation (Table 5.6) instead of the full ITT baseline characteristics (Table 5.5) used in the CS. Similarly the adverse event rates derived from the ITT concomitant LAMA subgroup as given in Table 5.12 were preferred instead of the ones in Table 5.10, which were used in the CS base-case.

The ERG incorporated these changes for consistency reasons; the company provided effectiveness and cost effectiveness evidence for the decision on the use of roflumilast for this population (patients who received triple therapy including LAMA).

Matters of judgement

6. Changing the maintenance costs associated with very severe COPD state:

The ERG believes that patients with very severe COPD visit the GP more frequently in one year than patients with severe COPD. In the company submission, patients in both groups visited the GP twice a year, whilst Oostenbrink et al. 2005[67] observed that patients in the very severe COPD group visited the GP four times a year. The ERG used this latter estimate of Oostenbrink et al. 2005[67] in their ERG base-case.

7. Using severe COPD specific annual decline rates: The ERG uses the annual decline rate of 38 ml per year specific to the severe COPD patients from Decramer and Cooper 2010[58] instead of 52 ml per year used in the CS.

The ERG judges the 38 ml per year estimate from Decramer and Cooper 2010[58] to be more plausible to use in the model compared to the 52 ml per year estimate from Lung Health Study[56], because the latter estimate is derived from a study which mostly consisted of moderate COPD patients (i.e. the baseline FEV1% predicted at baseline was 78%).

8. Using rate ratios obtained from the ITT population analysis instead of the PP population analysis in negative binomial regressions to estimate moderate and severe exacerbation rates.

The ERG judges the treatment effectiveness estimates (in terms of rate ratios) based on ITT population analysis to be more reliable, more in line with common practice in RCT statistical analysis, and more reflective of the clinical practice compared to the rate ratios based on PP population analysis as discussed in Section 5.2.6. Therefore, the ITT rate ratios, 0.767 (0.595–0.989) for severe and 0.934 (0.773–1.128) from Table 4.10, derived from the negative binomial regression that was performed on the concomitant LAMA subpopulation were used in the ERG preferred base-case.

Additional scenarios

The ERG conducted additional scenario analyses to explore further the structural uncertainties in the economic evaluation in the ERG preferred base-case. These additional scenarios are listed as below.

Scenario 1. Alternative assumptions on treatment effectiveness

Scenario 1a. Incorporating moderate and severe exacerbation rates from Table 14.2.1.76 and 14.2.1.77 the CSR of REACT trial, derived separately for COPD severe and very severe patients

In this scenario, different from the ERG preferred base-case, instead of using the rate ratios from Table 4.10 (which assumes the same roflumilast vs. placebo rate ratios for severe and very severe COPD patients), mean exacerbation rates separately derived from the severe and very severe COPD patients were used. The regression analyses that yielded these rates were performed on the ITT concomitant LAMA treatment subpopulation. These rates can be found from Table 14.2.1.76 and 14.2.1.77 the CSR of REACT trial as given below.

Table 5.33: The exacerbation rates separately derived from severe and very severe COPD patients from the concomitant LAMA patients in the ITT population

Moderate or Severe Exacerbations						
	Severe COPD patients, Poisson regression			**Very Severe COPD patients, Poisson regression**		
	Mean	**Lower 95% CI**	**Upper 95% CI**	**Mean**	**Lower 95% CI**	**Upper 95% CI**
roflumilast plus triple therapy rate	0.782	0.667	0.917	1.14	0.950	1.369
triple therapy rate	0.847	0.734	0.976	1.417	1.197	1.677
Rate ratio	0.924	0.746	1.144	0.805	0.628	1.032
Severe Exacerbations						
	Severe COPD patients, negative binomial regression			**Very Severe COPD patients, negative binomial regression**		
	Mean	**Lower 95% CI**	**Upper 95% CI**	**Mean**	**Lower 95% CI**	**Upper 95% CI**
roflumilast plus triple therapy rate	0.221	0.169	0.288	0.421	0.321	0.551
triple therapy rate	0.300	0.240	0.376	0.553	0.426	0.719
Rate ratio	0.736	0.520	1.042	0.761	0.523	1.106

Source: Table 14.2.1.76 and 14.2.1.77 the CSR of REACT trial
CI = confidence interval; COPD = chronic obstructive progressive disease

In Table 5.33, the moderate or severe exacerbation rate estimates were derived from Poisson regression, whereas the severe exacerbation rate estimates were derived from negative binomial regression. Assuming that negative binomial and Poisson regression estimates would give similar results, the moderate exacerbation rate estimates were calculated from the difference between the moderate or severe exacerbation rate and the severe exacerbation rate. Based on these calculations, the exacerbation rates used in the model in this scenario are given below in Table 5.34.

Table 5.34: Exacerbation rates used in the model

Treatment	Moderate exacerbations		Severe exacerbations	
	Severe COPD	Very severe COPD	Severe COPD	Very severe COPD
roflumilast plus triple therapy rate	0.561	0.719	0.221	0.421
triple therapy rate	0.547	0.864	0.300	0.553
COPD = chronic obstructive progressive disease				

Scenario 1b. Incorporating pooled rate ratios from REACT and RE2SPOND trials for moderate and severe exacerbations

In Table 4.10, the moderate or severe exacerbation rate ratio of roflumilast vs. placebo from the negative binomial regressions performed on the ITT population, concomitant LAMA subgroup in REACT trial was 0.871. When the results from RE2SPOND were taken into account, the pooled rate ratio for moderate or severe exacerbations (roflumilast vs. placebo) from REACT and RE2SPOND trials was increased to 0.90 (Table 1.1). In this scenario, we multiply the exacerbation rate ratios used in the ERG preferred base-case by a factor of (0.90/0.871), assuming that severe and moderate exacerbation rate ratios changed uniformly.

Scenario 2. Patients starting the model with very severe COPD (instead of severe COPD)

In this exploratory scenario analysis, it was assumed that all patients started the model in the very severe COPD state. In both CS and the ERG preferred base-case, all patients were assumed to start the model in the severe COPD state.

Scenario 3. Utility estimates from Solem et al. 2013[62]

In the ERG preferred base-case, health state utilities were taken from Rutten-van Mölken et al. 2006[46] and health state disutilities were from Hoogendoorn et al. 2011[65]. In this scenario, different HRQoL estimates for the COPD health state utilities and exacerbation disutilities from Solem et al. 2013[62] were used.

Scenario 4. Alternative assumptions surrounding COPD related mortality

Scenario 4a. Applying a single, uniform CFR for severe exacerbations, same for all ages

In this scenario, different from ERG preferred base-case, a uniform CFR (4.3%) from the 2014 UK National COPD Audit[59] was applied for severe exacerbations through all ages. In both CS and the ERG preferred base-case, the CFR from UK National COPD Audit[59] was adjusted according to the age of the cohort as explained in Section 5.2.6.

Scenario 4b. Applying the SMRs from Eckberg-Aronsson et al 2005[60], which included all COPD related deaths and excluding exacerbation CFRs.

In this scenario, different from ERG preferred base-case, SMRs (3.1 and 5 for severe and very severe COPD patients) from Eckberg-Aronsson et al 2005[60] were used. The SMRs in Eckberg-Aronsson et al 2005[60] were based on all COPD related deaths, including deaths due to exacerbations. Therefore, the CFRs were set to 0% in this scenario analysis. The SMRs used in CS and the ERG preferred base-case were based on Samyshkin et al. 2014[45], which was based on all COPD related deaths but exacerbation related deaths. The ERG could not trace how the SMRs from Samyshkin et al. 2014[45] were derived. This is also in line with the similar number of deaths in both arms (17 in the Roflumilast group and 18 in placebo group) as shown in Table 4.12.

Scenario 5. All adverse events incorporated instead of severe adverse events only
In this scenario analysis, all grade adverse events were considered instead of incorporating only severe adverse events as in the CS and ERG preferred base-case.

5.3.2. Results from the ERG preferred base-case and probabilistic sensitivity analysis

In the base-case analysis, roflumilast plus triple therapy resulted in a total (discounted) costs of £21,384 and QALYs of 6.10 (See Table 5.35). On the other hand, triple therapy alone resulted in a total (discounted) costs of £17,895 and QALYs of 6.01. Based on these results, roflumilast plus triple therapy produced an additional 0.10 QALYs at an incremental cost of £3,489 when compared to triple therapy alone, leading to an ICER of £35,821. This ICER is substantially higher than the company base-case ICER of £18,774.

Table 5.35: The ERG preferred base-case results

Technologies	Total costs	Total LYG	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER
roflumilast plus triple therapy	£21,384	8.75	6.10	£3,489	0.12	0.10	£35,821
triple therapy alone	£17,895	8.63	6.01	-	-	-	-
ICER = incremental cost effectiveness ratio; LYG = life years gained; QALYs = quality adjusted life years.							

Disaggregated results for effects and costs by health state are given in Table 5.36, below.

Table 5.36: Disaggregated costs and effects from the ERG preferred base-case analysis

	triple therapy alone	roflumilast plus triple therapy	Incremental
Costs-discounted			
Direct drug cost	£7,663	£11,779	£4,116
Exacerbation cost	£3,589	£2,846	-£743
Disease state cost	£6,576	£6,702	£126
Adverse event costs	£66	£57	-£9
Total costs	£17,895	£21,384	£3,489
Effects – undiscounted			
Total exacerbations	8.56	7.66	-0.90
Hospital exacerbations	2.88	2.26	-0.62
Effects – discounted			
Years in Severe State	5.37	5.40	0.03
Years in Very Severe State	3.27	3.35	0.08
Total Life years	8.63	8.75	0.12
Total QALYs	6.01	6.10	0.10
QALYs = quality adjusted life years.			

Based on the results above, similar to the CS, the incremental QALYs gained for roflumilast plus triple therapy were mostly due to the fewer exacerbations, and increased life expectancy (due to fewer exacerbation related deaths). The impact of TEAEs on the costs and QALYs was again negligible.

The ERG performed probabilistic sensitivity analyses on the ERG preferred base-case to explore the parametric uncertainty around the base-case parameters. In the PSA, if the standard error estimates for

the updated parameters could be found, those new estimates were used, otherwise it was assumed that the standard error estimates of the updated parameters would change in the same magnitude of the change in their means. The summary results of the PSA (10,000 iterations), which includes the mean and the 95 % CI of the costs, QALYs and resultant ICERs for the PSA are presented below (See Table 5.37) with corresponding scatterplots (See Figure 5.7) and CEACs (See Figure 5.8).

The PSA resulted in an incremental cost of £3,504, incremental QALYs of 0.10 and an ICER of £33,803 per QALY gained. These are comparable to the deterministic base-case results given in Table 5.35. From the scatterplot, it can be seen that the ICER of the simulation outputs are all scattered in the northeast quadrant and from the CEAC it can be seen that the probability that roflumilast plus triple therapy is cost effective compared to triple therapy alone is approximately 3% at a £20,000 per QALY gained threshold and 28% at a £30,000 per QALY gained threshold.

Table 5.37: PSA results of the ERG preferred base-case

Technologies	Total costs	95% CI	Total QALYs	95% CI	Incr. costs	Incr. QALYs	ICER
roflumilast plus triple therapy	£21,607	£18,695 to £24,918	6.15	5.44 to 6.91	£3,504	0.10	£33,803
triple therapy alone	£18,103	£15,435 to £21,197	6.05	5.35 to 6.8	-	-	-
ICER = incremental cost effectiveness ratio; LYG = life years gained; QALYs = quality adjusted life years.							

Figure 5.7: Incremental cost effectiveness scatterplot of the ERG preferred base-case analysis

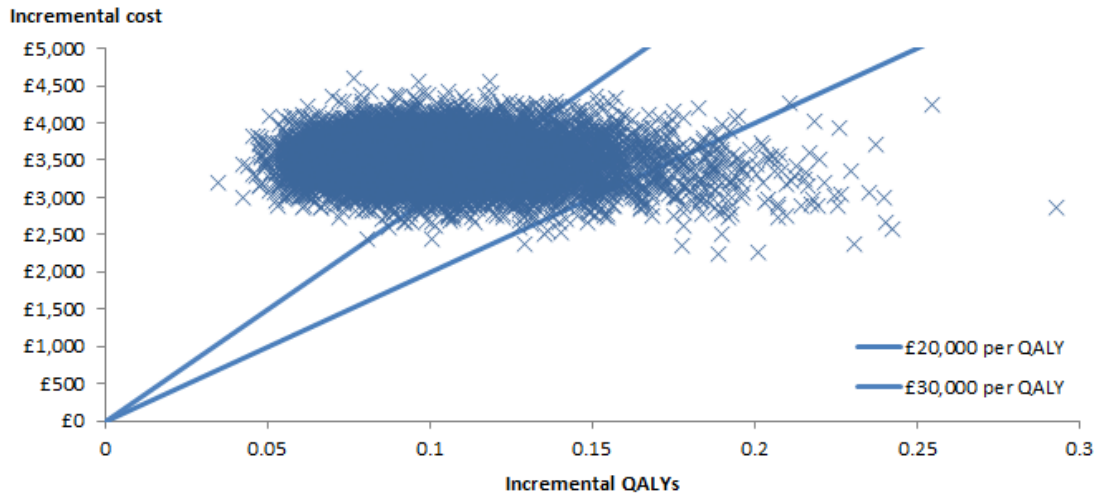
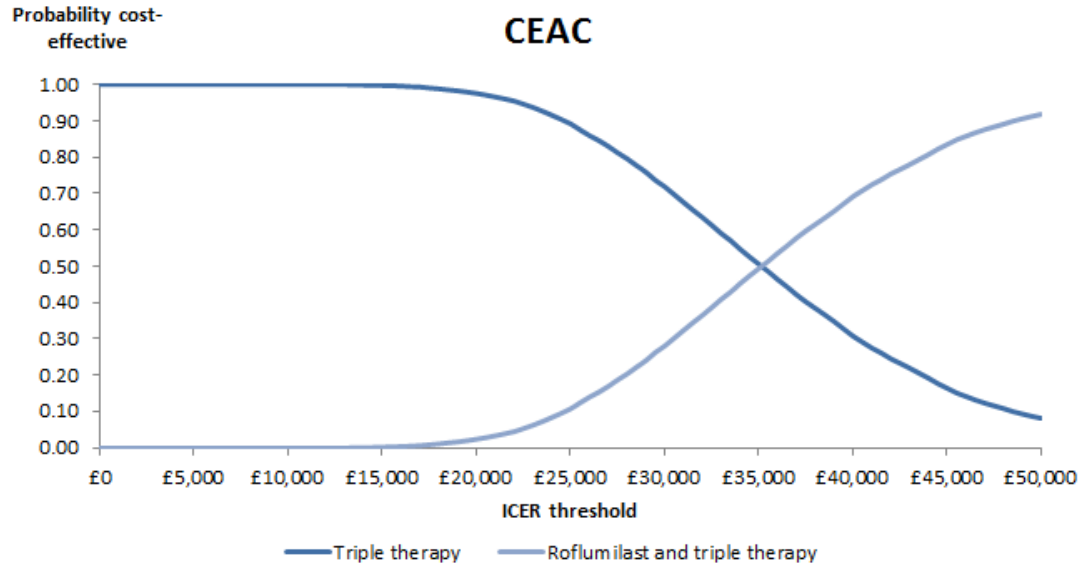


Figure 5.8: Cost effectiveness acceptability curve of the ERG preferred base-case



5.3.3. Results from the ERG additional exploratory scenario analyses

The results of the additional scenarios listed in Section 5.3.1, which were performed on the ERG preferred base-case are provided in Table 5.38 below.

Table 5.38: Results from the additional scenario analyses conducted on the ERG preferred base-case

Scenarios	roflumilast plus triple therapy		Triple therapy alone		Incr. costs	Incr. QALYs	ICER
	Total costs	Total QALYs	Total costs	Total QALYs			
CS base-case	£22,930	6.14	£19,933	5.98	£2,996	0.16	£18,774
ERG preferred base-case	£21,384	6.10	£17,895	6.01	£3,489	0.10	£35,821
Scenario 1a (Alternative effectiveness)	£22,147	5.95	£19,022	5.80	£3,125	0.15	£21,187
Scenario 1b (Pooled effectiveness)	£21,442	6.09	£17,895	6.01	£3,547	0.09	£41,592
Scenario 2 (Very severe population)	£25,205	4.93	£22,324	4.81	£2,881	0.12	£24,740
Scenario 3 (Utilities from Solem)	£21,384	5.84	£17,895	5.76	£3,489	0.08	£41,968
Scenario 4a (Uniform CFR)	£21,289	6.07	£17,785	5.96	£3,504	0.11	£32,348

Scenarios	roflumilast plus triple therapy		Triple therapy alone		Incr. costs	Incr. QALYs	ICER
	Total costs	Total QALYs	Total costs	Total QALYs			
Scenario 4b (all COPD SMR and no CFR)	£20,200	5.82	£17,149	5.80	£3,052	0.02	£149,564
Scenario 5 (all grade adverse events)	£21,410	6.09	£17,907	6.00	£3,503	0.09	£40,950
CFR = case fatality rate; COPD = chronic obstructive progressive disease; ICER = incremental cost effectiveness ratio; LYG = life years gained; QALYs = quality adjusted life years; SMR = standardized mortality ratio.							

From these results, it can be observed that the cost effectiveness results are very sensitive to the assumptions on the COPD related mortality (Scenario 4b). Applying SMRs including exacerbation related deaths (and therefore excluding CFRs) increased the ICER to £149,564 per QALY gained. This is easily explained by the fact that roflumilast prevents exacerbations, and without a CFR the current model structure does not allow for a subsequent impact on mortality.

Assumptions on exacerbation rates also impact the ICER. The ERG observed that incorporating the pooled results from REACT and RE2SPOND trials increased the ICER, whereas using exacerbation rates derived separately for severe and very severe COPD patients decreased the ICER considerably. However, as described in Section 5.3.1, both of these scenario implementations were based on assumptions, therefore the results of Scenario 1a and 1b should be interpreted with caution.

As can be seen from the results of Scenario 2, when all patients enter in the very severe COPD state the ICER decreases. This is in line with the exploratory scenarios conducted by the company on the CS base case as discussed in Section 5.2.11.

The choice for the utility source is another important driver for the cost effectiveness of roflumilast. If estimates for the COPD health state utilities and exacerbation disutilities were based on Solem et al. 2013[62], the ICER would be close to £42,000 per QALY gained. In the economic model, changing the base-case disutilities associated with exacerbations to disutilities from Solem et al. 2013[62] had a bigger impact than changing the base-case health state utilities to health state utilities from Solem et al. 2013[62].

Finally, including all grade adverse events have a significant impact on ICER, as was also seen in the company scenario analysis. If all adverse events were incorporated to the model instead of only serious adverse events, the ICER would be close to £41,000 per QALY gained. However, in this scenario the milder adverse events are assumed to have the same costs and disutilities as the serious adverse events. This is unlikely to be true in reality, and thus this scenario should be regarded as conservative.

5.4 Conclusions of the cost effectiveness section

The majority of the cost effectiveness searches in the CS were well documented, clearly structured and easily reproducible, and were carried out in line with the NICE guide to the methods of technology appraisal.[16] The ERG expressed concerns on restricting searches to English language and from eight countries only (UK, US, Canada, Germany, France, Italy, Spain and Australia). Furthermore, the ERG noted that stricter inclusion criteria were applied in this submission compared to the previous company submission of roflumilast (TA244), in terms of the intervention and comparators.

The economic model described in the CS is considered by the ERG to meet the NICE reference case to a reasonable extent (deviations occurred only in regards to measurement and valuation of HRQoL) and is in line with the decision problem formulated by the company (which is only partially in line the scope).

The ERG assessment indicated that the model was presented and reported appropriately. The company developed a three state (severe COPD, very severe COPD and death) Markov decision model to assess the cost effectiveness of roflumilast as an add-on to triple therapy in patients with (very) severe COPD associated with chronic bronchitis and a history of frequent exacerbations (≥ 2 moderate or severe COPD exacerbations within the previous year) despite triple therapy. The continuation of triple therapy without any additional medication is the only comparator in the submission. This is different from the scope, as other comparators (theophylline as an add-on to triple therapy, LAMA / LABA, LAMA / ICS, LABA / ICS, LAMA and LABA) were ignored.

In the model, patients are at risk of moderate or severe exacerbations. The exacerbation risks used in the model differ by health state, treatment, and exacerbation severity. Exacerbations lead to additional costs, a temporary decrease in quality of life, and additional mortality (only for severe exacerbations). The model inputs related to the disease progression, the COPD and exacerbation related mortality, costs, and utilities were taken from the literature whereas the baseline patient characteristics, treatment effectiveness (exacerbation rates) and safety parameters (adverse event rates) were derived from the REACT trial.

The addition of roflumilast to triple therapy (LAMA / LABA / ICS) is more costly (incremental costs £2,996), but also yields more QALYs (incremental QALYs: 0.16) than triple therapy only, resulting in an ICER of £18,774. The incremental QALY gains were mostly due to the fewer exacerbations, and increased life expectancy (due to fewer exacerbation related deaths). The increase in costs is mainly due to higher treatment costs.

The probabilistic sensitivity analysis showed that the probability that roflumilast / LAMA / LABA / ICS is cost effective compared to LAMA / LABA / ICS is approximately 70% at a £20,000 per QALY gained threshold. The company performed several scenario analyses including varying the severity of COPD of the baseline cohort. Roflumilast as an add-on therapy seems to be more cost effective for very severe COPD patients compared to severe COPD patients. From the other scenarios it was concluded that the changes in the use of standardised mortality ratios and quality of life utilities seem to have an important effect on ICERs, whereas assumptions on adverse events only had a minor influence.

The ERG's main concern with the company submission was the source of the exacerbation rates. The company used the exacerbation rates of the per protocol study population in the REACT trial while pooled estimates from the REACT and RE2SPOND trial might provide more robust treatment effectiveness estimates. Furthermore, the ERG considers the intention-to-treat population more in line with UK clinical practice than the per protocol population because it is likely that in clinical practice patients who do not strictly fulfil the inclusion criteria of REACT will receive treatment with roflumilast. Other concerns of the ERG were related to the model structure, translation of the exacerbation prevention to mortality gains, the generalisability of the REACT findings to the UK clinical practice, and model inputs used in transition probabilities as well as costs and utility inputs.

Accordingly, the ERG has incorporated various adjustments to the company base-case. Ideally, the adjustments would have included using exacerbation rate ratios based on the pooled ITT estimates from the REACT and RE2SPOND trial. However, the RE2SPOND trial did not report severe exacerbation rates specific to the LAMA subpopulation. Whilst speculative assumptions could be made, it was

decided to leave those for a scenario analysis, and base the ERG base case on ITT data from the REACT trial only.

The ERG base-case resulted in an ICER of £35,821 per QALY gained. The most influential adjustments/corrections made by the ERG were 1) using exacerbation rate ratios based on the ITT population from REACT (obtained from negative binomial regressions performed on patients who received concomitant LAMA treatment); 2) using severe COPD specific FEV1 decline rates from Decramer and Cooper 2010[58] and; 3) using exacerbation related utility decrements from Hoogendoorn et al. 2011[65]. From the PSA results, the probability that roflumilast plus triple therapy is cost effective compared to triple therapy alone is approximately 3% at a £20,000 per QALY gained threshold and 28% at a £30,000 per QALY gained threshold.

The ERG conducted some additional scenario analyses on the ERG preferred base-case to assess structural uncertainty.

One of the scenarios used different exacerbation rate ratios than the ERG preferred base-case (which assumes the same roflumilast vs. placebo rate ratios for severe and very severe COPD patients); instead using mean exacerbation rates separately derived from the severe and very severe COPD patients in the ITT concomitant LAMA treatment subpopulation. These rates were derived from the Poisson regression analyses for moderate or severe exacerbations and negative binomial regression analyses for severe exacerbations, which were provided in the CSR of the REACT trial. Assuming that negative binomial and Poisson regression estimates would give similar results, the moderate exacerbation rate estimates were calculated from the difference between the moderate or severe exacerbation rate and the severe exacerbation rate. This scenario resulted in an ICER of £21,187 per QALY gained.

