NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Roflumilast for treating chronic obstructive pulmonary disease [ID984]

The following documents are made available to the consultees and commentators:

1. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Astra Zeneca
   - Department of Health (no comment response)

2. **ERG Critique on the company's response to the ACD**
   - Erratum to critique

3. **Evidence Review Group factual accuracy response**

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

AstraZeneca Ltd – Response to ACD consultation – 28th February 2017

ID984 – Roflumilast for treating chronic obstructive pulmonary disease (Review of TA 244)

Executive summary:

We appreciate the opportunity to respond to the above ACD.

Roflumilast meets a high unmet need, recognised by the committee, in providing a new treatment (with an alternative mode of action) that reduces exacerbations in people with severe COPD, for whom limited other treatment options exist. These patients suffer from several exacerbations per year despite treatment with optimal, triple inhaled therapy, and such exacerbations are associated with poor prognosis and quality of life; and increased mortality risk. AstraZeneca's initial evidence submission sought a recommendation for patients exacerbating despite triple therapy in line with UK clinical experts; and the current GOLD Guidelines recommending treatment with roflumilast in this patient population where the unmet need; and therefore potential benefit is highest.

AstraZeneca recognises the committee's comments around the most appropriate data sources to inform the economic modelling (the pooled data from the REACT and RESPOND trials). We have used this clinical data to inform a revised modelling base case for the initial population submitted (patients exacerbating despite triple inhaled therapy), which results in an ICER of £24,976, being cost-effective at the £30,000 threshold.

We have applied three different model inputs in comparison to the ERG's modelling, which we believe results in a more accurate estimate of the cost-effectiveness of roflumilast in this 'triple therapy' population:

- Pooled clinical data from the REACT and RESPOND trials which are based on the full patient level data, as opposed to simply pooling the relative effect of roflumilast from both trials; therefore having the advantage of taking into account the rate of exacerbations for patients in the placebo arm
- New modelling assumption capturing post hospitalisation excess mortality, as suggested by the ERG (rather than mortality only occurring during an exacerbation period) to ensure that the benefit of roflumilast in reducing exacerbations is not underestimated.
- FEV1 decline in severe COPD patients taken from the most recent source

In this document, we have also presented clinical and cost effectiveness data for a new population (not included in the initial evidence submission), who would experience greater benefit from roflumilast: these are patients on triple therapy with prior hospitalisation. We believe that these patients have an even higher unmet need than the 'triple therapy population' as studies suggest that COPD-related hospitalisation history may indicate the patients most likely to experience further exacerbations.

In the 'prior hospitalised' population, we have used pooled data; and the adjusted modelling assumptions (described above) in a cost-effectiveness analysis, which results in a base case of £7,087/QALY, being cost-effective within £20,000/QALY threshold.

In conclusion, we would like to kindly request that in light of the provided data the committee revise the provisional 'not recommended'; and recommend roflumilast in a specified subgroup allowing clinicians and patients access to treatment where there is high unmet need.

Triple Therapy Population (population within initial manufacturer submission)

1. **Unmet Need**

As recognised by the committee, patients who are exacerbating despite triple therapy represent a high unmet need with limited treatment options available to them. UK clinical experts and the current GOLD Guidelines recommend treatment with roflumilast in this patient population where the unmet need and therefore potential benefit is highest.

2. **Clinical Data**

In response to the committee's concerns and preferred analyses, we have provided pooled ITT analyses of the REACT and RE2SPOND trials for the subgroup of patients addressed in our initial submission (Patients with severe COPD [FEV_1 post-bronchodilator < 50% predicted], associated with a history of exacerbation despite triple therapy). (denoted as the "triple therapy" population)

These analyses are different to the ERG's pooled results, presented previously, as they are based on the full patient level data; and therefore have the advantage of taking into account the rate of exacerbations for patients in the placebo arm as opposed to simply pooling the relative effect of roflumilast from both trials.

Results for the rate of moderate (treated with systemic steroids) or severe (leading to hospitalisation or death) COPD exacerbations per patient per year are provided below with further details provided in Table 1.

Subgroup: Patients with severe COPD (FEV_1 post-bronchodilator < 50% predicted), associated with a history of exacerbation despite triple therapy

In the pooled analyses compared with placebo, roflumilast as an add-on to LABA / LAMA /ICS reduced the rate of:

- [redacted]
- [redacted]

Table 1: Mean rate (95% CI) of COPD exacerbations per patient per year patients on Triple Therapy, ITT population (pooled REACT/RESPOND data)

Exacerbation severity	Roflumilast ITT: LABA / LAMA / ICS N=2147;	Placebo ITT: LABA / LAMA / ICS N=2140;	Roflumilast vs. placebo rate ratio
Moderate or severe	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]

p-values are based on a negative binomial regression
Source: AstraZeneca Data on File ROF-007-FEB2017

Data for baseline characteristics; and adverse events, included in the modelling are provided in the appendix.

3. Model Changes

Post Hospitalisation Excess Mortality

Following the discussion at the appraisal committee meeting, the ERG made it clear that it believed that the company model could have done more in terms of modelling mortality associated to hospitalised COPD exacerbations. Specifically that the probability of patients dying outside of hospital (i.e. after discharge) should be included in the model, which was further ratified by the clinical expert.

In the previous base case, mortality only occurs during an exacerbation period i.e. in the case of a hospitalised exacerbation this would occur whilst in hospital, but does not account for the probability of a patient dying post discharge. Given that roflumilast reduces the number of exacerbations from which patients suffer, the result of this omission is that the mortality and hence the QALY benefit of roflumilast is underestimated and therefore the resulting ICER is higher than the true value.

In order to include this post hospitalisation excess mortality risk in the model we have consulted the literature to gain some estimates of this increased risk and have identified the following publications:

- Connolly et al (2006)[2] which estimates 90 day mortality associated to a hospitalised COPD exacerbation at 15.3%
- Hartl et al (2013)[3] which estimates 90 day mortality associated to a hospitalised COPD exacerbation at 10.8%
- Roberts et al (2001)[4] which estimates 90 day mortality associated to a hospitalised COPD exacerbation at 13.7%

- Wildman et al (2008)[5] which estimates 180 day mortality associated to a hospitalised COPD exacerbation at 37.9%

- And Soler-Cataluna, (2005)[6] which estimates a permanent post hospitalisation mortality hazard ratio of 2.235

The excess mortality has been incorporated therefore in two ways:

Firstly as an increase to the current Case Fatality Rate (CFR) %, this method is used as the current model structure does not allow for temporary tunnel states post an exacerbation and therefore the entirety of the 90 day mortality risk must be applied at point of exacerbation. The disadvantage with this approach is that we are applying a 90 day mortality risk to a 30 day cycle and therefore this method will exclude the QALY gain from patients who would die at 90 days i.e. 2 cycles worth of QALYs. The findings from Wildman et al, however, suggest that even using this method the full impact of an exacerbation will be underestimated as a minimum of 20% more patients would die between day 90 and day 180.

The second method of applying this excess mortality has been to create 2 new states “Severe COPD – post hospitalisation” and “Very Severe COPD – post hospitalisation” where patients only transition to these states after having a severe (hospitalised) exacerbation, and patients transition between “Severe COPD – post hospitalisation” and “Very Severe COPD – post hospitalisation” at the same probability as that between Severe and Very Severe COPD. However patients within these post hospitalisation states have their background mortality rate inflated by the hazard ratio of 2.23. This method is further likely to underestimate the impact of a severe COPD exacerbation as it does not account for the frequency of exacerbations with the study showing a clear relationship between number of exacerbations and mortality risk.

The data from Connolly et al (2006)[2] has been chosen as base case as this provides the most recent UK specific estimate of COPD related mortality, however, the results from the scenario analyses in the appendix show that the ICER does not vary too much when using other estimates.

<u>FEV1 decline in Severe COPD patients</u>

Within their report the ERG makes the assertion that the yearly FEV1 decline, derived from the Lung Health Study of 52ml used in the company submission is less plausible than the 38ml per year derived from Decramer and Cooper 2010. While AstraZeneca agrees that Decramer and Cooper 2010 is a more specific estimate of FEV1 decline there is, however, a more recent meta-analysis, Tantucci and Modena 2012[1], which gives an estimate of 52ml per year FEV1 decline in patients with COPD.

Further, this paper specifically refers to the results from Decramer and Cooper 2010 as being unrepresentative of patients of COPD patients with severe COPD and removing this study from

the meta-analysis results in the average FEV1 decline estimate of between 56 and 59ml per year.

We have therefore incorporated this new data into the revised base case analysis, to be conservative the lower estimate of 52ml has been used as base case.

AstraZeneca's revised base case is therefore:

- FEV1 decline from Tantucci and Modena 2012[1] and mortality risk from Connolly et al 2006

4. Cost Effectiveness Results

Incorporating pooled REACT and RESPOND data and the modelling assumptions mentioned above results in a base case ICER of £24,976. Table 2 below shows the individual effects of each change on the ICER.

Table 2: Cost effectiveness results in Pooled REACT and RESPOND Triple Therapy population

Scenario		Total cost	∆ cost	Total QALYs	∆ QALYs	ICER
Pooled REACT/RESPOND only	roflumilast	£21,778		6.08		
	placebo	£18,098	£3,680	6.01	0.07	£54,979
FEV1 decline change only	roflumilast	£22,398		5.85		
	placebo	£18,816	£3,582	5.79	0.07	£52,987
Base Case	**roflumilast**	**£19,524**		**5.23**		
	placebo	**£16,016**	**£3,508**	**5.09**	**0.14**	**£24,976**

*All analyses are run from a base of pooled REACT and RESPOND Triple Therapy population inclusive of all ERG adjustments

Incorporating the revised pooled patient level clinical data causes the ERG's revised base case ICER of £71,365 to fall significantly to £54,979, this is because although the relative rates of exacerbations are similar the patient level analysis allows the rate of exacerbations for patients in the placebo arm to vary. The result of this is that the absolute number of exacerbations is higher in the placebo arm, and therefore the absolute number of exacerbations avoided is also higher.

Further to this, applying the FEV1 decline from Tantucci and Modena[1] causes the ICER to fall to £52,987 and applying additional mortality risk post hospitalisation of 15.3% gives an ICER of £24,976.

