NICE advice

# Chronic obstructive pulmonary disease: beclometasone, formoterol and glycopyrronium (Trimbow)

Evidence summary
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## Key points

The content of this evidence summary was up-to-date in May 2018. See summaries of product characteristics (SPCs), British national formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) or NICE websites for up-to-date information.

**Regulatory status:** Beclometasone/formoterol/glycopyrronium (Trimbow, Chiesi Limited) received a European marketing authorisation in July 2017. This triple-therapy inhaler contains an inhaled corticosteroid (ICS), long-acting beta-2 agonist (LABA) and long-acting muscarinic antagonist (LAMA). It is licensed for maintenance treatment of adults with moderate-to-severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an ICS and a LABA.

### Overview

This evidence summary discusses 3 randomised controlled trials (TRILOGY, TRINITY and TRIBUTE) looking at the safety and efficacy of beclometasone/formoterol/glycopyrronium in people with COPD with severe or very severe airflow limitation, symptoms despite treatment and a history of exacerbations.

Overall, the studies found small, statistically significant improvements in lung function, rates of moderate-to-severe exacerbations of COPD and health-related quality-of-life scores with beclometasone/formoterol/glycopyrronium compared with beclometasone/formoterol or indacaterol/glycopyrronium dual therapy, or tiotropium alone. The improvements may be of limited clinical importance.

In TRILOGY and TRINITY, improvements in primary outcomes relating to lung function and exacerbation rates just reached the level considered to be clinically important. For example, triple therapy with beclometasone/formoterol/glycopyrronium improved:

- pre-dose forced expiratory volume in 1 second ($FEV_1$) by 0.081 litre more than dual therapy with beclometasone/formoterol over 26 weeks, and
- the rate of moderate-to-severe exacerbations by 0.1 exacerbation per year compared with tiotropium over 52 weeks.

In TRIBUTE, the rate of moderate-to-severe exacerbations was reduced with beclometasone/formoterol/glycopyrronium compared with indacaterol/glycopyrronium. However, although the difference between the groups was statistically significant, it did not reach the level considered to be clinically important. There were few significant differences between the treatment groups for other outcomes in this study.

Beclometasone/formoterol/glycopyrronium did not improve symptoms of dyspnoea significantly more than beclometasone/formoterol. However, responder analyses showed that more people had a clinically important improvement in symptoms and health-related quality of life with triple therapy compared with dual therapy. Fixed triple therapy with a single beclometasone/formoterol/glycopyrronium inhaler was found to be similar to open triple therapy with beclometasone/formoterol plus tiotropium in 2 inhalers for all outcomes.

The adverse effect profile of beclometasone/formoterol/glycopyrronium is well understood because the active ingredients have been used for many years, alone and in combination. From the studies, there was no evidence that the safety of this triple therapy is worse than that of any of the comparators used in the 3 studies. The most frequently reported adverse effects included oral candidiasis, muscle spasms and dry mouth.

Beclometasone/formoterol/glycopyrronium may be an option for some people with moderate-to-severe COPD who have found triple therapy beneficial using more than 1 inhaler and can use a pressurised metered dose inhaler (with or without a spacer), but who have difficulty using multiple inhalers.

A summary to inform local decision-making is shown in table 1.

**Table 1 Summary of the evidence on effectiveness, safety, patient factors and resource implications**

**Effectiveness**

- In TRILOGY (Singh D et al. 2016), at week 26, triple therapy with beclometasone/formoterol/glycopyrronium improved **pre-dose $FEV_1$** (a co-primary outcome) compared with beclometasone/formoterol (adjusted mean difference 0.081 litre, 95% confidence interval [CI] 0.052 litre to 0.109 litre; p<0.001). Although general consensus is that an improvement below 0.100 litre is not clinically important, the European regulators (the European Medicines Agency) considered that 0.081 litre was a meaningful improvement in a population with severe COPD.

- In TRINITY (Vestbo J et al. 2017), at week 52, beclometasone/formoterol/glycopyrronium improved pre-dose $FEV_1$ (a secondary outcome) compared with tiotropium (adjusted mean difference 0.061 litre, 95% CI 0.037 litre to 0.086 litre; p<0.0001).

- In TRINITY, at week 52, fixed triple therapy with beclometasone/formoterol/glycopyrronium was found to be non-inferior to open triple therapy with beclometasone/formoterol and tiotropium for improving pre-dose $FEV_1$ (adjusted mean difference −0.003 litre, 95% CI −0.033 litre to 0.027 litre; p=0.85).

- In TRIBUTE, beclometasone/formoterol/glycopyrronium improved pre-dose $FEV_1$ (a secondary outcome) compared with indacaterol/glycopyrronium at some but not all time points. Averaged over 52 weeks, the mean improvement from baseline with the triple therapy compared with the dual therapy was 0.022 litre, which reached statistical significance (p<0.05).

- In TRILOGY, at week 26, there was no statistically significant difference between beclometasone/formoterol/glycopyrronium and beclometasone/formoterol in improvement in **Transition Dyspnoea Index (TDI) focal scores** (a co-primary outcome; p=0.160).

- TDI scores were not investigated in TRINITY or TRIBUTE.

- In TRILOGY, the rate of **moderate-to-severe exacerbations** was reduced by a relative 23% over 52 weeks with beclometasone/formoterol/glycopyrronium compared with beclometasone/formoterol (annualised rate 0.41 compared with 0.53 respectively; rate ratio [RR] 0.77, 95% CI 0.65 to 0.92; p=0.005).

- In TRINITY, beclometasone/formoterol/glycopyrronium reduced the rate of moderate-to-severe exacerbations by a relative 20% over 52 weeks compared with tiotropium alone (the

primary outcome; annualised rate 0.46 compared with 0.57 respectively; RR 0.80, 95% CI 0.69 to 0.92; p=0.0025).

- A 20% reduction in exacerbations was considered clinically important by the European Medicines Agency.
- In TRIBUTE, beclometasone/formoterol/glycopyrronium reduced the rate of moderate-to-severe exacerbations by 15% over 52 weeks compared with indacaterol/glycopyrronium (the primary outcome; annualised rate 0.50 compared with 0.59 respectively; RR 0.85, 95% CI 0.72 to 0.99; p=0.043). This reduction is **not** considered clinically important according to the criterion used by the European Medicines Agency. There were no significant differences between the groups for other exacerbation outcomes.
- **Responder analyses** in TRILOGY and TRINITY showed statistically significant, clinically important improvements in pre-dose $FEV_1$, symptoms of dyspnoea (TDI focal scores) and health-related quality of life (St George's Respiratory Questionnaire [SGRQ] scores) with triple therapy compared with dual or monotherapy.
- In TRIBUTE, there were no statistically significant differences between the groups in responder analyses for pre-dose $FEV_1$ or SGRQ scores.
- The use of **rescue medication** in puffs per day and the proportion of days without rescue medication were also significantly improved with triple therapy compared with dual or monotherapy in TRILOGY and TRINITY, but not TRIBUTE. These beneficial effects were not seen after 26 weeks in TRILOGY.

Safety

- The adverse effect profile of beclometasone/formoterol/glycopyrronium is well understood. None of the active substances are new and all have been used for many years, individually and in combination, for treating people with COPD of various grades of severity.
- The European public assessment report concludes that the known adverse events and serious adverse events of the active substances were of a frequency and nature to be expected, and can all be considered reversible with change or modification of treatment.
- The most frequent adverse effects (in 0.5% of people) include oral candidiasis, muscle spasms and dry mouth.
- Based on recommendations from the MHRA, the NICE guideline on COPD advises clinicians to be aware of the potential risk of developing adverse effects, including non-fatal pneumonia, in people with COPD treated with inhaled corticosteroids.

Patient factors

- The results of the studies may not apply to people with mild-to-moderate COPD, and it is unclear if benefits outweigh the risks in this population.
- People who had asthma, allergic rhinitis or atopy, clinically significant cardiovascular conditions or laboratory abnormalities, or unstable concurrent disease were excluded from TRILOGY and TRINITY, as were people with COPD exacerbations in the 4 weeks before screening or during the run-in period. Some of these populations were also excluded from TRIBUTE. The results of the studies therefore may not apply to the excluded populations.
- At baseline, study participants had, on average, only 1 exacerbation per year. The results of the studies may not apply to people who have more frequent exacerbations.
- Other than beclometasone/formoterol, tiotropium and indacaterol/glycopyrronium, it is not known how the efficacy and safety of triple therapy compares with other treatments for COPD, such as other combinations of ICS/LABA (alone or with a separate long-acting muscarinic antagonist [LAMA]) or other LABA/LAMAs.
- It is not known from the studies whether the fixed triple-therapy inhaler has any advantages over open triple therapy in terms of patient factors such as preference, adherence to treatment and ease of use of the device.
- Triple therapy in a single inhaler may be preferable for people who have difficulty using more than 1 device or who find their medication regimen difficult or confusing, and have trouble complying with treatment. However, triple therapy lacks flexibility and makes it difficult to amend the individual medicines if treatment needs changing for any reason.
- Some people may prefer a particular inhaler device or be able to use one device better than another. Some people with COPD are unable to use a spacer, others like to use one.
- Beclometasone/formoterol/glycopyrronium has not been compared with the triple-therapy inhaler containing fluticasone/umeclidinium/vilanterol.
- Beclometasone/formoterol/glycopyrronium is supplied in a pressurised metered dose inhaler and can be used with a spacer.
- Fluticasone/umeclidinium/vilanterol is supplied in a dry powder inhaler and cannot be used with a spacer.