In another scenario we assessed what impact might be expected from using pooled exacerbation rates based on the ITT populations from REACT and RE2SPOND. To that end, we multiplied the exacerbation rate ratios used in the ERG preferred base-case by a factor of (0.9/0.871), which is the ratio of the pooled moderate or severe RR from the ITT population, concomitant LAMA subgroup of REACT and RE2SPOND trials with the same RR from the REACT trial only. In this scenario, it was assumed that incorporating the RE2SPOND trial results would change the severe and moderate exacerbation rate ratios uniformly. This scenario resulted in an ICER of £41,592 per QALY gained.

From the results of these two scenarios, it became obvious that the assumptions about exacerbation rates impact the ICER considerably. Specifically, incorporating the pooled results from REACT and RE2SPOND trials increased the ICER, whereas using exacerbation rates derived separately for severe and very severe COPD patients decreased the ICER. However, both of these scenario implementations were based on assumptions, as the company had not provided the relevant analyses to estimate pooled exacerbation rates based on the ITT populations; therefore, the results of Scenario 1a and 1b should be interpreted with caution.

The ERG thinks that the most robust exacerbation rate would be the moderate and severe exacerbation rates derived separately for severe and very severe COPD patients from the negative binomial regression analyses performed on the pooled ITT population subgroup of LAMA concomitant patients from both REACT and RE2SPOND trials. And as this data is readily available to the company, the current uncertainty around the ICER stemming from uncertainty about the exacerbation rates can easily be resolved.

Whilst the source for estimation of exacerbation rates has a considerable impact on the ICER, the scenario analyses made it clear that how these exacerbations are translated to mortality is very important for the cost effectiveness results as well. Applying SMRs that included exacerbation related deaths and therefore not using exacerbation CFRs as explained in scenario 4b in Section 5.3.1 increased the ICER

to £149,564 per QALY gained. However, given that it is a known fact that exacerbations increase the probability of death, a model that does not account for this explicitly through a CFR will, by definition, underestimate the cost effectiveness of a treatment that reduces the number of exacerbations.

From the additional scenarios, it can be also seen that utility estimates, baseline population COPD states and adverse events also have an impact on ICER (ICERs ranging from £25,000 to £42,000). Thus, the ICER range from all the scenario analyses is from £21,000 to £150,000 per QALY gained.

In conclusion, based on the ERG base-case analysis, the ICER is estimated to be around £35,000 per QALY gained. This ICER value is larger than the £20,000 per QALY threshold. In addition, due to several assumptions regarding the exacerbation rates, and translation of exacerbations to mortality, the ERG deems that the uncertainty around the cost effectiveness of roflumilast is substantial.

6. IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

In Section 5.3 the ERG base-case was presented, which was based on various changes compared to the company base-case. Table 6.1 shows how each individual change impacts the ICER plus the combined effect of all changes simultaneously. The analyses numbers in Table 6.1 correspond to the analyses numbers reported in Section 5.3.

Table 6.1: Revised base case cost effectiveness analysis, incorporating corrections and amendments identified by the ERG

Scenarios	roflumilast plus triple therapy		Triple therapy alone		Incr. costs	Incr. QALYs	ICER
	Total costs	Total QALYs	Total costs	Total QALYs			
0. CS base-case	£22,930	6.14	£19,933	5.98	£2,996	0.16	£18,774
1. Fixing errors	£22,264	6.14	£19,006	5.98	£3,258	0.16	£20,416
(1+2). Fixing errors and using a more recent estimate for cost of ambulance transport	£22,301	6.14	£19,061	5.98	£3,240	0.16	£20,303
(1+3). Fixing errors and using exacerbation utility decrements from Hoogendoorn et al. 2011[65]	£22,264	6.15	£19,006	6.00	£3,258	0.15	£21,347
(1+4). Fixing errors and half cycle correction	£22,347	6.17	£19,073	6.01	£3,274	0.16	£20,516
(1+5). Fixing errors and concomitant LAMA population data for baseline characteristics and adverse events	£21,281	5.89	£18,158	5.73	£3,123	0.16	£20,025
(1+6). Fixing errors and changing the maintenance costs associated with very severe COPD state	£22,653	6.14	£19,381	5.98	£3,272	0.16	£20,498
(1+7). Fixing errors and using severe COPD state specific annual decline	£21,683	6.37	£18,294	6.22	£3,389	0.15	£21,875
(1+8). Fixing errors and using exacerbation rate ratios obtained from ITT population	£22,519	6.09	£19,006	5.98	£3,513	0.11	£33,015
(1 to 8 all): ERG preferred base-case	**£21,384**	**6.10**	**£17,895**	**6.01**	**£3,489**	**0.10**	**£35,821**

COPD = chronic obstructive progressive disease; CS = Company submission; ERG = Expert review group; ICER = incremental cost effectiveness ratio; Incr. = incremental; ITT = intention to treat; LAMA = Long acting Muscarinic-receptor Antagonist; LYG = life years gained; QALYs = quality adjusted life years.

7. OVERALL CONCLUSIONS

7.1 Statement of principal findings

The company has restricted the population, intervention and comparators. Regarding the comparators ignored in the submission, the company states "As the scope of intervention is restricted to roflumilast in combination with LABA / LAMA / ICS, mono- and dual therapy comparators are not considered relevant." If the committee agrees that the population can be restricted to adults with severe COPD associated with frequent exacerbations despite triple therapy, it might seem reasonable not to consider mono- and dual therapy comparators.

However, it is for the NICE appraisal committee to decide what the relevant population and relevant comparators are. There is evidence available to compare roflumilast in combination with LABA / ICS or in combination with triple therapy to most of the comparators listed in the scope. The company could have presented results for these comparisons. It is beyond the possibilities of the ERG within the STA timelines to perform these analyses, as this involves full data extraction of these trials, a full network meta-analysis and inclusion of these comparators in the economic model. However, it is certainly within the possibilities for the company, should the appraisal committee decide that these analyses are relevant for the decision problem.

Regarding the results as presented in the CS, the company has chosen the populations and analyses that showed the most favourable effects for roflumilast. Therefore, the company base-case analysis may overestimate the effectiveness of roflumilast. As presented in Section 4.2.5 the company uses a rate ratio of moderate to severe exacerbations of 0.799 (95% CI 0.670 to 0.952) for roflumilast versus placebo, based on the concomitant LAMA population from the REACT trial only, the per-protocol population, and the negative binomial model. Using ITT data instead of PP data from the REACT trial results in a rate ratio for moderate to severe exacerbations of 0.871 (95% CI: 0.741 to 1.024). Alternatively, the company could have used data from the total ITT populations from the REACT and RE2SPOND trials, based on the negative binomial model analyses. This would have resulted in a rate ratio of 0.90 (95% CI 0.82 to 0.99). The ERG prefers an analysis based on the concomitant LAMA ITT populations from the REACT and RE2SPOND trials combined, using the negative binomial model. This results in a rate ratio of moderate to severe exacerbations of 0.90 (95% CI 0.80 to 1.02).

Similarly, the company uses a rate ratio for severe exacerbations of 0.659 (95% CI 0.497 to 0.872) p=0.0035). Using ITT data instead of PP data from the REACT trial results in a rate ratio for severe exacerbations of 0.767 (95% CI: 0.595 to 0.989). An alternative analysis using data from the total ITT populations from the REACT and RE2SPOND trials, based on the negative binomial model analyses would have resulted in a rate ratio of 0.85 (95% CI 0.68 to 1.06). The ERG prefers an analysis based on the concomitant LAMA ITT populations from the REACT and RE2SPOND trials combined, using the negative binomial model. However, it is not possible for the ERG to calculate the rate ratio because we do not have these data from the RE2SPOND trial.

Table 7.1: Key finding from company and ERG analyses (Mean rate (95% CI) of COPD exacerbations per patient per year)

	Roflumilast vs placebo
Company preferred analyses	
Moderate to severe exacerbation*	RR 0.799 (95% CI: 0.670 to 0.952)
Severe exacerbation*	RR 0.659 (95% CI: 0.497 to 0.872)
Company analyses using ITT data instead of PP data from REACT only	
Moderate to severe exacerbation**	RR 0.871 (95% CI: 0.741 to 1.024)
Severe exacerbation**	RR 0.767 (95% CI: 0.595 to 0.989)
ERG preferred analyses	
Moderate to severe exacerbation***	RR 0.90 (95% CI 0.80 to 1.02)
Severe exacerbation****	RR 0.85 (95% CI 0.68 to 1.06)
* Based on PP population from the REACT trial, using the negative binomial regression model and the concomitant LAMA subgroup; ** Based on ITT population from the REACT trial, using the negative binomial regression model and the concomitant LAMA subgroup; *** Based on ITT populations from the REACT and RE2SPOND trials, using the negative binomial regression model and the concomitant LAMA subgroup; **** Based on ITT populations from the REACT and RE2SPOND trials, using the negative binomial regression model (data for the concomitant LAMA subgroup were not available).	

Adverse events were reported by 67% of the roflumilast group and 59% of the placebo group, with serious adverse events reported by 26% and 30% respectively. More people withdrew because of adverse events in the roflumilast group (11% compared with 5%). The most frequently reported adverse events were COPD exacerbations (15% with roflumilast compared with 19% with placebo), diarrhoea (10% compared with 4% respectively), weight loss (9% compared with 3% respectively) and nausea (6% compared with 2% respectively). Mortality rates were the same in both groups (2%); as were major adverse cardiovascular events (2% in both groups). There was no increase in the incidence of pneumonia with roflumilast.

The company base-case cost effectiveness analysis resulted in an ICER of £18,774 for QALYs gained for roflumilast plus triple therapy vs. triple therapy alone. The incremental QALY gains were mostly due to the fewer exacerbations, and increased life expectancy (due to fewer exacerbation related deaths). The higher costs are mainly due to higher treatment costs. The probabilistic sensitivity analysis performed on the CS base-case showed that the probability that roflumilast / LAMA / LABA / ICS is cost effective compared to LAMA / LABA / ICS is approximately 70% at a £20,000 per QALY gained threshold.

The ERG has incorporated various adjustments to the company base-case. Ideally, the adjustments would have included using exacerbation rate ratios based on the pooled ITT estimates from the REACT and RE2SPOND trial. However, the RE2SPOND trial did not report severe exacerbation rates specific to the LAMA subpopulation. Whilst speculative assumptions could be made, it was decided to leave those for a scenario analysis, and base the ERG base case on ITT data from the REACT trial only.

The ERG base-case resulted in an ICER of £35,821 per QALY gained. The most influential adjustments/corrections made by the ERG were 1) using exacerbation rate ratios obtained from the negative binomial regressions performed on the ITT population from REACT trial patients who received concomitant LAMA treatment; 2) using severe COPD specific FEV1 decline rates from

Decramer and Cooper 2010[58] and; 3) using exacerbation related utility decrements from Hoogendoorn et al. 2011[65]. The PSA results show that the probability that roflumilast plus triple therapy is cost effective compared to triple therapy alone is approximately 3% at a £20,000 per QALY gained threshold and 28% at a £30,000 per QALY gained threshold. The ERG conducted some additional scenario analyses on the preferred base-case to assess structural uncertainty. The ICER range from the scenario analyses are between £21,000 and £150,000 per QALY gained. From the results of the scenario analyses, as expected, it is obvious that the assumptions on exacerbation rates have a considerable impact on the ICER. Specifically, incorporating the pooled results from REACT and RE2SPOND trials increased the ICER, whereas using exacerbation rates derived separately for severe and very severe COPD patients decreased the ICER considerably.

Whilst the source for estimation of exacerbation rates has a considerable impact on the ICER, the scenario analyses made it clear that how these exacerbations are translated to mortality is very important for the cost effectiveness results as well. Applying SMRs that included exacerbation related deaths instead of applying exacerbation CFRs increased the ICER to £149,564 per QALY gained. However, given that it is a known fact that exacerbations increase the probability of death, a model that does not account for this explicitly through a CFR will, by definition, underestimate the cost effectiveness of a treatment that reduces the number of exacerbations. The additional scenario analyses show that utility estimates, baseline population COPD states, and adverse events also have an impact on ICER, though to a lesser extent. In conclusion, based on the ERG base-case analysis, the ICER is estimated to be around £35,000 per QALY gained. This ICER value is larger than the £20,000 per QALY threshold. In addition, due to several assumptions regarding the exacerbation rates, and translation of exacerbations to mortality, the ERG deems that the uncertainty around the cost effectiveness of roflumilast is substantial.

7.2 Strengths and limitations of the assessment

The main strength of the clinical effectiveness section of the company submission is the fact that the submission is supported by two large randomised controlled trials comparing roflumilast as add-on to triple therapy to triple therapy in patients with COPD. Unfortunately, the company decided to use only one of these trials (REACT).

A limitation of the clinical effectiveness section of the company submission is the fact that the company decided to use only the per-protocol population of one of the two trials that were relevant for the decision problem. Instead the company could have used pooled results from the ITT populations in both trials. In addition, the company ignored most of the interventions and comparators in the scope. There is evidence available to compare roflumilast in combination with LABA / ICS or in combination with triple therapy to most of the comparators listed in the scope. The company could have presented results for these comparisons. Finally, the ERG believes that the company has consistently chosen the populations and analyses that showed the most favourable effects for roflumilast. Therefore, the company base-case analysis may overestimate the effectiveness of roflumilast.

The main strength of the cost effectiveness section of the company submission relates to the transparency with which the cost effectiveness analysis has been reported. Additionally, a well-known and often used model structure was used and where input was sourced from literature, often well-known studies were selected. However, the model structure would have gained strength if it had incorporated the impact of exacerbations on the decline of lung function.

In line with the clinical effectiveness section, the main weakness of the cost effectiveness section of the company submission is the source for the exacerbations rates used in the model. The company used the exacerbation rates of the concomitant LAMA subgroup of the per protocol study population in the

REACT trial while pooled estimates from the concomitant LAMA subgroup from the ITT populations of REACT and RE2SPOND trial are likely to provide more robust treatment effectiveness estimates. And as this data is readily available to the company, the current uncertainty around the ICER stemming from uncertainty about the exacerbation rates can easily be resolved.

7.3 Suggested research priorities

For the cost effectiveness model inputs, the ERG thinks that the most robust exacerbation rate estimate would be the moderate and severe exacerbation rates derived separately for severe and very severe COPD patients from the negative binomial regression analyses performed on the pooled ITT population subgroup of LAMA concomitant patients from both REACT and RE2SPOND trials. This rate can be easily obtained from the patient level data from these trials.

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in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Roflumilast for the management of chronic obstructive pulmonary disease

ERRATUM

This document contains errata in respect of the ERG report in response to the company's factual accuracy check.

The table below lists the page to be replaced in the original document and the nature of the change:

Page nr:	**Change:**
16	"…an ICER of £35,821 per QALY gained." is changed to "…an ICER of £35,814 per QALY gained." In Table 1.2, in the "ERG preferred base-case" row: "£21,384" is changed to "£21,332" "£17,895" is changed to "£17,844" "£35,821" is changed to "£35,814"
17	"This scenario resulted in an ICER of £21,187 per QALY gained." is changed to "This scenario resulted in an ICER of £21,180 per QALY gained." "This scenario resulted in an ICER of £41,592 per QALY gained." is changed to "This scenario resulted in an ICER of £41,585 per QALY gained."
82	"Finally, the ERG found some small errors in the estimation or reporting of the ambulance costs and the costs of LABA / ICS. These errors were corrected in the ERG base-case (Section 5.3)" is changed to "Finally, the ERG found a small error in the estimation or reporting of the ambulance costs. This error was corrected in the ERG base-case (Section 5.3)" 6th row of Table 5.19 is deleted.
95	Removal of the bullet point e.
99	"…total (discounted) costs of £21,384 and QALYs…" is changed to "…total (discounted) costs of £21,332 and QALYs…" "…triple therapy alone resulted in a total (discounted) costs of £17,895 and QALYs…" is changed to "…triple therapy alone resulted in a total (discounted) costs of £17,844 and QALYs…" "…an incremental cost of £3,489 when compared to triple therapy alone, leading to an ICER of £35,821." Is changed to "…an incremental cost of £3,489 when compared to triple therapy alone, leading to an ICER of £35,814." Costs, incremental cost and ICER in Table 5.35 are updated accordingly. In Table 5.36, the numbers for "Direct drug cost" (third row) and for "Total costs" are updated accordingly
100	"The PSA resulted in an incremental cost of £3,504, incremental QALYs of 0.10 and an ICER of £33,803 per QALY gained." is changed to "The PSA resulted in an incremental cost of £3,498, incremental QALYs of 0.104 and an ICER of £33,727 per QALY gained."

	Table 5.37 is updated with the new PSA results Figure 5.7 is updated with the new scatterplot from the new PSA results
101	Figure 5.8 is updated with the new CEAC from the new PSA results Table 5.38 is updated with the new scenario analysis results
102	Table 5.38 is updated with the new scenario analysis results
104	"The ERG base-case resulted in an ICER of £35,821 per QALY gained." is changed to "The ERG base-case resulted in an ICER of £35,814 per QALY gained." "This scenario resulted in an ICER of £21,187 per QALY gained." is changed to "This scenario resulted in an ICER of £21,180 per QALY gained." "This scenario resulted in an ICER of £41,592 per QALY gained." is changed to "This scenario resulted in an ICER of £41,585 per QALY gained."
106	Table 6.1 is updated with the new results
108	"The ERG base-case resulted in an ICER of £35,821 per QALY gained." is changed with "The ERG base-case resulted in an ICER of £35,814 per QALY gained."

relevant evidence may have been missed as a consequence of this. Apart from a search of the American Thoracic Society Conference 2016, no additional efforts were made to find unpublished or supplementary information.

The main weakness of the clinical effectiveness section of the company submission is the fact that the company decided to use only the per-protocol population of one of the two trials that were relevant for the decision problem. Instead the company could have used pooled results from the ITT populations in both trials. Therefore, the company base-case analysis may overestimate the effectiveness of roflumilast. In addition, the company ignored most of the interventions and comparators in the scope. There is evidence available to compare roflumilast in combination with LABA / ICS or in combination with triple therapy to most of the comparators listed in the scope. The company could have presented results for these comparisons.

In line with the clinical effectiveness section, the main weakness of the cost effectiveness section of the company submission is the source for the exacerbations rates used in the model. The company used the exacerbation rates of the concomitant LAMA subgroup of the per protocol study population in the REACT trial while pooled estimates from the concomitant LAMA subgroup from the ITT populations of REACT and RE2SPOND trial might provide more robust treatment effectiveness estimates.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG has incorporated various adjustments to the company base-case. Ideally, the adjustments would have included using exacerbation rate ratios based on the pooled ITT estimates from the REACT and RE2SPOND trial. However, the RE2SPOND trial did not report severe exacerbation rates specific to the LAMA subpopulation. Whilst speculative assumptions could be made, it was decided to leave those for a scenario analysis, and base the ERG base case on ITT data from the REACT trial only.

The ERG base-case resulted in an ICER of £35,814 per QALY gained. The most influential adjustments/corrections made by the ERG were 1) using exacerbation rate ratios obtained from the negative binomial regressions performed on the ITT population from REACT trial patients who received concomitant LAMA treatment; 2) using severe COPD specific FEV1 decline rates from Decramer and Cooper 2010 and; 3) using exacerbation related utility decrements from Hoogendoorn et al. 2011. From the PSA results, the probability that roflumilast plus triple therapy is cost effective compared to triple therapy alone is approximately 3% at a £20,000 per QALY gained threshold and 28% at a £30,000 per QALY gained threshold. The key findings from company and ERG preferred analyses are given in Table 1.2

Table 1.1: Key finding from company and ERG analyses

Scenarios	roflumilast plus triple therapy		triple therapy		Incr. costs	Incr. QALYs	ICER
	Total costs	Total QALYs	Total costs	Total QALYs			
CS base-case	£22,930	6.14	£19,933	5.98	£2,996	0.16	£18,774
ERG preferred base-case	£21,332	6.10	£17,844	6.01	£3,489	0.10	£35,814

CS = company submission; ERG = expert review group; ICER = incremental cost effectiveness ratio; QALYs = quality adjusted life years.

The ERG conducted some additional scenario analyses on the preferred base-case to assess structural uncertainty.

One of the scenarios used different exacerbation rate ratios than the ERG preferred base-case (which assumes the same roflumilast vs. placebo rate ratios for severe and very severe COPD patients), instead using mean exacerbation rates separately derived from the severe and very severe COPD patients in the ITT concomitant LAMA treatment subpopulation. These rates were derived from the Poisson regression analyses for moderate or severe exacerbations and negative binomial regression analyses for severe exacerbations, which were provided in the CSR of the REACT trial. Assuming that negative binomial and Poisson regression estimates would give similar results, the moderate exacerbation rate estimates were calculated from the difference between the moderate or severe exacerbation rate and the severe exacerbation rate. This scenario resulted in an ICER of £21,180 per QALY gained.

In another scenario, we multiply the exacerbation rate ratios used in the ERG preferred base-case by a factor of (0.9/0.871), which is the ratio of moderate or severe RR from the ITT population, concomitant LAMA subgroup of REACT and RE2SPOND trials with the same RR from REACT trial only. In this scenario, it was assumed that incorporating RE2SPOND trial would change the severe and moderate exacerbation rate ratios uniformly. This scenario resulted in an ICER of £41,585 per QALY gained.

From the results of these two scenarios, it is obvious that the assumptions on exacerbation rates have a considerable impact on the ICER. Specifically, incorporating the pooled results from REACT and RE2SPOND trials increased the ICER, whereas using exacerbation rates derived separately for severe and very severe COPD patients decreased the ICER. However, both of these scenario implementations were based on assumptions, therefore the results of Scenario 1a and 1b should be interpreted with caution.

The ERG thinks that the most robust exacerbation rate would be the moderate and severe exacerbation rates derived separately for severe and very severe COPD patients from the negative binomial regression analyses performed on the pooled ITT population subgroup of LAMA concomitant patients from both REACT and RE2SPOND trials. And as these data are readily available to the company, the current uncertainty around the ICER stemming from uncertainty about the exacerbation rates can easily be resolved.

Whilst the source for estimation of exacerbation rates has a considerable impact on the ICER, the scenario analyses made it clear that how these exacerbations are translated to mortality is very important for the cost effectiveness results as well. Applying standardised mortality ratios (SMRs) that included exacerbation related deaths and therefore not using exacerbation case fatality rates (CFRs) as explained in scenario 4b in Section 5.3.1 increased the ICER to £149,564 per QALY gained.

From the additional scenarios, it can be also seen that utility estimates, baseline population COPD states and adverse events also have an impact on ICER. The ICER range from the scenario analyses are between £21,000 and £150,000.

In conclusion, based on the ERG base-case analysis, the ICER is estimated to be around £35,000 per QALY gained. This ICER value is larger than the £20,000 per QALY threshold. In addition, due to several assumptions regarding the exacerbation rates, and translation of exacerbations to mortality, the ERG deems that the uncertainty around the cost effectiveness of roflumilast is substantial.

ERG comment: The company did not identify all relevant articles with resource use and/or costs in the UK. A recent literature review[71] regarding cost effectiveness of maintenance treatment in COPD patients identified five UK studies of which the company only included one (Punekar et al. 2014[51]) in their review. Furthermore, it was not always clear how the company selected the resource use and unit costs for the economic analysis because the different studies reported different values.