Prior Hospitalised Population (new population, who would experience greater benefit from roflumilast)

1. **Unmet Need**

Hospitalizations for COPD exacerbations are associated with poor prognosis and survival. In fact, COPD exacerbations are the root cause of frequent hospitalizations, decreased quality of life, and increased mortality risk. Studies suggest that COPD-related hospitalization history may play a role in defining the patients most likely to experience further moderate to severe exacerbations. This is demonstrated by the comparison of the placebo arm rate of exacerbations in the triple versus the prior hospitalised population from the pooled REACT and RESPOND data within Table 3, which shows higher exacerbation rates in the prior hospitalised population.

Table 3: Mean rate (95% CI) of COPD exacerbations per patient per year patients on triple therapy, ITT population (pooled REACT/RESPOND data) versus patients on triple therapy and with at least 1 prior hospitalisation (pooled REACT/RESPOND data)

Exacerbation severity	Placebo ITT: LABA / LAMA / ICS N=1215;	Placebo ITT: LABA / LAMA / ICS and prior hospitalised N=405;
Moderate to severe	[redacted]	[redacted]
Severe	[redacted]	[redacted]
Moderate	[redacted]	[redacted]

Given this high level of unmet need, AstraZeneca have investigated the clinical; and cost-effectiveness of roflumilast in this subgroup of patients.

2. **Clinical Data**

Below, we provide a post-hoc analysis on a further subgroup of patients - patients with severe COPD [FEV_1 post-bronchodilator < 50% predicted], associated with a history of exacerbation and at least one hospitalisation for a COPD exacerbation in the prior year despite triple therapy. (Denoted as the “prior hospitalisation” population). It should be noted that this data has become available since our initial submission.

The mean rates of COPD exacerbation for patients on triple therapy and with a prior hospitalisation are provided in Table 4.

In patients with ≥ 1 hospitalisation for a COPD exacerbation, roflumilast as an add-on to LABA / LAMA /ICS compared with placebo significantly reduced the rate of;

- [redacted]
- [redacted]

Table 4: Mean rate of COPD exacerbation per year for patients on triple therapy and with at least 1 prior hospitalisation, ITT population (pooled REACT/RESPOND data)

Exacerbation severity	Roflumilast ITT: LABA / LAMA / ICS N=1225	Placebo ITT: LABA / LAMA / ICS N=1215	Roflumilast vs. placebo rate ratio
	Mean per patient per year (95% CI)		
Moderate or severe	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]

p-value are based on a negative binomial regression
p-value based on Poisson regression using robust error estimate with sandwich method as the negative binomial model did not converge
Source: AstraZeneca Data on File: ROF-008-FEB2017

Data for baseline characteristics; and adverse events, included in the modelling are provided in the appendix.

3. Model Changes

As with the triple therapy population, the model changes listed above regarding excess mortality and FEV1 decline have been used to calculate ICERs for the prior hospitalised population.

4. Cost Effectiveness Results

Incorporating pooled REACT and RESPOND data and the modelling assumptions mentioned above results in a base case ICER of £7,087. Table 5 below shows the individual effects of each change on the ICER.

Table 5: Cost effectiveness results in Pooled REACT and RESPOND Triple Therapy, Prior Hospitalisation Population

Scenario		Total cost	Δ cost	Total QALYs	Δ QALYs	ICER
Pooled REACT/RESPOND only	roflumilast	£23,373		6.20		
	placebo	£20,707	£2,666	5.94	0.26	£10,319
FEV1 decline change only	roflumilast	£24,123		5.95		
	placebo	£21,629	£2,493	5.69	0.27	£9,401
Base Case	**roflumilast**	**£20,173**		**5.16**		
	placebo	**£16,773**	**£3,401**	**4.68**	**0.48**	**£7,087**

*All analyses are run from a base of pooled REACT and RESPOND Triple Therapy Prior Hospitalised population inclusive of all ERG adjustments

Incorporating the data from the prior hospitalised population causes the ERG's revised base case ICER of £71,365 to fall significantly to £10,319, this is due to both a higher absolute rate of exacerbations and therefore a higher absolute reduction of exacerbations, but also because of a greater treatment effect of roflumilast in this population.

Further to this, applying the FEV1 decline from Tantucci and Modena[1] causes the ICER to fall to £9,401 and applying additional mortality risk post hospitalisation of 15.3% gives an ICER of £7,087

References

1. Tantucci C, Modina D. Lung Function Decline in COPD patients . Int J Chron Obstruct Pulmon Dis 2012;7:95-99.

2. Connolly MJ, Lowe D, Anstey K, Hosker HS, Pearson MG, Roberts CM; British Thoracic Society and the Royal College of Physicians Clinical Effectiveness Evaluation Unit (CEEu). Admissions to hospital with exacerbations of chronic obstructive pulmonary disease: Effect of age related factors and service organisation. Thorax. 2006 Oct;61(10):843-8.

3. Hartl S, Lopez-Campos JL, Pozo-Rodriguez F, Castro-Acosta A, Studnicka M, Kaiser B, Roberts CM. Risk of death and readmission of hospital-admitted COPD exacerbations: European COPD Audit. Eur Respir J. 2016 Jan;47(1):113-21.

4. Roberts C, Lowe D, Bucknall CE, Ryland I, Kelly Y, Pearson, M G. Clinical Audit indicatiors of outcome following admission to hospital with acute exacerbation of chronic obstructive pulmonary disease . Thorax 2002;57:137-141.

5. Wildman M J, Sanderson C, Groves J, Reeves B C, Ayres J, Harrison D, Young D, Rowan K.Predicting mortality for patients with exacerbations of COPD and Asthma in the COPD and Asthma Outcome Study. Q J Med 2009;102:389-399.

6. Soler-Cataluna J J, Martinez-Garcia M A, Sanchez P R, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax 2005;60:925-931

Appendix 1: Pooled analyses REACT and RES^{2}POND

Subgroup: Patients with severe COPD (FEV_1 post-bronchodilator < 50% predicted), associated with a history of exacerbation despite triple therapy

Baseline characteristics

Details of the baseline characteristics for the ITT pooled LAMA populations are provided in Table 6. The participants were well matched at baseline between the two treatment groups.

Table 6: Baseline characteristics for patients on Triple Therapy, ITT population (pooled REACT/RESPOND data)

Baseline characteristic	Roflumilast n=1225	Placebo N=1215
Age, n (%) ≤ 65 years >65 years	[redacted]	[redacted]
Male sex n (%)		
Body-mass index, n (%) < 18.5 kg / m^2 18.5 – < 25 kg / m^2 25 – < 30 kg / m^2 ≥ 30 kg / m^2	[redacted]	[redacted]
Smoking status, n (%) Current smoker Former smoker	[redacted]	[redacted]
Cigarette pack years <40 ≥40	[redacted]	[redacted]
COPD severity n (%) Mild Moderate (FEV_1 50 - < 80%) Severe (FEV_1 30 – < 50%) Very severe (FEV_1 < 30%) Missing	[redacted]	[redacted]
COPD severity group, n (%) GOLD A – low risk, less symptoms GOLD C – high risk, less symptoms GOLD D – high risk more symptoms Missing	[redacted]	[redacted]
CAT total score n (%)		

Baseline characteristic	Roflumilast n=1225	Placebo N=1215
< 10 ≥ 10 Missing	[redacted]	[redacted]
Historical exacerbations n (%)* <2 exacerbations 2 exacerbations 3 exacerbations >3 exacerbations Missing	[redacted]	[redacted]
Prior hospitalisations None At least one Missing	[redacted]	[redacted]

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.
*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

Source: AstraZeneca Data on File ROF-011-FEB2017

Adverse events

Details of key treatment emergent adverse events (TEAS) are provided in Table 7.The reporting of TEAE was comparable between the treatment groups (16.3% roflumilast vs. 16.1% placebo). TEAEs which occurred more frequently in the roflumilast group were weight decrease (1% vs 0% in the placebo arm), nausea (2% vs. 0% in the placebo arm and abdominal pain (4% vs. 0% in the placebo arm).

Table 7: Treatment emergent adverse events: Grade 3 serious AEs (excluding deaths) for patients on Triple Therapy, ITT population (pooled REACT/RESPOND data)

	Roflumilast group (n=1225) n (%)	Placebo group (n=1215) n (%)
Any AE	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Weight decrease	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]

Source: AstraZeneca Data on File: ROF-012-FEB2017

Cost Effectiveness Scenarios

AstraZeneca has undertaken several scenario analyses to investigate the impact of various different mortality assumptions on the ICER for roflumilast.

- Scenario 1 - FEV1 decline from Tantucci and Modena 2012 and mortality risk from Roberts et al 2001
- Scenario 2 - FEV1 decline from Tantucci and Modena 2012 and mortality risk from Soler-Cataluna 2005
- Scenario 3 - FEV1 decline from Tantucci and Modena 2012 and mortality risk from Hartl et al 2001
- Scenario 4 - FEV1 decline from Tantucci and Modena 2012 and mortality risk from Wildman et al (2008)

Table 8: Cost effectiveness results in Pooled REACT and RESPOND Triple Therapy population

		Total cost	Δ cost	Total QALYs	Δ QALYs	ICER
Scenario 1	roflumilast	£19,883		5.31		
	placebo	£16,358	£3,525	5.17	0.13	£26,526
Scenario 2	roflumilast	£17,606		4.82		
	placebo	£14,509	£3,097	4.72	0.10	£31,202
Scenario 3	roflumilast	£20,578		5.46		
	placebo	£17,027	£3,552	5.34	0.12	£30,349
Scenario 4	roflumilast	£15,760		4.38		
	placebo	£12,545	£3,214	4.18	0.20	£16,293

As mentioned above, the mortality risk assumed in the base case and scenarios 1, and 3 are likely to underestimate the mortality risk in COPD patients after an exacerbation due to the data source being limited to 90 days post hospitalisation, and the mortality risk assumed in scenario 2 is also likely to underestimate the true mortality risk as it does not take into account the number of hospitalisations a patient suffers from. While the mortality risk assumed in scenario 4 is likely to overestimate the QALY impact of this mortality due to a 180 day mortality risk being

applied to a 30 day period. The true ICER for this population is therefore likely to lie between £16,293 and £31,202.