- Beclometasone/formoterol/glycopyrronium is administered twice daily and fluticasone/umeclidinium/vilanterol is administered once daily.

**Resource implications**

- The acquisition cost of beclometasone/formoterol/glycopyrronium (Trimbow) is less than that of other combinations of ICS/LABA plus LAMA in 2 inhalers.
- A 30-day supply of treatment with beclometasone, formoterol and glycopyrronium costs £44.50 (excluding VAT) when the triple-therapy inhaler (Trimbow) is prescribed. This compares with £56.82 (excluding VAT) when beclometasone and formoterol are prescribed in a dual-therapy inhaler (Fostair or Fostair NEXThaler) and glycopyrronium in a monotherapy inhaler (Seebri Breezhaler).
- Triple therapy with beclometasone/formoterol/glycopyrronium (Trimbow) costs the same as triple therapy with fluticasone/umeclidinium/vilanterol (Trelegy; costs taken from the Drug Tariff and MIMS, March 2018).

## Introduction and current guidance

The NICE guideline on chronic obstructive pulmonary disease (COPD) is currently being updated (expected publication date November 2018). The current COPD guideline states that COPD is characterised by airflow obstruction that is usually progressive and not fully reversible, and is predominantly caused by smoking. COPD causes symptoms, disability and impaired quality of life, which may respond to pharmacological and other therapies that have limited or no measurable impact on the airflow obstruction. Exacerbations often occur, during which there is a rapid and sustained worsening of symptoms beyond normal day-to-day variations.

The current NICE guideline includes the following recommendations on using inhaled therapy for managing stable COPD:

- Short-acting bronchodilators, as necessary, should be the initial empirical treatment for the relief of breathlessness and exercise limitation.
- In people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as needed, the following should be offered as maintenance therapy:
    - if forced expired volume in 1 second ($FEV_1$) is 50% predicted or more: either a long-acting beta-2 agonist (LABA) or a long-acting muscarinic antagonist (LAMA)

  - if $FEV_1$ is less than 50% predicted: either a LABA with an inhaled corticosteroid (ICS) in a combination inhaler, or a LAMA. A LAMA should be considered in addition to a LABA if an ICS is declined or not tolerated.

- In people with stable COPD and an $FEV_1$ of 50% predicted or more who remain breathless or have exacerbations despite maintenance therapy with a LABA:
  - a LABA with an ICS in a combination inhaler should be considered
  - a LAMA in addition to a LABA should be considered where an ICS is declined or not tolerated.
- In people with COPD who remain breathless or have exacerbations despite using a LABA with an ICS, a LAMA should be offered in addition to the LABA and ICS, irrespective of $FEV_1$.
- A LABA with an ICS in a combination inhaler should be considered in addition to a LAMA for people with stable COPD who remain breathless or have exacerbations despite maintenance therapy with the LAMA, irrespective of $FEV_1$.
- The choice of medication should take into account the person's symptomatic response and preference, and the medicine's potential to reduce exacerbations, its side effects and its cost.

The NICE guideline on COPD was published in 2010, which was before any of the LABA/LAMA or ICS/LABA/LAMA combination inhalers were available in the UK. Following a recent review of the evidence, the guideline is being updated (expected publication date November 2018), although triple-therapy inhalers will not be included.

This evidence summary discusses the best available evidence for the safety and efficacy of the triple combination inhaler containing beclometasone (ICS), formoterol (LABA) and glycopyrronium (LAMA; Trimbow).

## Product overview

### *Mode of action*

Trimbow (Chiesi Limited) contains beclometasone dipropionate, formoterol fumarate dihydrate and glycopyrronium bromide. Beclometasone dipropionate is an inhaled corticosteroid (ICS), which suppresses inflammation in the lungs; formoterol fumarate dihydrate is a long-acting beta-2 agonist (LABA), which relaxes bronchial smooth muscle in people with reversible airways obstruction; and glycopyrronium bromide is a long-acting muscarinic antagonist (LAMA), which

blocks the bronchoconstrictor action of acetylcholine on airway smooth muscle cells, thereby dilating the airways (summary of product characteristics).

## *Regulatory status*

Beclometasone/formoterol/glycopyrronium (Trimbow) received a European marketing authorisation in July 2017. It is licensed for maintenance treatment of adults with moderate-to-severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an ICS and a LABA (European public assessment report).

## *Dosing information*

According to the summary of product characteristics, each delivered dose of beclometasone/formoterol/glycopyrronium (the dose leaving the mouthpiece) contains 87 micrograms of beclometasone dipropionate, 5 micrograms of formoterol fumarate dihydrate and 9 micrograms of glycopyrronium (as 11 micrograms glycopyrronium bromide). Each metered dose (the dose leaving the valve to be inhaled by the person) contains 100 micrograms of beclometasone dipropionate, 6 micrograms of formoterol fumarate dihydrate and 10 micrograms of glycopyrronium (as 12.5 micrograms glycopyrronium bromide).

The aerosol particles of beclometasone/formoterol/glycopyrronium are extrafine and, on average, much smaller than the particles delivered in non-extrafine formulations. For beclometasone dipropionate, this results in a more potent effect than formulations with a non-extrafine particle size distribution (100 micrograms of beclometasone dipropionate extrafine in Trimbow are equivalent to 250 micrograms of beclometasone dipropionate in a non-extrafine formulation).

The recommended (and maximum) dose of beclometasone/formoterol/glycopyrronium is 2 inhalations twice daily.

## *Cost*

A beclometasone/formoterol/glycopyrronium pressurised metered dose inhaler costs £44.50 and provides 120 inhalations (30 days' treatment; cost [excluding VAT] from MIMS, March 2018).

## Evidence review

A literature search was conducted which identified 90 references (see search strategy for full details). These references were screened using their titles and abstracts and 4 references were obtained and assessed for relevance.

Two randomised controlled trials (RCTs) identified from the search (Singh D et al. 2016 [TRILOGY] and Vestbo J et al. 2017 [TRINITY]) were included in this evidence summary. A further study was published after the searches were undertaken and was also included (Papi A et al. 2018 [TRIBUTE]). A summary of the included studies is shown in table 2 (see evidence tables for full details).

**Table 2 Summary of included studies**

| Study | Population | Intervention and comparison | Primary outcomes |
|---|---|---|---|
| Singh D et al. (2016) (TRILOGY)<br>RCT<br>159 sites in 14 countries | 1,368 adults aged ≥40 years with COPD and<br>• post-bronchodilator $FEV_1$ <50%<br>• $FEV_1$/FVC <0.7<br>• ≥1 moderate or severe exacerbation[a] in the last 12 months<br>• symptomatic despite treatment with ICS/LABA, ICS/LAMA, LABA/LAMA or LAMA monotherapy. | Triple therapy with beclometasone/formoterol/glycopyrronium bromide (100/6/12.5 micrograms) in a single metered dose inhaler (n=687)<br>versus<br>dual therapy with beclometasone/formoterol (100/6 micrograms) in a single matching metered dose inhaler (n=681[b]).<br>Both 2 puffs twice daily for 52 weeks. | Co-primary outcomes (assessed at week 26):<br>• change from baseline in pre-dose (morning) $FEV_1$<br>• change from baseline in 2-hour post-dose $FEV_1$ and<br>• TDI focal score (change in dyspnoea severity from baseline. |

| | | | |
|---|---|---|---|
| Vestbo J et al. (2017) (TRINITY)<br>RCT<br>224 sites in 15 countries | 2,691 adults aged ≥40 years with COPD and<br>• post-bronchodilator $FEV_1$ <50%<br>• $FEV_1$/FVC <0.7<br>• ≥1 moderate or severe exacerbation[a] in the last 12 months<br>• symptomatic despite treatment with ICS/LABA, ICS/LAMA, LABA/LAMA or LAMA monotherapy. | Fixed triple therapy with beclometasone/formoterol/glycopyrronium bromide (100/6/12.5 micrograms) in a single metered dose inhaler plus a dummy dry powder inhaler (n=1,078[b])<br>versus<br>tiotropium (18 micrograms) in a dry powder inhaler plus a dummy metered dose inhaler (n=1,075[c])<br>and<br>open triple therapy with beclometasone/formoterol (100/6 micrograms) in a metered dose inhaler plus tiotropium (18 micrograms) in a dry powder inhaler (n=538[b]).<br>2 puffs twice daily for the metered dose inhalers and 1 puff daily for the dry powder inhalers for 52 weeks. | Moderate-to-severe COPD exacerbation frequency over 52 weeks of treatment for fixed triple therapy versus tiotropium. |

