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

1st Appraisal Committee meeting

Background & Clinical Effectiveness

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For committee, projector and public

# Key issues: clinical effectiveness

- This appraisal is about the role of roflumilast in addition to inhaled and other therapies in the treatment of adults with severe COPD associated with frequent exacerbations
- Does the committee agree with the company's decision to exclude single and double inhaler therapy, and oral theophylline treatment, as comparators i.e. can the appraisal be restricted to adding roflumilast to inhaled triple therapy?
- Does the committee agree with the company's decision to present evidence for roflumilast based on only 1 (REACT) of 2 double-blind randomised trials (REACT and RE$^2$SPOND)? Is it more appropriate to pool the results from REACT and RE$^2$SPOND?
- What is the committees view on the company's decision to present only a subgroup of the REACT trial? Does the committee agree with the company's decision to present a "per protocol" rather than intention-to-treat analysis and to use a different statistical analysis than the one pre-specified?
- What is the committee's view on the clinical effectiveness of roflumilast? What is the committee's view of the quality and generalisability of the clinical evidence?

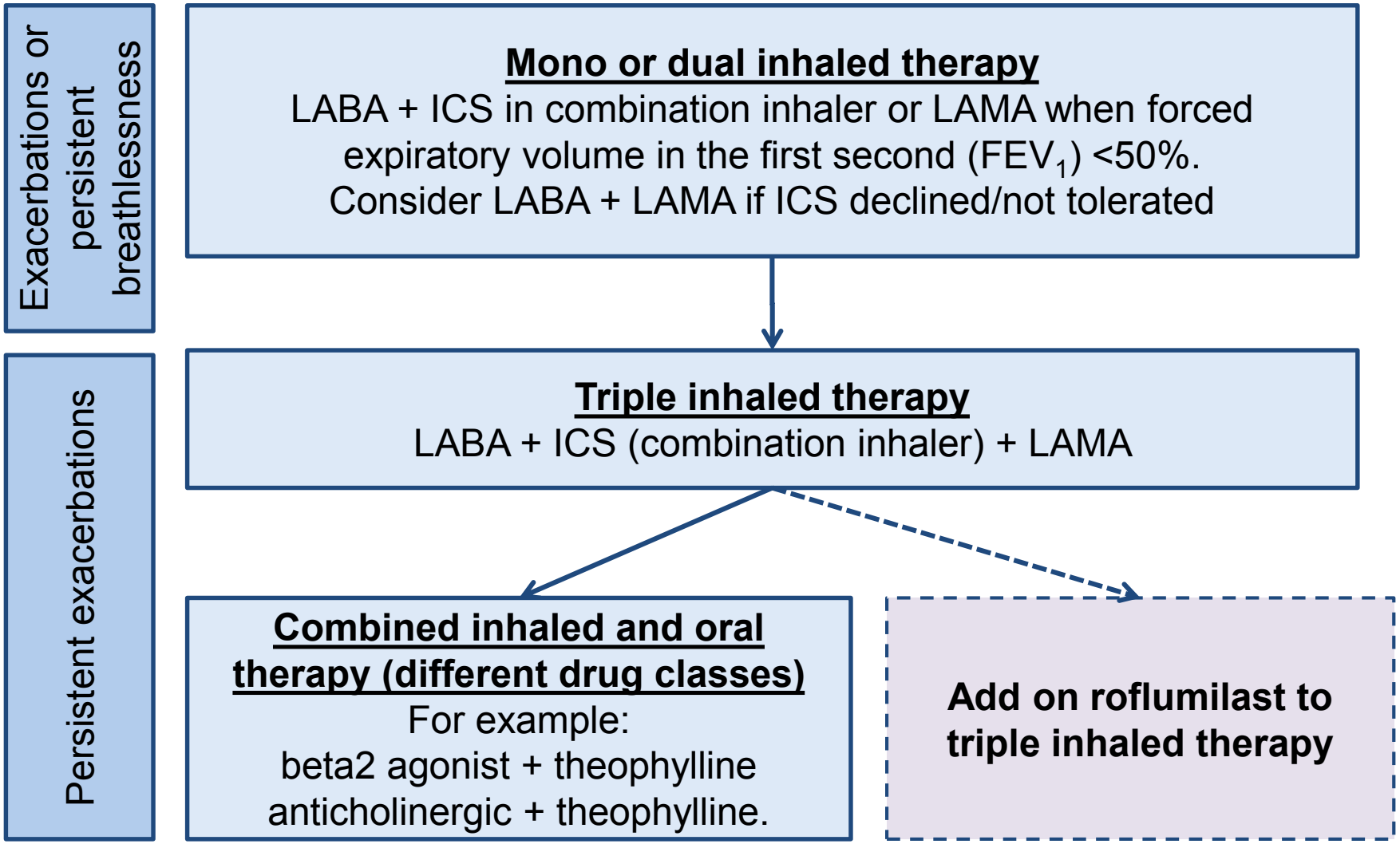
# Disease background

- Chronic obstructive pulmonary disease (COPD) includes chronic bronchitis and emphysema (and is also referred to chronic obstructive airways disease or chronic airflow limitation).
- COPD is characterised by chronic airways obstruction defined as a forced expiratory volume in 1 second ($FEV_1$) less than 80% predicted and a forced volume capacity ratio ($FEV_1$/FVC) less than 70%. Severe COPD is defined as a FEV1 less than 50%.
- Characteristic symptoms of COPD include chronic (and progressive) breathlessness, cough, and sputum production that can be variable from day-to-day.
- Approximately 1.2 million people in the UK have been diagnosed with COPD.
- The disease course is characterised by progressive worsening of airflow limitation over time with periodic acute exacerbations.
