Lead team presentation: Roflumilast for treating chronic obstructive pulmonary disease [ID984]

1st Appraisal Committee meeting

Cost Effectiveness

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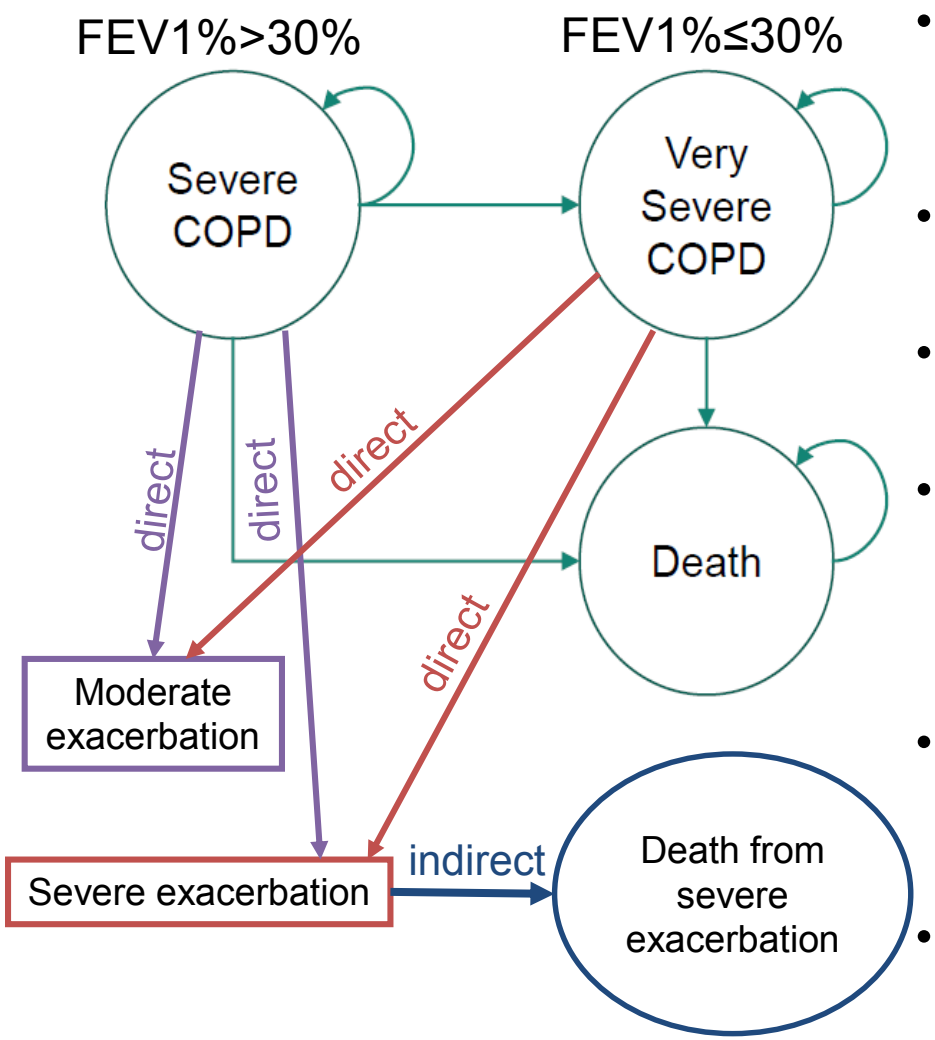
For committee, projector and public

Model structure



- Markov state transition model with 3 health states: severe, very severe and death.
- Two events: moderate and severe exacerbations.
- All patients start in severe COPD state (FEV1%=40%; assumption)
- Roflumilast directly reduces moderate and severe exacerbations, and indirectly reduces death from severe exacerbations.
- Baseline cohort based on all patients in ITT population from REACT (not LAMA subgroup)
- Time horizon: 40 years

Adapted from Figure 7 in the company submission

Clinical data used in company's model

Treatment effect (reduction in exacerbation)

- Uses data from REACT (LAMA subgroup)
- Per protocol analysis (excludes patients not taking concomitant LAMA)
- Negative binomial regression adjusting for COPD severity.