Subgroup: Patients with severe COPD (FEV_1 post-bronchodilator < 50% predicted), associated with a history of exacerbation and prior hospitalisation despite triple therapy

Baseline characteristics

Details of the baseline characteristics for the ITT pooled LAMA prior hospitalisation population are provided in Table 9. The participants were well matched at baseline between the two treatment groups.

Table 9: Baseline characteristics for patients on Triple Therapy with at least one prior hospitalisation ITT population (pooled REACT/RESPOND data)

Baseline characteristic	Roflumilast n=444	Placebo N=405
Age, n (%) ≤ 65 years >65 years	[redacted]	[redacted]
Male sex n (%)		
Body-mass index, n (%) < 18.5 kg / m^2 18.5 – < 25 kg / m^2 25 – < 30 kg / m^2 ≥ 30 kg / m^2	[redacted]	[redacted]
Smoking status, n (%) Current smoker Former smoker	[redacted]	[redacted]
Cigarette pack years <40 ≥40	[redacted]	[redacted]
COPD severity n (%) Moderate (FEV_1 50 - < 80%) Severe (FEV_1 30 – < 50%) Very severe (FEV_1 < 30%) Missing	[redacted]	[redacted]
COPD severity group, n (%) GOLD C – high risk, less symptoms GOLD D – high risk more symptoms Missing	[redacted]	[redacted]
CAT total score n (%) < 10 ≥ 10 Missing	[redacted]	[redacted]
Historical exacerbations n (%)* <2 exacerbations 2 exacerbations 3 exacerbations >3 exacerbations	[redacted]	[redacted]
Prior hospitalisations At least one	[redacted]	[redacted]

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.
*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

Source: AstraZeneca Data on File: ROF-009-FEB2017

Adverse events

Details of key treatment emergent adverse events (TEAS) are provided in Table 10. The reporting of TEAE was slighty higher in the placebo group (20.5% roflumilast vs. 24.9 % placebo).

Table 10: Treatment emergent adverse events: Grade 3 serious AEs (excluding deaths) for patients on Triple Therapy with at least one prior hospitalisation ITT population (pooled REACT/RESPOND data)

	Roflumilast group (n=444) n (%)	**Placebo group (n=405) n (%)**
Any AE	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Weight decrease	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]

Source: AstraZeneca Data on File: ROF-010-FEB2017

Cost Effectiveness Scenarios

AstraZeneca has undertaken several scenario analyses to investigate the impact of various different mortality assumptions on the ICER for roflumilast.

- Scenario 1 - FEV1 decline from Tantucci and Modena 2012 and mortality risk from Roberts et al 2001
- Scenario 2 - FEV1 decline from Tantucci and Modena 2012 and mortality risk from Soler-Cataluna 2005
- Scenario 3 - FEV1 decline from Tantucci and Modena 2012 and mortality risk from Hartl et al 2001
- Scenario 4 - FEV1 decline from Tantucci and Modena 2012 and mortality risk from Wildman et al (2008)

Table 11: Cost effectiveness results in Pooled REACT and RESPOND Prior Hospitalisation population

Scenario		Total cost	∆ cost	Total QALYs	∆ QALYs	ICER
Scenario 1	roflumilast	£20,641		5.26		
	placebo	£17,306	£3,335	4.80	0.46	£7,228
Scenario 2	roflumilast	£18,637		4.85		
	placebo	£16,322	£2,316	4.58	0.27	£8,549
Scenario 3	roflumilast	£21,567		5.45		
	placebo	£18,392	£3,175	5.03	0.42	£7,561
Scenario 4	roflumilast	£15,597		4.20		
	placebo	£12,000	£3,597	3.61	0.59	£6,136

*All analyses are run from a base of pooled REACT and RESPOND Triple Therapy Prior Hospitalised population inclusive of all ERG adjustments

As mentioned above, the mortality risk assumed in the base case and scenarios 1, and 3 are likely to underestimate the mortality risk in COPD patients after an exacerbation due to the data source being limited to 90 days post hospitalisation, and the mortality risk assumed in scenario 2 is also likely to underestimate the true mortality risk as it does not take into account the number of hospitalisations a patient suffers from. While the mortality risk assumed in scenario 4 is likely to overestimate the QALY impact of this mortality due to a 180 day mortality risk being applied to a 30 day period. The true ICER for this population is therefore likely to lie between £6,136 and £8,549. The ICER in this population remains cost effective at a £20,000 threshold regardless of the assumption used for mortality.

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Roflumilast for the management of chronic obstructive pulmonary disease
2nd ADDENDUM
Critique on the company's response to the ACD

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Introduction

The company has submitted revised analyses in response to the ACD issued by NICE.

The company changed three different model inputs in comparison to the ERG's modelling, which they believe results in a more accurate estimate of the cost-effectiveness of roflumilast in the 'triple therapy' population:

- Pooled clinical data from the REACT and RESPOND trials which are based on the full patient level data, as opposed to simply pooling the relative effect of roflumilast from both trials; therefore having the advantage of taking into account the rate of exacerbations for patients in the placebo arm
- New modelling assumption capturing post-hospitalisation excess mortality, as suggested by the ERG (rather than mortality only occurring during an exacerbation period) to ensure that the benefit of roflumilast in reducing exacerbations is not underestimated.
- FEV1 decline in severe COPD patients taken from the most recent source

The company has also presented clinical and cost effectiveness data for a new population (not included in the initial evidence submission), who would experience greater benefit from roflumilast, i.e. patients on triple therapy with prior hospitalisation. The company believe that these patients have a higher unmet need than the 'triple therapy population' as studies suggest that COPD-related hospitalisation history may indicate the patients most likely to experience further exacerbations.

We will discuss these two populations and the clinical effectiveness data submitted, the model changes performed by the company and the subsequent cost effectiveness results.

1. Triple Therapy Population (population within initial company submission)

1.1 Clinical Data

The company has provided pooled ITT analyses of the REACT and RE2SPOND trials for the subgroup of patients addressed in their initial submission (Patients with severe COPD [FEV_1 post-bronchodilator < 50% predicted], associated with a history of exacerbation despite triple therapy). (denoted as the "triple therapy" population).

These analyses are different to the ERG's pooled results, presented previously, as they are based on the full patient level data.

Results for the rate of moderate (treated with systemic steroids) or severe (leading to hospitalisation or death) COPD exacerbations per patient per year are provided in Table 1, both for the new company analysis and the ERG analysis.

Table 1: Comparison of revised company and original ERG analyses (Mean rate (95% CI) of COPD exacerbations per patient per year)

	Roflumilast vs placebo
Company preferred analyses	
Moderate to severe exacerbation*	RR [redacted]
Severe exacerbation*	RR [redacted]
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 ITT populations from the REACT and RE2SPOND trials (full patient level data), using the negative binomial regression equation and the concomitant LAMA subgroup; ** Based on ITT populations from the REACT and RE2SPOND trials, using the negative binomial regression equation and the concomitant LAMA subgroup; *** Based on ITT populations from the REACT and RE2SPOND trials, using the negative binomial regression equation (data for the concomitant LAMA subgroup were not available).	

As can be seen from Table 1, the two rate ratios are almost similar. Therefore, these data for the full triple therapy population seem accurate.

ERG comments: We were unable to check the new pooled analyses themselves as we have not received the full individual patient data from both trials. However, the company did not provide any details of their analysis methods, for example, whether the pooled analysis was adjusted for or stratified by study, to allow for the fact that there are two different studies. Therefore, we cannot comment on whether the analysis methods were appropriate. In addition, we cannot check the result for 'moderate exacerbations' as these data were not available in the original submission. Our result for 'severe exacerbations' is based on the full ITT populations of both trials (not the concomitant LAMA subgroup only), as these data were not available.

Table 2: Numbers of patients included in the REACT and RESPOND trials

Study design	REACT		RE2SPOND	
	Roflumilast	**Placebo**	**Roflumilast**	**Placebo**
All patients	**969**[d]	**966**[d]	**1178**[e]	**1174**[e]
LAMA use, n (%)	677 (70)	669 (69)	548 (47)	546 (47)
[d] Intent-to-treat population. [e] Safety population.				

In conclusion, at first glance the analyses seem correct, but we cannot check the analyses themselves as we have not received the full patient data from both trials and there is some uncertainty about the number of patients included in these analyses.

1.2 Model Changes

For the triple therapy (concomitant LAMA subpopulation), the company incorporated the following changes to the modified/corrected model used for the calculations in the Addendum to the ERG Report[1] from January 2017 (from here onwards referred to as "ERG addendum model"):

- Changing of the baseline characteristics and serious adverse event rates to reflect the pooled ITT triple therapy population from REACT and RE2SPOND trials
- Changing of the moderate/severe exacerbation rates in severe and very severe COPD states
- Incorporation of the post-hospitalisation excess mortality
- Changing the annual FEV1 decline rate used for severe COPD patients

Unfortunately, in the ACD Response provided by the company, only the last two changes were explained.[2] Below we provide explanations for each of the above changes implemented by the company.

1.2.1 Changes in the baseline characteristics and adverse event rates

In the ERG addendum model, the baseline characteristics and treatment emergent serious (TEASE) rates from the triple therapy ITT subpopulation of the REACT trial were used. These were updated by the company for the current model based on the pooled triple therapy ITT subpopulation data from both REACT and RE2SPOND trials. The baseline characteristics and adverse event rates used in the ERG addendum model versus the new company model are provided in Table 3 and

Table 4, respectively.