The ERG is especially concerned about the resource use of exacerbations. The company assumed that exacerbations are accompanied by additional GP visits, based upon Thomas et al. 2014[70]. However, Thomas et al. 2014[70] reports the number of GP visits according to the frequency of exacerbations in one year instead of the severity of exacerbations. The assumption of the company that the frequency of exacerbations in one year reflects the severity of exacerbations is incorrect. First, all patients within the model should be classified in the frequent exacerbation group since they need to have at least two exacerbations within the previous year to be eligible for roflumilast. Secondly, the classification of (in)frequent exacerbations implies that patients could have more than one exacerbation per year. However, the company assumes that all additional GP visits observed in Thomas et al. (2014)[70] should be assigned to one exacerbation, with a risk of double counting for patients with more than one exacerbation per year. In most other studies it is assumed that patients visit the GP one additional time in case of a moderate exacerbation.[41] Patients with a severe exacerbation have no additional GP visits, because these patients are hospitalised as a consequence of their exacerbation. Hence, the ERG will use this approach for the estimation of exacerbation costs (Table 5.19) in the ERG base-case (see Section 5.3).

The ERG also adjusted the costs of maintenance treatment for patients with very severe COPD and hospitalisation costs for treatment of severe exacerbations or pneumonia in the ERG base-case. The ERG increased the number of GP visits during maintenance treatment for patients with very severe COPD to four instead of two visits per year according to Oostenbrink et al. 2005.[67] Within the company submission, the hospitalisation costs were calculated as the weighted average of long- and short-term non-elective stay excluding costs of excess bed days. However, the costs of excess bed days are part of the total hospitalisation costs. Therefore, the ERG incorporated these in the total hospitalisation costs in the ERG base-case. In addition, the ERG was unable to reproduce the company reported hospitalisation costs of pneumonia from the weighted average of HRG DZ11. Therefore, the ERG estimated this weighted average, including the excess bed days.

Finally, the ERG found a small error in the estimation or reporting of the ambulance costs. This error was corrected in the ERG base-case (Section 5.3). All adjustments in cost parameters for the ERG base-case are reported in Table 5.19.

Table 5.2: ERG adjustment in cost parameters

Cost parameter	Value in company submission	Value in ERG Base-case
Very severe COPD	£106.90	£114.23
Moderate exacerbation	£103.85	£58.49
Severe exacerbation	£1,724.43	£1,455,17
Pneumonia	£2,518.00	£1,924.72
COPD = chronic obstructive progressive disease; ICS = inhaled corticosteroid; LABA = Long acting beta-adrenoceptor agonist.		

updated CS base-case as a starting point for its analysis. These adjustments made by the ERG/provided in the updated company base-case form the ERG base-case and were subdivided into three categories (derived from Kaltenthaler 2016[72]):

- Fixing errors (correcting the model were the company's submitted model was unequivocally wrong)
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (amending the model were the ERG considers that reasonable alternative assumptions are preferred)

After the ERG base-case analysis, additional scenario analyses were performed by the ERG in order to examine the potential impact of alternative assumptions on the cost effectiveness estimates.

5.3.1. Explanation of the ERG adjustments

Fixing errors

1. Fixing errors consisted of:
    a. Changing the cost of moderate exacerbations: the ERG considers the method to estimate the number of additional GP visits during exacerbations wrong, because moderate and severe exacerbations are not the same as infrequent and frequent exacerbations. The company overestimates the number of GP visit per exacerbations (2.03) as they did not take into account that patients may experience more than one exacerbation a year. To correct for this, the ERG applied one additional GP visits for patients with moderate exacerbations.
    b. Adjusting the number of GP visits for severe exacerbations: The ERG also deems that the additional number of GP visits for severe exacerbations are overestimated (8.03). In line with Oostenbrink et al. 2005[67], the ERG considers that patients do not visit the GP as they are all hospitalised for the severe exacerbation (0).
    c. Adjusting the unit cost for hospitalisation related to severe exacerbation: the ERG added the costs for excess bed days to the weighted average of short- and long-term non-elective hospital stay for COPD (£1,183.06 without excess bed days £1245.45 with excess bed days).
    d. Correcting the cost related to pneumonia costs: the ERG could not replicate the weighted average of the costs of short- and long-term non-elective hospital stay for pneumonia (£2518). Therefore, the ERG used their own calculated weighted average, whilst also including the excess bed days (£1,924.72).

Fixing violations

2. Changing the cost of ambulance transport according to the most recent available costs: the ERG used £233.02 from HRG code ASS02 "See and treat and convey" instead of £208.95 from Samyshkin et al. 2014[45] used in the model.

The ERG incorporated this change to the model to be in line with good modelling practice to use the most recently published cost and resource use data.

Scenario 5. All adverse events incorporated instead of severe adverse events only
In this scenario analysis, all grade adverse events were considered instead of incorporating only severe adverse events as in the CS and ERG preferred base-case.

5.3.2. Results from the ERG preferred base-case and probabilistic sensitivity analysis

In the base-case analysis, roflumilast plus triple therapy resulted in a total (discounted) costs of £21,332 and QALYs of 6.10 (See Table 5.35). On the other hand, triple therapy alone resulted in a total (discounted) costs of £17,844 and QALYs of 6.01. Based on these results, roflumilast plus triple therapy produced an additional 0.10 QALYs at an incremental cost of £3,489 when compared to triple therapy alone, leading to an ICER of £35,814. This ICER is substantially higher than the company base-case ICER of £18,774.

Table 5.3: The ERG preferred base-case results

Technologies	Total costs	Total LYG	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER
roflumilast plus triple therapy	£21,332	8.75	6.10	£3,489	0.12	0.10	£35,814
triple therapy alone	£17,844	8.63	6.01	-	-	-	-
ICER = incremental cost effectiveness ratio; LYG = life years gained; QALYs = quality adjusted life years.							

Disaggregated results for effects and costs by health state are given in Table 5.36, below.

Table 5.4: Disaggregated costs and effects from the ERG preferred base-case analysis

	triple therapy alone	roflumilast plus triple therapy	Incremental
Costs-discounted			
Direct drug cost	£7,612	£11,728	£4,115
Exacerbation cost	£3,589	£2,846	-£743
Disease state cost	£6,576	£6,702	£126
Adverse event costs	£66	£57	-£9
Total costs	£17,844	£21,332	£3,489
Effects – undiscounted			
Total exacerbations	8.56	7.66	-0.90
Hospital exacerbations	2.88	2.26	-0.62
Effects – discounted			
Years in Severe State	5.37	5.40	0.03
Years in Very Severe State	3.27	3.35	0.08
Total Life years	8.63	8.75	0.12
Total QALYs	6.01	6.10	0.10
QALYs = quality adjusted life years.			

Based on the results above, similar to the CS, the incremental QALYs gained for roflumilast plus triple therapy were mostly due to the fewer exacerbations, and increased life expectancy (due to fewer exacerbation related deaths). The impact of TEAEs on the costs and QALYs was again negligible.
The ERG performed probabilistic sensitivity analyses on the ERG preferred base-case to explore the parametric uncertainty around the base-case parameters. In the PSA, if the standard error estimates for

the updated parameters could be found, those new estimates were used, otherwise it was assumed that the standard error estimates of the updated parameters would change in the same magnitude of the change in their means. The summary results of the PSA (10,000 iterations), which includes the mean and the 95 % CI of the costs, QALYs and resultant ICERs for the PSA are presented below (See Table 5.37) with corresponding scatterplots (See Figure 5.7) and CEACs (See Figure 5.8).

The PSA resulted in an incremental cost of £3,498, incremental QALYs of 0.104 and an ICER of £33,727 per QALY gained. These are comparable to the deterministic base-case results given in Table 5.35. From the scatterplot, it can be seen that the ICER of the simulation outputs are all scattered in the northeast quadrant and from the CEAC it can be seen that the probability that roflumilast plus triple therapy is cost effective compared to triple therapy alone is approximately 3% at a £20,000 per QALY gained threshold and 28% at a £30,000 per QALY gained threshold.

Table 5.5: PSA results of the ERG preferred base-case

Technologies	Total costs	95% CI	Total QALYs	95% CI	Incr. costs	Incr. QALYs	ICER
roflumilast plus triple therapy	£21,546	£18,591 to £24,810	6.14	5.43 to 6.93	£3,498	0.104	£33,727
triple therapy alone	£18,047	£15,339 to £21,051	6.04	5.35 to 6.81	-	-	-
ICER = incremental cost effectiveness ratio; LYG = life years gained; QALYs = quality adjusted life years.							

Figure 5.1: Incremental cost effectiveness scatterplot of the ERG preferred base-case analysis

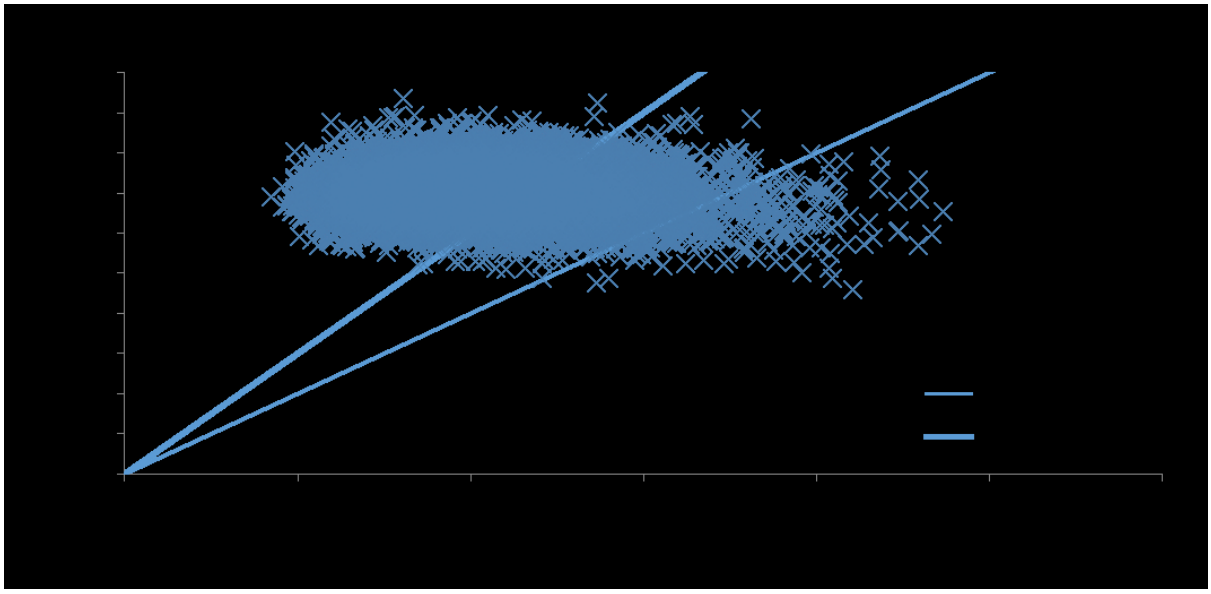
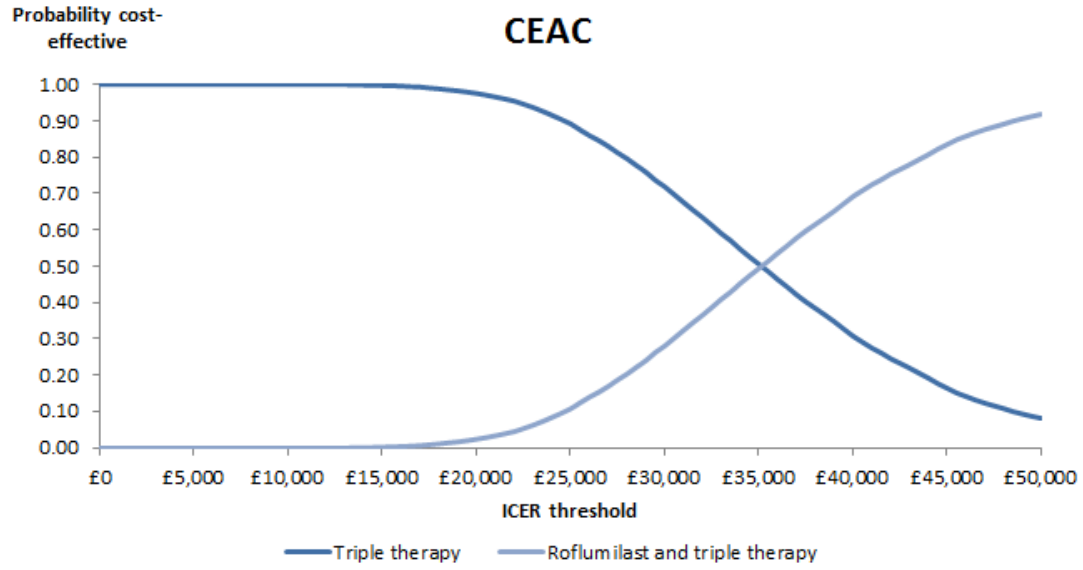


Figure 5.2: Cost effectiveness acceptability curve of the ERG preferred base-case



5.3.3. Results from the ERG additional exploratory scenario analyses

The results of the additional scenarios listed in Section 5.3.1, which were performed on the ERG preferred base-case are provided in Table 5.38 below.

Table 5.6: Results from the additional scenario analyses conducted on the ERG preferred base-case

Scenarios	roflumilast plus triple therapy		Triple therapy alone		Incr. costs	Incr. QALYs	ICER
	Total costs	Total QALYs	Total costs	Total QALYs			
CS base-case	£22,930	6.14	£19,933	5.98	£2,996	0.16	£18,774
ERG preferred base-case	£21,332	6.10	£17,844	6.01	£3,489	0.10	£35,814
Scenario 1a (Alternative effectiveness)	£22,096	5.95	£18,972	5.80	£3,124	0.15	£21,180
Scenario 1b (Pooled effectiveness)	£21,390	6.09	£17,844	6.01	£3,547	0.09	£41,585
Scenario 2 (Very severe population)	£25,159	4.93	£22,279	4.81	£2,880	0.12	£24,733
Scenario 3 (Utilities from Solem)	£21,332	5.84	£17,844	5.76	£3,489	0.08	£41,960
Scenario 4a (Uniform CFR)	£21,237	6.07	£17,734	5.96	£3,503	0.11	£32,341

Scenarios	roflumilast plus triple therapy		Triple therapy alone		Incr. costs	Incr. QALYs	ICER
	Total costs	Total QALYs	Total costs	Total QALYs			
Scenario 4b (all COPD SMR and no CFR)	£20,151	5.82	£17,099	5.80	£3,052	0.02	£149,564
Scenario 5 (all grade adverse events)	£21,359	6.09	£17,856	6.00	£3,502	0.09	£40,942
CFR = case fatality rate; COPD = chronic obstructive progressive disease; ICER = incremental cost effectiveness ratio; LYG = life years gained; QALYs = quality adjusted life years; SMR = standardized mortality ratio.							

From these results, it can be observed that the cost effectiveness results are very sensitive to the assumptions on the COPD related mortality (Scenario 4b). Applying SMRs including exacerbation related deaths (and therefore excluding CFRs) increased the ICER to £149,564 per QALY gained. This is easily explained by the fact that roflumilast prevents exacerbations, and without a CFR the current model structure does not allow for a subsequent impact on mortality.

Assumptions on exacerbation rates also impact the ICER. The ERG observed that incorporating the pooled results from REACT and RE2SPOND trials increased the ICER, whereas using exacerbation rates derived separately for severe and very severe COPD patients decreased the ICER considerably. However, as described in Section 5.3.1, both of these scenario implementations were based on assumptions, therefore the results of Scenario 1a and 1b should be interpreted with caution.

As can be seen from the results of Scenario 2, when all patients enter in the very severe COPD state the ICER decreases. This is in line with the exploratory scenarios conducted by the company on the CS base case as discussed in Section 5.2.11.

The choice for the utility source is another important driver for the cost effectiveness of roflumilast. If estimates for the COPD health state utilities and exacerbation disutilities were based on Solem et al. 2013[62], the ICER would be close to £42,000 per QALY gained. In the economic model, changing the base-case disutilities associated with exacerbations to disutilities from Solem et al. 2013[62] had a bigger impact than changing the base-case health state utilities to health state utilities from Solem et al. 2013[62].

Finally, including all grade adverse events have a significant impact on ICER, as was also seen in the company scenario analysis. If all adverse events were incorporated to the model instead of only serious adverse events, the ICER would be close to £41,000 per QALY gained. However, in this scenario the milder adverse events are assumed to have the same costs and disutilities as the serious adverse events. This is unlikely to be true in reality, and thus this scenario should be regarded as conservative.

5.4 Conclusions of the cost effectiveness section

The majority of the cost effectiveness searches in the CS were well documented, clearly structured and easily reproducible, and were carried out in line with the NICE guide to the methods of technology appraisal.[16] The ERG expressed concerns on restricting searches to English language and from eight countries only (UK, US, Canada, Germany, France, Italy, Spain and Australia). Furthermore, the ERG noted that stricter inclusion criteria were applied in this submission compared

from the REACT and RE2SPOND trial. However, the RE2SPOND trial did not report severe exacerbation rates specific to the LAMA subpopulation. Whilst speculative assumptions could be made, it was decided to leave those for a scenario analysis, and base the ERG base case on ITT data from the REACT trial only.

The ERG base-case resulted in an ICER of £35,814 per QALY gained. The most influential adjustments/corrections made by the ERG were 1) using exacerbation rate ratios based on the ITT population from REACT (obtained from negative binomial regressions performed on patients who received concomitant LAMA treatment); 2) using severe COPD specific FEV1 decline rates from Decramer and Cooper 2010[58] and; 3) using exacerbation related utility decrements from Hoogendoorn et al. 2011[65]. From the PSA results, the probability that roflumilast plus triple therapy is cost effective compared to triple therapy alone is approximately 3% at a £20,000 per QALY gained threshold and 28% at a £30,000 per QALY gained threshold.

The ERG conducted some additional scenario analyses on the ERG preferred base-case to assess structural uncertainty.

One of the scenarios used different exacerbation rate ratios than the ERG preferred base-case (which assumes the same roflumilast vs. placebo rate ratios for severe and very severe COPD patients); instead using mean exacerbation rates separately derived from the severe and very severe COPD patients in the ITT concomitant LAMA treatment subpopulation. These rates were derived from the Poisson regression analyses for moderate or severe exacerbations and negative binomial regression analyses for severe exacerbations, which were provided in the CSR of the REACT trial. Assuming that negative binomial and Poisson regression estimates would give similar results, the moderate exacerbation rate estimates were calculated from the difference between the moderate or severe exacerbation rate and the severe exacerbation rate. This scenario resulted in an ICER of £21,180 per QALY gained.

In another scenario, we assessed what impact might be expected from using pooled exacerbation rates based on the ITT populations from REACT and RE2SPOND. To that end, we multiplied the exacerbation rate ratios used in the ERG preferred base-case by a factor of (0.9/0.871), which is the ratio of the pooled moderate or severe RR from the ITT population, concomitant LAMA subgroup of REACT and RE2SPOND trials with the same RR from the REACT trial only. In this scenario, it was assumed that incorporating the RE2SPOND trial results would change the severe and moderate exacerbation rate ratios uniformly. This scenario resulted in an ICER of £41,585 per QALY gained.

From the results of these two scenarios, it became obvious that the assumptions about exacerbation rates impact the ICER considerably. Specifically, incorporating the pooled results from REACT and RE2SPOND trials increased the ICER, whereas using exacerbation rates derived separately for severe and very severe COPD patients decreased the ICER. However, both of these scenario implementations were based on assumptions, as the company had not provided the relevant analyses to estimate pooled exacerbation rates based on the ITT populations; therefore, the results of Scenario 1a and 1b should be interpreted with caution.

The ERG thinks that the most robust exacerbation rate would be the moderate and severe exacerbation rates derived separately for severe and very severe COPD patients from the negative binomial regression analyses performed on the pooled ITT population subgroup of LAMA concomitant patients from both REACT and RE2SPOND trials. And as this data is readily available to the company, the current uncertainty around the ICER stemming from uncertainty about the exacerbation rates can easily be resolved.

6. IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

In Section 5.3 the ERG base-case was presented, which was based on various changes compared to the company base-case. Table 6.1 shows how each individual change impacts the ICER plus the combined effect of all changes simultaneously. The analyses numbers in Table 6.1 correspond to the analyses numbers reported in Section 5.3.

Table 6.7: Revised base case cost effectiveness analysis, incorporating corrections and amendments identified by the ERG

Scenarios	roflumilast plus triple therapy		Triple therapy alone		Incr. costs	Incr. QALYs	ICER
	Total costs	Total QALYs	Total costs	Total QALYs			
0. CS base-case	£22,930	6.14	£19,933	5.98	£2,996	0.16	£18,774
1. Fixing errors	£22,211	6.14	£18,954	5.98	£3,257	0.16	£20,409
(1+2). Fixing errors and using a more recent estimate for cost of ambulance transport	£22,248	6.14	£19,009	5.98	£3,239	0.16	£20,296
(1+3). Fixing errors and using exacerbation utility decrements from Hoogendoorn et al. 2011[65]	£22,211	6.15	£18,954	6.00	£3,257	0.15	£21,340
(1+4). Fixing errors and half cycle correction	£22,294	6.17	£19,020	6.01	£3,273	0.16	£20,509
(1+5). Fixing errors and concomitant LAMA population data for baseline characteristics and adverse events	£21,230	5.89	£18,109	5.73	£3,122	0.16	£20,018
(1+6). Fixing errors and changing the maintenance costs associated with very severe COPD state	£22,600	6.14	£19,329	5.98	£3,271	0.16	£20,492
(1+7). Fixing errors and using severe COPD state specific annual decline	£21,629	6.37	£18,241	6.22	£3,388	0.15	£21,869
(1+8). Fixing errors and using exacerbation rate ratios obtained from ITT population	£22,466	6.09	£18,954	5.98	£3,513	0.11	£33,009
(1 to 8 all): ERG preferred base-case	**£21,332**	**6.10**	**£17,844**	**6.01**	**£3,489**	**0.10**	**£35,814**

COPD = chronic obstructive progressive disease; CS = Company submission; ERG = Expert review group; ICER = incremental cost effectiveness ratio; Incr. = incremental; ITT = intention to treat; LAMA = Long acting Muscarinic-receptor Antagonist; LYG = life years gained; QALYs = quality adjusted life years.

Table 7.8: Key finding from company and ERG analyses (Mean rate (95% CI) of COPD exacerbations per patient per year)

	Roflumilast vs placebo
Company preferred analyses	
Moderate to severe exacerbation*	RR 0.799 (95% CI: 0.670 to 0.952)
Severe exacerbation*	RR 0.659 (95% CI: 0.497 to 0.872)
Company analyses using ITT data instead of PP data from REACT only	
Moderate to severe exacerbation**	RR 0.871 (95% CI: 0.741 to 1.024)
Severe exacerbation**	RR 0.767 (95% CI: 0.595 to 0.989)
ERG preferred analyses	
Moderate to severe exacerbation***	RR 0.90 (95% CI 0.80 to 1.02)
Severe exacerbation****	RR 0.85 (95% CI 0.68 to 1.06)
* Based on PP population from the REACT trial, using the negative binomial regression model and the concomitant LAMA subgroup; ** Based on ITT population from the REACT trial, using the negative binomial regression model and the concomitant LAMA subgroup; *** Based on ITT populations from the REACT and RE2SPOND trials, using the negative binomial regression model and the concomitant LAMA subgroup; **** Based on ITT populations from the REACT and RE2SPOND trials, using the negative binomial regression model (data for the concomitant LAMA subgroup were not available).	

Adverse events were reported by 67% of the roflumilast group and 59% of the placebo group, with serious adverse events reported by 26% and 30% respectively. More people withdrew because of adverse events in the roflumilast group (11% compared with 5%). The most frequently reported adverse events were COPD exacerbations (15% with roflumilast compared with 19% with placebo), diarrhoea (10% compared with 4% respectively), weight loss (9% compared with 3% respectively) and nausea (6% compared with 2% respectively). Mortality rates were the same in both groups (2%); as were major adverse cardiovascular events (2% in both groups). There was no increase in the incidence of pneumonia with roflumilast.