| | | | |
|---|---|---|---|
| Papi A et al. 2018 (TRIBUTE)<br>RCT<br>187 sites in 17 countries | 1,532 adults aged ≥40 years with COPD and<br>• post-bronchodilator $FEV_1$ <50%<br>• $FEV_1$/FVC <0.7<br>• ≥1 moderate or severe exacerbation[a] in the last 12 months<br>• symptomatic despite treatment with ICS/LABA, ICS/LAMA, LABA/LAMA or LAMA monotherapy. | Triple therapy with beclometasone/formoterol/glycopyrronium bromide (100/6/12.5 micrograms) in a single metered dose inhaler plus a dummy dry powder inhaler (n=764)<br>versus<br>dual therapy with indacaterol/glycopyrronium bromide (110/63 micrograms) in a single matching dry powder inhaler plus a dummy metered dose inhaler (n=768).<br>2 puffs twice daily for the metered dose inhalers and 1 puff daily for the dry powder inhalers for 52 weeks. | Moderate-to-severe COPD exacerbation frequency over 52 weeks of treatment. |
| [a] Defined as sustained worsening of respiratory symptoms that required treatment with systemic corticosteroids and/or antibiotics or need for hospitalisation.<br>[b] 1 person did not receive the allocated therapy.<br>[c] 1 person received the first dose of study medication, but withdrew consent before providing any post-baseline data, and is included in the safety population but not the efficacy population. | | | |
| **Abbreviations:** COPD, chronic obstructive pulmonary disease; FVC, forced vital capacity; $FEV_1$, forced expiratory volume in 1 second; TDI, Transition Dyspnoea Index; RCT, randomised controlled trial. | | | |

The remaining 2 references were excluded. These are listed in excluded studies with reasons for their exclusion.

## *Clinical effectiveness*

An overview of the results for clinical effectiveness can be found in the results tables.

### Lung function

The **TRILOGY study** (Singh D et al. 2016) found that, at week 26, triple therapy with beclometasone/formoterol/glycopyrronium improved pre-dose forced expiratory volume in 1 second ($FEV_1$; a co-primary outcome) by 0.081 litre more than dual therapy with beclometasone/formoterol (0.082 litre compared with 0.001 litre respectively; 95% confidence interval [CI] 0.052 litre to 0.109 litre; p<0.001). The European public assessment report for beclometasone/formoterol/glycopyrronium states that, although there is no consensus statement on what constitutes a minimally clinical important difference for pre-dose $FEV_1$ for people with airflow obstruction, some published literature suggests a threshold of 0.100 litre for clinical trials may be appropriate. Also, a threshold for meaningful change is considered more meaningful for people with severe or very severe disease than for those with mild-to-moderate disease. In other words, small improvements in outcomes may be more noticeable for people with severe COPD than those with mild-to-moderate COPD. The Committee for Medicinal Products for Human Use (CHMP) concluded that, considering the severity of the condition of the target population, the improvement over baseline in pre-dose $FEV_1$ of 0.081 litres for beclometasone/formoterol/glycopyrronium compared with beclometasone/formoterol is a meaningful benefit for this population who had severe COPD.

In TRILOGY, 2-hour post-dose $FEV_1$ also improved more with triple therapy than with dual therapy at 26 weeks (a co-primary outcome), with a statistically significant difference between the groups (adjusted mean difference 0.117 litre, 95% CI 0.086 litre to 0.147 litre; p<0.001).

In responder analyses, pre-dose $FEV_1$ improved by at least 0.100 litre in more participants using triple therapy compared with dual therapy at weeks 26 and 52 (for example, 38% compared with 23% respectively at 52 weeks; odds ratio [OR] 2.06, 95% CI 1.62 to 2.62; p<0.001).

In the **TRINITY study** (Vestbo J et al. 2017), a bigger improvement in pre-dose $FEV_1$ (a secondary outcome) was seen with beclometasone/formoterol/glycopyrronium compared with tiotropium at week 52 (0.082 litre compared with 0.021 litre respectively; adjusted mean difference 0.061 litre, 95% CI 0.037 litre to 0.086 litre; p<0.0001) and the difference between the groups was statistically significant.

Fixed triple therapy with beclometasone/formoterol/glycopyrronium was found to be non-inferior to open triple therapy with beclometasone/formoterol and tiotropium (adjusted mean difference −0.003 litre, 95% CI −0.033 litre to 0.027 litre; p=0.85; the lower confidence interval is above the predefined non-inferiority margin of −0.050 litre).

Pre-dose $FEV_1$ improved by at least 0.100 litre in more participants using triple therapy compared with tiotropium at weeks 26 and 52 (both p<0.0001; see the results tables for more details). No statistically significant differences were seen between fixed and open triple therapy at either time point (p=0.69 and p=0.63 respectively).

In the **TRIBUTE study** (Papi A et al. 2018), a statistically significant improvement in pre-dose $FEV_1$ (a secondary outcome) was seen with beclometasone/formoterol/glycopyrronium compared with indacaterol/glycopyrronium at weeks 12 and 40 (both p<0.01), but not weeks 4, 26 and 52 (p values not reported). When averaged over 52 weeks, the mean improvement from baseline with the triple therapy compared with the dual therapy was 0.022 litre, which reached statistical significance (p<0.05).

Pre-dose $FEV_1$ improved by at least 0.100 litre in around 20% of participants using beclometasone/formoterol/glycopyrronium and indacaterol/glycopyrronium at weeks 26 and 52, and there were no statistically significant differences between the groups (p=0.194 and p=0.198 respectively).

## Dyspnoea

In the **TRILOGY study**, at week 26, there was no statistically significant difference between beclometasone/formoterol/glycopyrronium and beclometasone/formoterol in improvement in Transition Dyspnoea Index (TDI) focal scores (a co-primary outcome; p=0.160).

More than 50% of participants in each group reported clinically important improvements of at least 1 unit in TDI focal scores at week 26 and week 52. However, although there was a statistically significant difference between the groups at week 26 (57% compared with 52% respectively; OR 1.28, 95% CI 1.03 to 1.59; p=0.027), there was no significant difference at week 52 (p=0.430).

Dyspnoea was not investigated in the **TRINITY** or **TRIBUTE** studies.

## Exacerbations of COPD

In the **TRILOGY study**, the rate of moderate-to-severe exacerbations was reduced by 23% over 52 weeks (annualised rate 0.1 exacerbation) with beclometasone/formoterol/glycopyrronium

compared with beclometasone/formoterol (annualised rate 0.41 compared with 0.53 respectively; rate ratio [RR] 0.77, 95% CI 0.65 to 0.92; p=0.005).

Triple therapy prolonged the time to the first moderate-to-severe exacerbation compared with dual therapy (hazard ratio [HR] 0.80, 95% CI 0.67 to 0.97; p=0.020).

In the **TRINITY study**, beclometasone/formoterol/glycopyrronium reduced the rate of moderate-to-severe exacerbations by 20% over 52 weeks compared with tiotropium alone (the primary outcome; annualised rate 0.46 compared with 0.57 respectively; RR 0.80, 95% CI 0.69 to 0.92; p=0.0025). The European public assessment report for beclometasone/formoterol/glycopyrronium states that a 20% reduction in moderate-to-severe exacerbations is suggested to be a minimally clinically important difference in people with COPD. For this outcome, there was no statistically significant difference between fixed triple therapy with beclometasone/formoterol/glycopyrronium and open triple therapy with beclometasone/formoterol and tiotropium (p=0.89).

Fixed triple therapy prolonged the time to the first moderate-to-severe exacerbation compared with tiotropium (HR 0.84, 95% CI 0.72 to 0.97; p=0.0154). There was no statistically significant difference between fixed triple therapy and open triple therapy (p=0.57). Similar results were seen for the time to the first severe COPD exacerbation and time to the first moderate COPD exacerbation (see the results tables for more details).

In the **TRIBUTE study**, the rate of moderate-to-severe exacerbations (the primary outcome) was reduced by 15% over 52 weeks (annualised rate 0.1 exacerbation) with beclometasone/formoterol/glycopyrronium compared with indacaterol/glycopyrronium (annualised rate 0.50 compared with 0.59 respectively; RR 0.85, 95% CI 0.72 to 0.99; p=0.043). This reduction is **not** considered clinically important according to the criterion used in the European public assessment report (20% reduction).

There were no statistically significant differences between beclometasone/formoterol/glycopyrronium and indacaterol/glycopyrronium in the rate of moderate exacerbations or the rate of severe exacerbations (p=0.118 and p=0.189 respectively). However, the study was not statistically powered to compare the groups for these outcomes. There were also no statistically significant differences between the triple therapy and the dual therapy in the time to the first moderate-to-severe exacerbation or the time to the first severe exacerbation (p=0.219 and p=0.405 respectively).