- Exacerbations are thought to contribute to disease burden, by accelerating disease progression and reducing quality of life. Exacerbations are also associated with an increased risk of death.

# Clinical management of severe COPD

- NICE clinical guideline on COPD (2010 update of 2004 guideline, due to be updated again) recommends smoking cessation and a number of treatment options including optimising inhaled therapy, oral therapy, pulmonary rehabilitation and long term oxygen therapy to manage stable COPD.
- NICE 2010 guideline did not include an update on the treatment of acute exacerbations.
- Some differences between NICE (2010) and GOLD (Global initiative for chronic obstructive lung disease) guidelines (2016) but main treatments options include:
  - Inhaled dual therapy such as long acting beta$_2$ agonist (LABA) + inhaled corticosteroid (ICS) or LABA + long acting muscarinic antagonist (LAMA) if ICS declined or not tolerated
  - Inhaled triple therapy with LABA + LAMA + ICS
  - Other alternative combination therapies including inhaled therapy and oral theophylline.

# NICE guidance on managing stable COPD with exacerbations




Source: NICE clinical guideline 101 (2010) - to be updated

# GOLD 2016 guideline on management of COPD

- GOLD classifies COPD disease severity (A–D) based on symptoms, exacerbation history and airway limitation.
- Company suggest GOLD categories C & D relevant ($FEV_1$ <50% predicted)
  - Group C have few symptoms but a high risk of exacerbations
  - Group D have many symptoms and high risk, based on either severe airflow limitation or frequent exacerbations.

| GOLD | First line | Alternative choice | Other possible treatments |
|---|---|---|---|
| C | ICS + LABA **or** LAMA | LABA + LAMA **or** LABA + phosphodiesterase-4 (PDE4) inhibitor **or** LAMA + PDE4 | Short acting $beta_2$ agonist (SABA) **and/or** short acting muscarinic antagonist (SAMA) as required; Theophylline |
| D | ICS + LABA and / or LAMA | ICS + LABA + LAMA **or** ICS + LABA + PDE4 **or** LABA + LAMA **or** LAMA / PDE4 | Carbocysteine; N-acetycysteine; SABA **and / or** SAMA as required; Theophylline |