The company base-case cost effectiveness analysis resulted in an ICER of £18,774 for QALYs gained for roflumilast plus triple therapy vs. triple therapy alone. The incremental QALY gains were mostly due to the fewer exacerbations, and increased life expectancy (due to fewer exacerbation related deaths). The higher costs are mainly due to higher treatment costs. The probabilistic sensitivity analysis performed on the CS base-case showed that the probability that roflumilast / LAMA / LABA / ICS is cost effective compared to LAMA / LABA / ICS is approximately 70% at a £20,000 per QALY gained threshold.

The ERG has incorporated various adjustments to the company base-case. Ideally, the adjustments would have included using exacerbation rate ratios based on the pooled ITT estimates from the REACT and RE2SPOND trial. However, the RE2SPOND trial did not report severe exacerbation rates specific to the LAMA subpopulation. Whilst speculative assumptions could be made, it was decided to leave those for a scenario analysis, and base the ERG base case on ITT data from the REACT trial only.

The ERG base-case resulted in an ICER of £35,814 per QALY gained. The most influential adjustments/corrections made by the ERG were 1) using exacerbation rate ratios obtained from the negative binomial regressions performed on the ITT population from REACT trial patients who

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

ADDENDUM TO:

Roflumilast for the management of chronic obstructive pulmonary disease

This addendum consists of three parts. The first part contains the results of additional scenario analyses based on data provided in the company's response to the factual accuracy check.

The following scenarios were explored:

i. Scenario analysis in which the additional GP visits due to moderate exacerbation is 2 (instead of 1) and additional GP visits due to severe exacerbation is 1 (instead of 0). These numbers were proposed by the company in its response to the FEC, in issue 3.
ii. Scenario analysis in which LABA / ICS daily cost is £1.14 instead of £1.30, the new estimate was proposed by the company in its response to the FEC, in issue 3.
iii. Scenario analysis in which pooled moderate and severe exacerbation rate ratios from the REACT and RE2SPOND trials were used (patients on triple therapy, ITT population). The rate ratios from the RE2SPOND trial for the relevant population were provided in the company's response to the factual accuracy check.

The second part contains the tables with the exacerbation rates and rate ratios used in the economic model in the company submission base case, in the ERG preferred base case and in the ERG exploratory scenario analyses.

The third part contains a revised ERG base case. The ERG has revised its preferred base case according to scenario analysis iii above.

Part-I: Additional scenario analyses based on data provided in the company's response to the factual accuracy check

i. Scenario analysis based on new estimates for additional GP visits due to moderate and severe exacerbations

In its response to the factual accuracy check, the company suggested new estimates for additional GP visits due to moderate (2 additional GP visits instead of 1) and severe (1 additional GP visits instead of 0) exacerbations. When the corresponding changes were made in the additional number of GP visits due to moderate and severe exacerbations as proposed by the company, the incremental cost effectiveness results below are obtained (Table 1).

Table 1: Additional scenario analysis with the company's additional GP visit estimates (for moderate and severe exacerbations)

Technologies	Total costs	Total LYG	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER
roflumilast plus triple therapy	£21,601	8.75	6.10	£3,456	0.12	0.10	£35,481
triple therapy alone	£18,145	8.63	6.01	-	-	-	-
ICER = incremental cost effectiveness ratio; LYG = life years gained; QALYs = quality adjusted life years.							

ii. Scenario analysis based on new estimate for the daily LABA / ICS drug costs

In its response to the factual accuracy check, the company suggested new estimate for the daily LABA / ICS drug costs (£1.14 per day instead of £1.30 per day). When the corresponding changes were made in the daily cost of LABA/ICS as proposed by the company, the following incremental cost effectiveness results in Table 2 are obtained.

Table 2: Additional scenario analysis with the company's new estimate for the daily LABA / ICS drug costs

Technologies	Total costs	Total LYG	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER
roflumilast plus triple therapy	£20,824	8.75	6.10	£3,482	0.12	0.10	£35,746
triple therapy alone	£17,342	8.63	6.01	-	-	-	-
ICER = incremental cost effectiveness ratio; LYG = life years gained; QALYs = quality adjusted life years.							

iii. Scenario analysis in which pooled moderate and severe exacerbation rate ratios from the REACT and RE2SPOND trials were used (patients on triple therapy, ITT population).

In this scenario, the exacerbation rate ratios obtained from the pooled analysis of the REACT and RE2SPOND trials were used. These rate ratios were from negative binomial regression models conducted on the concomitant LAMA subgroup of ITT population of both trials. This is different from the scenario 1b in the section 5.3 of the ERG report, in which a common multiplier factor (0.90/0.871), based on moderate to severe patients, was applied to both moderate and severe exacerbation rate ratios. The rate ratios that were obtained from the pooled analysis are given in Table 3 for moderate and severe exacerbations, respectively.

Table 3: Pooled rate ratios for moderate and severe exacerbations from REACT and RE2SPOND studies

Moderate Exacerbations (roflumilast vs. placebo)			
Study	Rate Ratio	Lover 95%	Upper 95%
REACT*	0.934	0.773	1.128
RE2SPOND**	0.920	0.773	1.095
Pooled Rate Ratio	0.926	0.815	1.053
Severe Exacerbations (roflumilast vs. placebo)			
Study	Rate Ratio	Lover 95%	Upper 95%
REACT*	0.767	0.595	0.989
RE2SPOND**	1.04	0.76	1.43
Pooled Rate Ratio	0.880	0.654	1.184
Source: * Table 4.10 in the ERG report; ** Table 50 provided in company's response to the FEC			

The negative binomial model was chosen as it was the most consistently reported across the two trials. To estimate the moderate exacerbation and severe exacerbation rates, the coefficient for "Roflumilast" in the regression function of the economic model was set to the logarithm of the corresponding pooled rate ratio, and the following incremental cost effectiveness results in Table 4 are obtained.

Table 4: Scenario analysis in which pooled moderate and severe exacerbation rate ratios from the REACT and RE2SPOND trials were used (patients on triple therapy, ITT population)

Technologies	Total costs	Total LYG	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER
Roflumilast plus triple therapy	£21,548	8.81	6.06	£3,704	0.12	0.05	£71,365
Triple therapy alone	£17,844	8.68	6.01	-	-	-	-
ICER = incremental cost effectiveness ratio; LYG= life years gained; QALYs = quality adjusted life years.							

Note that in this scenario analysis, all the other regression coefficients (constants and coefficients for "very severe COPD state") are still based on the original regression model from the company submission, based on data from per protocol population from the REACT trial only.

Part-II: Exacerbation rates and rate ratios used in the economic model

In Table 5, the actual moderate and severe annual exacerbation rates used in the economic model for severe and very severe COPD states for the company preferred analysis, ERG preferred analysis, original scenario 1b of the ERG report and updated scenario 1b in this addendum are given. Note that the exacerbation rates for the triple therapy are the same in all scenarios, because all scenarios use the same regression model, but each of them uses a different covariate for the "Roflumilast" treatment, which is the logarithm of the rate ratio.

Table 5: Actual moderate and severe exacerbation rates used in the economic model for different scenarios

	roflumilast plus triple therapy		**Triple therapy**		**Roflumilast vs placebo**
	Severe COPD	**Very Severe COPD**	**Severe COPD**	**Very Severe COPD**	**Rate Ratio**
Company preferred analysis based on REACT PP analysis, concomitant LAMA rate ratios					
Moderate exacerbation	0.384	0.607	0.434	0.685	0.887
Severe exacerbation	0.115	0.270	0.175	0.411	0.656
ERG preferred analysis based on REACT ITT analysis, concomitant LAMA rate ratios					
Moderate exacerbation	0.405	0.640	0.434	0.685	0.934
Severe exacerbation	0.134	0.316	0.175	0.411	0.767
Scenario 1b in the ERG report, based on an approximation for the pooled exacerbation rate ratios from REACT and RE2SPOND ITT, concomitant LAMA analyses					
Moderate exacerbation	0.418	0.661	0.434	0.685	0.965
Severe exacerbation	0.139	0.326	0.175	0.411	0.793
Scenario analysis iii in this addendum, based on the pooled exacerbation rate ratios from REACT and RE2SPOND ITT, concomitant LAMA analyses					
Moderate exacerbation	0.401	0.634	0.434	0.685	0.926
Severe exacerbation	0.154	0.362	0.175	0.411	0.88

Furthermore, in scenario 1a in the ERG report, the exacerbation rates from the clinical study report were directly used in the economic model. The rate ratios calculated from these rates are presented in Table 6 below. As it can be seen, the rate ratios are different between severe and very severe COPD patients.

Table 6: Exacerbation rate and rate ratios used in scenario 1a of the ERG report

Treatment	**Moderate exacerbations**		**Severe exacerbations**	
	Severe COPD	**Very severe COPD**	**Severe COPD**	**Very severe COPD**
roflumilast plus triple therapy rate	0.561	0.719	0.221	0.421
triple therapy rate	0.547	0.864	0.3	0.553
Rate ratio	1.026	0.832	0.737	0.761
Source = Table 5.34 in the ERG report COPD = chronic obstructive progressive disease				

Part-III: Revised ERG base case

Based on the additional evidence provided by the company in its response to the factual accuracy check, the ERG decided to revise its preferred base case and use the treatment effectiveness (exacerbation rate) estimates based on pooled results from REACT and RE2SPOND trials as in the scenario analysis iii (Table 3) in this addendum. As discussed in the ERG report, the ERG considers the pooled results from REACT and RE2SPOND might provide robust treatment effectiveness estimates.

Even though the new company estimates for exacerbation related additional GP visits and for LABA/ICS daily costs might be deemed plausible, we decided not to incorporate these estimates in the revised ERG preferred base case. The reasons for not including them are:

1. Their impact on ICER is very limited, as seen in Table 1 and Table 2 in this addendum.
2. The plausibility of these estimates should be validated by clinicians.

The construction of the revised ERG preferred base case is shown in Table 7, which therefore updates Table 6.1 in the ERG report.

Table 7: Revised base case cost effectiveness analysis, incorporating corrections and amendments identified by the ERG including additional analyses based on additional evidence provided in the FEC

Scenarios	roflumilast plus triple therapy		Triple therapy alone		Incr. costs	Incr. QALYs	ICER
	Total costs	Total QALYs	Total costs	Total QALYs			
0. CS base-case	£22,930	6.14	£19,933	5.98	£2,996	0.16	£18,774
1. Fixing errors	£22,211	6.14	£18,954	5.98	£3,257	0.16	£20,409
(1+2). Fixing errors and using a more recent estimate for cost of ambulance transport	£22,248	6.14	£19,009	5.98	£3,239	0.16	£20,296
(1+3). Fixing errors and using exacerbation utility decrements from Hoogendoorn et al. 2011[65]	£22,211	6.15	£18,954	6.00	£3,257	0.15	£21,340
(1+4). Fixing errors and half cycle correction	£22,294	6.17	£19,020	6.01	£3,273	0.16	£20,509
(1+5). Fixing errors and concomitant LAMA population data for baseline characteristics and adverse events	£21,230	5.89	£18,109	5.73	£3,122	0.16	£20,018
(1+6). Fixing errors and changing the maintenance costs associated with very severe COPD state	£22,600	6.14	£19,329	5.98	£3,271	0.16	£20,492
(1+7). Fixing errors and using severe COPD state specific annual decline	£21,629	6.37	£18,241	6.22	£3,388	0.15	£21,869
(1+8). Fixing errors and using exacerbation rate ratios obtained from pooled ITT, concomitant LAMA population data from REACT and RESPOND trials	£22,706	6.04	£18,954	5.98	£3,752	0.06	£66,859
(1 to 8 all): ERG preferred base-case	£21,548	6.06	£17,844	6.01	£3,704	0.05	£71,365

COPD = chronic obstructive progressive disease; CS = Company submission; ERG = Expert review group; ICER = incremental cost effectiveness ratio; Incr. = incremental; ITT = intention to treat; LAMA = Long acting Muscarinic-receptor Antagonist; LYG = life years gained; QALYs = quality adjusted life years.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Roflumilast for treating chronic obstructive pulmonary disease

(review of technology appraisal guidance TA244) [ID984]

You are asked to check the ERG report from Klejinen Systematic Reviews Ltd to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, 9 December 2016** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 REACT Trial: Intention to Treat, Valid Case Set and Per-Protocol Analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Throughout the ERG report the ERG have referred to the ITT population of the REACT trial as being the most appropriate source of data for this appraisal as opposed to the PP population - AstraZeneca disagrees and believes that there may have been a misinterpretation by the ERG of the PP population and what this consists of.	AstraZeneca believes that the ERG should base it's base case on the concomitant LAMA (triple therapy) subgroup in the PP population from the REACT trial. The Full Analysis Set (FAS) included all randomised patients who took at least one dose of either roflumilast or placebo after randomisation. Patients were assigned to the treatment group based on the treatment to which they are randomised ('as randomised' analysis). The intention-to-treat (ITT) analysis was based on the FAS. The per-protocol (PP) analysis is based on the valid cases set (VCS) which consisted of all patients (including those patients terminating the trial prematurely) of the FAS without any major protocol violations. Similarly to the ITT analysis, the PP was performed on an 'as randomised' basis. The PP analysis was used to assess the robustness of the results and was performed for the primary endpoint and key-secondary endpoints. The PP population was selected over the ITT population in the manufacturer submission; and economic model base case for a range of reasons: • The ITT population included randomised patients who took at least 1 dose of study drug following	This requires amending due to the considerable proportion of patients who are included in the ITT population of REACT who A) Do not meet the license requirements of roflumilast B) Do not meet the population requirements of the scope of this appraisal Therefore AstraZeneca proposes that the ERG base case is based on the triple therapy subgroup of the PP population from the REACT trial. The effect of basing the analysis on the triple therapy, REACT, PP population would be to reduce the ERG preferred Base Case ICER as demonstrated below.	Not a factual error. All the arguments are explained in the CS and the ERG report.

	randomisation and incorporated all data until the patient discontinued (prematurely or as scheduled) the trial. The ITT population included a substantial proportion of patients with protocol violations (16.0%) meaning these patients (16.0%) did not meet either the licence criteria for roflumilast and / or the decision problem criteria* for this technology appraisal, and would therefore result in a biased estimate of the treatment effect for the decision problem in this submission. • The PP population, however, included only those patients without major protocol violations (note: patients who discontinued treatment were included in the PP population provided there were no major protocol violations). The PP population was identified as being more appropriate (than the ITT population) and aligned to the patient subgroup defined in the decision problem. Based upon the above key weaknesses the ITT population should not be considered as the most appropriate source of evidence for this appraisal The diagram in Appendix 1 illustrates the protocol pathway which patients followed in the enrolment phase of the REACT trial. As shown, there were a significant number of patients who were filtered out of the study for not meeting the inclusion criteria, however, as the study progressed there was a protocol amendment		

	which allowed patients who had presented with an FEV1 >50% to re-enter the trial and results in a significant number of major protocol violations (and thus unlicensed patients) being present in the ITT REACT population. *Decision problem population from the scope - Adults with severe chronic obstructive pulmonary disease (FEV1 post bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations		

Issue 2 LAMA sub-group in RESPOND

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG have stated in their report that they were unable to find data for severe exacerbations in the LAMA subgroup within the RESPOND paper or the CSR. AstraZeneca would like to clarify the references for this data in the paper; and CSR (moderate or severe exacerbations); and provide additional data for the severe exacerbations (not in the CSR or the paper).	Please see the separate pdf file for a summary of the relevant data. However, AstraZeneca maintains that the RE^{2}SPOND trial is not an appropriate source of evidence for this appraisal due to the following reasons: 1. The RE^{2}SPOND trial required patients to be taking an ICS/LABA +/- LAMA for a minimum of 3 months prior to baseline. Given that the entry criteria required patients to have 2 or more exacerbations in the prior year, we cannot conclude that patients included in the trial were uncontrolled on ICS/LABA +/- LAMA therapy (i.e. patients may have had exacerbations on a previous treatment prior to progressing onto an ICS/LABA +/- LAMA and still have met the entry criteria). In contrast, in the REACT trial patients were required to have been on their ICS/LABA +/- LAMA for at least 1 year and have had 2 or more exacerbations in the year prior to trial entry. "The expected clinical position for roflumilast in the UK is for COPD patients already receiving maximal inhaled therapy with ICS/LABA+ LAMA; and who are still experiencing 2 or more exacerbations per year. This group of patients would typically be receiving maximal inhaled therapy for at least a year before additional therapy is considered, as reflected in the inclusion criteria of the REACT trial. This was not the case in the RE^{2}SPOND trial". (Data on File	The inclusion of the RE^{2}SPOND trial in the ERG sensitivity analyses introduces a significant number of patients into the analysis who are not appropriate to the appraisal and therefore significantly reduced the robustness of the outcome Removing the RE^{2}SPOND trial from the ERG sensitivity analyses would reduce the uncertainty within the ERG list of sensitivity analyses as presented below.	Not a factual error. We thank the company for providing these data, but it's too late for us to do any additional analyses. If the Committee wants the cost effectiveness results based on pooled moderate and severe exacerbation rate ratios from the LAMA concomitant patients in the REACT and RE2SPOND trials, the ERG can provide an additional analysis before the committee meeting (Scenario 1b in Section 5.3 of the ERG report without assumption on moderate severe exacerbation rate ratio).

	ROF-006-NOV2016) (previously provided) 2. The REACT trial included a greater proportion of patients matching the specific population (subgroup) for which AstraZeneca seeks a NICE recommendation (adults with severe COPD (FEV1 post-bronchodilator < 50% predicted) associated with chronic bronchitis and a history of frequent exacerbations (≥2 exacerbations in the prior 12 months) despite triple therapy with LABA / LAMA / ICS.) The REACT trial includes 70% of patients who were prescribed triple therapy (ICS/LABA/LAMA) at baseline compared with 47% of patients in the RE^{2}SPOND trial. 3. The RE^{2}SPOND trial includes patients, who were using the US licensed dose of fluticasone/salmeterol 250/50ug as background therapy. Conversely, the fluticasone/salmeterol dose used as background therapy in the REACT trial was the UK and EU licensed dose of 500/50ug. Therefore, the REACT trial is more applicable to the UK as it is reflective of the background therapy used in UK clinical practice. 4. Very few patients included in the RE^{2}SPOND trial are from Western Europe (1 from Italy and 12 from Spain) from a total of 2352 patients in the trial (0.6 %) vs. 29.5% of patients from Western Europe in the REACT trial. 5. Finally, the RE^{2}SPOND trial used a formulation of roflumilast which is not currently approved for use in the UK. The US FDA-approved uncoated formulation was used in the RE^{2}SPOND trial. The EMA-approved enteric film-		

	coated formulation was used in the REACT trial.		

Issue 3 Explanation of ERG adjustments

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
ERG report page 94: The ERG have labelled a group of their adjustments as “fixing errors”, AstraZeneca believes that the adjustments made are not solely errors and include aspects which are matters of judgement. Furthermore, we have identified some errors within the calculations for background therapy drug costs	AstraZeneca proposes that the following points are re-categorised as matters of judgement and the incorrect adjustments are corrected in the ERG base case. The ERG have noted that moderate and severe exacerbations are not the same as infrequent and frequent exacerbations and have amended the resource use in the model (specifically adjusting the number of GP visits for both moderate and severe exacerbations), however, while AstraZeneca agrees that moderate and severe exacerbations are not the same as infrequent and frequent exacerbations, we believe the adjustment made by the ERG to be a matter judgement and should be labelled accordingly: 1. AstraZeneca agrees with the ERG that a patient suffering from a moderate exacerbation would attend 1 GP visit at the point of exacerbation, however, it is also reasonable to assume that a patient would be followed up by the GP after the prescribed course of oral corticosteroids (OCS) has been completed. AstraZeneca therefore believes that a value of 2 GP visits for a moderate exacerbation is appropriate. 2. AstraZeneca also agrees with the ERG that a patient suffering from a severe	These errors require correcting for 2 reasons 1. The title of “fixing errors (correcting the model where the company’s submitted model was unequivocally wrong)” is in itself misleading and therefore requires altering 2. AstraZeneca believes that 3 of the 5 adjustments made by the ERG in this section are themselves inappropriate and therefore require amending. The effect of these changes would be to alter the ERGs base case from £35,821 to £35,412, when using the ITT population, which as previously stated AstraZeneca does not support. The impact of making these changes and using the PP population would be to alter the base case ICER to £21,897.	The ERG considers using the estimates for “frequent” and “infrequent” exacerbations for “moderate” and “severe” exacerbations is unequivocally wrong, and was an obvious misinterpretation. Therefore, the ERG provided its own estimates based upon other evidence from the literature. The company might not agree with these estimates, but they are not factual errors. If the Committee finds the new estimates from the company more useful, the ERG can provide an additional analysis before the committee meeting.

	exacerbation would also have an inpatient hospitalisation, however, as with moderate exacerbations it is reasonable to assume that patients would also be followed up, either in primary care or via an outpatient visit. This is confirmed by NICE treatment pathways for managing exacerbations of COPD which state that "arrangements for follow-up and home-care (such as visiting nurse, oxygen delivery, referral for other support) should be made before discharge" (NICE Pathways)[1]. Therefore AstraZeneca believes that a value of at least 1 additional GP visit is appropriate. 3. The ERG notes that there is an error in the calculation of the cost of LABA/ICS and suggests that adding the cost of LABA to the cost of ICS is the most appropriate way of calculating this. There are two issues here: (1) This would result in the use of unlicensed medication given that ICS as a mono component is not licensed in COPD (2) The ERG have made an error in their calculation as they have mistaken Symbicort 400/12 and 200/6 as LABA and Seretide 500 as ICS while all 3 compounds are ICS/LABA combination products and therefore would be inappropriate to use together. AstraZeneca, however, acknowledges that there has been an error in calculating the cost of ICS/LABA as several products have been omitted from		The ERG agrees that the way LABA / ICS costs were calculated in the ERG preferred base case is wrong, and agrees to use the LABA / ICS cost estimate (£1.30) used in the CS. The ERG appreciates the drug costs of additional comparators; however, it is too late to verify these costs and incorporate them to the model. If the Committee considers incorporating the costs of these new LABA / ICS formulations, the ERG can provide an additional analysis before the committee meeting.

	the calculation (Duoresp 180/4.5 and 360/9 (both £0.50), Fostair 100/6 (£0.49) and AirFluSal 500 (£0.55)). Therefore AstraZeneca has recalculated the cost of ICS/LABA as £1.14 per day and proposes that the ERG use this cost in its base case and scenario analyses.		