Table 3: Baseline characteristics of the ITT, concomitant LAMA subgroup

Patient characteristic	Baseline values in the ERG Addendum (REACT)	Baseline values in the new company model (REACT and RE2SPOND)
Age (years)	65.0[1]	[redacted]
Proportion male	74.50%[1]	[redacted]
Mean height (cm, males)	170.6[1]	[redacted]
Mean height (cm, females)	160[1]	[redacted]
Sources: 1-Based on response to the clarification letter document[3], p18. 2- Based on Table 6 in the response to the ACD[3], p9. 3-Could not be replicated by the ERG from the evidence in the response to the ACD[2]		

Table 4: Occurrence rate of the TEASEs based on ITT, concomitant LAMA subpopulation

	ERG Addendum (REACT)[1]		New company model (REACT and RE2SPOND)[2]	
TESAEs	**Roflumilast arm mean (SE)**	**Comparator arm mean (SE)**	**Roflumilast arm (mean)**	**Comparator arm (mean)**
Diarrhoea	0.15% (0.15%)	0.30% (0.21%)	[redacted]	[redacted]
Weight loss	0.44% (0.26%)	0.00% (0.00%)	[redacted]	[redacted]
Nausea*	0.00% (0.00%)	0.00% (0.00%)	[redacted]	[redacted]
Pneumonia	2.95% (0.65%)	3.44% (0.70%)	[redacted]	[redacted]
Source: 1-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 in REACT and therefore not reported. Assumed to be zero. 2- From Table 7 in the response to the ACD[2], p10				

ERG Comments: The ERG could not verify the correctness of the newly used baseline characteristics and the AE rates as these values and the details of the related calculations were not reported.

1.2.2 Changes in the moderate/severe exacerbation rates for patients in the severe and very severe COPD state

In the ERG addendum model, the pooled moderate/severe exacerbation rate ratios from the rate ratios in the REACT and RE2SPOND trials were used. The rate ratios in the REACT and RE2SPOND trials were derived from the negative binomial regression equations conducted on the triple therapy subgroup of ITT population from each trial, and the inverse variance method was used in pooling the rate ratios. In the ERG addendum model, the logarithms of these pooled rate ratios were plugged into the predictive negative binomial regression equations that were reported in the original company submission model, which were based on the exacerbation data from the PP, concomitant LAMA subpopulation in the REACT trial.

However, in the current response from the company, no details are provided on how the newly estimated, pooled, rate ratios have been translated into health state specific, treatment specific and exacerbation severity specific exacerbation rates.

The actual exacerbation rates used in the ERG addendum model and the new model are presented below in

Table 5. The coefficients for the “roflumilast” covariate used in the predictive regression equations in the economic model ([redacted] and [redacted] for moderate and severe exacerbations, respectively) are very similar to the rate ratios provided in Table 1 of the response to the ACD document[2] ([redacted] and [redacted] for moderate and severe exacerbations, respectively).

Table 5: Actual moderate and severe exacerbation rates used in the economic models

	roflumilast plus triple therapy		Triple therapy		Roflumilast vs placebo
	Severe COPD	**Very Severe COPD**	**Severe COPD**	**Very Severe COPD**	**Rate Ratio**
ERG addendum model, based on the pooled exacerbation rate ratios from REACT and RE2SPOND ITT, concomitant LAMA subpopulation.					
Moderate exacerbation	0.401	0.634	0.434	0.685	0.926
Severe exacerbation	0.154	0.362	0.175	0.411	0.88
The new model from the company					
Moderate exacerbation	0.560	0.789	0.610	0.859	0.918
Severe exacerbation	0.163	0.335	0.191	0.394	0.85

ERG Comments: In the new electronic company model, the ERG noticed that the company updated the predictive regression equation coefficients for the estimation of annual moderate/severe exacerbation rates for patients in severe/very severe COPD states. Since the details on how the regression coefficients were derived are missing, the ERG cannot assess the validity of the resulting exacerbation rate inputs used in the new economic model.

Since the company did not provide any details of their analysis methods, it is not clear to the ERG whether the pooled analysis was adjusted for or stratified by study, to allow for the fact that patient level data come from two different studies. Pooling patient level data without any adjustments/stratifications from REACT and RE2SPOND as if they were from a single trial might overlook the potential impact of the differences in REACT and RE2SPOND trials (e.g. in terms of patient inclusion criteria).

1.2.3 Incorporation of the post-hospitalization excess mortality due to severe exacerbations

In the ERG addendum model, a case fatality rate (CFR) of 4.3% was applied for each severe exacerbation, which was taken from the 2014 National UK Audit.[4] The COPD-associated mortality (but not taking inpatient exacerbation related deaths) was applied to the original company model, by applying the standardized mortality ratios of 2.5 and 3.85 on top of UK life table mortality rates for severe COPD and very severe COPD patients, respectively. These SMRs were calculated in Samyshkin et al. 2014.[5] Details on these inputs were explained in the main ERG report.

In the new company model, the company incorporated excess mortality (after hospitalisation) due to severe exacerbations. In its base case, the company applied the 90 day mortality (15.3%), associated to a hospitalised COPD patient due to exacerbation from Connolly et al (2006)[6] as the CFR, for each severe exacerbation in the model. The company justified their choice of Connolly et al (2006)[6] by arguing that it provides the most recent UK specific COPD related mortality estimate.

ERG Comments: Concerning the model changes related to the post-hospitalisation mortality, the ERG considers that the way post-hospitalisation mortality is incorporated into the new company model causes a double counting issue for exacerbation related deaths after hospital discharge.

In the new company model, applying the 90-day post-hospitalisation mortality risk as the CFR for severe exacerbations causes a double counting problem for post-hospitalisation deaths that happen after hospital discharge. The reason for this double counting issue is because these deaths were already taken into account while calculating the SMRs used in the original company model. This double counting of

deaths leads to an underestimation of QALYs and LYs left estimated by the new company model regardless of treatment. In terms of incremental results, the correction of the double counting problem would slightly decrease the ICER, because with lower SMRs, life expectancy would be higher for each patient who does not have an exacerbation and patients have fewer exacerbations on roflumilast. Or, in other words, due to the slight increase in life-years in both groups, roflumilast has more time to prevent exacerbations.

In the response to the ACD document, the company argued that applying post-hospitalisation mortality as CFR in the economic model would be a conservative approach, because under this approach, the alive days of a patient, who died at day 90 after his/her severe exacerbation, were not taken into account. The ERG agrees that the alive days of a patient who died after hospital discharge are overlooked in this approach, but thinks that this is slightly more beneficial for the roflumilast arm in terms of incremental QALYs gained, as there are more severe exacerbation deaths (and therefore more overlooked alive days after hospital discharge) in the placebo arm.

The ERG noted that the most recent 90-day post-hospitalisation mortality estimate from the UK National COPD Audit 2014[4] which is 12% would be a more plausible choice for the post-hospitalisation risk mortality than the estimate from Connolly et al (2006).[6] The estimate from Connolly et al (2006)[6] was based on data before 2006, and in the audit,[4] a historical reduction in 90-day post-hospitalisation mortality (from the hospital admission) was reported. While the mortality was 16.3% in 2003, it dropped to 14.2% in 2008; and to 12% in 2014. As the most recent (2014) UK specific estimate for post-hospitalisation mortality, 12% from the UK National COPD Audit would be the preferred post-hospitalisation mortality input for the model according to the ERG.

1.2.4 Changing the annual FEV1 decline rate used for severe COPD patients

In the ERG addendum model, an annual FEV1 decline rate of 38 ml per year, which was derived from Decramer and Cooper (2010)[7] using data from the UPLIFT trial, was assumed for the annual FEV1 decline for severe COPD patients.

The company, in its new model, used the FEV1 decline rate estimate of 52 ml per year from Tantucci and Modina (2012),[8] which is a recent meta-analysis. Furthermore, in the response to the ACD, the company mentioned that the estimate from the Decramer and Cooper 2010[7] study was deemed as "*as being unrepresentative of patients of COPD patients with severe COPD*" by Tantucci and Modina (2012)[8]

ERG Comments: Concerning the change of the annual FEV1 decline in the new company model, the company used the 52 ml per year estimate from Tantucci and Modina[8], and argued that 38 ml estimate from Decramer and Cooper 2010[7] was deemed unrepresentative for severe COPD patients. The ERG identified the 52 ml estimate from Tantucci and Modina,[8] and it seems that this estimate is derived from one study,[9] focusing on patients with alpha-1 antitrypsin deficiency-related emphysema. The ERG considers the patient population from this study might be a specific subgroup of COPD patients.

In Tantucci and Modina,[8] the UPLIFT study, from which the original 38 ml estimate was derived, was excluded from the meta-analysis. The research question of the meta-analysis was the annual FEV1 decline in the natural history of COPD, and therefore the placebo arms of randomized clinical trials were included in the meta-analysis. The UPLIFT trial was not among the included studies, because in the UPLIFT control arm, patients received on average at least 2 active drugs. Even though for the meta-analysis in Tantucci and Modina,[8] it might be reasonable to exclude UPLIFT trial from the meta-analysis, the ERG still considers that 38 ml is a more plausible estimate for the economic model, because

the 'placebo' patients in the REACT also received at least 2 active ingredients during the trial and therefore the FEV1 decline from the UPLIFT trial might depict the annual FEV1 decline of severe COPD patients in the REACT trial better.

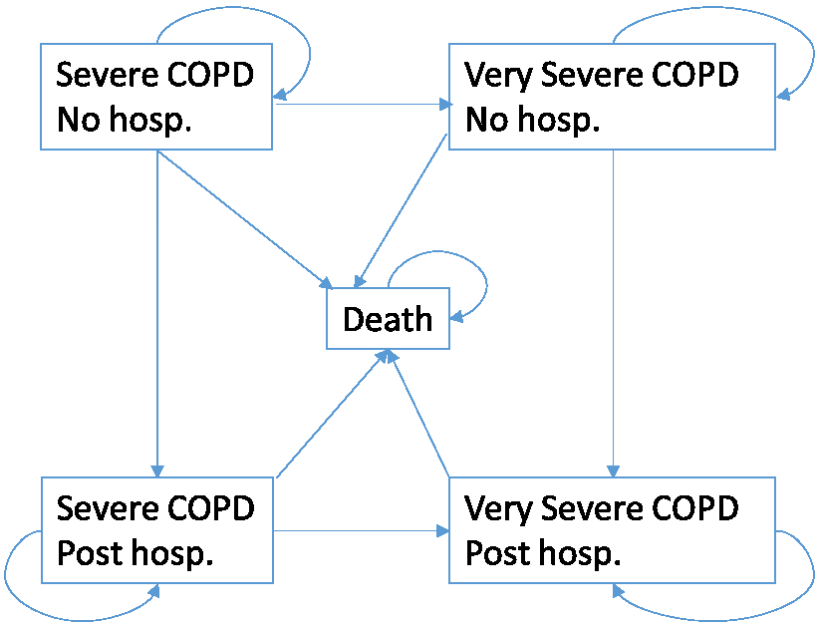
1.2.5 Additional scenario analyses on the new company base case concerning the excess mortality due to severe exacerbations

After the changes above were implemented in the new company model, the following scenario analyses were conducted on the excess mortality due to severe exacerbations:

- Instead of 15.3% from Connolly et al (2006),[6] 90 day mortality estimate (10.8%) from Hartl et al (2013)[10] was applied as the CFR.
- Instead of 15.3% from Connolly et al (2006),[6] 90 day mortality estimate (13.7%) from Roberts et al (2001)[11] was applied as the CFR.
- Instead of 15.3% from Connolly et al (2006),[6] 180 day mortality estimate (37.9%) from Wildman et al (2008)[12] was applied as the CFR.
- CFR is not changed from the ERG addendum model, but the post-hospitalization mortality hazard ratio of 2.235 from Soler-Cataluna (2005)[13] was applied to the SMRs for severe and very severe COPD patients.