## Health-related quality of life

In the **TRILOGY study**, clinically relevant improvements of at least 4 units in St George's Respiratory Questionnaire (SGRQ) scores were reported with beclometasone/formoterol/glycopyrronium compared with beclometasone/formoterol, with statistically significant differences between the groups at weeks 26 and 52 (for example, 43% compared with 36% respectively at 52 weeks; OR 1.33, 95% CI 1.06 to 1.66; p=0.014).

In the **TRINITY study**, SGRQ scores improved by at least 4 units in more participants using triple therapy compared with tiotropium at weeks 26 and 52 (p=0.0024 and p=0.0019 respectively; see the results tables for more details). Fixed triple therapy was found to be better than open triple therapy at 26 weeks but not 52 weeks (p=0.0486 and p=0.37 respectively).

In the **TRIBUTE study**, SGRQ scores improved by at least 4 units in around 40% of participants using beclometasone/formoterol/glycopyrronium and indacaterol/glycopyrronium at weeks 26 and 52, and there were no statistically significant differences between the groups (p=0.255 and p=0.068 respectively).

## Use of rescue medication

In the **TRILOGY study**, the use of rescue medication in puffs per day was significantly lower with beclometasone/formoterol/glycopyrronium compared with beclometasone/formoterol up to week 26 (for example, during weeks 13 to 26, −0.21 puffs compared with −0.02 puffs respectively; adjusted mean difference −0.19 puffs, 95% CI −0.35 puffs to −0.02 puffs; p=0.029). However, no significant difference was seen after this time point.

Participants using triple therapy had a higher proportion of days without rescue medication than those using dual therapy up to week 12 (for example, during weeks 5 to 12, 6.23% compared with 3.18% respectively; adjusted mean difference 3.05%, 95% CI 0.15% to 5.95%; p=0.039). No difference was seen after this time point.

In the **TRINITY study**, participants using triple therapy had fewer puffs of rescue medication per day compared with participants using tiotropium at all time points (all p<0.0001). No statistically significant differences were seen between fixed and open triple therapy at any time point (all p≥0.359).

Participants using triple therapy also had a higher proportion of days without rescue medication than those using tiotropium (all p<0.0001). No statistically significant differences were seen between fixed and open triple therapy at any time point (all p≥0.455).

In the **TRIBUTE study**, there was no statistically significant difference between beclometasone/formoterol/glycopyrronium and indacaterol/glycopyrronium in the average number of puffs of rescue medication (p=0.517) or the proportion of days without rescue medication (p=0.361).

## *Safety and tolerability*

The European public assessment report states that, overall, the adverse effect profile of beclometasone/formoterol/glycopyrronium is well understood. None of the active substances are new and all have been used for many years, individually and in combination, for treating people with COPD of various grades of severity. The report concludes that the known adverse events and serious adverse events of the active substances were of a frequency and nature to be expected, and can all be considered reversible with change or modification of treatment.

In **TRILOGY**, a similar proportion of participants using beclometasone/formoterol/glycopyrronium and beclometasone/formoterol had treatment-emergent adverse events (54% compared with 56% respectively). Most of these were COPD-related (58% and 63% respectively), and most were mild or moderate in severity. About 3% of participants in each group had pneumonia, and about 2% of participants in each group had major adverse cardiovascular events. One treatment-related serious adverse event occurred (atrial fibrillation) in a person in the triple therapy group. This event resolved in 15 days and did not cause study medicine discontinuation.

Treatment-emergent adverse events resulted in death in a similar proportion of participants in the 2 groups (2%). None of the deaths were considered to be related to the study medicine. The number of treatment-emergent adverse events leading to discontinuation of treatment was also similar between the groups (5%).

In **TRINITY**, a similar proportion of participants using beclometasone/formoterol/glycopyrronium (fixed triple and open triple) and tiotropium had treatment-emergent adverse events (55%, 58% and 58% respectively). As in TRILOGY, most of these were COPD-related (59%, 54% and 62% respectively), and most were mild or moderate in severity. In each group, 2–3% of participants had pneumonia, and 1–2% of participants had major adverse cardiovascular events. One treatment-related serious adverse event was seen (angina pectoris) in the tiotropium group. Although the person recovered, the adverse event resulted in withdrawal from the study.

Treatment-emergent adverse events resulted in death in 1–3% of participants in the 3 groups. The most common treatment-emergent adverse events leading to death related to cardiac disorders or COPD exacerbations (European public assessment report). No deaths were considered related to study treatment. Fewer participants experienced adverse events leading to discontinuation of

study treatment in the 2 triple therapy groups compared with the tiotropium group (both 3% compared with 6% respectively.

As in the other 2 studies, in **TRIBUTE**, a similar proportion of participants using beclometasone/formoterol/glycopyrronium and indacaterol/glycopyrronium had treatment-emergent adverse events (64% compared with 67% respectively). In both groups, 56% of these were COPD-related, and most were mild or moderate in severity. Pneumonia was seen in 4% of participants in each group, and adverse cardiovascular events were seen in 6% of participants using beclometasone/formoterol/glycopyrronium and 7% of participants using indacaterol/glycopyrronium. Two treatment-related serious adverse events were reported: dysuria in the triple therapy group and atrial fibrillation in the dual-therapy group.

In the beclometasone/formoterol/glycopyrronium group, 5% of participants had adverse events that led to discontinuation of treatment compared with 6% in the indacaterol/glycopyrronium group. The most common adverse events leading to treatment discontinuation were exacerbations of COPD. Adverse events resulted in 37 deaths across both groups, none of which were considered to be related to the study treatment.

According to the summary of product characteristics, the adverse events reported most frequently during the clinical development of beclometasone/formoterol/glycopyrronium were:

- oral candidiasis (0.5%), which is normally associated with inhaled corticosteroids
- muscle spasms (0.5%), which can be attributed to the long-acting beta-2agonist, and
- dry mouth (0.5%), which is a typical anticholinergic effect.

An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, has been observed in people with COPD receiving ICS. Based on recommendations from the MHRA, the NICE guideline on COPD advises clinicians to be aware of the potential risk of developing adverse effects, including non-fatal pneumonia, in people with COPD treated with inhaled corticosteroids.

An overview of the results for safety and tolerability can be found in results tables.

## *Evidence strengths and limitations*

TRILOGY and TRINITY were the key randomised controlled trials for licensing the beclometasone/formoterol/glycopyrronium triple-therapy inhaler. The European public assessment report states that their design and methodology was appropriate, and key outcomes were in line with guidance

on undertaking studies in COPD. Randomisation and blinding were robust, statistical methods were acceptable, and the studies were of sufficient duration to measure exacerbation rate. The TRIBUTE study had a similar design and methodology.

All 3 studies included people with COPD with severe or very severe airflow limitation, symptoms despite treatment and a history of exacerbations who were current or ex-smokers. Just over half of the participants were aged less than 65 years, approximately three quarters were male, and most were of white ethnicity and had at least 1 concurrent disease. In both studies, the groups were comparable in terms of demography, lung function and symptoms. Most participants in the studies were using dual combination COPD therapy at study entry. In TRILOGY and TRINITY around 74% of participants were using ICS/LABA combinations compared with 61% in TRIBUTE. The European public assessment report notes that the participants enrolled in TRILOGY and TRINITY were representative of the target population for the therapeutic indication.

People with asthma, allergic rhinitis or atopy, clinically significant cardiovascular conditions or laboratory abnormalities, or unstable concurrent disease that might have affected the efficacy or safety of beclometasone/formoterol/glycopyrronium were not eligible to take part in TRILOGY or TRINITY, nor were people currently using triple therapy with an ICS, LABA and LAMA. Some of these populations were also excluded from TRIBUTE. It is unclear if the results of the studies apply to populations other than those recruited; for example, people with mild-to-moderate COPD for whom it is possible that any benefits of treatment might not outweigh the risks of adverse effects.

The TRILOGY study had 3 co-primary outcomes that were assessed according to a pre-specified hierarchy. The first 2 primary outcomes were disease-oriented and assessed changes in lung function. The third primary outcome assessed patient-oriented changes in dyspnoea using TDI score. Although TDI focal score improved more with beclometasone/formoterol/glycopyrronium than with beclometasone/formoterol, the difference between the groups was not statistically significant. According to the pre-specified success criterion, this means that TRILOGY failed to show that triple therapy was superior to dual therapy for this outcome.

The study authors stated that the need for participants to recall their previous symptoms is a potential problem when measuring TDI, and that this may have affected the result for this outcome, particularly as the study lasted 52 weeks. The authors of TRILOGY also observed a mean improvement in TDI focal score in the beclometasone/formoterol control group, which exceeded the minimum clinically important difference threshold, and an improvement in SGRQ total score which was close to the threshold, despite no change in treatment. They note that a trial effect on patient reported outcomes has been observed in previous COPD clinical trials.