Source: Table 6 from company submission

# Roflumilast

| | |
|---|---|
| UK Marketing authorisation | Maintenance treatment of severe COPD ($FEV_1$ <50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add on to bronchodilator treatment. |
| Mode of administration | Administered as an oral therapy. |
| Mechanism of action | Long-acting selective PDE4 enzyme inhibitor with anti-inflammatory activity (inflammation thought to be important in COPD). |
| Dosage | The recommended dose is 500 micrograms (one tablet) roflumilast once daily. |
| Cost | • £37.71 per pack of 30 tablets, list price (BNF, edition 67)<br>• Cost per year of treatment £458.88<br>• No patient access scheme |
| Eligible population | Company estimates 122,391 people in England may be eligible for treatment with roflumilast. |

# Patient Issues

- No submissions from patient groups were received

# Decision problem

| | **NICE scope** | **Company's decision problem** |
|---|---|---|
| Population | Adults with severe COPD ($FEV_1$ <50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations | Adults with severe COPD ($FEV_1$ <50% predicted) associated with chronic bronchitis and a history of frequent exacerbations (≥2 exacerbations in prior 12 months) despite triple therapy with LABA + LAMA + ICS |
| Intervention | Roflumilast plus maintenance bronchodilator treatment - single or double/triple therapy (LABA or LAMA alone or combined with ICS, LAMA plus LABA if ICS not tolerated) | Roflumilast in combination with maintenance triple therapy: LABA + LAMA + ICS |
| Comparator | • LAMA in combination with LABA and ICS<br>• LAMA + LABA<br>• LAMA or LABA (with or without ICS)<br>• Theophylline plus inhaled maintenance bronchodilator | LAMA in combination with LABA and ICS (LABA + LAMA + ICS)<br>As the scope of intervention is restricted to roflumilast in combination with LABA + LAMA + ICS, mono- and dual therapy comparators were not considered relevant |

# Decision problem

| | **NICE scope** | **Company's decision problem** |
|---|---|---|
| Outcomes | • lung function<br>• symptom control (e.g. shortness of breath)<br>• health-related quality of life<br>• incidence and severity of acute exacerbations, including hospitalisation<br>• mortality<br>• adverse effects of treatment | • lung function as measured by $FEV_1$<br>• health related quality of life<br>• rate of moderate to severe exacerbations (including hospitalisation)<br>• rate of severe exacerbations (requiring hospitalisation)<br>• mortality<br>• adverse effects of treatment |
| Subgroups | None | None |

# Rationale for differences in scope vs. decision problem

- Company seeking recommendation for the use of roflumilast as add-on to triple therapy (LAMA + LABA + ICS) in patients with severe COPD ($FEV_1$< 50% predicted), symptoms of chronic bronchitis and frequent exacerbations (≥ 2 / year).
- Therefore the company excluded some treatments as comparators:
  - monotherapy and dual therapy (for example LAMA or LABA alone, LABA + LAMA) are outside of the company's decision problem as appraisal restricted to add on to triple therapy
  - theophylline use is low in UK (particularly as add on to triple therapy), there are serious treatment limiting side effects (seizures and cardiac arrhythmias) and it is difficult to use (requires monitoring of plasma levels with higher doses).

# Evidence review group's (ERG) comments

- Company's proposed population is more restricted compared with NICE scope and many interventions and comparators listed in the scope have been excluded.
  - Difficult for NICE to issue guidance for any treatment involving roflumilast, other than roflumilast in combination with triple therapy (LABA plus LAMA plus ICS).
  - Is it reasonable not to consider mono and dual therapy as comparators?
  - Theophylline clearly specified by NICE in the scope as a relevant comparator and ERG does not agree with rationale for excluding.
  - There is evidence to compare roflumilast in combination with dual or triple therapy to most of the comparators listed in scope using indirect comparison.

# Company's clinical effectiveness trials

- 3 trials identified by the company:
  - **REACT**: multicentre double blind randomised controlled trial comparing roflumilast vs. placebo as add on to LABA + ICS (with or without LAMA) in people with severe COPD, including in the UK. Pre-specified subgroup (those having triple therapy) identified by company as most relevant.
  - **RE²SPOND**: similar to REACT but LABA + ICS dosing according to FDA licence, low number of Western European patients (n=13), less than half (47%, n=1,094 of 2352 in the safety population) were on triple therapy, and used FDA rather than EMA approved formulation of roflumilast. Not considered to be aligned with UK practice and therefore not presented in detail.
  - Randomised controlled study (open label) presented in conference abstract but authors did not provide information. Not discussed further in submission.