Minor changes in the model structures were needed to implement the last scenario above. Two additional states were created: "Severe COPD – post hospitalisation" and "Very Severe COPD – post hospitalisation", where patients only transition to these states from "prior hospitalisation" states, after having a severe (hospitalised) exacerbation. The transition between "Severe COPD – post hospitalisation" and "Very Severe COPD – post hospitalisation" is the same as the transition probability between "Severe COPD – prior hospitalisation" and "Very Severe COPD – prior hospitalisation". In the last scenario analysis explained above, the patients within these post hospitalisation states have their background mortality rate inflated by a factor of 2.23 from the hazard ratio estimate in Soler-Cataluna (2005).[13] The updated model structure for this scenario analysis is given in **Error! Reference source not found.** below.

Figure 1: Updated model structure for one of the scenario analyses (using HR from Soler-Cataluna (2005)[13]) to incorporate excess exacerbation mortality



ERG Comments: In the scenarios in which post-hospitalisation risks were applied as CFR (i.e. Hartl et al (2013)[10], Roberts et al (2001)[11] and Wildman et al (2008)[12]), the same issues discussed above for the base case analysis (i.e. double counting of post-hospitalisation deaths and the underestimation of the alive days when a patient dies after s/he is discharged from the hospital) are relevant, as well.

The ERG considers that the estimate from Wildman et al (2008)[12] is not plausible, because different from other studies, in Wildman et al (2008)[12], only the patients that were admitted into ICUs (not general wards) were analysed, which represents the mortality risk of a more severe patient population than other studies.

In the scenario in which post-hospitalisation mortality is applied as SMRs using additional states, the company argued that the impact of a severe exacerbation was underestimated, because the frequency of severe exacerbations would not have an effect on the mortality. The ERG has some doubts about this argument because firstly, CFRs for severe exacerbations derived from in-hospital deaths are still applied in this scenario, and therefore the frequency of severe exacerbations would still have an effect on the mortality. Secondly, in Figure 2 from Soler-Cataluna 2005[13] it was demonstrated that the difference between the Kaplan Meier survival curves from the patients who were hospitalised once and from the patients who were hospitalised more than once was not statistically significant. Furthermore, the ERG could not find the HR value that the company used in the new model, 2.23, in the paper.

Finally, the ERG identified a logical inconsistency in the implementation of this scenario. In the model, it was assumed that all patients were not previously hospitalised in the baseline, even though there were patients with hospitalisation history already in the baseline of REACT and RE2SPOND trials. Correcting for this inconsistency is expected to increase the CFR of this scenario analysis slightly, as the number of non-hospitalised patients in the baseline, who would benefit from less number of severe exacerbations in the roflumilast arm, would be less.

1.3 Cost Effectiveness Results

By implementing the changes above to the ERG addendum model, the ICER decreased to £24,976 per QALY gained from £71,365 per QALY gained in the ERG addendum model. Table 6 shows how each individual change impacts the ICER plus the combined effect of all changes simultaneously.

As it can be seen from Table 6, incorporating the post-hospitalization mortality as a CFR in the economic model has the biggest impact on the ICER (decreased ICER to £32,515 per QALY gained), additionally, using exacerbation rates derived from pooled REACT and RE2SPOND trials decreased the ICER as well (decreased ICER to £54,305 per QALY gained).

Furthermore, the company conducted several scenario analyses on mortality and applied the mortality rates from Roberts et al 2001[11], Soler-Cataluna 2005[13], Hartl et al. 2005[10] and Wildman et al 2008[12], respectively. The results from these analyses are also presented in Table 6. The ICER in these scenarios range from £16,293 per QALY gained (when the 180 day mortality risk after hospitalization from Wildman et al 2008[12] is applied as the CFR for severe exacerbation in the economic model) to £31,202 per QALY gained (when the post-hospitalization mortality hazard ratio of 2.235 from Soler-Cataluna (2005)[13] was applied to the SMRs for post-hospitalization severe and very severe COPD patients, two newly added states in the economic model).

ERG Comments: In the company's response to the ACD document[2], the ERG identified a number of reporting errors/inconsistencies in the tables. For instance, in Table 2 and Table 5 from the response to the ACD document[2], it reads as if the company reported the effects of applying each model change

separately, however the ERG noticed from the economic model that these reported results actually denote the effects of applying the changes jointly in a stepwise manner.

On top of the company scenarios, the ERG conducted the following scenario analyses.

- Instead of 15.3% from Connolly et al (2006)[6], 90 day mortality estimate (12%) from the UK National COPD Audit 2014[4] was applied as the CFR.
- Instead of 52 ml from Tantucci and Modina (2012),[8] 38ml FEV1 decline from Decramer and Cooper 2010[7] is used.
- Both post-hospitalisation mortality and annual FEV1 decline estimates are changed as above

The incremental results from these scenarios are also presented in Table 6. Using these more plausible inputs (Scenario 7) increased the ICER to £29,156 per QALY gained

On the presumption that the calculations of the baseline characteristics, adverse event and exacerbation rates are right, for the population within the initial company submission (triple therapy, severe/very severe COPD with frequent exacerbations), the ICER estimate is expected to be between and £25,000 and £35,000 per QALY gained, and it is very sensitive to the assumptions on mortality.

Table 6: Revised base case cost effectiveness analysis, incorporating changes mentioned by the company and additional scenarios

Additional changes implemented by the company and company's new base case	roflumilast plus triple therapy		Triple therapy alone		Incr. costs	Incr. QALYs	ICER
	Total costs	Total QALYs	Total costs	Total QALYs			
0. ERG addendum model	£21,548	6.06	£17,844	6.01	£3,704	0.05	£71,365
1. Updating the baseline characteristics and adverse event rates according to REACT and RE2SPOND trials	£21,720	6.09	£17,965	6.04	£3,755	0.05	£72,455
2. Updating moderate and severe exacerbation rates according to the pooled patient level data from REACT and RE2SPOND trials	£21,606	6.05	£17,977	5.98	£3,629	0.07	£54,305
3. Incorporating post-hospitalization excess mortality after exacerbation (from Connolly et al 2006[6])	£[illegible]	[illegible]	£[illegible]	[illegible]	£3,541	0.11	£32,515
4. Changing the annual FEV1 decline for severe COPD patients	£22,180	5.83	£18,584	5.78	£3,602	0.05	£67,884
(1 to 4 all). Company's preferred base-case in the response to ACD	**£19,524**	**5.23**	**£16,016**	**5.09**	**£3,508**	**0.14**	**£24,976**
Additional scenarios on the mortality rate assumption	**roflumilast plus triple therapy**		**Triple therapy alone**		**Incr. costs**	**Incr. QALYs**	**ICER**
	Total costs	**Total QALYs**	**Total costs**	**Total QALYs**			
1. 90-day post-hospitalization mortality risk from Roberts et al 2011[11]	£19,388	5.31	£16,135	5.17	£3,525	0.13	£26,526
2. Post mortality HR from Soler-Cataluna 2005[13]	£17,606	4.82	£14,509	4.72	£3,097	0.10	£31,202
3. 90-day post-hospitalization mortality risk from Hartl et al 2001[10]	£20,578	5.46	£17,027	5.34	£3,552	0.12	£30,349
4. 180-day post-hospitalization mortality risk from Wildman et al 2008[12]	£15,760	4.38	£12,545	4.18	£3,214	0.20	£16,293
5*. 90-day post-hospitalization mortality risk from UK COPD Audit[4]	**£20,283**	**5.39**	**£16,742**	**5.27**	**£3,541**	**0.12**	**£28,569**
6*. 38ml FEV1 decline from Decramer and Cooper 2010[7]	**£19,086**	**5.45**	**£15,497**	**5.31**	**£3,589**	**0.14**	**£25,368**
7*. 90-day post-hospitalization mortality risk from UK COPD Audit[4] AND 38ml FEV1 decline from Decramer and Cooper 2010[7]	**£19,799**	**5.62**	**£16,173**	**5.50**	**£3,626**	**0.12**	**£29,166**

* Scenarios 5, 6 and 7 were conducted by the ERG on the new company base case. The scenario 7 uses more preferable input estimates for post-hospitalisation mortality and annual FEV1 decline

2. Prior Hospitalised Population (new population)

2.1 Clinical Data

The company provided a post-hoc analysis on a subgroup of patients - patients with severe COPD [FEV_1 post-bronchodilator < 50% predicted], associated with a history of exacerbation **and at least one hospitalisation for a COPD exacerbation in the prior year** despite triple therapy (denoted as the "prior hospitalisation" population). According to the company, these data have become available since their initial submission.

We checked the CSRs of both trials, but we were not able to find data for this subgroup. Therefore, we are not able to check any of these data.