Severe to very severe COPD

- Transition probability (1.2% monthly) based on constant rate of FEV1 decline.
- Decline in FEV1 from Lung Health Study (52ml/year)
- FEV1% predicted calculated using Crapo et al (1981) equations.

Progression to death

- UK lifetables inflated with standardised mortality ratio (SMR) associated with COPD (2.5 for severe COPD and 3.85 for very severe COPD)
- Risk of death from severe exacerbation from case fatality rate in UK National COPD Audit Report 2014 (4.3% died during hospital admission for severe exacerbation); adjusted for age.

Health related quality of life (HRQoL)

- REACT trial used COPD Assessment Test (CAT) to collect quality of life data:
  - significant reduction from baseline CAT scores in each group but no significant difference between groups (mean difference: -0.285 (95% CI -0.711 to 0.142).
- Systematic review identified 15 studies measuring HRQoL of people with severe & very severe COPD:
  - None conducted in UK
  - 2 studies used EQ-5D UK value set (Rutten-van Molken 2006 and Menn 2010)
- Company's base case uses Rutten-van Molken studies.
- Company's scenario analysis uses alternative sources of HRQoL data including US study Solem (2013).

Utility values used in company's model

Analysis	State	Data source	Mean (SE)
Base-case	Health states	Rutten van Molken (2006) COPD patients, EQ-5D UK weights	Severe: 0.750 (0.009) Very severe: 0.647 (0.025)
	Exacerbations	Rutten van Molken (2009) Vignettes valued with time trade-off by sample of Dutch public	Moderate: -0.010 (0.007) Severe: -0.042 (0.009)
	Treatment emergent adverse events	Assumption: equal to a severe exacerbation from Rutten-van Molken (2009)	-0.042 (first month of treatment)
Scenario	Health states	Solem (2013) COPD patients EQ-5D at time of interview and recall of exacerbation health status US weights	Severe: 0.707 (0.013) Very severe: 0.623 (0.021)
	Exacerbation severity (base case)		Moderate: -0.103 (0.013) Severe: -0.157 (0.023) (converts to -0.009 for moderate and -0.013 over exacerbation duration)

Source: Table 40 and 69 in company submission

Adverse events

- Company's base case includes pneumonia (most common serious adverse event) and diarrhoea, weight decrease and nausea (most common adverse events of any grade) from REACT.
- Company's base case applies treatment emergent serious adverse events only and assumes:
  - It's appropriate to apply adverse event rates for the entire trial period in the 1st month only, as long term events are not expected
  - The cost of managing diarrhoea, weight loss & nausea is equivalent to the cost of a GP visit (£44)
  - The cost of pneumonia (£2,518) is a weighted average of non-elective inpatient short stay and long stay.
- Scenario analyses assess impact of including all treatment emergent adverse events, or excluding them from the analysis.
- Discontinuation of treatment is not built into the model.

Costs and resource use

- Systematic review identified 5 studies reporting data on cost and resource use in severe and very severe COPD
  - 3 studies conducted in UK, 1 in Germany and 1 Canada but not used to inform model inputs.
- NHS reference costs applied to severe (hospitalised) exacerbations- otherwise managed in primary care (GP visits).

Resource use	Components	Cost
[redacted]		
Very severe COPD monthly maintenance	As above but 4 days spirometry per year and 6.08 days per month on oxygen therapy	£106.90
[redacted]		
Severe exacerbations	Excess GP consultations (n=8.03), hospital admission and ambulance transport	£1,724.43

Source: Tables 41, 47, 49 and 50 in company submission

Other assumptions in company's model

- Base case model assumes
  - No additional lung function benefit from treatment with roflumilast.
  - Patients with severe & very severe COPD have 2 GP visits a year for general maintenance.
  - During a moderate exacerbation, 50% of patients will be treated with a 7-day course of prednisolone and 50% with a 14-day course.
  - During a severe exacerbation, 90% of patients will be transported to hospital by ambulance.
  - Exacerbations are associated with increased risk of death, costs and disutilities.