Issue 4 Results from the additional scenario analyses conducted on the ERG preferred base-case

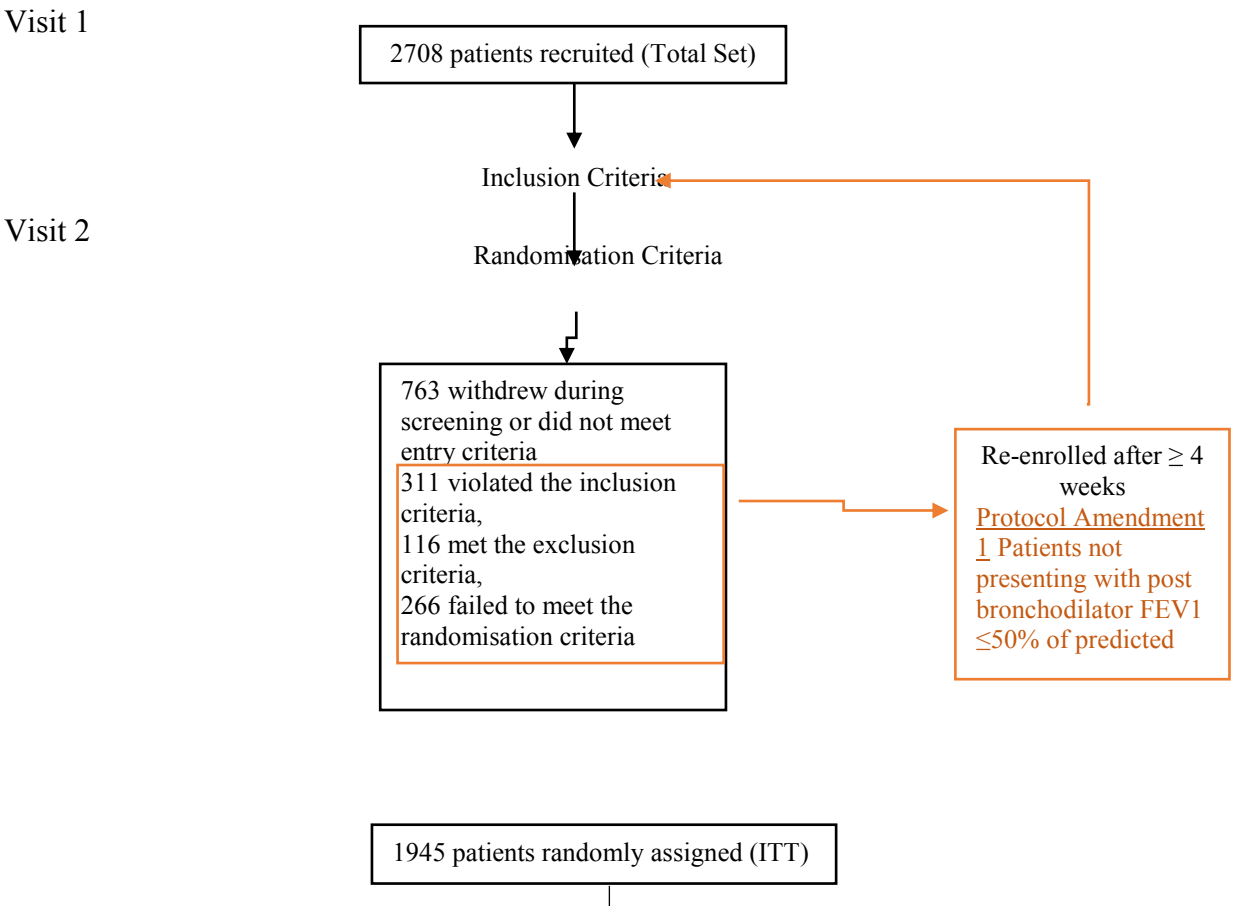
Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
ERG report page 100/101: The ERG has presented a table of analyses which show the ICER ranging from £21,187 to £149,564, AstraZeneca believes this table overestimate the uncertainty in the ICER as several of the scenarios are based on unrealistic assumptions	1. The ERGs preferred base case and the scenario analyses resulting from the further analyses, not only incorporate some inappropriate assumptions listed in Issue 3 (incorrect cost of ICS/LABA and an underestimation of GP visits associated to moderate and severe exacerbations), but also use data from the full ITT population rather than the PP population from REACT. As described above, the ITT population is not appropriate to the decision problem as a significant proportion of these patients would either be excluded from the licensed population; and hence out of scope of the appraisal or unlicensed, specifically ruled out under the population defined in the scope of this appraisal, or both. Therefore	AstraZeneca believe that the ERG base case and sensitivity analyses presented in table 5.38 on pages 100 and 101 are based on both less appropriate data and improbable assumptions for the cost effectiveness analysis of roflumilast as add-on to triple therapy. AstraZeneca believe that due to this, the ERG base case should be revised without incorporating the full ITT population and focus on the PP population utilised in the company base case with the effect being that the ERG base case ICER decreases from £35,821 to £21,897	Not a factual error. All the arguments are explained in the ERG report.

	AstraZeneca proposes that each sensitivity analysis conducted by the ERG should be based on the concomitant LAMA subgroup of the PP population in the REACT trial. 2. Scenario 1b uses the less appropriate data from the ITT population in REACT and also adds in data from the RE^{2}SPOND trial which, as described above in Issue 2, is also inappropriate to this decision problem. While AstraZeneca accepts that this is a valid sensitivity analysis, it should be made clear within the text that this is an implausible estimate for UK clinical practice. 3. Scenario 4b assumes that there is no excess risk of death from an exacerbation, again this is an improbable assumption. It is clearly demonstrated in the literature that COPD exacerbations are highly associated with an excess risk of death, and therefore it is completely unsafe to incorporate this into the economic model even as a sensitivity analysis. As a minimum therefore AstraZeneca proposes that it is made clear that this sensitivity analysis has been conducted to understand the impact of mortality on the ICER and is an implausible estimate of the true ICER. 4. Scenario 5 includes adverse events of all severities in the economic model and while AstraZeneca does not disagree	AstraZeneca believe that owing to the inconsistencies and implausible assumptions highlighted in the previous column, these scenario analyses should be revised by taking into account the changes suggested in column 2, with the effect being a more robust ICER for roflumilast as add-on to triple therapy.	

	that these events have an impact on patients' lives, we believe that the manner in which they have been incorporated into the model is inappropriate. Due to the highly conservative assumption made regarding the utility decrement (i.e. assuming this is the same as a severe exacerbation) the impact of including all treatment related adverse events (TRAEs) is vastly overestimated, to the point of being uninformative, for example, in this scenario a low grade nausea event is given the same disutility as a hospitalised COPD exacerbation. AstraZeneca therefore proposes that this sensitivity analysis is removed given that the potential QALY loss associated to all adverse events has already been covered in the company base case assumptions. Should the ERG still wish to explore this analysis of including all adverse events in the model, AstraZeneca would suggest that using the disutility associated with a moderate exacerbation would be more appropriate for low grade adverse events, however, we believe that this analysis would still be highly conservative and should be clearly stated as such.		

[1] NICE Pathways - Managing exacerbations of COPD https://pathways.nice.org.uk/pathways/chronic-obstructive-pulmonary-disease#path=view%3A/pathways/chronic-obstructive-pulmonary-disease/managing-exacerbations-of-copd.xml&content=view-index (last accessed Dec 2016)

Appendix 1:



Appendix 1:

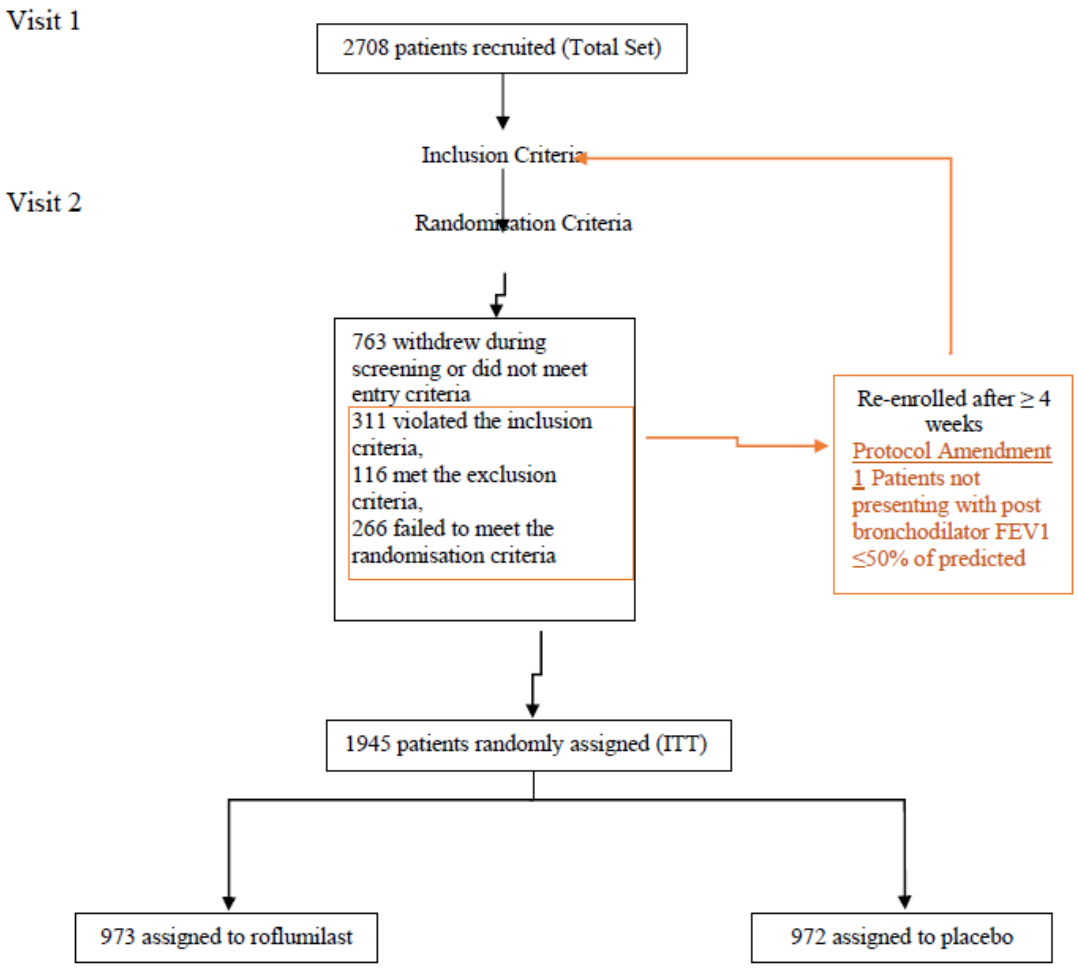

Visit 1
2708 patients recruited (Total Set)
Inclusion Criteria
Visit 2
Randomisation Criteria
763 withdrew during screening or did not meet entry criteria
311 violated the inclusion criteria,
116 met the exclusion criteria,
266 failed to meet the randomisation criteria
Re-enrolled after ≥ 4 weeks
Protocol Amendment 1 Patients not presenting with post bronchodilator FEV1 ≤50% of predicted
1945 patients randomly assigned (ITT)
973 assigned to roflumilast
972 assigned to placebo

Table 50. Rate of COPD Exacerbations per patient per Year:
ITT population
By LAMA use

		Placebo (N= 1174)		Roflumilast 500 µg (N= 1178)		Placebo vs Roflumilast rate ratio			
Exacerbation	Subgroup LAMA use	n	Rate (95% CI)	n	Rate (95% CI)	Rate ratio	Standard error	% change	p-value
Moderate or severe	Yes	546	1.45(1.29,1.62)	548	1.36(1.20,1.53)	0.94(0.79, 1.11)	0.085	-6.3%	0.4438
	No	628	1.12(0.99,1.27)	630	1.00(0.87,1.14)	0.89(0.74, 1.07)	0.094	-10.9%	0.2211
Severe	Yes	546	0.32(0.26,0.40)	548	0.34(0.27,0.42)	1.04(0.76, 1.43)	0.161	4.1%	0.8042
	No	628	0.26(0.21,0.33)	630	0.22(0.18,0.29)	0.85(0.60, 1.20)	0.175	-14.9%	0.3556
Moderate or severe and/or treated with antibiotics	Yes	546	1.69(1.51,1.88)	548	1.52(1.35,1.71)	0.90(0.77, 1.06)	0.081	-10.0%	0.1947
	No	628	1.25(1.11,1.41)	630	1.13(1.00,1.28)	0.90(0.76, 1.07)	0.088	-9.8%	0.2409
Moderate	Yes	546	0.94(0.83,1.05)	548	0.86(0.76,0.97)	0.92(0.77, 1.09)	0.087	-8.3%	0.3211
	No	628	0.71(0.62,0.81)	630	0.67(0.58,0.76)	0.94(0.77, 1.13)	0.098	-6.5%	0.4967
Moderate and/or treated with antibiotics	Yes	546	1.40(1.27,1.54)	548	1.28(1.15,1.42)	0.91(0.79, 1.05)	0.071	-8.7%	0.2008
	No	628	1.04(0.93,1.15)	630	0.98(0.88,1.09)	0.94(0.81, 1.10)	0.078	-5.7%	0.4525

SE = Standard error of the rate ratio. Change (%) = (rate ratio – 1)*100.
Rates, 95% CI, rate ratio, SE, p-value are based on a negative binomial regression with treatment as factor.
A rate ratio < 1 represents a favorable outcome for the test treatment.

Pre-meeting briefing
Roflumilast for treating chronic obstructive pulmonary disease [ID984]

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting.

Disease background

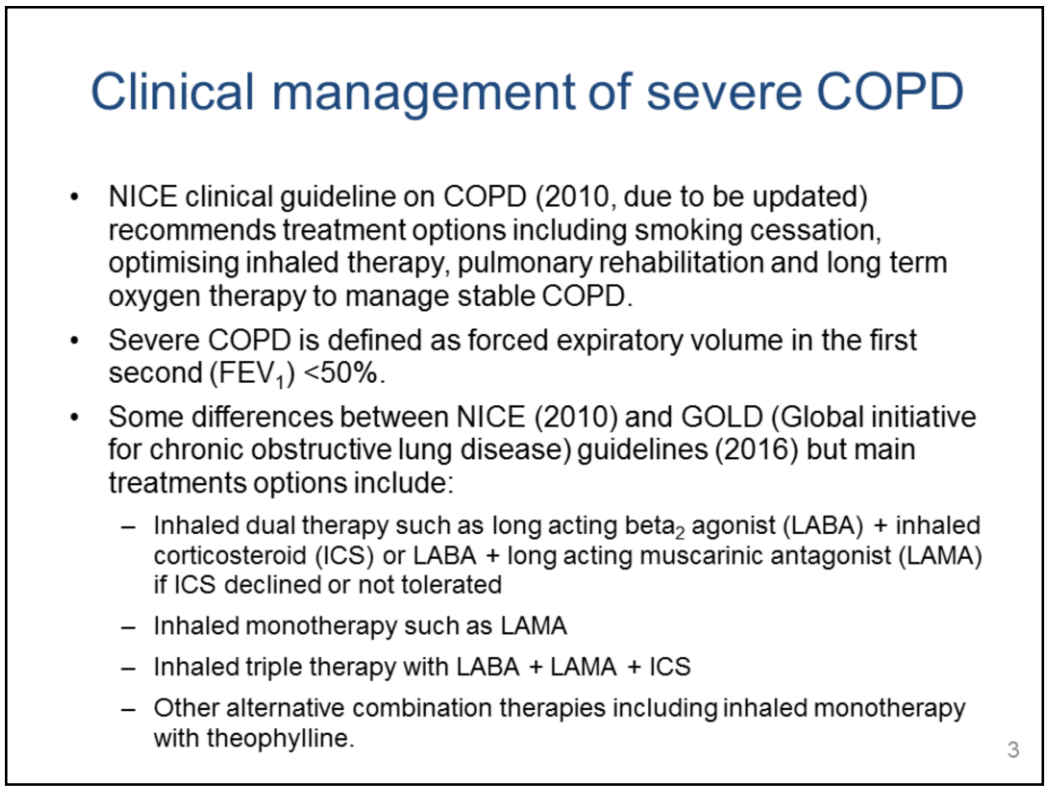
- Chronic obstructive pulmonary disease (COPD) includes chronic bronchitis, emphysema, chronic obstructive airways disease and chronic airflow limitation.
- COPD is characterised by consistent airways obstruction defined as FEV_1 (forced expiratory volume in 1 second) less than 80% predicted and FEV_1/FVC (forced volume capacity) ratio less than 70% and there is a long-term progressive decline in persistent airflow limitation that is accompanied by exacerbations.
- Exacerbations significantly contribute to disease burden accelerating disease progression, increasing the risk of mortality and morbidity, and reducing quality of life.
- Characteristic symptoms of COPD include chronic and progressive dyspnoea, cough, and sputum production that can be variable from day-to-day.
- Approximately 1.2 million people in the UK have been diagnosed with COPD.

2

Further detail and discussion on the disease background can be found in section 3.1 of company submission (pages 27 to 35) and section 2.1 of ERG report (pages 18 to 20).

To note:

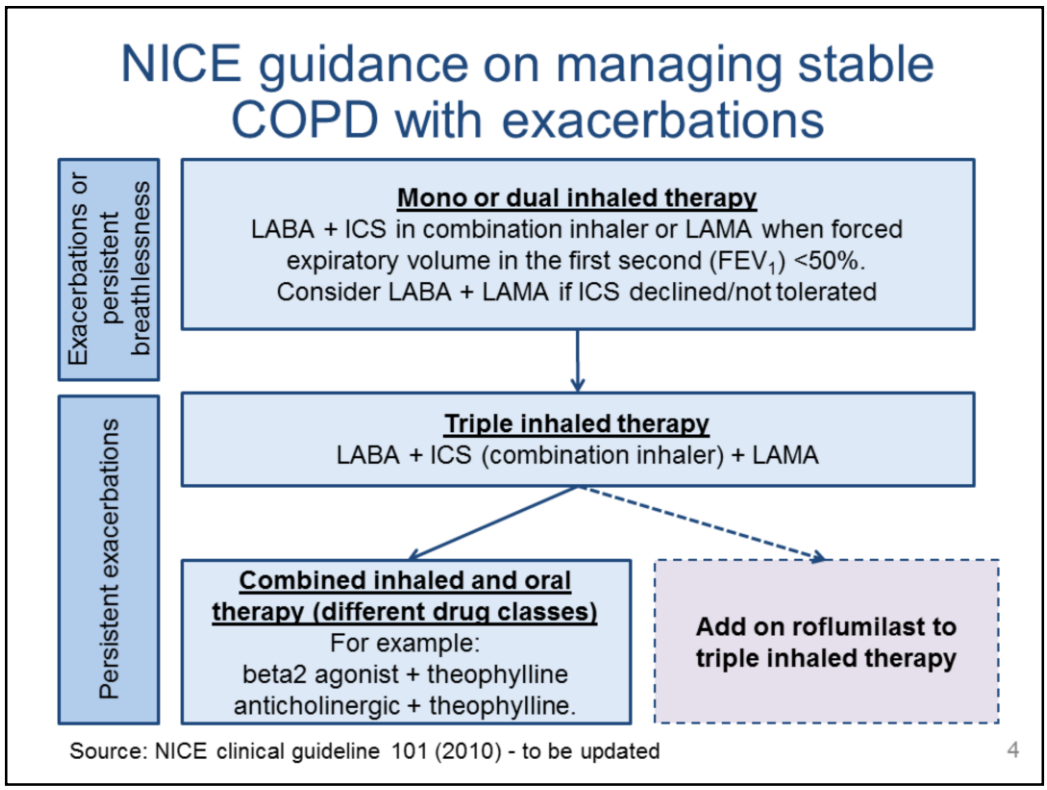
- COPD is a common preventable and treatable disease.
- Roflumilast is indicated for maintenance treatment of severe COPD associated with chronic bronchitis. Patients with COPD are often assigned a clinical phenotype of chronic bronchitis or emphysema, reflecting the prevalent mechanism of airflow limitation. Chronic bronchitis is a common clinical phenotype associated with COPD – published data report that 14 to 74% of COPD patients have chronic bronchitis. Chronic bronchitis is defined 'as chronic productive cough for 3 months in each of 2 successive years, in a patient in whom other causes of productive chronic cough have been excluded'. Chronic bronchitis may precede or follow the onset of airflow obstruction.
- The company estimates that 122,391 people in England are eligible for treatment with roflumilast (page 188 in company submission).



Further detail and discussion on the clinical management of COPD can be found in section 3.2 of company submission (pages 35 to 37) and section 2.2 of ERG report (pages 20 and 21).

To note:

- The company highlighted that the GOLD guidelines (2016) are more up to date than NICE's clinical guideline 101 (2010) and therefore that GOLD should take precedence over the NICE guidance. The NICE clinical guideline is due to be updated but timelines have not yet been confirmed. The company also state that the section on inhaled therapies has been identified as one of the sections for review and update.
- The company stated that there are subtle variations between local UK guidelines but that they are, in general, aligned with NICE clinical guideline 101 and the GOLD 2016 guideline.
- Based on a review of available local UK treatment guidelines, the company believes that current clinical practice in the management of COPD is considered to be well-established. There are only very subtle variations between local UK guidelines. These minor differences are not believed to be significant issues in current clinical practice.



Further detail and discussion on the current management of COPD can be found in section 3.2 of the company submission (pages 35 to 37).

To note:

- The company has excluded theophylline because it does not consider it to be standard care in the UK.
- NICE clinical guideline 101 recommendation 1.2.4.1 states: If patients remain symptomatic on monotherapy, their treatment should be intensified by combining therapies from different drug classes. Effective combinations include:
    - $beta_2$ agonist and theophylline
    - anticholinergic and theophylline. **[2004]**

GOLD 2016 guideline on management of COPD

- GOLD classifies COPD disease severity (A–D) based on symptoms, exacerbation history and airway limitation.
- Company suggest GOLD categories C & D relevant (FEV_1 <50% predicted)
  - Group C have few symptoms but a high risk of exacerbations
  - Group D have many symptoms and high risk, based on either severe airflow limitation or frequent exacerbations.

GOLD	First line	Alternative choice	Other possible treatments
C	ICS + LABA **or** LAMA	LABA + LAMA **or** LABA + phosphodiesterase-4 (PDE4) inhibitor **or** LAMA + PDE4	Short acting $beta_2$ agonist (SABA) **and/or** short acting muscarinic antagonist (SAMA) as required; Theophylline
D	ICS + LABA and / or LAMA	ICS + LABA + LAMA **or** ICS + LABA + PDE4 **or** LABA + LAMA **or** LAMA / PDE4	Carbocysteine; N-acetycysteine; SABA **and / or** SAMA as required; Theophylline

Source: Table 6 from company submission

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Further detail and discussion on the GOLD 2016 guidelines can be found in section 3.4 (clinical guidance and guidelines) of the company submission (pages 40 to 42).

To note:

- GOLD was launched in 1997 in collaboration with the National Heart, Lung, and Blood Institute, National Institutes of Health, USA, and the World Health Organization.
- Roflumilast is indicated in patients with severe airflow limitation (FEV_1 <50% predicted) associated with chronic bronchitis and a history of exacerbations, which broadly overlaps with GOLD groups C and D. However, patients with less severe airflow may fall into groups C and D due to their high exacerbation risk and are not included in the licensed indication.
- Medicines listed in the column 'other possible treatments' are listed in alphabetical order, and therefore not necessarily in order of preference.
- GOLD guidelines state theophylline can be used if long-acting inhaled bronchodilators are unavailable or unaffordable.

Roflumilast

UK Marketing authorisation	Maintenance treatment of severe COPD (FEV_1 <50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add on to bronchodilator treatment.
Mode of administration	Administered as an oral therapy.
Mechanism of action	Long-acting selective PDE4 enzyme inhibitor which targets cells and mediators in the body believed to be important in COPD.
Dosage	The recommended dose is 500 micrograms (one tablet) roflumilast once daily.
Cost	• £37.71 per pack of 30 tablets, list price (BNF, edition 67) • Cost per year of treatment £458.88 • No patient access scheme
Eligible population	Company estimates 122,391 people in England may be eligible for treatment with roflumilast.

6

Further detail and discussion on roflumilast is given on page 22 of section 2.1 (description of the technology) and page 189 of section 6.8 (annual budget impact on NHS in England) in the company submission.

To note:

- Roflumilast was granted a UK marketing authorisation in July 2010.
- The company is seeking a more specific recommendation for use as add-on to triple therapy (LABA / LAMA / ICS).
- The company anticipates that treatment with roflumilast will be initiated in secondary care and maintained in primary care.

Decision problem

	NICE scope	Company's decision problem
Population	Adults with severe COPD (FEV_1 <50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations	Adults with severe COPD (FEV_1 <50% predicted) associated with chronic bronchitis and a history of frequent exacerbations (≥2 exacerbations in prior 12 months) despite triple therapy with LABA + LAMA + ICS
Intervention	Roflumilast plus maintenance bronchodilator treatment (LABA or LAMA alone or combined with ICS, LAMA plus LABA if ICS not tolerated)	Roflumilast in combination with maintenance triple therapy: LABA + LAMA + ICS
Comparator	• LAMA in combination with LABA and ICS • LAMA + LABA • LAMA or LABA (with or without ICS) • Theophylline plus inhaled maintenance bronchodilator	LAMA in combination with LABA and ICS (LABA + LAMA + ICS) As the scope of intervention is restricted to roflumilast in combination with LABA + LAMA + ICS, mono- and dual therapy comparators are not considered relevant

7

Further detail of the company's decision problem can be found in table 1 in the company submission (page 13) and section 3 of the ERG report (pages 22 to 27).