2.2 Model Changes

For the prior hospitalization subgroup, the company incorporated the following changes to the ERG addendum model:

- Changing of the baseline characteristics and serious adverse event rates to reflect the prior hospitalized, pooled ITT triple therapy population from REACT and RE2SPOND trials
- Changing of the moderate/severe exacerbation rates in severe and very severe COPD states reflecting the prior hospitalized, pooled ITT triple therapy population from REACT and RE2SPOND trials
- Incorporation of the post-hospitalisation excess mortality
- Changing the annual FEV1 decline rate used for severe COPD patients

The last two model changes (in post-hospitalisation mortality and FEV1 decline) for the prior hospitalised subgroup are the same as explained in sections 1.2.3 and 1.2.4, respectively.

The baseline characteristics and serious adverse event rates used in the prior hospitalised group in the new model are provided in Table 7 and Table 8, respectively. The ERG could not replicate these values used in the model from the response to the ACD document.

Table 7: Baseline characteristics of the prior hospitalized, ITT, concomitant LAMA subgroup

Patient characteristic	Baseline values in the new model (REACT and RE2SPOND)
Age (years)	[redacted]
Proportion male	[redacted]
Mean height (cm, males)	[redacted]
Mean height (cm, females)	[redacted]

Table 8: Occurrence rate of the TEASEs based on ITT, concomitant LAMA subpopulation

	New model (REACT and RE2SPOND)	
TESAEs	**Roflumilast arm (mean)**	**Comparator arm (mean)**
Diarrhoea	[redacted]	[redacted]
Weight loss	[redacted]	[redacted]
Nausea*	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]

For the prior hospitalised subgroup, the exacerbation rates used in the model were also updated. The actual exacerbation rates used in the new model for the prior hospitalized subpopulation are presented in Table 9. These rates were derived from the predictive regression equations in the economic model.

The coefficients for the "roflumilast" covariate used in the predictive regression equations in the economic model for the prior hospitalised subpopulation analysis ([redacted] and [redacted] for moderate and severe exacerbations, respectively) are almost same as the rate ratios ([redacted] and [redacted] for moderate and severe exacerbations, respectively) provided in Table 4 of the response to the ACD document[2].

Table 9: Actual moderate and severe exacerbation rates used in the economic models

	roflumilast plus triple therapy		Triple therapy		Roflumilast vs placebo
	Severe COPD	**Very Severe COPD**	**Severe COPD**	**Very Severe COPD**	**Rate Ratio**
The new model from the company					
Moderate exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG Comments: In the subgroup analysis for the prior hospitalised subpopulation, the ERG could not verify the correctness of the baseline characteristics and the AE rates as the patient level data of this specific subgroup was not provided.

Similarly, the ERG could not verify the correctness of the exacerbation rate results from the negative binomial regression equations used for this subpopulation in the economic model, as the patient level data and specifics of the negative binomial regressions were not provided. For the mortality and FEV1 decline changes, the critique discussed above for the base case analysis is valid for subgroup population, as well.

2.3 Cost Effectiveness Results

In the new subgroup analysis, in which pooled exacerbation rates from REACT and RE2SPOND ITT, triple therapy and prior hospitalised subpopulation were used, the ICER has decreased to £7,087 per QALY gained.

Similar to the base case, the company conducted several scenario analyses on mortality and applied the mortality rates from Roberts et al 2001[11], Soler-Cataluna 2005[13], Hartl et al. 2005[10] and Wildman et al 2008[12], respectively.

The results from these subgroup and scenario analyses are presented in Table 10. The ICER in these scenarios are ranging from £6,136 per QALY gained (when the 180 day mortality risk after hospitalization from Wildman et al 2008[12] is applied as the CFR for severe exacerbation in the economic model) to £8,549 per QALY gained (when the post-hospitalization mortality hazard ratio of 2.235 from Soler-Cataluna (2005)[13] was applied to the SMRs for post-hospitalization severe and very severe COPD patients, two newly added states in the economic model).

For the prior hospitalised subpopulation, on the presumption that the calculations on the baseline characteristics, adverse event and exacerbation rates are right, the ICER estimate is expected to be less than £10,000 per QALY gained, and the estimate seems to be less sensitive to the assumptions on mortality.

Table 10: Revised base case cost effectiveness analysis, incorporating changes mentioned by the company and additional scenarios

Results from the analysis conducted on the new subpopulation	roflumilast plus triple therapy		Triple therapy alone		Incr. costs	Incr. QALYs	ICER
	Total costs	Total QALYs	Total costs	Total QALYs			
Prior hospitalised, ITT, triple therapy subpopulation from REACT and RE2SPOND trials	**£20,173**	**5.16**	**£16,773**	**4.68**	**£3,401**	**0.48**	**£7,087**
Additional scenarios on the mortality rate assumption	**roflumilast plus triple therapy**		**Triple therapy alone**		**Incr. costs**	**Incr. QALYs**	**ICER**
	Total costs	**Total QALYs**	**Total costs**	**Total QALYs**			
1. 90-day post-hospitalization mortality risk from Roberts et al 2006[11]	£20,241	5.21	£16,906	4.80	£3,335	0.46	£7,228
2. Post mortality HR from Soler-Cataluna 2005[13]	£18,637	4.85	£16,322	4.58	£2,316	0.27	£8,549
3. 90-day post-hospitalization mortality risk from Hartl et al 2001[10]	£21,567	5.45	£18,392	5.03	£3,175	0.42	£7,561
4. 180-day post-hospitalization mortality risk from Wildman et al 2008[12]	£15,597	4.20	£12,000	3.61	£3,597	0.59	£6,136

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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
2nd ADDENDUM
Critique on the company's response to the ACD

ERRATUM

26 April 2017

This document contains errata in respect of the ERG 2nd addendum (date 3 April 2017) 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:**
8	"In the response to the ACD document, the company argued that applying post-hospitalisation mortality as CFR in the economic model would be a conservative approach, because under this approach, the alive days of a patient, who died at day 90 after his/her severe exacerbation, were not taken into account." is changed to "In the response to the ACD document, the company argued that applying post-hospitalisation mortality as CFR in the economic model is likely to overstate the impact of mortality. They also stated that applying a 90 day CFR is conservative on the basis that some of the evidence suggests that the increased mortality risk might extend to 180 days."
10	"In the scenario in which post-hospitalisation mortality is applied as SMRs using additional states, the company argued that the impact of a severe exacerbation was underestimated, because the frequency of severe exacerbations would not have an effect on the mortality." is changed to "In the scenario in which post-hospitalisation mortality is applied as SMRs using additional states, the company argued that the impact of a severe exacerbation was underestimated, because in this scenario, the frequency of severe exacerbations would not have any effect on the COPD related mortality in the model, contrary to clinical expectations." "Furthermore, the ERG could not find the HR value that the company used in the new model, 2.23, in the paper." is changed to "Furthermore, the ERG could not find the HR value that the company used in the new model, 2.23, in the paper. At factual accuracy check stage the company corrected this error and confirmed the correct value as 2.94." "…hazard ratio of 2.235 from Soler-Cataluna (2005)13 was applied …" is changed to "…hazard ratio of 2.94 from Soler-Cataluna (2005)13 was applied …"
11	The following text has been added: "Furthermore, at factual accuracy check stage the company informed the ERG of an error in the PSA implementation of the array formulae for the uncertainty of the treatment effects was identified in the model. The correction of this error seems not to change the main conclusions drawn on the probabilistic results in the original ERG report"

12	Table 6, Additional scenario 2, has been updated to reflect the correct results for the modified post mortality HR from Soler-Cataluna 2005.
14	"…hazard ratio of 2.235 from Soler-Cataluna (2005)13 was applied …" is changed to "…hazard ratio of 2.94 from Soler-Cataluna (2005)13 was applied …"
15	Table 10, Additional scenario 2, has been updated to reflect the correct results for the modified post mortality HR from Soler-Cataluna 2005.

double counting of deaths leads to an underestimation of QALYs and LYs left estimated by the new company model regardless of treatment. In terms of incremental results, the correction of the double counting problem would slightly decrease the ICER, because with lower SMRs, life expectancy would be higher for each patient who does not have an exacerbation and patients have fewer exacerbations on roflumilast. Or, in other words, due to the slight increase in life-years in both groups, roflumilast has more time to prevent exacerbations.

In the response to the ACD document, the company argued that applying post-hospitalisation mortality as CFR in the economic model is likely to overstate the impact of mortality. They also stated that applying a 90 day CFR is conservative on the basis that some of the evidence suggests that the increased mortality risk might extend to 180 days.. The ERG agrees that the alive days of a patient who died after hospital discharge are overlooked in this approach, but thinks that this is slightly more beneficial for the roflumilast arm in terms of incremental QALYs gained, as there are more severe exacerbation deaths (and therefore more overlooked alive days after hospital discharge) in the placebo arm.

The ERG noted that the most recent 90-day post-hospitalisation mortality estimate from the UK National COPD Audit 2014,[4] which is 12%, would be a more plausible choice for the post-hospitalisation risk mortality than the estimate from Connolly et al (2006).[6] The estimate from Connolly et al (2006)[6] was based on data before 2006, and in the audit,[4] a historical reduction in 90-day post-hospitalisation mortality (from the hospital admission) was reported. While the mortality was 16.3% in 2003, it dropped to 14.2% in 2008; and to 12% in 2014. As the most recent (2014) UK specific estimate for post-hospitalisation mortality, 12% from the UK National COPD Audit would be the preferred post-hospitalisation mortality input for the model according to the ERG.

1.2.4 Changing the annual FEV1 decline rate used for severe COPD patients

In the ERG addendum model, an annual FEV1 decline rate of 38 ml per year, which was derived from Decramer and Cooper (2010)[7] using data from the UPLIFT trial, was assumed for the annual FEV1 decline for severe COPD patients.