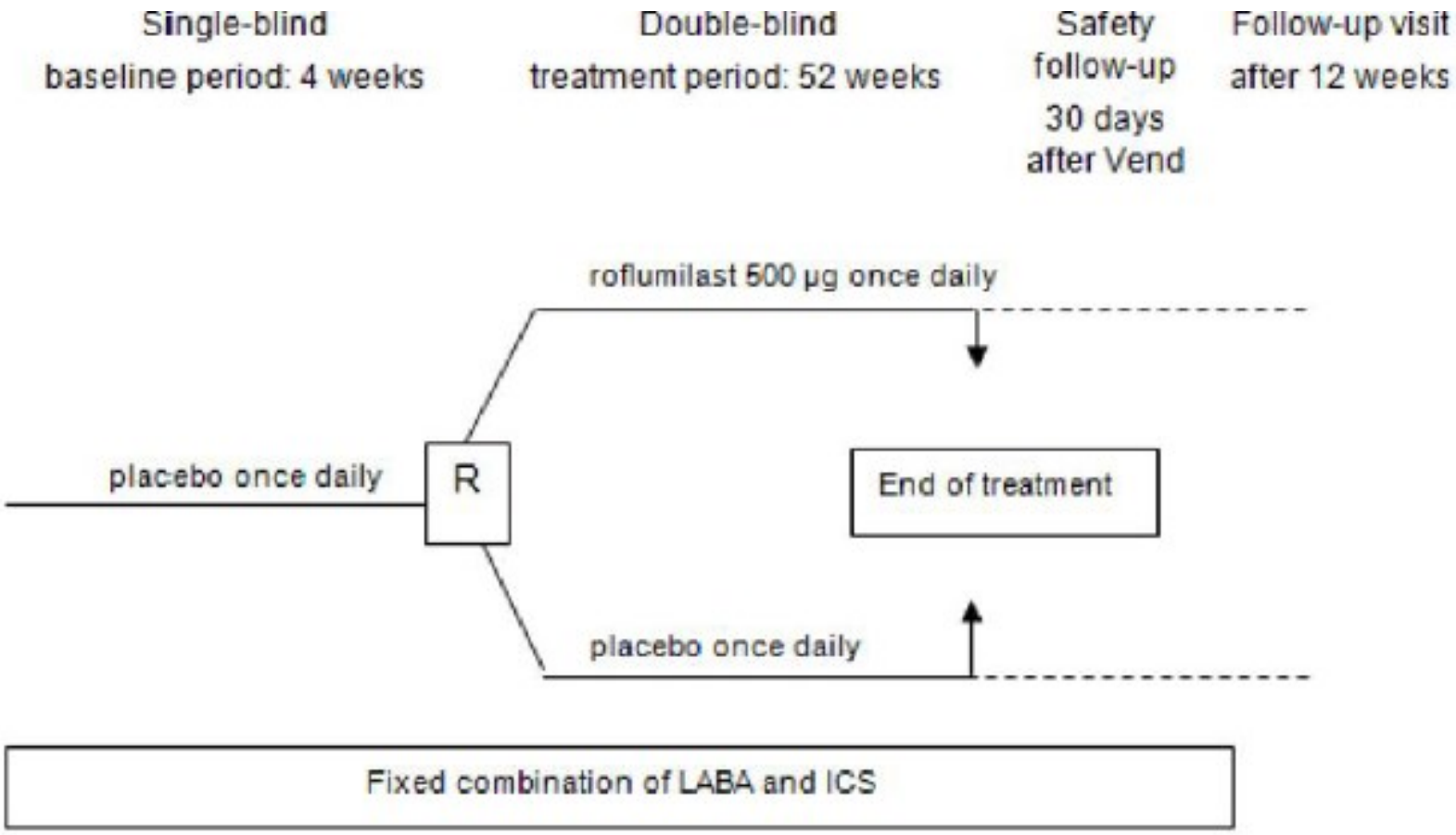
# ERG's comments on the clinical trials

- RE$^2$SPOND trial is also relevant to the decision problem and similar enough to REACT trial to pool results.