To note:

- The company use a more restricted population, intervention and comparator compared with the NICE scope and the rationale for this is discussed in later slides.

Decision problem

	NICE scope	Company's decision problem
Outcomes	• lung function • incidence and severity of acute exacerbations, including hospitalisation • symptom control (e.g. shortness of breath) • mortality • adverse effects of treatment • health-related quality of life	• rate of moderate to severe exacerbations (including hospitalisation) • rate of severe exacerbations (requiring hospitalisation) • lung function as measured by FEV_1 • mortality • health related quality of life • adverse effects of treatment
Subgroups	None	None

8

Further detail of the company's decision problem can be found in table 1 in the company submission (page 13) and section 3 of the ERG report (pages 22 to 27).

ERG comments to note

- The company's submission does not report symptom control (e.g. shortness of breath). COPD Symptom Scores were reported in the clinical study report (Tables 14.2.3.5 to 14.2.3.7). In addition health related quality of life is not reported in the clinical effectiveness section of the submission. Quality of Life (COPD Assessment Test) data were presented in the clinical study report. See section 4.2.5 of the ERG report for more information on these outcomes.

Rationale for differences in scope vs. decision problem

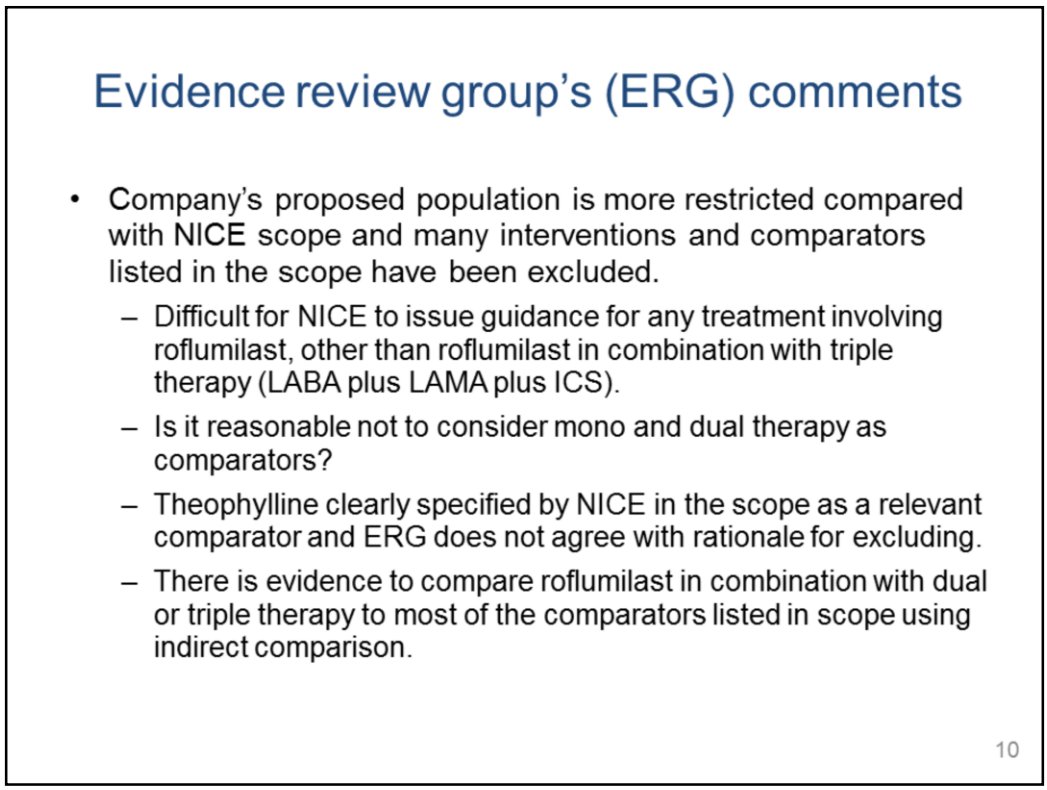
- Company seeking recommendation for the use of roflumilast as add-on to triple therapy (LAMA + LABA + ICS) in patients with severe COPD (FEV_1< 50% predicted), symptoms of chronic bronchitis and frequent exacerbations (≥ 2 / year).
- Therefore the company excludes some treatments as comparators:
  - monotherapy and dual therapy (for example LAMA or LABA alone, LABA + LAMA) are outside of the company's decision problem as appraisal restricted to add on to triple therapy
  - theophylline use is low in UK (particularly as add on to triple therapy), there are serious treatment limiting side effects (seizures and cardiac arrhythmias) and it is difficult to use (requires monitoring of plasma levels with higher doses).

9

Further details can be found in section 3.2 of the company submission (pages 36 & 37) and section 3.3 of the ERG report (pages 26 and 27).

To note:

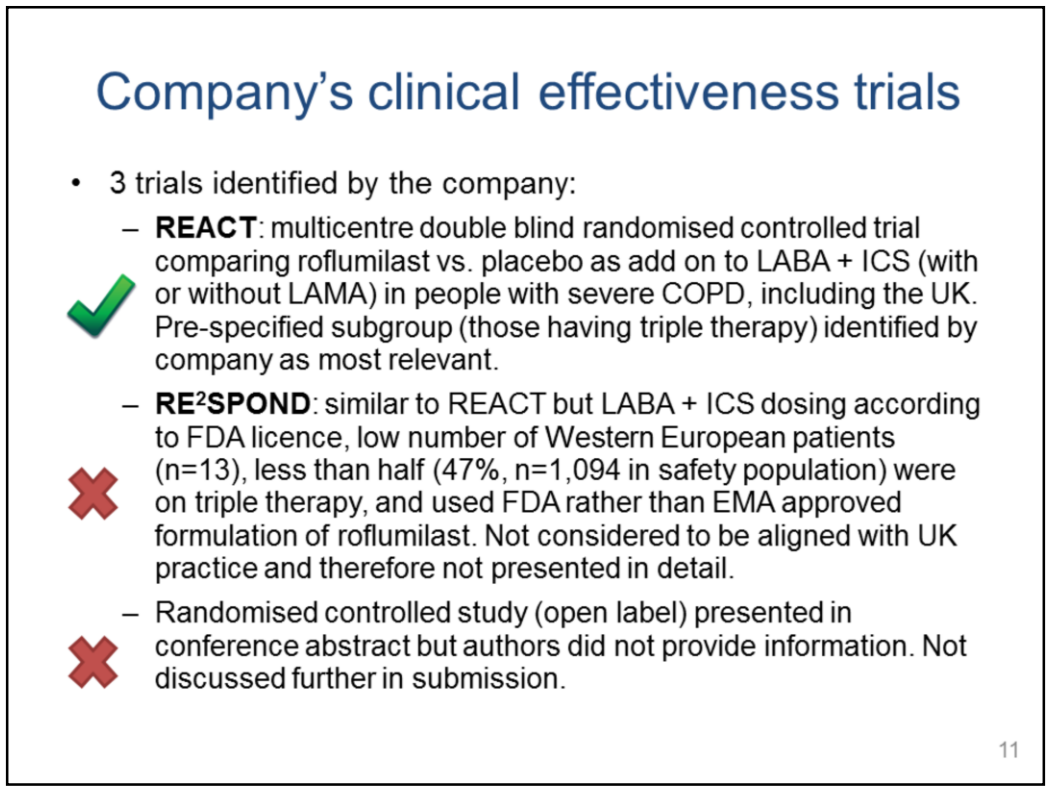
- The company states that there is no evidence on the use of theophylline as add-on to triple therapy and its impact on exacerbation rates in patients with severe COPD and frequent exacerbations. The theophylline study most relevant to the decision problem is a pilot clinical trial, in which patients with severe COPD were treated with oral low-dose theophylline added to ICS+LABA. In this placebo-controlled study theophylline failed to prevent exacerbations.
- The company highlights that the challenges associated with theophylline are reflected in the GOLD guidelines which recommend that theophylline is considered only if long-acting bronchodialators are not available or affordable.



Further details can be found in section 3 of the ERG report (pages 22 to 27).

ERG comments to note:

- If the population is restricted to adults who have severe COPD despite triple therapy, it seems reasonable that the intervention is roflumilast in addition to triple therapy.
- Trials have been performed in patients with severe COPD comparing triple therapy with dual therapy (e.g. FORWARD and WISDOM). Therefore, the company could have presented evidence showing the comparative effectiveness of roflumilast versus dual therapy using indirect comparisons.



Further details on the randomised controlled trials (RCTs) that the company considered relevant can be found in section 4.2 of the company's submission (page 46 to 49).

To note:

- The company carried out a systematic review to identify RCTs of roflumilast as an add-on to triple therapy (LABA / LAMA / ICS) in patients with severe / very severe COPD, as defined in the pre-2013 GOLD report as stages 3 and 4.
- The company concludes that REACT is the most relevant trial to the decision problem and as such is presented as the primary trial in the submission.

ERG's comments on the clinical trials

- RE²SPOND trial is also relevant to the decision problem and similar enough to REACT trial to pool results.

Design	REACT trial	RE²SPOND trial
Population	1,935 in ITT analysis	2,352 in safety population
Treatment	500 µg roflumilast or placebo + fixed dose combination of ICS/LABA (no limit to the % of participants allowed LAMA)	500 µg roflumilast or placebo + fixed dose combination of ICS/LABA (+ up to 60% of participants allowed LAMA)
LABA + ICS dose	fluticasone/salmeterol 500/50 µg or 250/50 µg (1 inhalation twice daily)	fluticasone/salmeterol 250/50 µg (1 inhalation twice daily)
Roflumilast formulation	Film-coated tablets	Uncoated tablets
Definition of primary outcome	Moderate: required oral/parenteral corticosteroid treatment Severe: resulting in hospitalisation and/or leading to death Exacerbations occurring within 10 days counted as 1 exacerbation	

Source: Table 4.14 in ERG report

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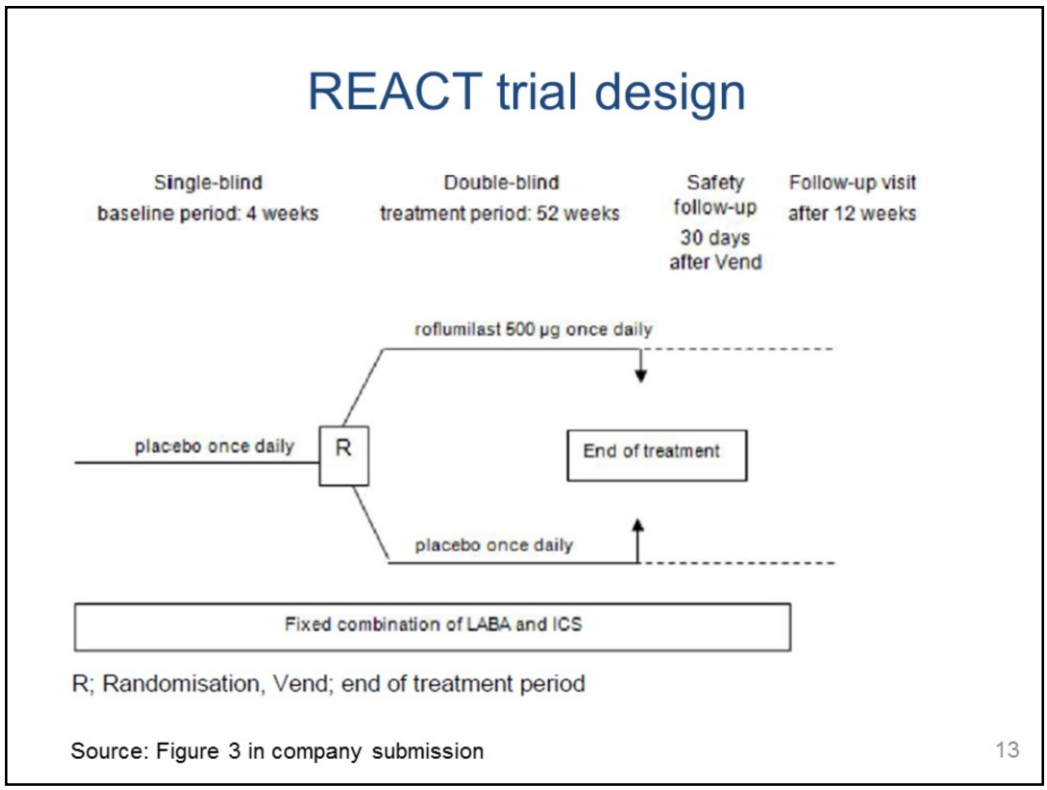
Further detail on RE²SPOND trial can be found in section 4.5 of ERG report (pages 50 to 54).

ERG comments to note:

- The RE²SPOND trial is a 52-week, phase 4, double-blind, placebo controlled trial including participants aged 40 years or older with severe/very severe chronic obstructive pulmonary disease, chronic bronchitis, 2 or more exacerbations and/or hospitalisations in the previous year, and receiving inhaled corticosteroid/long-acting b2-agonist with or without LAMA daily for 3 or more months.
- Participants were randomised to once-daily roflumilast, 500 mg (n = 1,178), or placebo (n = 1,176). Stratification was based on LAMA use and 47% of the population was on additional LAMA therapy.



Further details on the design of the REACT trial can be found in section 4.3 of the company's submission (pages 49 to 57).

To note:

- The trial consisted of a 4-week, single-blind baseline period during which patients received placebo.
- This was followed by a 52-week double-blind treatment period during which patients received either roflumilast or placebo.
- After the treatment phase, there was a 12-week follow-up period with a final visit at week 64. For those patients who were experiencing an adverse event at the end of the double-blind treatment phase (i.e. when they stopped study drug treatment) there was also safety follow-up at 30 days.

REACT study

Parameter	Description
Patients	Roflumilast (n=969) & placebo (n=966)
Inclusion criteria	History of COPD associated with chronic bronchitis, FEV_1 ≤ 50% predicted, age ≥ 40 years, smoking history ≥ 20 pack-years, history of ≥ 2 moderate or severe exacerbations in the previous year, pre-treated with ICS and LABA for at least 12 months before baseline; and at a constant dose
Location	21 countries including United Kingdom (n=105 recruited & 55 randomised)
Trial design	1 year prospective, multicentre, phase 3-4 trial (double blind)
Trial drugs	Roflumilast 500 µg or placebo once daily for 52 weeks (double blind)
Primary outcomes	Rate of moderate or severe COPD exacerbations per patient per year (moderate exacerbations defined as requiring oral or parenteral glucocorticosteroids and severe exacerbations as requiring hospitalisations and/or leading to death)
Secondary outcomes	Change in post-bronchodilator FEV_1, rate of severe COPD exacerbations per patient per year, time to exacerbation, COPD assessment test, mortality & adverse events, time to withdrawal *NB: 12 pre-planned subgroups (concomitant LAMA used for this appraisal)*

Table 10 in company submission

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To note:

- Inclusion criteria included history of COPD (according to GOLD 2009 for at least 12 months prior to baseline) associated with symptoms of chronic bronchitis (chronic product cough for 3 months in each of the 2 years prior to baseline), post-bronchodilator FEV_1 of ≤50% predicted, history of ≥ 2 moderate or severe exacerbations (separated by at least 10 days) in the previous year, pre-treatment with inhaled ICS and LABA combination for at least 12 months before baseline; and at a constant dose (the maximum approved dose of the combination) as a fixed combination in the 3 months prior to baseline.
- Patients were recruited from secondary care and primary care. There was no dose titration and the protocol did not permit dose adjustments. Patients who were already taking an inhaled LAMA (tiotropium bromide) prior to the start of the trial were allowed to continue this treatment (company's subgroup of interest).

RE²SPOND study

Parameter	Description
Patients	Roflumilast (n=1,178) & placebo (n=1,174) in ITT population
Inclusion criteria	Eligible participants were 40 years of age or older with severe to very severe COPD, chronic bronchitis, two or more exacerbations and/or hospitalisations in the previous year, and were receiving ICS/LABA with or without LAMA daily for 3 months or longer. Participants had to remain on the same COPD maintenance treatment from screening through randomisation.
Location	17 countries (United States, Ukraine, Argentina, Russia, Philippines, Peru, Romania, Serbia, Canada, Malaysia, Thailand, Mexico, Spain, Taiwan, Colombia, Italy, and Chile).
Trial design	1 year prospective, multicentre, phase 4 trial (double blind)
Trial drugs	Roflumilast 500 µg or placebo once daily for 52 weeks (double blind)
Primary outcomes	Rate of moderate or severe COPD exacerbations per patient per year (moderate exacerbations defined as those that required oral or parenteral corticosteroid treatment and severe exacerbations as those that resulted in hospitalization and/or led to death).
Secondary outcomes	Rate of severe exacerbations, rate of moderate or severe antibiotic-treated COPD exacerbations, and mean change from baseline in pre-dose FEV_1 over 52 weeks.

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To note:

- Eligible participants were ≥40 years of age with a COPD history associated with chronic productive cough ≥12 months prior to screening (3 months in each of 2 consecutive years, with other causes of productive cough excluded), ≥2 documented moderate or severe COPD exacerbations in the 12 months prior to screening, and an FEV_1/forced vital capacity ratio <70% and postbronchodilator FEV_1 ≤50% of predicted. Additionally, participants must have been receiving an FDC ICS/LABA treatment for ≥3 months prior to screening, and those previously treated with a LAMA must have been on a stable dose for ≥3 months before screening. Participants were required to remain on the same COPD maintenance treatment from screening through randomisation.
- The efficacy analysis (i.e. intention-to-treat [ITT]) population comprised all randomised participants who took at least one dose of double-blind investigational product; participants were assigned to the treatment group based on the treatment to which they were randomised. The safety analysis population included all participants who were randomised and took at least one dose of double-blind investigational product; participants were assigned to the treatment they actually received.

Company's analysis of data from REACT

LAMA subgroup

- Company identified the pre-specified subgroup of patients having triple therapy (LABA + LAMA + ICS) as the most relevant:
  - 70% (677/969) in roflumilast group and 69% (669/966) in placebo group

Population included in analysis

- Per protocol (PP) analysis considered to be most relevant because the intention to treat (ITT) population included a substantial proportion of patients with protocol violations (e.g. FEV_1>50%, fewer than 2 exacerbations, not treated with ICS + LABA for prior year).
  - PP population reduces the number of patients to 1,122 (58% of the total ITT population)

Statistical model

- Negative binomial model considered more appropriate than Poisson as low event rate reduced study power and allows different exacerbation rates across patients (risk of exacerbation differs in COPD patients).

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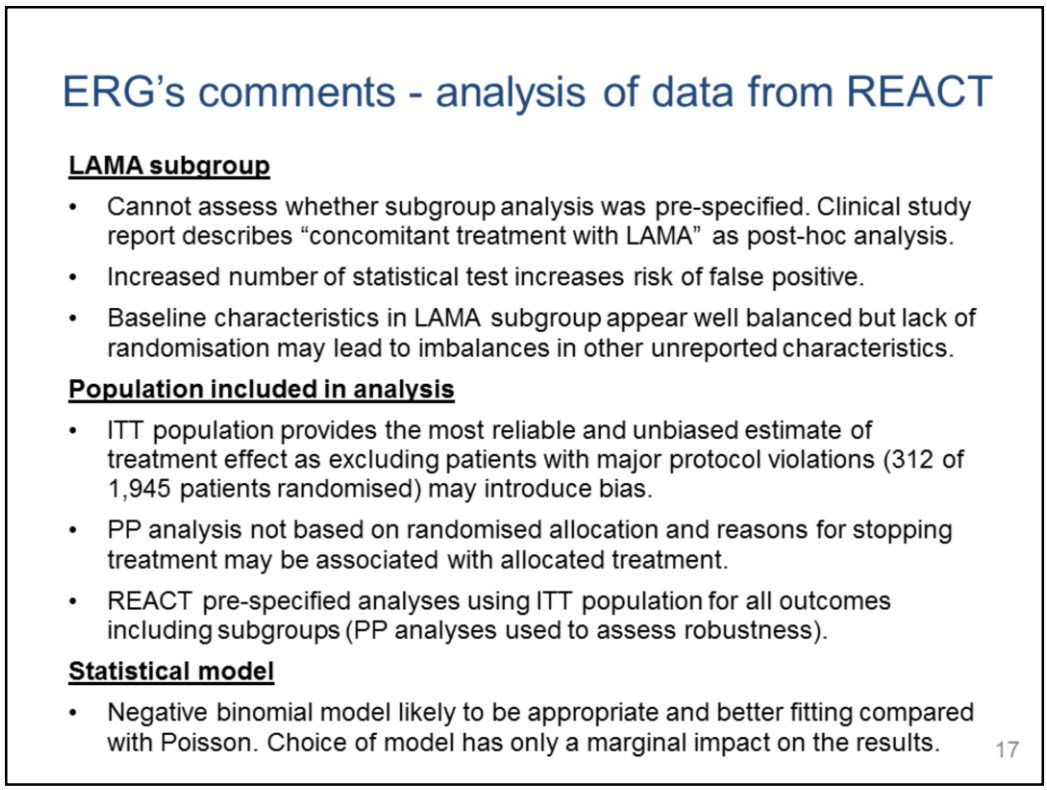
For further detail on the statistical analysis of the REACT trial, see section 4.4 of the company submission (pages 57 to 61) and section 4.7 (pages 72 to 75) for the company's preferred clinical effectiveness results.

To note:

- The pre-specified negative binomial model (which accounts for over dispersion) assumes that individuals' exacerbations follow a Poisson process with an underlying rate that is distributed as a gamma distribution. The primary analysis for the primary outcome (and subgroup analyses) used the ITT analysis and a Poisson regression model.
- The ITT population included randomised patients who took at least 1 dose of study drug following randomisation and incorporated all data until the patient discontinued (prematurely or as scheduled) the trial. The per protocol population included only those patients without major protocol violations (note: patients who discontinued treatment were included in the per protocol population provided there were no major protocol violations).
- 16.8% of patients in the roflumilast group and 15.3% in the placebo group had at least 1 major protocol deviation: 5.9% in the roflumilast group and 4.9% in the placebo group had FEV_1 % predicted >50% at V0 (start of the single-blind baseline period), 4.2% and 3.8% were not pre-treated with LABA/ICS for at least 12 months prior to V0, or did not use a fixed combination of LABA/ICS on a constant daily dose throughout the trial and 1.1% and 0.8% had less than 2 documented moderate or severe COPD exacerbations within 1 year prior to V0.



Further details can be found in section 4.2.2 and 4.2.3 of the ERG report (pages 36 to 40)

ERG comments to note:

- Any per-protocol analysis is likely to be biased as it is no longer based on the randomised allocation and the reasons that patients may not comply with the treatment protocol could be related to their allocated treatment (see section 4.2.2 and 4.2.3 of ERG report).
- 312 out of 1,945 randomised patients had major protocol deviations. For example there were 105 patients (table 4.5 on page 38 of ERG report) who had postbronchodilator FEV_1>50 % at the start of the single-blind baseline period (not in line with the inclusion criteria). At the clarification stage the company stated that as the study progressed there was a protocol change to allow patients to enter with FEV_1>50%. However, the ERG state that the company did not make it clear whether this protocol change accounted for the 105 patients with FEV_1>50 % , nor did the company explain the other major protocol deviations.
- The ERG concluded that the company have not provided adequate justification for the major protocol amendments and thus the production of the per protocol population and so continue to believe that the ITT population is superior.