The company, in its new model, used the FEV1 decline rate estimate of 52 ml per year from Tantucci and Modina (2012),[8] which is a recent meta-analysis. Furthermore, in the response to the ACD, the company mentioned that the estimate from the Decramer and Cooper 2010[7] study was deemed as "*as being unrepresentative of patients of COPD patients with severe COPD*" by Tantucci and Modina (2012)[8]

ERG Comments: Concerning the change of the annual FEV1 decline in the new company model, the company used the 52 ml per year estimate from Tantucci and Modina[8], and argued that 38 ml estimate from Decramer and Cooper 2010[7] was deemed unrepresentative for severe COPD patients. The ERG identified the 52 ml estimate from Tantucci and Modina,[8] and it seems that this estimate is derived from one study,[9] focusing on patients with alpha-1 antitrypsin deficiency-related emphysema. The ERG considers the patient population from this study might be a specific subgroup of COPD patients. In Tantucci and Modina,[8] the UPLIFT study, from which the original 38 ml estimate was derived, was excluded from the meta-analysis. The research question of the meta-analysis was the annual FEV1 decline in the natural history of COPD, and therefore the placebo arms of randomized clinical trials were included in the meta-analysis. The UPLIFT trial was not among the included studies, because in the UPLIFT control arm, patients received on average at least 2 active drugs. Even though for the meta-analysis in Tantucci and Modina,[8] it might be reasonable to exclude UPLIFT trial from the meta-analysis, the ERG still considers that 38 ml is a more plausible estimate for the economic model,

ERG Comments: In the scenarios in which post-hospitalisation risks were applied as CFR (i.e. Hartl et al (2013)[10], Roberts et al (2001)[11] and Wildman et al (2008)[12]), the same issues discussed above for the base case analysis (i.e. double counting of post-hospitalisation deaths and the underestimation of the alive days when a patient dies after s/he is discharged from the hospital) are relevant, as well.

The ERG considers that the estimate from Wildman et al (2008)[12] is not plausible, because different from other studies, in Wildman et al (2008)[12], only the patients that were admitted into ICUs (not general wards) were analysed, which represents the mortality risk of a more severe patient population than other studies.

In the scenario in which post-hospitalisation mortality is applied as SMRs using additional states, the company argued that the impact of a severe exacerbation was underestimated, because in this scenario, the frequency of severe exacerbations would not have any effect on the COPD related mortality in the model, contrary to clinical expectations. The ERG has some doubts about this argument because firstly, CFRs for severe exacerbations derived from in-hospital deaths are still applied in this scenario, and therefore the frequency of severe exacerbations would still have an effect on the mortality. Secondly, in Figure 2 from Soler-Cataluna 2005[13], it was demonstrated that the difference between the Kaplan Meier survival curves from the patients who were hospitalised once and from the patients who were hospitalised more than once was not statistically significant. Furthermore, the ERG could not find the HR value that the company used in the new model, 2.23, in the paper. At factual accuracy check stage the company corrected this error and confirmed the correct value as 2.94.

Finally, the ERG identified a logical inconsistency in the implementation of this scenario. In the model, it was assumed that all patients were not previously hospitalised in the baseline, even though there were patients with hospitalisation history already in the baseline of REACT and RE2SPOND trials. Correcting for this inconsistency is expected to increase the ICER of this scenario analysis slightly, as the number of non-hospitalised patients in the baseline, who would benefit from less number of severe exacerbations in the roflumilast arm, would be less.

1.3 Cost Effectiveness Results

By implementing the changes above to the ERG addendum model, the ICER decreased to £24,976 per QALY gained from £71,365 per QALY gained in the ERG addendum model. Table 1 shows how each individual change impacts the ICER plus the combined effect of all changes simultaneously.

As it can be seen from Table 1, incorporating the post-hospitalization mortality as a CFR in the economic model has the biggest impact on the ICER (decreased ICER to £32,515 per QALY gained), additionally, using exacerbation rates derived from pooled REACT and RE2SPOND trials decreased the ICER as well (decreased ICER to £54,305 per QALY gained).

Furthermore, the company conducted several scenario analyses on mortality and applied the mortality rates from Roberts et al 2001[11], Soler-Cataluna 2005[13], Hartl et al. 2005[10] and Wildman et al 2008[12], respectively. The results from these analyses are also presented in Table 1. The ICER in these scenarios range from £16,293 per QALY gained (when the 180 day mortality risk after hospitalization from Wildman et al 2008[12] is applied as the CFR for severe exacerbation in the economic model) to £31,202 per QALY gained (when the post-hospitalization mortality hazard ratio of 2.94 from Soler-Cataluna (2005)[13] was applied to the SMRs for post-hospitalization severe and very severe COPD patients, two newly added states in the economic model).

ERG Comments: In the company's response to the ACD document[2], the ERG identified a number of reporting errors/inconsistencies in the tables. For instance, in Table 2 and Table 5 from the response

to the ACD document[2], it reads as if the company reported the effects of applying each model change separately, however the ERG noticed from the economic model that these reported results actually denote the effects of applying the changes jointly in a stepwise manner.

Furthermore, at factual accuracy check stage the company informed the ERG of an error in the PSA implementation of the array formulae for the uncertainty of the treatment effects was identified in the model. The correction of this error seems not to change the main conclusions drawn on the probabilistic results in the original ERG report.

On top of the company scenarios, the ERG conducted the following scenario analyses.

- Instead of 15.3% from Connolly et al (2006)[6], 90 day mortality estimate (12%) from the UK National COPD Audit 2014[4] was applied as the CFR.
- Instead of 52 ml from Tantucci and Modina (2012),[8] 38ml FEV1 decline from Decramer and Cooper 2010[7] is used.
- Both post-hospitalisation mortality and annual FEV1 decline estimates are changed as above

The incremental results from these scenarios are also presented in Table 1. Using these more plausible inputs (Scenario 7) increases the ICER to £29,166 per QALY gained

On the presumption that the calculations on the baseline characteristics, adverse event and exacerbation rates are right, for the population within the initial company submission (triple therapy, severe/very severe COPD with frequent exacerbations), the ICER estimate is expected to be between and £25,000 and £35,000 per QALY gained, and it is very sensitive to the assumptions on mortality.

Table 1: Revised base case cost effectiveness analysis, incorporating changes mentioned by the company and additional scenarios

Additional changes implemented by the company and company's new base case	roflumilast plus triple therapy		Triple therapy alone		Incr. costs	Incr. QALYs	ICER
	Total costs	Total QALYs	Total costs	Total QALYs			
0. ERG addendum model	£21,548	6.06	£17,844	6.01	£3,704	0.05	£71,365
1. Updating the baseline characteristics and adverse event rates according to REACT and RE2SPOND trials	£21,720	6.09	£17,965	6.04	£3,755	0.05	£72,455
2. Updating moderate and severe exacerbation rates according to the pooled patient level data from REACT and RE2SPOND trials	£21,606	6.05	£17,977	5.98	£3,629	0.07	£54,305
3. Incorporating post-hospitalization excess mortality after exacerbation (from Connolly et al 2006[6])	£18,857	5.44	£15,316	5.333	£3,541	0.11	£32,515
4. Changing the annual FEV1 decline for severe COPD patients	£22,186	5.83	£18,584	5.78	£3,602	0.05	£67,884
(1 to 4 all). Company's preferred base-case in the response to ACD	**£19,524**	**5.23**	**£16,016**	**5.09**	**£3,508**	**0.14**	**£24,976**
Additional scenarios on the mortality rate assumption	**roflumilast plus triple therapy**		**Triple therapy alone**		**Incr. costs**	**Incr. QALYs**	**ICER**
	Total costs	**Total QALYs**	**Total costs**	**Total QALYs**			
1. 90-day post-hospitalization mortality risk from Roberts et al 2001[11]	£19,883	5.31	£16,358	5.17	£3,525	0.13	£26,526
2. Post mortality HR from Soler-Cataluna 2005[13]	£16,152	4.49	£13,195	4.38	£2,957	0.11	£26,177
3. 90-day post-hospitalization mortality risk from Hartl et al 2001[10]	£20,578	5.46	£17,027	5.34	£3,552	0.12	£30,349
4. 180-day post-hospitalization mortality risk from Wildman et al 2008[12]	£15,760	4.38	£12,545	4.18	£3,214	0.20	£16,293
5*. 90-day post-hospitalization mortality risk from UK COPD Audit[4]	**£20,283**	**5.39**	**£16,742**	**5.27**	**£3,541**	**0.12**	**£28,569**
6*. 38ml FEV1 decline from Decramer and Cooper 2010[7]	**£19,086**	**5.45**	**£15,497**	**5.31**	**£3,589**	**0.14**	**£25,368**
7*. 90-day post-hospitalization mortality risk from UK COPD Audit[4] AND 38ml FEV1 decline from Decramer and Cooper 2010[7]	**£19,799**	**5.62**	**£16,173**	**5.50**	**£3,626**	**0.12**	**£29,166**

* Scenarios 5, 6 and 7 were conducted by the ERG on the new company base case. The scenario 7 uses more preferable input estimates for post-hospitalisation mortality and annual FEV1 decline

For the prior hospitalised subgroup, the exacerbation rates used in the model were also updated. The actual exacerbation rates used in the new model for the prior hospitalized subpopulation are presented in Table 2. These rates were derived from the predictive regression equations in the economic model.

The coefficients for the "roflumilast" covariate used in the predictive regression equations in the economic model for the prior hospitalised subpopulation analysis ([redacted] and [redacted] for moderate and severe exacerbations, respectively) are almost same as the rate ratios ([redacted] and [redacted] for moderate and severe exacerbations, respectively) provided in Table 4 of the response to the ACD document[2].

Table 2: Actual moderate and severe exacerbation rates used in the economic models

	roflumilast plus triple therapy		**Triple therapy**		**Roflumilast vs placebo**
	Severe COPD	**Very Severe COPD**	**Severe COPD**	**Very Severe COPD**	**Rate Ratio**
The new model from the company					
Moderate exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG Comments: In the subgroup analysis for the prior hospitalised subpopulation, the ERG could not verify the correctness of the baseline characteristics and the AE rates as the patient level data of this specific subgroup was not provided.

Similarly, the ERG could not verify the correctness of the exacerbation rate results from the negative binomial regression equations used for this subpopulation in the economic model, as the patient level data and specifics of the negative binomial regressions were not provided. For the mortality and FEV1 decline changes, the critique discussed above for the base case analysis is valid for subgroup population, as well.

2.3 Cost Effectiveness Results

In the new subgroup analysis, in which pooled exacerbation rates from REACT and RE2SPOND ITT, triple therapy and prior hospitalised subpopulation were used, the ICER has decreased to £7,087 per QALY gained.

Similar to the base case, the company conducted several scenario analyses on mortality and applied the mortality rates from Roberts et al 2001[11], Soler-Cataluna 2005[13], Hartl et al. 2005[10] and Wildman et al 2008[12], respectively.