Company's base case results

	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER
Deterministic results							
Roflumilast	£22,930	8.95	6.14	£2,996	0.18	0.16	£18,774
Triple therapy	£19,933	8.77	5.98	-	-	-	-
Probabilistic results							
Roflumilast	£23,129	-	6.18	£2,996	-	0.17	£17,855
Triple therapy	£20,133	-	6.01	-	-	-	-

ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, Life years gained; QALYs, quality-adjusted life years;

- Probabilistic results show triple therapy plus roflumilast has a 72% probability of being cost effective at £20,000 per QALY gained, increasing to 100% at £30,000 per QALY gained

Company's deterministic sensitivity analyses

- In all of the company's sensitivity analyses the ICER was under £25,000 per QALY gained.
- Most influential parameters include:
  - transition probability from severe to very severe COPD for both treatment groups
  - starting age of cohort
  - mortality rate for very severe COPD

Company's scenario analyses
Starting population 100% very severe or mixed COPD

- Base case assumes all patients start in severe COPD state
  - scenario 1 all patients start with very severe COPD
  - scenario 2 mixed population of severe & very severe COPD (as in REACT trial)

	Total costs (£)	**Total LYG**	**Total QALYs**	**Inc. costs (£)**	**Inc. LYG**	**Inc. QALYs**	**ICER**
[redacted]							
All very severe COPD	£26,014	8.23	5.18	£2,343	0.22	0.19	£12,337
[redacted]							

All ICERS from deterministic results. Abbreviations: ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, Life years gained; QALYs, quality-adjusted life years.
*69% severe COPD and 31% very severe COPD (from subgroup analysis in REACT)

Source: Tables 57 and 61 in company submission

Company's additional scenario analyses

1) LAMA included as covariate (base case analysis excluded people not taking LAMA)
2) Higher mortality rates for COPD assumed (standardised mortality ratios of 3.1 and 5.0 for severe and very severe COPD compared with 2.5 and 3.85 in the base case analysis)
3) Inclusion of additional lung function benefit from roflumilast (base case excluded this additional benefit)
4) Inclusion of all treatment emergent adverse events (base case included only serious ones)
5) Removal of all treatment emergent adverse events

All scenario analyses resulted in ICERs below £21,000 per QALY gained

Company's scenario analysis results

	ICER per QALY gain by severity of COPD in starting population		
Company's base case	£18,774	-	-
Higher mortality rate for severe COPD	£20,906	£13,186	£18,207
All grade treatment emergent adverse events included	£19,498	£12,708	£17,109

All ICERS from deterministic results. Abbreviations: ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, Life years gained; QALYs, quality-adjusted life years.
*Estimated based on exacerbations over 1 year period (under the assumption that lung function benefit persists for 1 year).

Source: Tables 65, 66, 68, 71 and 72 in company submission

Company's scenario analysis
Alternative sources of HRQoL data

- Base case uses Rutten-van Molken studies for COPD utility scores. Company used data from Solem (2013) in scenario analysis:
  - US study of 314 patients (190 with severe COPD and 124 with very severe COPD)
  - Used the EQ-5D and the St George's Respiratory Questionnaire.
- Scenario analyses using various combinations of utilities and disutilities from Rutten van-Molken (2006), Rutten van-Molken (2009) and Solem (2013).

COPD severity of starting population	**ICER (£ per QALY gained)**
[redacted]	
Very severe	£12,337 to £17,937
[redacted]	

Source: Table 70 in company submission

ERG's comments on cost effectiveness

- ERG's main concern is company's choice of exacerbation rates (from per protocol analysis in REACT). ERG has strong preference for ITT results. Pooled results from REACT and RE^{2}SPOND may give more robust estimates.
- ERG also concerned about:
  - model structure (does not account for patient heterogeneity and impact of exacerbations on COPD progression)
  - model inputs used in transition probabilities as well as costs and utility inputs (alternatives proposed)
- ERG suggest several adjustments under 3 categories:
  - Errors (correct company's model as unequivocally wrong)
  - Violations (correct company's model as ERG consider NICE reference case, scope or best practice not followed)
  - Matters of judgement (amend company's model using ERG's preferred alternative assumptions).