| Design | REACT trial | RE$^2$SPOND trial |
|---|---|---|
| Population | 1,935 in ITT analysis | 2,352 in safety population |
| Treatment | 500 µg roflumilast or placebo + fixed dose combination of ICS/LABA (no limit to the % of participants allowed LAMA) | 500 µg roflumilast or placebo + fixed dose combination of ICS/LABA (+ up to 60% of participants allowed LAMA) |
| LABA + ICS dose | fluticasone/salmeterol 500/50 µg or 250/50 µg (1 inhalation twice daily) | fluticasone/salmeterol 250/50 µg (1 inhalation twice daily) |
| Roflumilast formulation | Film-coated tablets | Uncoated tablets |
| Definition of primary outcome | Moderate: required oral/parenteral corticosteroid treatment<br>Severe: resulting in hospitalisation and/or leading to death<br>Exacerbations occurring within 10 days counted as 1 exacerbation | |

Source: Table 4.14 in ERG report

# REACT trial design




R; Randomisation, Vend; end of treatment period

Source: Figure 3 in company submission

# REACT trial

| Parameter | Description |
|---|---|
| | |
| **Inclusion criteria** | History of COPD associated with chronic bronchitis, $FEV_1$ ≤ 50% predicted, age ≥ 40 years, smoking history ≥ 20 pack-years, history of ≥ 2 moderate or severe exacerbations in the previous year, pre-treated with ICS and LABA for at least 12 months before baseline; and at a constant dose |
| | |
| **Trial design** | 1 year prospective, multicentre, phase 3-4 trial (double blind) |
| | |
| **Primary outcomes** | Rate of moderate or severe COPD exacerbations per patient per year (moderate exacerbations defined as requiring oral or parenteral glucocorticosteroids and severe exacerbations as requiring hospitalisations and/or leading to death) |
| | |

Table 10 in company submission

# RE²SPOND trial

| Parameter | Description |
|---|---|
| | |
| **Inclusion criteria** | Eligible participants were 40 years of age or older with severe to very severe COPD, chronic bronchitis, two or more exacerbations and/or hospitalisations in the previous year, and were receiving ICS/LABA with or without LAMA daily for 3 months or longer. Participants had to remain on the same COPD maintenance treatment from screening through randomisation. |
| | |
| **Trial design** | 1 year prospective, multicentre, phase 4 trial (double blind) |
| | |
| **Primary outcomes** | Rate of moderate or severe COPD exacerbations per patient per year (moderate exacerbations defined as those that required oral or parenteral corticosteroid treatment and severe exacerbations as those that resulted in hospitalization and/or led to death). |
| | |

# Baseline characteristics in REACT and RE²SPOND trials

| | REACT trial | | RE²SPOND trial | |
|---|---|---|---|---|
| **Baseline characteristic** | **Roflumilast (n=969)** | **Placebo (n=966)** | **Roflumilast (n=1,178)** | **Placebo (n=1,174)** |
| **Age (years), mean (SD)** | 65 (8.4) | 65 (8.4) | 64.4 (8.8) | 64.5 (8.4) |
| **Male** | 718 (74) | 725 (75) | 821 (70) | 794 (68) |
| **Current smoker** | 411 (42) | 432 (45) | 462 (39) | 464 (40) |
| **Moderate COPD** | 18 (2) | 16 (2) | 1 (<1) | 0 |
| **Severe COPD** | 658 (68) | 677 (70) | 697 (59) | 720 (61) |
| **Very Severe COPD** | 291 (30) | 273 (28) | 474 (40) | 446 (38) |
| **% predicted post-bronchodilator FEV1, mean (SD)** | 35.4 (9.25) | 35.5 (8.76) | 33.00 (9.04) | 32.97 (8.88) |
| **2 exacerbations in past year** | 855 (88) | 859 (89) | 874 (74) | 876 (75) |
| **>2 exacerbations in past year** | 103 (11) | 100 (10) | 291 (25) | 288 (25) |
| Unless specified data is reported as number of participants (%) | | | | |