Summary of results from REACT

	Intention to treat in all patients (n=1,935) Primary analysis	Per protocol analysis in LAMA subgroup (n=1,122) Company's preferred data	Intention to treat analysis in LAMA subgroup (n=1,346) ERG's preferred data
Moderate to severe exacerbation rate (95% confidence interval)			
Rate roflumilast	0.805 (0.724 to 0.895)	0.858 (0.754 to 0.978)	0.924 (0.821 to 1.040)
Rate placebo	0.927 (0.843 to 1.020)	1.075 (0.954 to 1.211)	1.061 (0.950 to 1.185)
Rate ratio (RR)	**0.868 (0.753 to 1.002)***	**0.799 (0.670 to 0.952)**	**0.871 (0.741 to 1.024)**
Severe exacerbation rate (95% confidence interval)			
Rate roflumilast	0.239 (0.201 to 0.283)	0.260 (0.21 to 0.322)	0.287 (0.237 to 0.347)
Rate placebo	0.315 (0.270 to 0.368)	0.395 (0.329 to 0.475)	0.374 (0.315 to 0.443)
RR	**0.757 (0.601 to 0.952)****	**0.659 (0.497 to 0.872)**	**0.767 (0.595 to 0.989)**
Moderate exacerbation rate (95% confidence interval)			
Rate roflumilast	Not reported	0.593 (0.511 to 0.689)	0.631 (0.550 to 0.725)
Rate placebo		0.669 (0.582 to 0.769)	0.676 (0.564 to 0.770)
RR		**0.886 (0.722 to 1.087)**	**0.934 (0.773 to 1.128)**

NB: Rates are per patient year. Company and ERG preferred data are from negative binomial model. * from Poisson model; ** from negative binomial model

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Results from REACT are discussed on pages 75 to 79, table 16 and 17 of the company submission and in section 4.2.5 of the ERG report (pages 41 to 49 and table 4.10 on page 47).

To note:

- In the REACT trial the primary endpoint (moderate to severe exacerbations) was analysed using a Poisson regression model for comparability with previous studies, with an accompanying pre-specified negative binomial analysis (used to assess robustness).
- The company suggests that a secondary endpoint of particular relevance to the decision problem is the rate of severe exacerbations. Severe exacerbations were defined as exacerbations that required hospitalisation and / or lead to death. Due to the low event rate (and as per the statistical plan), this endpoint was analysed by negative binomial regression.

ERG's comments on the clinical data

- RE²SPOND trial results are also relevant to the decision problem

Outcome	REACT trial RR (95% CI)	RE²SPOND trial RR (95% CI)
Moderate to severe exacerbations (primary endpoint)*	0.87 (0.75 to 1.00)	0.92 (0.81 to 1.04)
Moderate to severe exacerbations per participant per year (sensitivity analysis)†	0.86 (0.74 to 0.995)	Not applicable
Severe exacerbations†	0.76 (0.60 to 0.95)	0.95 (0.75 to 1.19)
Moderate or severe or antibiotic-treated exacerbations*	0.84 (0.74 to 0.95)	0.90 (0.80 to 1.02)
Severe exacerbations in participants with a prior history of hospitalisation†	0.65 (0.48 to 0.89)	0.79 (0.56 to 1.10)

*analysed using Poisson model in ITT population in REACT and negative binomial model in ITT population in RE²SPOND
† analysed using negative binomial model in ITT population in REACT and RE²SPOND

Source: Table 4.16 in ERG report

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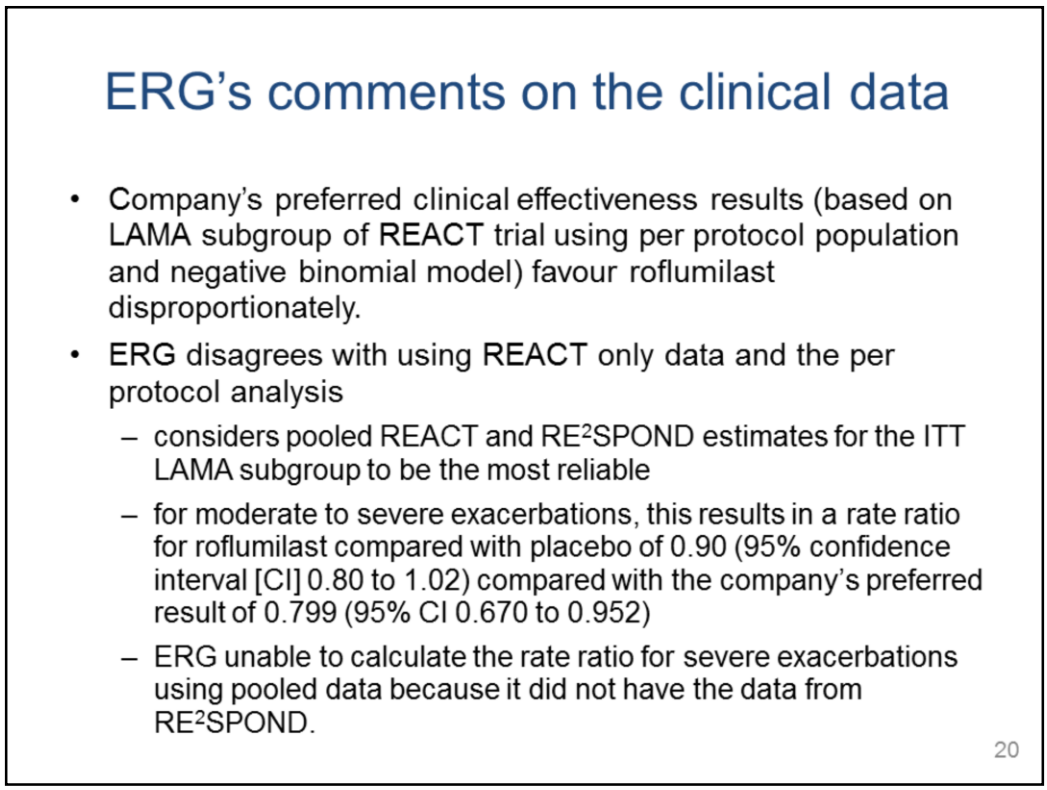
Further detail on RE²SPOND trial can be found in section 4.5 of ERG report (pages 50 to 54).



ERG comments to note:

- The results from RE²SPOND showed that the addition of roflumilast produced an 8.5% reduction in moderate or severe exacerbations but that the between group difference was not statistically significant. The time to the first exacerbation event was also not different between the two groups.

Adverse events – all patients in REACT

- 67% of patients in roflumilast group and 59% of patients in placebo group reported adverse events.
- Serious adverse events were reported by 26% of patients in the roflumilast group and 30% in placebo group.
- Most reactions reported were mild or moderate and occurred mainly in the first weeks of therapy and mostly resolved on continued treatment.
- Most common events in roflumilast group were diarrhoea (10% vs 4% in the placebo arm), weight decrease (9% vs 3%) and nausea (6% vs 2%).
- No increase in the incidence of pneumonia or other pulmonary infections during treatment with roflumilast (4%) compared with placebo (5%).

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Further detail on the adverse events can be found in section 4.12 of the company submission (pages 83 to 86) and pages 48 and 49 in the ERG report.

To note:

- The overall adverse event rate was similar to that reported in less severely affected patients in Rabe et al. (2010) and in a previous 12-month study of roflumilast (Calverley et al. 2009).
- The rate of pneumonia in both groups was higher than reported in previous roflumilast studies reflecting the known risks of ICS for COPD-related pneumonia in this population.
- Patients who received roflumilast in REACT reported the anticipated range of pharmacologically predictable side effects.

Key safety outcomes - REACT

- Body weight - pre-specified safety endpoint (mean weight loss in roflumilast group 2.65 kg [SD 4.37 kg] compared with 0.15 kg [SD 3.69 kg] in placebo). Consistent with previous studies.
  - During the 12 week end of treatment follow up period, 6% (37/657) of patients continued on commercial roflumilast. Bodyweight partially recovered in patients who discontinued roflumilast and appeared relatively stable in those who continued on commercial roflumilast.
- Other safety outcomes included mortality and major adverse cardiovascular events (2% in both groups).
- CHMP flagged psychiatric disorders as potential safety concern. In REACT study depression was reported by 2% of patients in roflumilast group vs. 1.1% in placebo.

Source: Table 21 in company submission

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Further detail on key safety outcomes can be found on pages 85 and 86 of the company submission and table 4.12 (page 49) of the ERG report.

To note:

- Body weight was a pre-specified safety endpoint and an identified safety issue of concern. This magnitude of weight loss associated with roflumilast use was consistent with previous studies and equated to a ~4% reduction in body weight from baseline (mean weight at baseline of the ITT population of the roflumilast group was 75.07 kg SD 17.275 kg).

Indirect comparison

- Company searched for studies to carry out an indirect comparison to incorporate all potential comparators in the severe to very severe COPD population.
- None of the 10 trials identified were considered relevant and an indirect comparison was not carried out
  - study by Cosio (2016) highlighted as potentially relevant (theophylline + ICS + LABA compared with LABA + ICS) but discarded because theophylline not considered a relevant comparator.
- ERG state that an indirect comparison is possible when including comparators from NICE scope
  - appraisal committee to decide whether these analyses are relevant for the decision problem.

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Further detail on identified trials for an indirect comparison can be found in section 4.10 of the company submission (pages 80 to 83).

To note:

- The systematic review for indirect and mixed treatment comparisons was conducted with a broader scope than the review for RCTs (see section 4.1 of the company submission) to incorporate any and all potential comparators in the severe to very severe COPD population. The review included RCTs of at least 24 weeks (6 months) duration.
- The ERG state there is evidence available to compare roflumilast in combination with LABA / ICS or in combination with triple therapy to most of the comparators listed in the scope. The ERG produce a possible network of studies that would allow a comparison of roflumilast in combination with triple therapy to triple therapy, LABA / LAMA, LABA / ICS and LABA / ICS in combination with theophylline (see figure 4.1 on page 34 of the ERG report).
- The ERG also note that if the committee agrees that the population can be restricted to adults with severe COPD associated with frequent exacerbations despite triple therapy, it might seem reasonable not to consider mono- and dual therapy comparators.

Key issues: clinical effectiveness

- Does the committee agree that the appraisal can be restricted to adults with severe COPD associated with frequent exacerbations despite background triple therapy?
- Does the committee agree with the company's decision to exclude monotherapy, dual therapy and theophylline as comparators?
- Does the committee agree with the company's decision to present evidence for roflumilast based on 1 double-blind randomised trial (REACT)?
  - What is the committee's view on the clinical effectiveness of roflumilast?
  - What is the committee's view of the quality and generalisability of the clinical evidence?
- Is it appropriate to pool the results from REACT and RE^{2}SPOND?
- Does the committee agree with the company's preferred analyses, that is, per protocol analyses from the REACT trial on the basis that the ITT population includes patients with protocol violations?

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Cost effectiveness evidence

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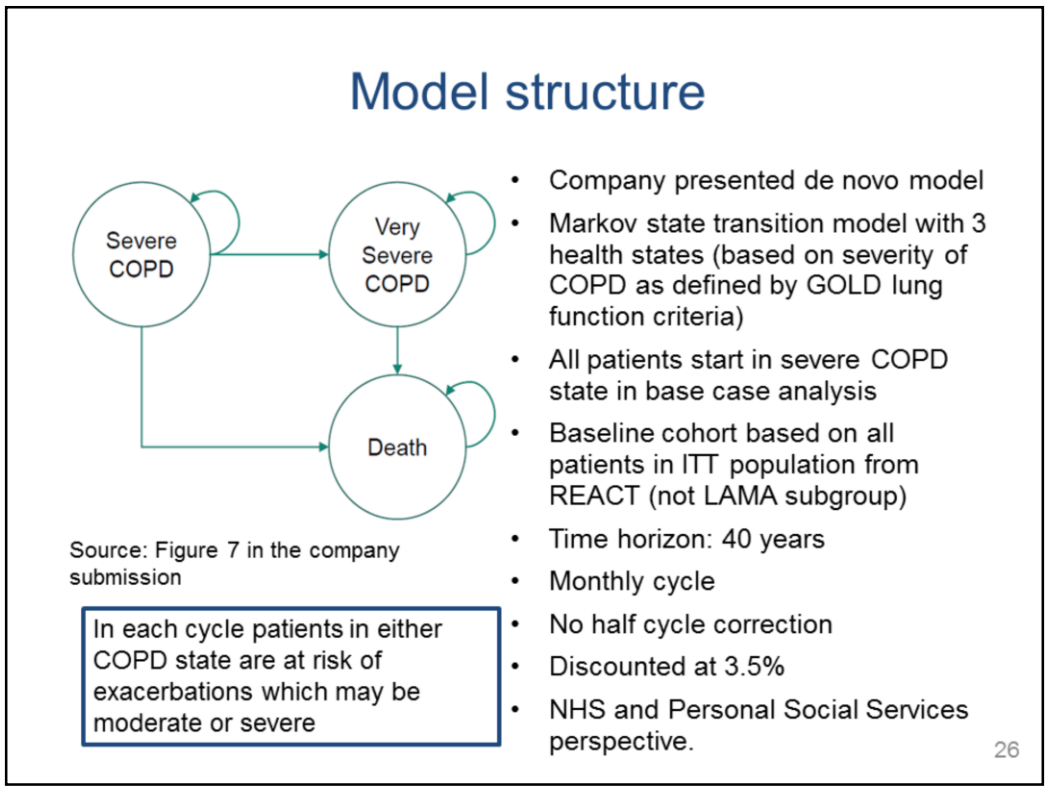
- The company presents the cost effectiveness evidence in section 5 of the company submission.
- The ERG discusses the cost effectiveness evidence in chapter 5 of the ERG report.



Further detail can be found on pages 97 to 99 in section 5.2 of the company submission.

To note:

- Using GOLD criteria the threshold for severe COPD is below 50% FEV_1 predicted and for very severe COPD is below 30% FEV_1 predicted.
- In each cycle the model predicts the proportion of patients who progress from severe COPD to very severe COPD or die. Patients in either COPD state are at risk of suffering exacerbations which may be moderate to severe.
- The model structure is similar to the one used in NICE technology appraisal 244, Samyshkin et al. (2014), and in the NICE COPD clinical guideline (CG101) but it has been updated to include differential moderate and severe exacerbation rates and to focus on roflumilast as add-on to triple therapy rather than dual therapy.
- The average age of the cohort was 64.7 years. Patients entering the model were considered to have severe COPD and suffering from at least 2 moderate to severe exacerbations in the last year.
- The ERG note that the model structure excluded many important aspects of COPD progression.

Clinical data used in company's model

- Model uses REACT data from subgroup who received concomitant LAMA (LABA + LAMA + ICS + roflumilast vs. LABA + LAMA +ICS) and uses data from per protocol analysis (negative binomial regression).
- Model estimates rate of moderate and severe exacerbations separately:
  - Base case controls for COPD severity and treatment arm and excludes patients not taking concomitant LAMA
  - Scenario analysis includes all patients (in the per protocol population), with concomitant LAMA use adjusted for as a covariate, along with COPD severity and treatment arm.
- Clinical benefit of roflumilast is larger with severe exacerbations compared with moderate exacerbations using both modelling approaches.

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Further detail can be found in section 5.2 (pages 97 and 98) and section 5.3 (pages 103 and 104) of the company submission.

To note:

- As the REACT trial showed a significant reduction in the rate of severe exacerbations and because severe exacerbations have more important consequences than moderate exacerbations, the model estimates the rate of exacerbations separately for moderate and severe exacerbations.
- The company suggest that negative binomial regression likely offers a more precise estimate, particularly as exacerbations in patients who received placebo were less frequent in REACT than was expected when the trial was designed.

Transition probabilities

Parameter	Details
Progression from severe (<50% FEV_1) to very severe COPD (<30% FEV_1 predicted)	Average FEV_1% predicted at start of model for patients with severe COPD is midpoint (40%) of the FEV_1% range for severe COPD (30% to 50%). Rate of FEV_1 assumed to decline at 52ml per year for all patients (Lung Health Study 2000). Equations from Crapo et al (1981) used to estimate predicted FEV_1 values using baseline characteristics from REACT. Predicted average time to very severe COPD is 6.97 years (monthly transition probability of 1.20%).
Progression to death due to very severe exacerbation	Based on case fatality rate from UK National COPD Audit Report 2014 (4.3% died during hospital admission for severe exacerbation). Adjusted for age using same approach as Samyshkin (2014) to avoid overestimating rate when younger than 72 years (mean age in audit).
Progression to death in stable COPD	Based on all cause mortality rate in general population using UK life tables and standardised mortality ratios (SMRs) with adjustment for impact of stable COPD and exacerbation specific mortality. Same SMR used as in Samyshkin 2014 (2.5 for severe COPD and 3.85 for very severe COPD). Estimated from all cause mortality from Ekberg-Aronsson 2005 (Swedish study) with severe exacerbation mortality deducted.

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Further detail can be found in section 5.3 (clinical parameters and variables) of the company submission (pages 100 to 101 for progression from severe to very severe COPD and page 108 for progression to death in stable COPD).

To note:

Progression to death due to severe exacerbation

- In Samyshkin (2014) the ratio of the age specific risk of death in the general population to the risk of death at the age of 72 years has been used to adjust the reported case fatality rate (CFR). For example, the ratio of the risk of death for patients 70 years of age compared to those 72 years of age is 0.78. The CFR for patients 72 years of age, adjusted accordingly, is 3.4%.

Progression to death in stable COPD

- The rates of exacerbations and case fatality rate used in the company's model are lower compared with Samyshkin (2014) and there is the possibility that the SMR of 2.5 and 3.85 are underestimating the true SMR. Therefore the company conducted scenario analyses with a higher mortality rate for severe COPD.

Health related quality of life (HRQoL)

- REACT trial used COPD Assessment Test (CAT) to collect quality of life data:
  - significant reduction from baseline CAT scores in each group but no significant difference between groups (mean difference: -0.285 (95% CI -0.711 to 0.142).
- Systematic review identified 15 studies measuring HRQoL of people with severe & very severe COPD:
  - None conducted in UK
  - 2 studies used EQ-5D UK value set (Rutten-van Molken 2006 and Menn 2010)
- Company's base case uses Rutten-van Molken studies.
- Company's scenario analysis uses alternative sources of HRQoL data including US study Solem (2013).

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Further details can be found in section 5.4 of the company submission pages 108 to 118.

To note:

- Hoyle et al. (2016) developed an algorithm to estimate EQ-5D based preference weights (utilities) based on CAT. Hoyle et al (2016) state their algorithm is likely to underestimate utilities for both low HRQoL (utility<0.5) and at near full health (utility≥0.9). Mapped CAT-based utility data would require further analyses to derive relevant parameter estimates for the model. CAT data is not considered in company's analysis.
- The search strategies for systematic review were designed to capture data from eight countries: UK, US, Canada, Germany, France, Italy, Spain and Australia.

Utility values used in company's model

State	Data source	Mean (SE)
COPD severity (base case)	Rutten van Molken (2006) used UK general population weights	Severe: 0.750 (0.009) Very severe: 0.647 (0.025)
COPD severity (scenario)	Solem (2013)	Severe: 0.707 (0.013) Very severe: 0.623 (0.021)
Exacerbation severity (base case)	Rutten van Molken (2009) EQ-5D time trade-off (Dutch time trade-off tariff)	Moderate: -0.010 (0.007) Severe: -0.042 (0.009)
Exacerbation severity (scenario)	Solem (2013)	Moderate: -0.103 (0.013) Severe: -0.157 (0.023)
Treatment emergent adverse events	Conservative assumption*	-0.042
*equal to a severe exacerbation from Rutten-van Molken (2009)		

Source: Table 40 and 69 in company submission

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For more details see section 5.4 of company's submission (pages 108 to 122, table 40 on page 122) and pages 181 to 183 (table 69 on page 182) for the utilities used in the scenario analyses.

To note:

- Due to their reduced lung function, patients with COPD have impaired HRQoL. Rutten-van Molken et al. (2006) sampled 1,235 patients across 13 countries including 513 patients with severe COPD and 91 patients with very severe COPD using the EQ-5D questionnaire, and UK general population preference weights (EQ-5D UK tariff).
- Rutten-van Molken et al. (2009) sampled 239 Dutch adults, also based on EQ-5D, but used the Dutch time trade-off tariff. The decrements for exacerbations represent the aggregate reduction in quality of life across exacerbations rather than annual utility values.
- Solem et al (2013) sampled 314 US patients (190 with severe COPD and 124 with very severe COPD) using the EQ-5D and the St George's Respiratory Questionnaire (SGRQ). As the mean length of moderate and severe exacerbations was 10.7 days (± 8.4 days) and 9.7 days (± 5.8 days) respectively, it was assumed that this disutility is only applied for one month, i.e. the values reported are divided by 12. This provides a smaller disutility then those provided by Rutten van Molken (2009).

Adverse events

- Company's base case includes pneumonia (most common serious adverse event) and diarrhoea, weight decrease and nausea (most common adverse events of any grade) from REACT.
- Discontinuation of treatment is not built into the model so treatment effect includes patients who discontinued treatment.
- Company's base case applies treatment emergent serious adverse events only and assumes:
  - It's appropriate to apply adverse event rates for the entire trial period in the 1st month only, as long term events are not expected
  - The cost of managing diarrhoea, weight loss & nausea is equivalent to the cost of a GP visit (£44)
  - The cost of pneumonia (£2,518) is a weighted average of non-elective inpatient short stay and long stay.
- Scenario analyses assess impact of including all treatment emergent adverse events, or excluding them from the analysis.

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See pages 119 of the company submission for details on adverse events, page 184 for further details of the scenario analyses and section 5.5 (pages 122 to 143) for costs.

To note

- Owing to time constraints associated to the acquisition of roflumilast, the company stated it was not possible to build discontinuation into the economic model. Consequently, with the treatment effect being inclusive of those patients who discontinued, the company states that the base case analysis is a conservative estimate of the cost effectiveness of roflumilast.
- The company's base case applies rates for treatment emergent serious adverse events only because the majority of treatment emergent adverse events are of grade 1 and 2 severity, which is not significant enough to impact costs or disutilities.
- The company assume that the majority of patients with uncontrolled adverse reactions will discontinue treatment. It is also assumed that long-term adverse events were not likely given that 95.3% of treatment emergent adverse events in REACT occurred within the first year post-treatment initiation.

Costs and resource use

- Systematic review identified 5 studies reporting data on cost and resource use in severe and very severe COPD
  - 3 studies conducted in UK, 1 in Germany and 1 Canada but not used to inform model inputs.
- NHS reference costs applied to severe (hospitalised) exacerbations- otherwise managed in primary care (GP visits).

Resource use	Components	Cost
Severe COPD monthly maintenance	GP consultation every 6 months (BMJ Best Practice), 2 days spirometry, influenza vaccination in 75% patients & 1.22 days per month on oxygen therapy (Oostenbrink 2005)	£32.57
Very severe COPD monthly maintenance	As above but 4 days spirometry per year and 6.08 days per month on oxygen therapy	£106.90
Moderate exacerbations	Excess GP consultations and prednisolone treatment	£103.85
Severe exacerbations	Excess GP consultations, hospital admission and ambulance transport	£1,724.43

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Source: Tables 41, 47, 49 and 50 in company submission

Further detail in section 5.5 of the company submission (pages 122 to 143).

To note:

For COPD maintenance:

- BMJ Best Practice (2016) states that stable COPD patients should be assessed at 6-month intervals, and the company assume patients in both severe and very severe COPD states visit a GP twice a year.
- Other maintenance resource use was assumed to be the same as in Samyshkin (2014) in which resource use estimates were based on Oostenbrink et al. conducted alongside a clinical trial. These resource use assumptions were also used elsewhere.

For COPD exacerbations:

- BMJ Best Practice for COPD states that patients with frequent exacerbations should be followed at 2-week to 1-month intervals. Thomas et al. (2014) reports primary care contacts by exacerbation frequency (none, infrequent and frequent). The median number of primary care contacts per year is less than recommended in BMJ Best Practice. The model applies an assumption that the ratio of contacts (Table 48) between non-exacerbators, infrequent and frequent exacerbators can be applied to the recommended number of primary care visits to estimate the number of visits for patients with and without exacerbations (recommended two contacts per year).