ERG's correction of errors

Parameter	Company	ERG
GP visits	• 2.03 visits per moderate exacerbation (infrequent exacerbators) • 8.03 visits per severe exacerbations (frequent exacerbators)	• severity not same as frequency and can have multiple exacerbations per year • Additional GP visits due to moderate exacerbation is 1 and additional visits for severe exacerbation is 0
Hospital stay	Cost of hospitalisation due to severe exacerbation (£1183.06) and cost of pneumonia (£2518) based on weighted average of non-elective inpatient short and long stay.	ERG add costs for excess bed days to hospitalisation (£1245.45).
Pneumonia		Could not replicate company's estimate so ERG calculated weighted average and include excess bed days (£1924.72).

ERG's corrections of violations

Parameter	Company	ERG
Ambulance transport	£208.95 from Samyshkin et al. (2014).	HRG code used as most recently published cost data (£233.02).
Utility decrements due to exacerbations	0.01 and 0.042 for moderate and severe exacerbations (Rutten-van Molken 2009, time trade-off valuations by Dutch general public).	Data from Hoogendoorn 2011 (0.0166 for moderate exacerbations and 0.0482 for severe). EQ-5D and valued with the UK-tariff.
Half cycle correction	No half cycle correction due to short cycle length.	Half cycle correction added (impact small but good practice).
Baseline population and adverse events	Full ITT analysis from REACT.	ITT analysis from LAMA subgroup in REACT for consistency with effectiveness data.

ERG's preferred assumptions

Parameter	Company	ERG
Maintenance costs (severe and very severe COPD)	• Assumes 2 GP visits per year for both groups • Monthly maintenance cost £32.57 for severe COPD and £106.90 for very severe.	• Assumes more GP visits with very severe COPD compared with severe. • Use 4 times per year (Oostenbrink et al. 2005) for very severe COPD.
Progression from severe to very severe COPD	• Reference equations to translate FEV_1 to % FEV_1 predicted from Crapo (1981) • Lung function decline 52 ml per year (Lung Health Study 2000).	• Reference equation from Hankinson et al. (1999). • Use more plausible lung function decline 38 ml per year (Decramer & Cooper 2010)
Exacerbation rates	Rate ratios from REACT (LAMA subgroup, per protocol analysis) • Moderate (RR 0.887, 95% CI 0.723 to 1.087) • Severe (RR 0.656, 0.496 to 0.868)	Rate ratios from REACT (LAMA subgroup, ITT analysis) • Moderate (RR 0.934, 0.773 to 1.128) • Severe (RR 0.767, 0.595 to 0.989)

ERG's base case results
(ICERs for add on roflumilast vs. triple therapy)

Parameter	Inc. costs	Inc. QALYs	ICER
Company's base case	**£2,996**	**0.16**	**£18,774**
1. Correct all errors (GP visits, cost of hospitalisation and pneumonia)	£3,257	0.16	£20,409
2. Correct errors and update ambulance cost	£3,239	0.16	£20,296
3. Correct errors and use exacerbation utility from UK tariff	£3,257	0.15	£21,340
4. Correct errors and add half cycle correction	£3,273	0.16	£20,509
5. Correct errors and use LAMA subgroup for baseline characteristics and adverse events	£3,122	0.16	£20,018
6. Correct errors and increase maintenance costs for very severe COPD	£3,271	0.16	£20,492
7. Correct errors and lower lung function decline	£3,388	0.15	£21,869
8. Correct errors and use ITT exacerbation rates (REACT)	£3,513	0.11	£33,009
ERG preferred base case (1 to 8)	**£3,489**	**0.10**	**£35,814**

All ICERS from deterministic results. Abbreviations: ICER, incremental cost-effectiveness ratio; Inc, incremental; QALYs, quality-adjusted life years.