Source: Table 4.15 in ERG report

# Company's analysis of data from REACT

**LAMA subgroup**

- Company identified the pre-specified subgroup of patients having triple therapy (LABA + LAMA + ICS) as the most relevant:
  - 70% (677/969) in roflumilast group and 69% (669/966) in placebo group

**Population included in analysis**

- Per protocol (PP) analysis considered to be most relevant because the intention to treat (ITT) population included a substantial proportion of patients with protocol violations (e.g. $FEV_1$>50%, fewer than 2 exacerbations, not treated with ICS + LABA for prior year).
  - PP population reduces the number of patients to 1,122 (58% of the total ITT population)

**Statistical model**

- Poisson regression model was prespecified for the primary endpoint but a negative binomial model was considered more appropriate as the low event rate reduced study power and allows different exacerbation rates across patients (risk of exacerbation differs in COPD patients).

# ERG's comments - analysis of data from REACT

**LAMA subgroup**

- Cannot assess whether this subgroup analysis was pre-specified (prospective). Clinical study report describes "concomitant treatment with LAMA" as a post-hoc (retrospective) analysis.
- Increased number of statistical test increases risk of false positive.
- Baseline characteristics in LAMA subgroup appear well balanced but lack of randomisation may lead to imbalances in other unreported characteristics.

**Population included in analysis**

- ITT population provides the most reliable and unbiased estimate of treatment effect as excluding patients with major protocol violations (312 of 1,945 patients randomised) may introduce bias.
- PP analysis not based on randomised allocation and reasons for stopping treatment may be associated with allocated treatment.
- REACT pre-specified analyses using ITT population for all outcomes including subgroups (PP analyses used to assess robustness).

**Statistical model**

- Negative binomial model likely to be appropriate and better fitting compared with Poisson. Choice of model has only a marginal impact on the results.

# Summary of results from REACT

| | **Intention to treat in all patients (n=1,935)**<br>**Primary analysis** | **Per protocol analysis in LAMA subgroup (n=1,122)**<br>**Company's preferred data** | **Intention to treat analysis in LAMA subgroup (n=1,346)**<br>**ERG's preferred data** |
|---|---|---|---|
| Moderate to severe exacerbation rate (95% confidence interval) | | | |
| Rate roflumilast | 0.805 (0.724 to 0.895) | 0.858 (0.754 to 0.978) | 0.924 (0.821 to 1.040) |
| Rate placebo | 0.927 (0.843 to 1.020) | 1.075 (0.954 to 1.211) | 1.061 (0.950 to 1.185) |
| **Rate ratio (RR)** | **0.868 (0.753 to 1.002)*** | **0.799 (0.670 to 0.952)** | **0.871 (0.741 to 1.024)** |
| Severe exacerbation rate (95% confidence interval) | | | |
| Rate roflumilast | 0.239 (0.201 to 0.283) | 0.260 (0.21 to 0.322) | 0.287 (0.237 to 0.347) |
| Rate placebo | 0.315 (0.270 to 0.368) | 0.395 (0.329 to 0.475) | 0.374 (0.315 to 0.443) |
| **RR** | **0.757 (0.601 to 0.952)**** | **0.659 (0.497 to 0.872)** | **0.767 (0.595 to 0.989)** |
| Moderate exacerbation rate (95% confidence interval) | | | |
| Rate roflumilast | Not reported | 0.593 (0.511 to 0.689) | 0.631 (0.550 to 0.725) |
| Rate placebo | | 0.669 (0.582 to 0.769) | 0.676 (0.564 to 0.770) |
| **RR** | | **0.886 (0.722 to 1.087)** | **0.934 (0.773 to 1.128)** |
| NB: Rates are per patient year. Company and ERG preferred data are from negative binomial model. * from Poisson model; ** from negative binomial model | | | |