Other assumptions in company's model

- Base case model assumes
  - No additional lung function benefit from treatment with roflumilast.
  - Patients with severe & very severe COPD have 2 GP visits a year for general maintenance.
  - During a moderate exacerbation, 50% of patients will be treated with a 7-day course of prednisolone and 50% with a 14-day course.
  - During a severe exacerbation, 90% of patients will be transported to hospital by ambulance.
  - Exacerbations are associated with increased risk of death, costs and disutilities.

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Further detail can be found in the company submission (pages 144 to 146).

Company's base case results

	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER
Deterministic results							
Roflumilast	£22,930	8.95	6.14	£2,996	0.18	0.16	£18,774
Triple therapy	£19,933	8.77	5.98	-	-	-	-
Probabilistic results							
Roflumilast	£23,129	-	6.18	£2,996	-	0.17	£17,855
Triple therapy	£20,133	-	6.01	-	-	-	-

ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, Life years gained; QALYs, quality-adjusted life years;

- Probabilistic results show triple therapy plus roflumilast has a 72% probability of being cost effective at £20,000 per QALY gained, increasing to 100% at £30,000 per QALY gained

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Further detail can be found in section 5.7 of the company submission (pages 146 to 158).

To note

- The company provided updated PSA results that were provided in the response to the clarification letter, which included the correction of the programming error that the ERG identified and inclusion of the correlation of the regression coefficients. These update results are used here.
- The following parameters were made probabilistic (statistical distribution): FEV_1 decline per annum (Gamma); Exacerbation regression equations (Normal); treatment emergent adverse events and serious treatment adverse events rates (Beta); Resource use (Beta or Gamma) except prednisolone use, hospital admission and ambulance transport; Unit costs (Gamma) except spirometry, influenza vaccination and oxygen therapy; COPD health state utilities (Beta); COPD exacerbation disutilities (Beta); Standardised mortality ratios (Gamma); Severe exacerbation case fatality rate (Beta).
- The PSA involved undertaking 10,000 simulations, each involved a random draw from each distribution.

Company's deterministic sensitivity analyses

- In all of the company's sensitivity analyses the ICER was under £25,000 per QALY gained.
- Most influential parameters include:
  - transition probability from severe to very severe COPD for both treatment groups
  - starting age of cohort
  - mortality rate for very severe COPD

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Further detail can be found in section 5.8 of the company submission (pages 157 and 158).

To note

- Each parameter was set to either the upper and lower limits of the 95% CI, 20% higher or lower than the base case value (where a 95% CI was not available) or standard upper and lower limits (i.e. cost and outcomes discount rates were set to 6% and 0%) , holding all other parameters constant.
- The most influential parameter is the monthly transition probability for the LABA / LAMA / ICS treatment group. Although these changes in monthly transitions (± 0.24%) may seem minor they are equivalent to 17 additional or fewer months in the severe COPD state.
- The ERG noticed that some of the parameters were not included into the deterministic sensitivity analysis, such as the treatment effect parameters. The justification for the parameter inclusion criteria used by the company for deterministic sensitivity analysis is not clear to the ERG. The ERG conducted several scenarios exploring the treatment effectiveness (see Section 5.3 of ERG report).

Company's scenario analyses

Starting population 100% very severe or mixed COPD

- Base case assumes all patients start in severe COPD state
  - scenario 1 all patients start with very severe COPD
  - scenario 2 mixed population of severe & very severe COPD (as in REACT trial)

	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER
Base case (all severe COPD)	£22,930	8.95	6.14	£2,996	0.18	0.16	£18,774
All very severe COPD	£26,014	8.23	5.18	£2,343	0.22	0.19	£12,337
Mixed population*	£23,892	8.72	5.84	£2,792	0.19	0.17	£16,519

All ICERS from deterministic results. Abbreviations: ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, Life years gained; QALYs, quality-adjusted life years.
*69% severe COPD and 31% very severe COPD (from subgroup analysis in REACT)

Source: Tables 57 and 61 in company submission

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Further detail can be found in the company submission pages 159 to 179.

To note

- The company reports ICERs separately for a starting population of all severe COPD patients, all very severe COPD patients and the mixed population based on the proportion reported in REACT (the ICERs are presented on next slide).
- Probabilistic results are also included for these scenario analyses in the company submission (pages 165 to 169 for very severe COPD and pages 175 to 179 for mixed population.)
- The company concludes that the "probabilistic results are highly comparable to the base case deterministic results demonstrating that the model is stable".

Company's additional scenario analyses

1) LAMA included as covariate (base case analysis excluded people not taking LAMA)
2) Higher mortality rates for COPD assumed (standardised mortality ratios of 3.1 and 5.0 for severe and very severe COPD compared with 2.5 and 3.85 in the base case analysis)
3) Inclusion of additional lung function benefit from roflumilast (base case excluded this additional benefit)
4) Inclusion of all treatment emergent adverse events (base case included only serious ones)
5) Removal of all treatment emergent adverse events

All scenario analyses resulted in ICERs below £21,000 per QALY gained

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Further detail can be found in the company submission pages 159 to 184.

Rationale for scenario analyses

- Concomitant LAMA use was not found in the trial to impact on the relative effectiveness of roflumilast in terms of exacerbation reduction (hence no interaction term is included), and controlling for LAMA use allows differences in the underlying rate of exacerbations to differ by LAMA usage, without sacrifice of data. Therefore scenario analyses with LAMA as covariate were conducted.
- The rates of exacerbations and case fatality rate used in the company's model are lower compared with Samyshkin (2014) and there is the possibility that the SMRs of 2.5 and 3.85 for severe and very severe COPD underestimate the true SMRs. Therefore scenario analyses with a higher mortality rate were conducted.
- In the REACT trial, add on roflumilast resulted in a 56 ml (95% CI 38 to 73) improvement in post-bronchodilator FEV_1 over 52 weeks compared with triple therapy alone. The company suggests that "It is possible that some degree of reduction in exacerbation rates seen in REACT may be attributable to lung function improvement." Therefore scenario analyses with additional lung function benefit in the roflumilast arm were conducted.

Company's scenario analysis results

	ICER per QALY gain by severity of COPD in starting population		
Scenario	Severe	Very severe	Mixed severe & very severe
Company's base case	£18,774	-	-
LAMA use included as a covariate	£16,326	£12,385	£15,030
Higher mortality rate for severe COPD	£20,906	£13,186	£18,207
Additional lung function benefit (1 year*)	£18,159	£14,049	£16,834
All grade treatment emergent adverse events included	£19,498	£12,708	£17,109
All treatment emergent adverse events removed	£18,711	£12,292	£16,462

All ICERS from deterministic results. Abbreviations: ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, Life years gained; QALYs, quality-adjusted life years.
*Estimated based on exacerbations over 1 year period (under the assumption that lung function benefit persists for 1 year).

Source: Tables 65, 66, 68, 71 and 72 in company submission

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Further detail can be found in the company submission pages 159 to 184.

Company's scenario analysis
Alternative sources of HRQoL data

- Base case uses Rutten-van Molken studies for COPD utility scores. Company used data from Solem (2013) in scenario analysis:
  - US study of 314 patients (190 with severe COPD and 124 with very severe COPD)
  - Used the EQ-5D and the St George's Respiratory Questionnaire.
- Scenario analyses using various combinations of utilities and disutilities from Rutten van-Molken (2006), Rutten van-Molken (2009) and Solem (2013).

COPD severity of starting population	ICER (£ per QALY gained)
Severe (base case)	£18,774 to £26,069
Very severe	£12,337 to £17,937
Mixed	£16,519 to £23,305

Source: Table 70 in company submission

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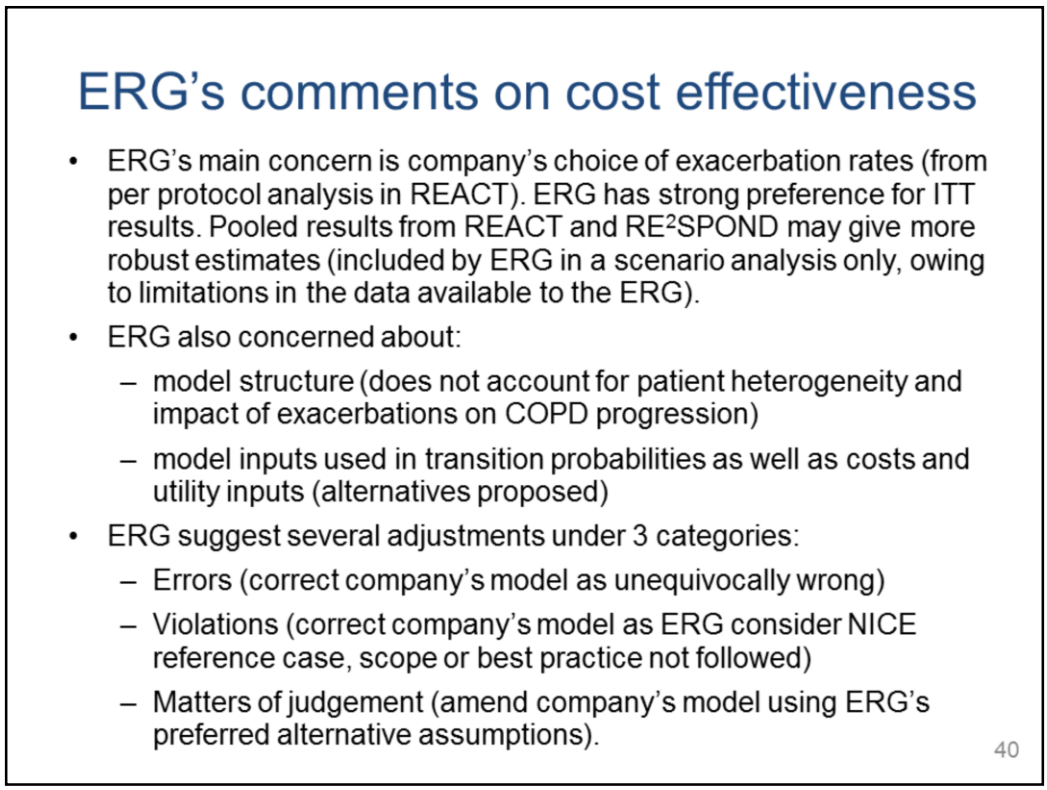
Further detail can be found in the company submission pages 181 to 183.

To note

- The company states that "As the mean length of moderate and severe exacerbations in Solem (2013) was 10.7 days (± 8.4 days) and 9.7 days (± 5.8 days) respectively, it was assumed that this disutility is only applied for one month, i.e. the values reported are divided by 12. This provides a smaller disutility than those provided by Rutten van Molken 2009."
- The company suggests that the utility values for Rutten van-Molken 2006 are the most appropriate given that they are based on UK general population weights, therefore the ICER is likely to only range up to £22,206 when varying disutility values with considerable smaller disutilities for exacerbations.



Further detail can be found in section 1.5 of the ERG report (pages 14 and 15).

ERG comments to note:

- The company used the exacerbation rates of the per protocol population in the REACT trial whereas the ERG state that pooled estimates from the REACT and RE²SPOND trial might provide more robust effectiveness estimates. Furthermore, the ERG considers the intention-to-treat population more in line with UK clinical practice than the per protocol population because it is likely that in clinical practice patients who do not strictly fulfil the inclusion criteria of REACT will receive treatment with roflumilast.
- The ERG considers the company's model to be a simplistic representation of COPD progression, which does not take patient heterogeneity, as well as the impact of exacerbation on disease progression, into account. Even though estimating the direction of bias without a formal analysis would be speculative, the ERG believes that not incorporating some of these modelling aspects, for instance the impact of previous exacerbation history on future exacerbations, might have resulted in a more conservative estimate of the ICER.

ERG's correction of errors

Parameter	Company	ERG
GP visits	• 2.03 visits per moderate exacerbation (infrequent exacerbators) • 8.03 visits per severe exacerbations (frequent exacerbators)	• severity not same as frequency and can have multiple exacerbations per year • add 1 additional visit for moderate exacerbation and reduce to 0 for severe exacerbation (Oostenbrink et al. 2005) as patients are in hospital.
Hospital stay	Cost of hospitalisation due to severe exacerbation (£1183.06) and cost of pneumonia (£2518) based on weighted average of non-elective inpatient short and long stay.	ERG add costs for excess bed days to hospitalisation (£1245.45).
Pneumonia		Could not replicate company's estimate so ERG calculated weighted average and include excess bed days (£1924.72).

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Further detail can be found in section 5.3.1 of the ERG report (page 94).

ERG comments to note:

GP visits

- The ERG considers the method to estimate the number of additional GP visits during exacerbations to be incorrect because moderate and severe exacerbations are not the same as infrequent and frequent exacerbations.
- The ERG also considers that the company overestimates the number of GP visit per exacerbations (2.03) as they did not take into account that patients may experience more than one exacerbation a year.
- The ERG also considers that the additional number of GP visits for severe exacerbations is overestimated (8.03).

ERG's corrections of violations

Parameter	Company	ERG
Ambulance transport	£208.95 from Samyshkin et al. (2014).	HRG code used as most recently published cost data (£233.02).
Utility decrements due to exacerbations	0.01 and 0.042 for moderate and severe exacerbations (Rutten-van Molken 2009, time trade-off valuations by Dutch general public).	Data from Hoogendoorn 2011 (0.0166 for moderate exacerbations and 0.0482 for severe). EQ-5D and valued with the UK-tariff.
Half cycle correction	No half cycle correction due to short cycle length.	Half cycle correction added (impact small but good practice).
Baseline population and adverse events	Full ITT analysis from REACT.	ITT analysis from LAMA subgroup in REACT for consistency with effectiveness data.

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Further detail can be found in in section 5.3.1 of the ERG report (pages 94 and 95)

ERG comments to note:

Ambulance transport

- The ERG incorporated this change to the model to reflect good modelling practice to use the most recently published cost and resource use data.

Utility decrements due to exacerbation

- The ERG incorporated this change to the model, because the current estimates from Rutten-van Mölken et al. (2009) were not derived from the EQ-5D but from time trade-off valuations of COPD health profiles by the Dutch general public. Therefore, to be more in line with the NICE reference case, the estimates from Hoogendoorn et al. (2011) were used for moderate and severe exacerbations, since they were derived from patient-reported EQ-5D and valued with the UK-tariff.

ERG's preferred assumptions

Parameter	Company	ERG
Maintenance costs (severe and very severe COPD)	• Assumes 2 GP visits per year for both groups • Monthly maintenance cost £32.57 for severe COPD and £106.90 for very severe.	• Assumes more GP visits with very severe COPD compared with severe. • Use 4 times per year (Oostenbrink et al. 2005) for very severe COPD.
Progression from severe to very severe COPD	• Reference equations to translate FEV_1 to % FEV_1 predicted from Crapo (1981) • Lung function decline 52 ml per year (Lung Health Study 2000).	• Reference equation from Hankinson et al. (1999). • Use more plausible lung function decline 38 ml per year (Decramer & Cooper 2010)
Exacerbation rates	Rate ratios from REACT (LAMA subgroup, per protocol analysis) • Moderate (RR 0.887, 95% CI 0.723 to 1.087) • Severe (RR 0.656, 0.496 to 0.868)	Rate ratios from REACT (LAMA subgroup, ITT analysis) • Moderate (RR 0.934, 0.773 to 1.128) • Severe (RR 0.767, 0.595 to 0.989)

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Further detail can be found in in section 5.3.1 of the ERG report (page 95).

ERG comment to note:

Progression from severe to very severe COPD

- The ERG judges the 38 ml per year estimate from Decramer and Cooper (2010) to be more plausible to use in the model compared with the 52 ml per year estimate from Lung Health Study, because the latter estimate is derived from a study which mostly consisted of moderate COPD patients (i.e. the baseline FEV1% predicted at baseline was 78%).

ERG's amended base case results

Parameter	Inc. costs	Inc. QALYs	ICER
Company's base case	**£2,996**	**0.16**	**£18,774**
1. Correct all errors (GP visits, cost of hospitalisation and pneumonia)	£3,257	0.16	£20,409
2. Correct errors and update ambulance cost	£3,239	0.16	£20,296
3. Correct errors and use exacerbation utility from UK tariff	£3,257	0.15	£21,340
4. Correct errors and add half cycle correction	£3,273	0.16	£20,509
5. Correct errors and use LAMA subgroup for baseline characteristics and adverse events	£3,122	0.16	£20,018
6. Correct errors and increase maintenance costs for very severe COPD	£3,271	0.16	£20,492
7. Correct errors and lower lung function decline	£3,388	0.15	£21,869
8. Correct errors and use ITT exacerbation rates (REACT)	£3,513	0.11	£33,009
ERG preferred base case (1 to 8)	**£3,489**	**0.10**	**£35,814**

All ICERS from deterministic results. Abbreviations: ICER, incremental cost-effectiveness ratio; Inc, incremental; QALYs, quality-adjusted life years.

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Further detail can be found in table 6.7 of the erratum of ERG report (page 106).

ERG comment to note:

- The most influential adjustments/corrections made by the ERG were
    1. using exacerbation rate ratios based on the ITT population from REACT (obtained from negative binomial regressions performed on patients who received concomitant LAMA treatment);
    2. using severe COPD specific FEV_1 decline rates from Decramer and Cooper (2010) and;
    3. using exacerbation related utility decrements from Hoogendoorn et al. (2011)
- The ERG note that their base case ICER is substantially higher than the company's base case ICER of £18,774.

ERG's deterministic and probabilistic results

	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER
Deterministic results							
Company	-	-	-	-	-	-	£18,774
Roflumilast	£21,332	8.75	6.10	£3,489	0.12	0.10	£35,814
Triple therapy	£17,844	8.63	6.01	-	-	-	-
Probabilistic results							
Company	-	-	-	-	-	-	£17,855
Roflumilast	£21,546	-	6.14	£3,498	-	0.104	£33,727
Triple therapy	£18,047	-	6.04	-	-	-	-

ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, Life years gained; QALYs, quality-adjusted life years;

Using the ERG's preferred assumptions, triple therapy plus roflumilast has a 3% probability of being cost effective at £20,000 per QALY gained, increasing to 28% at £30,000 per QALY gained.

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Further detail can be found in section 5.3.2 of the ERG report (pages 98 to 100) and tables 5.3 (page 99) and table 5.5 (page 100) of the ERG erratum.

ERG comments to note:

- Based on the results above, similar to the company model, the incremental QALYs gained for roflumilast plus triple therapy were mostly due to fewer exacerbations, and increased life expectancy (due to fewer exacerbation related deaths). The impact of treatment emergent adverse events on the costs and QALYs was negligible.
- The ERG performed probabilistic sensitivity analyses (PSA) on the ERG preferred base-case to explore the parametric uncertainty around the base-case parameters. In the PSA, if the standard error estimates for the updated parameters could be found, those new estimates were used, otherwise it was assumed that the standard error estimates of the updated parameters would change in the same magnitude of the change in their means.

ERG's scenario analysis
exacerbation rates from pooled results

- No data from RE²SPOND on severe exacerbation rates in ITT population in LAMA subgroup were available to ERG.
- ERG estimates the treatment effects if RE²SPOND was incorporated
  - use severe exacerbation rate ratio of 0.767 from ERG base case (ITT analysis in LAMA subgroup of REACT trial)
  - multiply this by ratio of treatment effect from pooled studies: treatment effect from REACT for moderate to severe exacerbation (0.9/0.871)
  - assume incorporating RE²SPOND trial would change moderate and severe exacerbations rate ratios uniformly
  - scenario is based on assumptions so interpret with caution.

Outcome in LAMA subgroup	REACT trial results	Pooled results (REACT and RE²SPOND)
Moderate to severe exacerbation in ITT population	RR 0.871 (0.741 to 1.024)	RR 0.90 (0.80 to 1.02)
Severe exacerbation in ITT population	RR 0.767 (0.595 to 0.989)	Not reported in RE²SPOND trial

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Further detail can be found in scenario 1b in the ERG report (page 97).

ERG comments to note:

The ERG's main concern with the company submission was the source of the exacerbation rates. The company used the exacerbation rates of the per protocol study population in the REACT trial while pooled estimates from the REACT and RE²SPOND trial might provide more robust treatment effectiveness estimates. Furthermore, the ERG considers the intention-to-treat population more in line with UK clinical practice than the per protocol population because it is likely that in clinical practice patients who do not strictly fulfil the inclusion criteria of REACT will receive treatment with roflumilast.

ERG's additional scenario analyses
(based on ERG's amended base case)

Scenario	Inc. costs (£)	Inc. QALYs	ICER (add on roflumilast vs. triple therapy)
Company base case	**£2,996**	**0.16**	**£18,774**
ERG preferred base case	**£3,489**	**0.10**	**£35,814**
Separate exacerbation rates for severe and very severe COPD	£3,124	0.15	£21,180
Use pooled results* for exacerbations	£3,547	0.09	£41,585
All patients start with very severe COPD	£2,880	0.12	£24,733
Use Solem (2013) for utilities	£3,489	0.08	£41,960
Single mortality rate for severe exacerbations	£3,503	0.11	£32,341
Use SMRs from all COPD related deaths (including deaths due to exacerbation)	£3,052	0.02	£149,564
Include all grade adverse events	£3,502	0.09	£40,942

*Effectiveness estimate from RE²SPOND and REACT trials. All ICERS from deterministic results.
Abbreviations: ICER, incremental cost-effectiveness ratio; Inc, incremental; QALYs, quality-adjusted life years.

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Further detail can be found in section 5.3.1 in the ERG report (pages 96 to 98) and table 5.6 in the ERG erratum (page 101 and 102)

ERG comments to note:

- Incorporating pooled exacerbation rates from REACT and RE²SPOND increased the ICER whereas estimating the rates separately for patients with severe and very severe COPD decreased the ICER. However, as described in Section 5.3.1 of the ERG report, both scenarios were based on assumptions and should be interpreted with caution.
- The ERG believes that the most robust exacerbation rate would be the moderate and severe exacerbation rates derived separately for severe and very severe COPD patients from the negative binomial regression analyses performed on the pooled ITT population subgroup of LAMA concomitant patients from both REACT and RE²SPOND trials. It also states that, as these data are readily available to the company, the current uncertainty around the ICER could easily be resolved.
- The cost effectiveness results are sensitive to the assumptions on COPD related mortality (Scenario 4b in ERG report). Applying SMRs including exacerbation related deaths (and therefore excluding case fatality rates (CFRs) increased the ICER to £149,564 per QALY gained. The ERG commented that this is easily explained by the fact that roflumilast prevents exacerbations, and without a CFR the current model structure does not allow for a subsequent impact on mortality.
- If all adverse events were included in the model instead of only serious ones, the ICER is close to £41,000 per QALY gained. However, milder adverse events are assumed to have the same costs and disutilities as serious adverse events which the ERG stated is unlikely to be true in reality.

Innovation & equalities

- The company considers roflumilast to be innovative as:
  - It is the only approved oral treatment with a specific anti-inflammatory mechanism of action that targets COPD inflammation.
  - It provides a further step in the treatment pathway post-triple therapy (LABA / LAMA / ICS) where currently there is no treatment available.
  - It is expected to reduce exacerbations and therefore reduce the comorbidities associated with frequent use of oral corticosteroids (which is not captured in the QALY calculation).
- Company did not identify any potential equality issues.

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Further detail can be found on page 26 of the company's submission.

Key issues: cost effectiveness

- What is the committee's view of the company's modelling approach?
- The choice of exacerbation rate impacts the ICER considerably - which rates are most appropriate?
- What is the committee's view on the best data source for HRQol?
- Which approach for incorporating adverse events is appropriate?
- What is the committee's view on assumptions around COPD related mortality?
- Does the committee consider roflumilast to be an innovative therapy?

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