Specialists involved in producing the evidence summary noted that triple therapy is generally considered only in people who have frequent exacerbations of COPD (more than 2 per year) despite dual inhaler therapy (for example a LABA/ICS or LABA/LAMA). At baseline, participants in the studies had, on average, 1 exacerbation per year, not 'frequent exacerbations'. The results of the studies may not apply to people who have 'frequent exacerbations'.

The exacerbation rate was reportedly lower than anticipated during all 3 studies during the 52-week follow-up, despite the requirement for participants to have a history of at least 1 exacerbation in the year before study entry. The authors of the studies consider that this might be because participants in interventional studies often receive improved care, with regular, detailed clinic visits. Also, treatment adherence in clinical trials is generally higher than that seen in clinical practice. Adherence was 94–95% in TRILOGY and TRINITY, and 98.5% in TRIBUTE.

According to the European public assessment report, evaluation of the safety of the beclometasone/formoterol/glycopyrronium triple inhaler was difficult because of the nature of the study populations. Participants were generally frail older people, with advanced lung disease and often other significant health problems.

TRILOGY compared triple therapy (beclometasone/formoterol/glycopyrronium) with dual therapy (beclometasone/formoterol) and TRINITY compared beclometasone/formoterol/glycopyrronium with tiotropium and open triple therapy with beclometasone/formoterol plus tiotropium. TRIBUTE compared beclometasone/formoterol/glycopyrronium with dual therapy (indacaterol/glycopyrronium). Therefore, it is not known how the efficacy and safety of fixed triple therapy compares with other treatments for COPD, such as other combinations of ICS/LABA (alone or with a separate LAMA) or other LABA/LAMAs.

It is also not known from the studies whether the fixed triple-therapy inhaler has any advantages over open triple therapy in terms of patient factors such as preference, adherence to treatment and ease of use of the device.

An overview of the quality assessment of each included study can be found in evidence tables.

## Estimated impact for the NHS

### *Other treatments*

The beclometasone/formoterol/glycopyrronium (metered dose) inhaler (Trimbow) was the first triple therapy combination inhaler licensed for COPD in the UK. A second triple therapy (dry

powder) inhaler containing fluticasone, vilanterol and umeclidinium (Trelegy) has also been licensed in the UK and is the subject of a separate evidence summary.

Four dual-therapy LAMA/LABA combination inhalers are currently available for treating symptoms of COPD:

- aclidinium/formoterol (Duaklir Genuair)
- indacaterol/glycopyrronium (Ultibro Breezhaler)
- tiotropium/olodaterol (Spiolto Respimat) and
- umeclidinium/vilanterol (Anoro Ellipta).

Combination ICS/LABA inhalers currently licensed for treating COPD include:

- beclometasone/formoterol metered dose inhaler (Fostair) and dry powder inhaler (Fostair NEXThaler)
- budesonide/formoterol dry powder inhalers (DuoResp Spiromax, Fobumix and Symbicort Turbohaler)
- fluticasone propionate/salmeterol dry powder inhalers (Aerivio Spiromax, AirFluSal Forspiro, Seretide Accuhaler)
- fluticasone/vilanterol dry powder inhaler (Relvar Ellipta).

Note that not all strengths of all these products are licensed for treating COPD; some strengths are licensed only for treating asthma. Please see the summaries of product characteristics for more information.

ICS are not licensed for monotherapy in COPD and are only available in combination with LABAs. Four single-component LABAs are currently licensed for treating COPD:

- formoterol (Atimos Modulite, Formoterol Easyhaler, Foradil and Oxis Turbohaler)
- indacaterol (Onbrez Breezhaler)
- olodaterol (Striverdi Respimat) and
- salmeterol (Neovent, Serevent Accuhaler and Serevent Evohaler).

Single-component LAMAs licensed for treating COPD are:

- aclidinium (Eklira Genuair)
- glycopyrronium (Seebri Breezhaler)
- tiotropium (Braltus Zonda, Spiriva Handihaler and Spiriva Respimat) and
- umeclidinium (Incruse Ellipta).

Examples of branded products are given but the lists are not intended to be comprehensive. Some originator brands are now off-patent and further generic versions may be available.

## *Costs of other treatments*

Table 3 lists comparative costs for a range of mono, dual and triple-therapy inhalers for COPD compared with the beclometasone/formoterol/glycopyrronium metered dose inhaler (Trimbow). Table 4 gives examples of a range of costs for triple therapy using either a triple-therapy inhaler or a combination of a dual-therapy inhaler containing an ICS/LABA plus a monotherapy inhaler containing a LAMA. These tables do not include all of the currently licensed products or all of the options for triple therapy, but give an indication of the range of treatments and triple therapy options, and their associated acquisition costs (excluding VAT).

**Table 3 Examples of costs of inhalers for treating COPD**

| Treatment | Usual dosage[a,b] | 30-day cost excluding VAT |
|---|---|---|
| **Single-component LABAs** | | |
| Formoterol 12 micrograms (Formoterol Easyhaler) | 1 puff twice daily | £11.87[c,d] |
| Indacaterol 150 micrograms and 300 micrograms (Onbrez Breezhaler) | 1 puff daily | £32.19[c] |
| Olodaterol 2.5 micrograms (Striverdi Respimat) | 2 puffs once daily | £26.35[c] |
| Salmeterol 50 micrograms (Serevent Accuhaler) | 1 puff twice daily | £35.11[c,d] |

| | | |
|---|---|---|
| **Single-component LAMAs** | | |
| Aclidinium 322 micrograms (Eklira Genuair) | 1 puff twice daily | £28.60[c] |
| Glycopyrronium 44 micrograms (Seebri Breezhaler) | 1 puff daily | £27.50[c] |
| Tiotropium 10 micrograms, dry powder (Braltus) | 1 puff daily | £25.80[c] |
| Tiotropium 2.5 micrograms, aerosol (Spiriva Respimat) | 2 puffs once daily | £23.00[c] |
| Umeclidinium 55 micrograms (Incruse Ellipta) | 1 puff daily | £27.50[c] |
| **Combination LAMA/LABA inhalers** | | |
| Tiotropium/olodaterol 2.5/2.5 micrograms (Spiolto Respimat) | 2 puffs once daily | £32.50[c] |
| Aclidinium/formoterol 340/12 micrograms (Duaklir Genuair) | 1 puff twice daily | £32.50[c] |
| Indacaterol/glycopyrronium 85/43 micrograms (Ultibro Breezhaler) | 1 puff daily | £32.49[c] |
| Umeclidinium/vilanterol 55/22 micrograms (Anoro Ellipta) | 1 puff daily | £32.50[c] |
| **Combination ICS/LABA inhalers** | | |
| Beclometasone/formoterol 100/6 micrograms (Fostair or Fostair NEXThaler) | 2 puffs twice daily | £29.32[c] |
| Budesonide/formoterol 320/9 micrograms (Fobumix Easyhaler) | 1 puff twice daily | £26.99[e,d] |
| Fluticasone furoate/vilanterol 92/22 micrograms (Relvar Ellipta) | 1 puff daily | £22.00[c] |
| Fluticasone propionate/salmeterol 500/50 micrograms (Aerivio Spiromax and AirFluSal Forspiro) | 1 puff twice daily | £29.97[e,d] |
| **Triple ICS/LABA/LAMA inhalers** | | |
| Beclometasone/formoterol/glycopyrronium 87/5/9 micrograms (Trimbow) | 2 puffs twice daily | £44.50[e] |
| Fluticasone/vilanterol/umeclidinium 92/55/22 micrograms (Trelegy) | 1 puff daily | £44.50[e] |

[a] Doses taken from the relevant summary of product characteristics.

[b] The doses shown do not represent the full range that can be used and they do not imply therapeutic equivalence.

[c] Costs taken from the Drug Tariff (March 2018). All costs include the inhaler device.

[d] Lowest cost dry powder formulations selected; other brands and formulations are available.

[e] Costs taken from MIMS (March 2018). All costs include the inhaler device.