# ERG's comments on the clinical data

## Results from REACT and RE²SPOND in all patients

- RE²SPOND trial results are also relevant to the decision problem

| Outcome | REACT trial RR (95% CI) | RE²SPOND trial RR (95% CI) |
|---|---|---|
| Moderate to severe exacerbations (primary endpoint)* | 0.87 (0.75 to 1.00) | 0.92 (0.81 to 1.04) |
| Moderate to severe exacerbations per participant per year (sensitivity analysis)† | 0.86 (0.74 to 0.995) | Not applicable |
| Severe exacerbations† | 0.76 (0.60 to 0.95) | 0.95 (0.75 to 1.19) |
| Moderate or severe or antibiotic-treated exacerbations* | 0.84 (0.74 to 0.95) | 0.90 (0.80 to 1.02) |
| Severe exacerbations in participants with a prior history of hospitalisation† | 0.65 (0.48 to 0.89) | 0.79 (0.56 to 1.10) |
| *analysed using Poisson model in ITT population in REACT and negative binomial model in ITT population in RE²SPOND<br>† analysed using negative binomial model in ITT population in REACT and RE²SPOND | | |

Source: Table 4.16 in ERG report

# ERG's comments on the clinical data

- Company's preferred clinical effectiveness results (based on LAMA subgroup of REACT trial using per protocol population and negative binomial model) favour roflumilast disproportionately.
- ERG disagrees with using REACT only data and the per protocol analysis
  - considers pooled REACT and RE$^2$SPOND estimates for the ITT LAMA subgroup to be the most reliable
  - for moderate to severe exacerbations, this results in a rate ratio for roflumilast compared with placebo of 0.90 (95% confidence interval [CI] 0.80 to 1.02) compared with the company's preferred result of 0.799 (95% CI 0.670 to 0.952)

# Adverse events – all patients in REACT

- 67% of patients in roflumilast group and 59% of patients in placebo group reported adverse events.
- Serious adverse events were reported by 26% of patients in the roflumilast group and 30% in placebo group.
- Most reactions reported were mild or moderate and occurred mainly in the first weeks of therapy and mostly resolved on continued treatment.
- Most common events in roflumilast group were diarrhoea (10% vs 4% in the placebo arm), weight decrease (9% vs 3%) and nausea (6% vs 2%).
- No increase in the incidence of pneumonia or other pulmonary infections during treatment with roflumilast (4%) compared with placebo (5%).

# Key safety outcomes - REACT

- Body weight - pre-specified safety endpoint (mean weight loss in roflumilast group 2.65 kg [SD 4.37 kg] compared with 0.15 kg [SD 3.69 kg] in placebo). Consistent with previous studies.
  - During the 12 week end of treatment follow up period, 6% (37/657) of patients continued on commercial roflumilast. Bodyweight partially recovered in patients who discontinued roflumilast and appeared relatively stable in those who continued on commercial roflumilast.
- Other safety outcomes included mortality and major adverse cardiovascular events (2% in both groups).
- CHMP flagged psychiatric disorders as potential safety concern. In REACT study depression was reported by 2% of patients in roflumilast group vs. 1.1%  in placebo.

Source: Table 21 in company submission

# Indirect comparison

- Company searched for studies to carry out an indirect comparison to incorporate all potential comparators in the severe to very severe COPD population.
- None of the 10 trials identified were considered relevant and an indirect comparison was not carried out
  - study by Cosio (2016) highlighted as potentially relevant (theophylline + ICS + LABA compared with LABA + ICS) but discarded because theophylline not considered a relevant comparator (although was in NICE Decision Problem).
- ERG state that an indirect comparison is possible when including comparators from NICE scope
  - appraisal committee to decide whether these analyses are relevant for the decision problem.

# Key issues: clinical effectiveness

- This appraisal is about the role of roflumilast in addition to inhaled and other therapies in the treatment of adults with severe COPD associated with frequent exacerbations
- Does the committee agree with the company's decision to exclude single and double inhaler therapy, and oral theophylline treatment, as comparators i.e. can the appraisal be restricted to adding roflumilast to inhaled triple therapy?
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