The results from these subgroup and scenario analyses are presented in Table 3. The ICER in these scenarios are ranging from £6,136 per QALY gained (when the 180 day mortality risk after hospitalization from Wildman et al 2008[12] is applied as the CFR for severe exacerbation in the economic model) to £8,549 per QALY gained (when the post-hospitalization mortality hazard ratio of 2.94 from Soler-Cataluna (2005)[13] was applied to the SMRs for post-hospitalization severe and very severe COPD patients, two newly added states in the economic model).

For the prior hospitalised subpopulation, on the presumption that the calculations on the baseline characteristics, adverse event and exacerbation rates are right, the ICER estimate is expected to be less than £10,000 per QALY gained, and the estimate seems to be less sensitive to the assumptions on mortality.

Table 3: Revised base case cost effectiveness analysis, incorporating changes mentioned by the company and additional scenarios

Results from the analysis conducted on the new subpopulation	**roflumilast plus triple therapy**		**Triple therapy alone**		**Incr. costs**	**Incr. QALYs**	**ICER**
	Total costs	**Total QALYs**	**Total costs**	**Total QALYs**			
Prior hospitalised, ITT, triple therapy subpopulation from REACT and RE2SPOND trials	**£20,173**	**5.16**	**£16,773**	**4.68**	**£3,401**	**0.48**	**£7,087**
Additional scenarios on the mortality rate assumption	**roflumilast plus triple therapy**		**Triple therapy alone**		**Incr. costs**	**Incr. QALYs**	**ICER**
	Total costs	**Total QALYs**	**Total costs**	**Total QALYs**			
1. 90-day post-hospitalization mortality risk from Roberts et al 2001[11]	£20,641	5.26	£17,306	4.80	£3,335	0.46	£7,228
2. Post mortality HR from Soler-Cataluna 2005[13]	£16,918	4.49	£14,606	4.20	£2,312	0.29	£8,053
3. 90-day post-hospitalization mortality risk from Hartl et al 2001[10]	£21,567	5.45	£18,392	5.03	£3,175	0.42	£7,561
4. 180-day post-hospitalization mortality risk from Wildman et al 2008[12]	£15,597	4.20	£12,000	3.61	£3,597	0.59	£6,136

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 critique on the company's response to the ACD, 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, 19 April 2017** 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 Clarification on the pooling of REACT and RESPOND

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 4, Section 1.1 We would like to respond to the following ERG statement and provide clarification on the analysis methods used for the pooled analysis "We were unable to check the new pooled analyses themselves as we have not received the full individual patient data from both trials. However, the company did not provide any details of their analysis methods, for example, whether the pooled analysis was adjusted for or stratified by study, to allow for the fact that there are two different studies. Therefore, we cannot comment on whether the analysis methods were appropriate" The analysis methods used for the pooled analysis are as follows: **1.1 Pooled Analysis Objectives** To investigate the effect of roflumilast 500 µg tablets once daily versus placebo on exacerbation rate in chronic obstructive pulmonary disease	Not applicable,	To provide the Appraisal Committee with further information to inform and ensure confidence in the accuracy of the efficacy results.	Thank you for providing more information about the trials and statistical methods for pooling. As the pooled analyses were adjusted for trial the ERG are satisfied that the analyses accounted for the fact that the data were from different trials.

(COPD) patients who are concomitantly treated with a fixed combination of long-acting β2-agonists (LABA) and inhaled glucocorticosteroid (ICS). To obtain data on safety and tolerability of roflumilast in COPD patients who are concomitantly treated with a fixed combination of LABA and ICS. To investigate the effect of roflumilast on major cardiovascular events (MACE) To provide exploratory analysis of subgroups. Lung function endpoints are not part of the pooled analysis as in REACT post-bronchodilator measurements were collected during the treatment period only and for RESPOND pre-bronchodilator measurements. **1.2 Trial Design** Each of the two trials to be combined in this pooled analysis was designed as a 52-week randomized, double-blind, parallel group, multicenter, placebo-controlled, phase III/IV trial. The trials were performed in severe or very severe COPD patients and			

included two parallel treatment arms (roflumilast 500 µg once daily vs. placebo once daily) concomitantly treated with a fixed combination of LABA and ICS. The first visit, Visit 0 [V0] or Visit 1 [V1], depending on the study, will be referenced as “Screening", Visit 2 [V2] as “Randomization". Visit VPK, interim telephone contacts and visits after Week 52 will not be considered in any pooled analysis. **1.3 Randomization** In both trials patients were randomized (1:1 ratio) to roflumilast or placebo at the end of the baseline period. In the RESPOND trial randomization was stratified by LAMA use (LAMA use vs no LAMA use). **1.3.1 Visit Windows** For the pooled analysis the visits will be presented as weeks: Week 0, Week 4, Week 12, Week 20, Week 28, Week 40 and Week 52. The visit structure “ready for analyses" from the individual trials will be taken over and adjusted, if needed, to reflect the week presentation. At the time of the			

performing of the pooled analysis additional considerations regarding the visit presentation may be done. **2. ANALYSIS SETS** In accordance with ICH recommendations in guidelines E3 and E9, the following analysis sets will be defined: total set, full analysis set, and safety set. Analysis based on per-protocol set is not part of the pooled analysis. All tables and graphs will be based on Clinical Data Interchange Standards Consortium Study Data Tabulation Models and Analysis Data Models (CDISC SDTMs and ADaMs). The individual study specific SDTMs and ADaMs will be used for the pooled analysis without any further changes or updates. For the pooled analysis a new set of ADaMs will be generated based on study specific SDTMs and/or ADaMs to support the analyses described in this document. All regression analyses included trial as a covariate to control for differences between trials.			

Issue 2 Corrected HR value

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 12, Section 1.2.5. The ERG state: "Furthermore, the ERG could not find the HR value that the company used in the new model, 2.23, in the paper." This is due to an error in the AstraZeneca response and the correct HR value is 2.94, use of the correct HR alters the ICER in this scenario to £26,177.	"Furthermore, the ERG could not find the HR value that the company used in the new model, 2.23, in the paper. At factual accuracy check stage the company correct this error and confirmed the correct value as 2.94."	To amend a factual inaccuracy within the AstraZeneca response and provide the Appraisal Committee with the correct information and corresponding ICER.	The following sentence has been added: "At factual accuracy check stage the company corrected this error and confirmed the correct value as 2.94." Additionally, the CE results based on this HR were updated in Table 6 and 10 of the addendum.

Issue 3 Misrepresentation of impact of applying post-hospitalisation mortality 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 8, Section 1.2.3. The following ERG statement is incorrect and does not accurately reflect the AstraZeneca ACD consultation response. The ERG appear to have confused our comments on post-hospitalisation and the application of a 90-day mortality risk to a 30 day cycle: "In the response to the ACD document, the company argued	To amend the text "In the response to the ACD document, the company argued that applying post-hospitalisation mortality as CFR in the economic model is likely to overstate the impact of mortality. They also stated that applying a 90 day CFR is conservative on the basis that evidence suggests that the increased mortality risk actually extends to 180 days."	To accurately reflect the AstraZeneca response to the ACD	The text is changed as follows to avoid confusion: "In the response to the ACD document, the company argued that applying post-hospitalisation mortality as CFR in the economic model is likely to overstate the impact of mortality. They also stated that applying a 90 day CFR is conservative on the basis that some of the evidence suggests

that applying post-hospitalisation mortality as CFR in the economic model would be a conservative approach, because under this approach, the alive days of a patient, who died at day 90 after his/her severe exacerbation, were not taken into account." Within our response to the ACD we stated that the approach of applying post-hospitalisation mortality may **overstate** the impact of mortality we did not suggest it was conservative. It is however correct to state that applying a 90 day CFR is conservative as there is evidence to suggest that the increased mortality risk actually extends to 180 days.			that the increased mortality risk might extend to 180 days."

Issue 4 Misrepresentation of impact of applying post-hospitalisation mortality 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 10, Section 1.2.5 The following ERG statement is incorrect and does not accurately reflect the AstraZeneca ACD consultation response: "In the scenario in which post-hospitalisation mortality is applied as SMRs using additional states,	To amend the text as follows: "In the scenario in which post-hospitalisation mortality is applied as SMRs using additional states, the company argued that the impact of a severe exacerbation was underestimated, because the frequency of severe exacerbations would ~~not~~ have an effect on the mortality."	To accurately reflect the AstraZeneca response to the ACD	The text is changed as follows to avoid confusion: "In the scenario in which post-hospitalisation mortality is applied as SMRs using additional states, the company argued that the impact of a severe exacerbation was underestimated, because in

the company argued that the impact of a severe exacerbation was underestimated, because the frequency of severe exacerbations would not have an effect on the mortality." To clarify: within our response we stated that the impact of severe exacerbation was underestimated on the basis that the frequency of exacerbations would have an effect on mortality. Patients in the model are able to experience more than one exacerbation. The impact of this in terms of mortality is not taken into account using the HR considered.			this scenario, the frequency of severe exacerbations would not have any effect on the COPD related mortality in the model, contrary to clinical expectations."

Issue 5 Error discovered in PSA in economic model

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
We would like to inform the ERG of an error in the PSA and model included in the initial AstraZeneca submission document, which we have recently become aware of. When calculating the parameter values for the PSA on the treatment effect the "MMULT" function had been applied only to the row as opposed to the entire	No amendments to the ERG report are required as probabilistic results are not reported in the current document,	While amendments to the current ERG report are not required, it should be noted that correcting the error has minor implications on the probabilistic results of the model.	Thank you for pointing out this error. The ERG can confirm that the correction of this error seems not to change the main conclusions drawn on the probabilistic results of the original model. Following sentence is added on page 11: "Furthermore, at factual

covariance matrix, ad had not been applied as an array formula. This has been corrected and the amended model provided alongside this response. Correcting the error has minor implications on the probabilistic results of the model.			accuracy check stage the company informed the ERG of an error in the PSA implementation of the array formulae for the uncertainty of the treatment effects was identified in the model. The correction of this error seems not to change the main conclusions drawn on the probabilistic results in the original ERG report. ”