**Abbreviations:** ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist.

**Table 4 Examples of costs of triple therapy for treating COPD**

| | | 30-day cost excluding VAT[a] |
|---|---|---|
| **Combination ICS/LABA inhaler plus a separate LAMA inhaler** | | |
| Beclometasone/formoterol 100/6 micrograms (Fostair[b] or Fostair NEXThaler) | Aclidinium 322 micrograms (Eklira Genuair) | £57.92 |
| | Glycopyrronium 44 micrograms (Seebri Breezhaler) | £56.82 |
| | Tiotropium 10 micrograms, dry powder (Braltus) | £55.12 |
| | Tiotropium 2.5 micrograms, aerosol (Spiriva Respimat) | £52.32 |
| | Umeclidinium 55 micrograms (Incruse Ellipta) | £56.82 |
| Budesonide/formoterol 320/9 micrograms (Fobumix Easyhaler) | Aclidinium 322 micrograms (Eklira Genuair) | £55.59 |

| | | |
|---|---|---|
| | Glycopyrronium 44 micrograms (Seebri Breezhaler) | £54.49 |
| | Tiotropium 10 micrograms, dry powder (Braltus) | £52.79 |
| | Tiotropium 2.5 micrograms, aerosol (Spiriva Respimat) | £49.99 |
| | Umeclidinium 55 micrograms (Incruse Ellipta) | £54.49 |
| Fluticasone furoate/vilanterol 92/22 micrograms (Relvar Ellipta) | Aclidinium 322 micrograms (Eklira Genuair) | £50.60 |
| | Glycopyrronium 44 micrograms (Seebri Breezhaler) | £49.50 |
| | Tiotropium 10 micrograms, dry powder (Braltus) | £47.80 |
| | Tiotropium 2.5 micrograms, aerosol (Spiriva Respimat) | £45.00 |
| | Umeclidinium 55 micrograms (Incruse Ellipta) | £49.50 |
| Fluticasone propionate/salmeterol 500/ 50 micrograms (Aerivio Spiromax and AirFluSal Forspiro) | Aclidinium 322 micrograms (Eklira Genuair) | £58.57 |
| | Glycopyrronium 44 micrograms (Seebri Breezhaler) | £57.47 |
| | Tiotropium 10 micrograms, dry powder (Braltus) | £55.77 |

| | | |
|---|---|---|
| | Tiotropium 2.5 micrograms, aerosol (Spiriva Respimat) | £52.97 |
| | Umeclidinium 55 micrograms (Incruse Ellipta) | £57.47 |
| **Triple ICS/LABA/LAMA inhalers** | | |
| Beclometasone/formoterol/glycopyrronium 87/5/9 micrograms (Trimbow)[b] | | £44.50 |
| Fluticasone/vilanterol/umeclidinium 92/55/22 micrograms (Trelegy) | | £44.50 |
| [a] Costs taken from the Drug Tariff (March 2018) or MIMS (March 2018). Lowest cost dry powder formulations selected unless footnoted otherwise; other brands and formulations are available. All costs include the inhaler device. See table 3 for more details.<br>[b] Pressurised metered dose inhaler. | | |
| **Abbreviations:** ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist. | | |

A 30-day supply of combination therapy with beclometasone, formoterol and glycopyrronium costs £44.50 (excluding VAT) when the triple-therapy inhaler (Trimbow) is prescribed. This compares with £56.82 (excluding VAT) when beclometasone and formoterol are prescribed in a dual-therapy inhaler (Fostair or Fostair NEXThaler) together with glycopyrronium in a single therapy inhaler (Seebri Breezhaler). It is the same price as the fluticasone, vilanterol and umeclidinium triple-therapy inhaler (Trelegy).

The acquisition cost of a 30-day supply of combination ICS/LABA inhaler plus a separate LAMA inhaler using the products listed in the table above ranges from about £45.00 to £58.00 (excluding VAT), compared with £44.50 (excluding VAT) for triple-therapy inhaler. This suggests that using triple therapy could lead to annual savings of between £6 and £160 per year when these products are used (based on using 12 inhalers per year; note that inhaler strengths and dosages vary and they may not be equivalent). The tables include the lowest cost dry powder formulations so the saving with triple therapy would be higher where more expensive brands and formulations are currently used.

## *Current or estimated usage*

It is not possible to provide estimated usage of the beclometasone/formoterol/glycopyrronium triple-therapy inhaler based on the available data. This is because it is not currently possible to determine whether prescribing of inhalers is for asthma or COPD, or whether inhalers are used alone or in combination as part of triple therapy.

Results from a retrospective cohort study based on the UK Clinical Practice Research Database (n=3,199) found that, over 2 years, 39% of people with COPD who were initially prescribed an ICS in combination with a long-acting bronchodilator (usually a LABA) stepped up to an open triple therapy regimen. The majority of people who were initially using open triple therapy stepped down to a LABA/ICS (25%) or LAMA (31%) during the 2-year follow-up (Wusrt KE et al. 2014). However, the study included a relatively small number of people only, and it started in January 2008 and may not be applicable to current practice.

## *Likely place in therapy*

The NICE guideline on COPD (currently being updated) recommends that triple therapy should be considered in people who remain breathless or have exacerbations despite using an ICS/LABA (add a LAMA) or a LAMA (add an ICS/LABA), irrespective of $FEV_1$. (The NICE guideline was published before any of the LABA/LAMA or ICS/LABA/LAMA combination inhalers were available in the UK). The choice of medication should take into account the person's symptomatic response and preference, and the medicine's potential to reduce exacerbations, its side effects and its cost.

The TRILOGY and TRINITY studies found modest statistically significant improvements in lung function, rates of moderate-to-severe exacerbations of COPD and health-related quality-of-life scores with beclometasone/formoterol/glycopyrronium compared with beclometasone/formoterol dual therapy or tiotropium alone. Improvements in lung function and exacerbation rates generally reached the level considered to be clinically important. Beclometasone/formoterol/glycopyrronium did not improve symptoms of dyspnoea significantly more than beclometasone/formoterol. However, responder analyses showed that more participants had a clinically important improvement in symptoms and health-related quality of life with triple therapy compared with dual therapy. Fixed triple therapy with a single beclometasone/formoterol/glycopyrronium inhaler was found to be similar to open triple therapy with beclometasone/formoterol plus tiotropium in 2 inhalers for all outcomes.

The TRIBUTE study found that beclometasone/formoterol/glycopyrronium reduced the rate of moderate-to-severe exacerbations compared with indacaterol/glycopyrronium. However, although

the difference between the groups was statistically significant, it may not have been clinically important. For other outcome measures, beclometasone/formoterol/glycopyrronium and indacaterol/glycopyrronium were generally found to be similar. For example, there were no statistically significant differences between the groups for rates of moderate exacerbations, severe exacerbations, or time to first moderate-to-severe or severe exacerbation. Also, responder analyses showed no difference in terms of the proportion of people who had a clinically important improvement in lung function or health-related quality of life.

The adverse effect profile of beclometasone/formoterol/glycopyrronium is well understood because the active ingredients have been used for many years, alone and in combination. The most frequent adverse effects include oral candidiasis, muscle spasms and dry mouth.

The acquisition cost of the beclometasone/formoterol/glycopyrronium triple-therapy inhaler (Trimbow) is less than that of other combinations of ICS/LABA plus LAMA in 2 inhalers. It costs the same as triple therapy with fluticasone/umeclidinium/vilanterol (Trelegy) (£44.50 for a 30 day's treatment [excluding VAT]; MIMS, March 2018).

Some people may prefer a particular inhaler device or be able to use one device better than another. Some people with COPD are unable to use a spacer, others like to use one. Beclometasone/formoterol/glycopyrronium is supplied in a pressurised metered dose inhaler and can be used with a spacer. Fluticasone/umeclidinium/vilanterol is supplied in a dry powder inhaler and cannot be used with a spacer. Beclometasone/formoterol/glycopyrronium is administered twice daily and fluticasone/umeclidinium/vilanterol is administered once daily.

Until recently, administering triple therapy needed more than 1 inhaler, sometimes using 2 different types of device. Triple therapy in a single inhaler may be preferable for people who have difficulty using more than 1 device or who find their medication regimen difficult or confusing, and have trouble complying with treatment. However, triple therapy lacks flexibility and makes it difficult to amend the individual medicines if treatment needs changing for any reason.

Beclometasone/formoterol/glycopyrronium may be suitable for some people with moderate-to-severe COPD who have found triple therapy beneficial using more than 1 inhaler and can use a pressurised metered dose inhaler (with or without a spacer), but who have difficulty using multiple inhalers.

Local decision makers will need to take safety, efficacy, cost and patient factors into account when considering the likely place in therapy of beclometasone/formoterol/glycopyrronium.

## Information for the public about medicines

Evidence summaries provide an overview of the best evidence that is available about specific medicines. They also give general information about the condition that the medicine might be prescribed for, how the medicine is used, how it works, and what the aim of treatment is.

Evidence summaries aim to help healthcare professionals and patients decide whether medicines are safe to use and if they are likely to work well, especially when there isn't another suitable medicine that has a licence for the condition. They don't contain recommendations from NICE on whether the medicine should be used.

### *Information about licensing of medicines*

In the UK, medicines need to have a licence before they can be widely used. To get a licence, the manufacturer of the medicine has to provide evidence that shows that the medicine works well enough and is safe enough to be used for a specific condition and for a specific group of patients, and that they can manufacture the medicine to the required quality. Evidence summaries explain whether a medicine has a licence, and if it does what the licence covers.

There is more information about licensing of medicines on NHS Choices.