ERG's deterministic and probabilistic results
(ICERs for add on roflumilast vs. triple therapy)

	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER
Deterministic results							
Company	-	-	-	-	-	-	£18,774
Roflumilast	£21,332	8.75	6.10	£3,489	0.12	0.10	£35,814
Triple therapy	£17,844	8.63	6.01	-	-	-	-
Probabilistic results							
Company	-	-	-	-	-	-	£17,855
Roflumilast	£21,546	-	6.14	£3,498	-	0.104	£33,727
Triple therapy	£18,047	-	6.04	-	-	-	-

ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, Life years gained; QALYs, quality-adjusted life years;

Using the ERG's preferred assumptions, triple therapy plus roflumilast has a 3% probability of being cost effective at £20,000 per QALY gained, increasing to 28% at £30,000 per QALY gained.

ERG's additional scenario analyses

(ICERs for add on roflumilast vs. triple therapy based on ERG's base case)

Scenario	Inc. costs (£)	Inc. QALYs	ICER
Company base case	**£2,996**	**0.16**	**£18,774**
ERG preferred base case RR for moderate exacerbation =0.934 (0.773 to 1.128) RR for severe exacerbation =0.767 (0.595 to 0.989)	**£3,456**	**0.10**	**£35,814**
Separate exacerbation for severe and very severe COPD Moderate exacerbation [severe=RR 1.026, very severe=RR 0.832] Severe exacerbation [severe =RR 0.737, very severe =RR 0.761]	£3,124	0.15	£21,180
Pooled effectiveness (REACT and RE^{2}SPOND) RR for moderate exacerbation = 0.926 (0.815 to 1.053) RR for severe exacerbation = 0.880 (0.654 to 1.184)	£3,704	0.05	£71,365
All patients start with very severe COPD	£2,880	0.12	£24,733
Use Solem (2013) for utilities	£3,489	0.08	£41,960
Mortality from severe exacerbations same for all ages	£3,503	0.11	£32,341
Use SMRs from all COPD related deaths (CRF=0)	£3,052	0.02	£149,564
Include all grade adverse events	£3,502	0.09	£40,942

ERG's revised base case results
(ICERs for add on roflumilast vs. triple therapy)

Parameter	Inc. costs	Inc. QALYs	ICER
Company's base case	**£2,996**	**0.16**	**£18,774**
1. Correct all errors (GP visits, cost of hospitalisation and pneumonia)	£3,257	0.16	£20,409
2. Correct errors and update ambulance cost	£3,239	0.16	£20,296
3. Correct errors and use exacerbation utility from UK tariff	£3,257	0.15	£21,340
4. Correct errors and add half cycle correction	£3,273	0.16	£20,509
5. Correct errors and use LAMA subgroup for baseline characteristics and adverse events	£3,122	0.16	£20,018
6. Correct errors and increase maintenance costs for very severe COPD	£3,271	0.16	£20,492
7. Correct errors and lower lung function decline	£3,388	0.15	£21,869
8. Correct errors and use pooled exacerbation rates	£3,752	0.06	£66,859
ERG preferred base case (1 to 8)	**£3,704**	**0.05**	**£71,365**

All ICERS from deterministic results. Abbreviations: ICER, incremental cost-effectiveness ratio; Inc, incremental; QALYs, quality-adjusted life years.

Innovation & equalities

- The company considers roflumilast to be innovative as:
  - It is the only approved oral treatment with a specific anti-inflammatory mechanism of action that targets COPD inflammation.
  - It provides a further step in the treatment pathway post-triple therapy (LABA / LAMA / ICS) where currently there is no treatment available.
  - It is expected to reduce exacerbations and therefore reduce the comorbidities associated with frequent use of oral corticosteroids (which is not captured in the QALY calculation).
- Company did not identify any potential equality issues.

Key issues: cost effectiveness

- What is the committee's view of the company's modelling approach?
- The choice of exacerbation rate ratio (effect of roflumilast on exacerbations) impacts the ICER considerably - which rate ratios are most appropriate?
- What is the committee's view on the best data source for HRQol?
- Which approach for incorporating adverse events is appropriate?
- What is the committee's view on assumptions around COPD related mortality?
- Does the committee consider roflumilast to be an innovative therapy?