Medicines can be prescribed if they don't have a licence (unlicensed) or for 'off-label' use. Off-label means that the person prescribing the medicine wants to use it in a different way than that stated in its licence. This could mean using the medicine for a different condition or a different group of patients, or it could mean a change in the dose or that the medicine is taken in a different way. If a healthcare professional wants to prescribe an unlicensed medicine, or a licensed medicine off-label, they must follow their professional guide, for example for doctors the General Medical Council's good practice guidelines. These include giving information about the treatment and discussing the possible benefits and harms so that the person has enough information to decide whether or not to have the treatment. This is called giving informed consent.

### *Questions that might be useful to ask about medicines*

- Why am I being offered this medicine?
- Why am I being offered a medicine that is unlicensed or is being used off-label?
- What does the treatment involve?

- What are the benefits I might get?
- How good are my chances of getting those benefits?
- Could having the treatment make me feel worse?
- Are there other treatments I could try?
- What are the risks of the treatment?
- Are the risks minor or serious? How likely are they to happen?
- What could happen if I don't have the treatment?

## Relevance to other NICE programmes

The beclometasone/formoterol/glycopyrronium triple-therapy inhaler was not considered appropriate for a NICE technology appraisal and is not currently planned into any other NICE work programme.

In 2010, NICE published a clinical guideline on chronic obstructive pulmonary disease (NICE guideline CG101), which has been incorporated into a NICE interactive flowchart on COPD. The guideline is currently being updated (expected publication date November 2018).

## References

Papi A, Vestbo J, Fabbri L et al. (2018) Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. Lancet 391: 1076–84

Singh D, Papi A, Corradi M et al. (2016) Single inhaler triple therapy versus inhaled corticosteroid plus long-acting $\beta_2$-agonist therapy for chronic obstructive pulmonary disease: a double-blind, parallel group, randomised controlled trial. Lancet 388: 963–73

Wurst KE, Punekar YS, Shukla A (2014) Treatment Evolution after COPD Diagnosis in the UK Primary Care Setting. PLoS ONE 9(9): e105296

Vestbo J, Papi A, Corradi M et al. (2017) Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial. Lancet 389:1919–29

# Evidence tables

**Table 5 Singh D et al. 2016 (TRILOGY)**

| | |
|---|---|
| **Study reference** | Singh D, Papi A, Corradi M et al. (2016) Single inhaler triple therapy versus inhaled corticosteroid plus long-acting $\beta_2$-agonist therapy for chronic obstructive pulmonary disease: a double-blind, parallel group, randomised controlled trial. Lancet 388: 963–73 |
| **Unique identifier** | NCT01917331 |
| **Study type** | Randomised, parallel group, double blind, active-controlled study. |
| **Aim of the study** | Compared the efficacy and safety of single inhaler triple therapy with beclometasone dipropionate, formoterol fumarate, and glycopyrronium bromide with that of dual therapy with beclometasone dipropionate and formoterol fumarate in people with COPD with severe or very severe airflow limitation, symptoms despite treatment and a history of exacerbations. |
| **Study dates** | 21 March 2014 to 14 January 2016. |
| **Setting** | 159 sites in 14 countries: 18 primary care, 99 secondary care, 28 tertiary care and 14 specialist investigation units. |
| **Number of participants** | 1,368 participants were randomly assigned to treatment (1 person did not receive the allocated therapy). |
| **Population** | Adults aged 40 years or older who were current or ex-smokers and had a diagnosis of COPD for at least 12 months (76% male, 100% white, mean age 63 years, 47% current smokers and 53% ex-smokers, mean time since diagnosis 7.7 years, 84% with at least 1 concurrent disease). |

| | |
|---|---|
| **Inclusion criteria** | • Post-bronchodilator $FEV_1$ <50% predicted (mean 37%) and $FEV_1$/FVC ratio <0.7 (mean 0.4).<br>• At least 1 moderate or severe COPD exacerbation[a] in the previous 12 months (mean 1.2 exacerbations).<br>• Use for at least 2 months before screening of:<br>– an ICS plus a LABA (as a free or fixed combination, 73%),<br>– an ICS plus a LAMA (1%),<br>– a LABA plus a LAMA (as a free or fixed combination, 15%) or<br>– LAMA monotherapy (11%).<br>• Symptomatic, classified as a CAT total score of ≥10 (mean 20.8) and a BDI focal score of ≤10 at screening (mean 5.4), with the BDI criterion also confirmed at the randomisation visit. |
| **Exclusion criteria** | • Diagnosis of asthma.<br>• History of allergic rhinitis or atopy.<br>• A COPD exacerbation in the 4 weeks before screening or during the run-in period.<br>• Clinically significant cardiovascular conditions or laboratory abnormalities.<br>• Unstable concurrent disease that might have affected efficacy or safety (as judged by the investigator).<br>• Current triple therapy with an ICS, LABA and LAMA. |
| **Intervention(s)** | Beclometasone dipropionate 100 micrograms, formoterol fumarate 6 micrograms and glycopyrronium bromide 12.5 micrograms in a single pressurised metered dose inhaler (2 puffs twice daily) (n=687). |
| **Comparator(s)** | Beclometasone dipropionate 100 micrograms and formoterol fumarate 6 micrograms in a single matching metered dose inhaler (2 puffs twice daily) (n=681). |

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|---|---|
| **Length of follow-up** | During a 2-week open-label run-in period, all participants received beclometasone dipropionate and formoterol fumarate.<br>After the run-in period, they were randomly assigned 1:1 to 1 of the 2 treatment groups for a 52-week treatment period (median exposure 365 days, compliance 95%). |
| **Outcomes** | Co-primary outcomes (assessed at week 26):<br>• change from baseline in pre-dose (morning) $FEV_1$,<br>• change from baseline in 2-hour post-dose $FEV_1$, and<br>• TDI focal score (change in dyspnoea severity from baseline). |
| | Secondary outcomes:[b]<br>• pre-dose $FEV_1$ at all other clinic visits, averaged over the treatment period<br>• $FEV_1$ response[c] at weeks 26 and 52<br>• 2-hour post-dose $FEV_1$ at all other clinic visits<br>• TDI focal score at all other clinic visits<br>• TDI response[d] at weeks 26 and 52<br>• SGRQ total score at all clinic visits<br>• SGRQ response[e] at weeks 26 and 52<br>• percentage of days without rescue medication use<br>• average number of puffs of rescue medication (salbutamol 100 micrograms) per day<br>• moderate-to-severe COPD exacerbation[f] frequency over 52 weeks<br>• time to first moderate-to-severe COPD exacerbation. |
| | Safety outcomes:<br>• treatment-emergent adverse events<br>• treatment-related adverse events. |

| | | |
|---|---|---|
| **Source of funding** | Chiesi Farmaceutici SpA. | |
| **Overall risk of bias/quality assessment** (CASP RCT checklist) | Did the trial address a clearly focused issue? | Yes |
| | Was the assignment of patients to treatments randomised? | Yes[g] |
| | Were patients, health workers and study personnel blinded? | Yes |
| | Were the groups similar at the start of the trial? | Yes |
| | Aside from the experimental intervention, were the groups treated equally? | Yes |
| | Were all of the patients who entered the trial properly accounted for at its conclusion? | Yes |
| | How large was the treatment effect? | See table 8 |
| | How precise was the estimate of the treatment effect? | See table 8 |
| | Can the results be applied in your context? (or to the local population) | Yes |
| | Were all clinically important outcomes considered? | Yes |
| | Are the benefits worth the harms and costs? | See key points |

| | |
|---|---|
| **Study limitations** | • The study included people with COPD with severe or very severe airflow limitation, symptoms despite treatment and a history of exacerbations and at least 1 moderate-to-severe exacerbation in the previous 12 months, who were symptomatic despite treatment. The results of the study may not apply to other populations with COPD.<br>• People who had asthma, allergic rhinitis or atopy, clinically significant cardiovascular conditions or laboratory abnormalities, or unstable concurrent disease were excluded from the study, as were people with COPD exacerbations in the 4 weeks before screening or during the run-in period. The results of the study may not apply to these populations.<br>• 2 of the co-primary outcomes are disease-oriented, rather than patient-oriented outcomes.<br>• Measuring TDI relies on participants remembering what their symptoms were like previously, which may be difficult, especially over 52 weeks. This can lead to recall bias.<br>• 73% of participants formerly took an ICS/LABA and the results may not apply to those formerly using other treatments such as a LABA/LAMA.<br>• It is not known from the study how the efficacy and safety of beclometasone/formoterol/glycopyrronium compares with treatments for COPD apart from beclometasone/formoterol, such as other combinations of ICS/LABA (alone or with a separate LAMA).<br>• It is also not known from the study whether the triple-therapy inhaler has any advantages over using a ICS/LABA with a separate LAMA in terms of patient factors such as adherence to treatment and ease of use of the device.<br>• The exacerbation rate seen during the study was lower than that seen before the study even in the control group whose treatment was generally similar in both time periods. This may have been because of regular follow up and improved compliance with treatment. |

| | |
|---|---|
| **Comments** | [a] Defined as sustained worsening of the person's condition (dyspnoea, cough and/or sputum production or purulence), from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a person with underlying COPD that includes prescriptions of systemic corticosteroids and/or antibiotics or need for hospitalisation.<br>[b] Not all of these secondary outcomes are discussed in this evidence summary. See the paper for more details.<br>[c] Change from baseline in pre-dose $FEV_1$ ≥0.100 litre.<br>[d] A TDI focal score of ≥1 was deemed the minimum clinically important difference.<br>[e] A decrease from baseline in SGRQ total score ≥4 was deemed the minimum clinically important difference.<br>[f] Defined as a worsening of the person's respiratory symptoms that in the view of their healthcare provider required treatment with systemic corticosteroids, antibiotics, or hospital admission, or a combination of these. Severe exacerbations were those requiring hospital admission or resulting in death.<br>[g] The method of randomisation used suggests allocation was concealed. |
| **Abbreviations:** BDI, Baseline Dyspnoea Index; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FVC, forced vital capacity; $FEV_1$, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; SGRQ, St George's Respiratory Questionnaire (measuring health-related quality of life); TDI, Transition Dyspnoea Index. | |

**Table 6 Vestbo J et al. 2017 (TRINITY)**

| | |
|---|---|
| **Study reference** | Vestbo J, Papi A, Corradi M et al. (2017) Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial. Lancet 389: 1919–29 |
| **Unique identifier** | NCT01911364 |
| **Study type** | Randomised, parallel group, double blind, double dummy, active-controlled study. |

| | |
|---|---|
| **Aim of the study** | Primarily compared the efficacy and safety of single inhaler triple therapy with beclometasone dipropionate, formoterol fumarate, and glycopyrronium bromide with that of monotherapy with tiotropium in people with COPD with severe or very severe airflow limitation, symptoms despite treatment and a history of exacerbations.<br>Also compared the triple-therapy inhaler with a dual-therapy inhaler containing beclometasone dipropionate and formoterol fumarate plus a monotherapy inhaler containing tiotropium (fixed triple versus open triple). |
| **Study dates** | 21 January 2014 to 18 March 2016. |
| **Setting** | 224 sites in 15 countries (including the UK): 17 primary care, 121 secondary care, 48 tertiary care and 38 specialist investigation units. |
| **Number of participants** | 2,691 participants were randomly assigned to treatment (2 people did not receive the allocated therapy. 1 person randomised to the open triple-therapy group received only tiotropium and was included in the tiotropium arm for the safety analyses). |
| **Population** | Adults aged 40 years or older who were current or ex-smokers and had with a diagnosis of COPD for at least 12 months (76% male, 99% white, mean age 63 years, 48% current smokers and 52% ex-smokers, mean time since diagnosis 8 years, 84% with at least 1 concurrent disease). |
| **Inclusion criteria** | • Post-bronchodilator $FEV_1$ <50% predicted (mean 37%) and $FEV_1$/FVC ratio <0.7 (mean 0.4).<br>• At least 1 moderate or severe COPD exacerbation[a] in the previous 12 months (mean 1.3 exacerbations).<br>• Use for at least 2 months before screening of:<br>– an ICS plus a LABA (as a free or fixed combination, 74%),<br>– an ICS plus a LAMA (3%),<br>– a LABA plus a LAMA (as a free or fixed combination, 12%) or<br>– LAMA monotherapy (11%).<br>• Symptomatic, classified as a CAT total score of ≥10 (mean 21.6). |

| | |
|---|---|
| **Exclusion criteria** | • Diagnosis of asthma.<br>• History of allergic rhinitis or atopy.<br>• A COPD exacerbation in the 4 weeks before screening or during the run-in period.<br>• Clinically significant cardiovascular conditions or laboratory abnormalities.<br>• Unstable concurrent disease that might have affected efficacy or safety (as judged by the investigator).<br>• Current triple therapy with an ICS, LABA and LAMA. |
| **Intervention(s)** | Beclometasone dipropionate 100 micrograms, formoterol fumarate 6 micrograms and glycopyrronium bromide 12.5 micrograms in a single pressurised metered dose inhaler (2 puffs twice daily) plus a dummy dry powder inhaler (1 puff daily) (fixed triple therapy; n=1,078). |
| **Comparator(s)** | Tiotropium 18 micrograms in a dry powder inhaler (Handihaler; 1 puff daily) plus a dummy pressurised metered dose inhaler (2 puffs twice daily) (n=1,075).<br>Beclometasone dipropionate 100 micrograms and formoterol fumarate 6 micrograms in a pressurised metered dose inhaler (2 puffs twice daily) plus tiotropium 18 micrograms in a dry powder inhaler (1 puff daily) (open triple therapy; n=538). |
| **Length of follow-up** | During a 2-week open-label run-in period, all participants received tiotropium.<br>After the run-in period, they were randomly assigned 2:2:1 to the fixed triple group, tiotropium group or open triple group for a 52-week treatment period (median exposure 365 days, compliance 94–95%). |
| **Outcomes** | Primary outcome.<br>• Moderate-to-severe COPD exacerbation[b] frequency over 52 weeks of treatment for fixed triple therapy versus tiotropium. |

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| | Key secondary outcomes: change from baseline in pre-dose<br>$FEV_1$ at week 52<br>• for fixed triple therapy versus tiotropium<br>• for fixed triple therapy versus open triple therapy (non-inferiority analysis).<br>Other secondary outcomes:[c]<br>• time to first moderate-to-severe COPD exacerbation<br>• time to first severe COPD exacerbation<br>• rate of severe and of moderate COPD exacerbations over 52 weeks of treatment<br>• change from baseline in pre-dose $FEV_1$ at other time points<br>• mean pre-dose $FEV_1$ averaged over the treatment period<br>• $FEV_1$ response[d] at weeks 26 and 52<br>• pre-dose inspiratory capacity at all clinic visits<br>• SGRQ total score at all clinic visits<br>• SGRQ response[e] at weeks 26 and 52<br>• percentage of days without rescue medication use<br>• average number of puffs of rescue medication (salbutamol 100 micrograms) per day. |
| | Safety outcomes:<br>• treatment-emergent adverse events<br>• treatment-related adverse events. |
| **Source of funding** | Chiesi Farmaceutici SpA |

| | | |
|---|---|---|
| **Overall risk of bias/quality assessment** (CASP RCT checklist) | Did the trial address a clearly focused issue? | Yes |
| | Was the assignment of patients to treatments randomised? | Yes[f] |
| | Were patients, health workers and study personnel blinded? | Yes |
| | Were the groups similar at the start of the trial? | Yes |
| | Aside from the experimental intervention, were the groups treated equally? | Yes |
| | Were all of the patients who entered the trial properly accounted for at its conclusion? | Yes |
| | How large was the treatment effect? | See table 9 |
| | How precise was the estimate of the treatment effect? | See table 9 |
| | Can the results be applied in your context? (or to the local population) | Yes |
| | Were all clinically important outcomes considered? | Yes |
| | Are the benefits worth the harms and costs? | See key points |

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|---|---|
| **Study limitations** | • The study included people with COPD with severe or very severe airflow limitation and at least 1 moderate-to-severe exacerbation in the previous 12 months, who were symptomatic despite treatment. The results of the study may not apply to other populations with COPD.<br>• People who had asthma, allergic rhinitis or atopy, clinically significant cardiovascular conditions or laboratory abnormalities, or unstable concurrent disease were excluded from the study, as were people with COPD exacerbations in the 4 weeks before screening or during the run-in period. The results of the study may not apply to these populations.<br>• 74% of participants formerly took an ICS/LABA and the results may not apply to those formerly using other treatments such as a LABA/LAMA.<br>• It is not known from the study how the efficacy and safety of beclometasone/formoterol/glycopyrronium compares with treatments for COPD apart from tiotropium alone and open triple therapy.<br>• It is also not known from the study whether the triple-therapy inhaler has any advantages over using a ICS/LABA with a separate LAMA in terms of patient factors such as adherence to treatment and ease of use of the device.<br>• The exacerbation rate seen during the study was lower than that seen before the study even in the control group whose treatment was generally similar in both time periods. This may have been because of regular follow up and improved compliance with treatment. |

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|---|---|
| Comments | [a] Defined as sustained worsening of the person's condition (dyspnoea, cough and/or sputum production or purulence), from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a person with underlying COPD that includes prescriptions of systemic corticosteroids and/or antibiotics or need for hospitalisation.<br>[b] Defined as a worsening of the person's respiratory symptoms that in the view of their healthcare provider required treatment with systemic corticosteroids, antibiotics, or hospital admission, or a combination of these. Severe exacerbations were those requiring hospital admission or resulting in death.<br>[c] Not all of these secondary outcomes are discussed in this evidence summary. See the paper for more details.<br>[d] Change from baseline in pre-dose $FEV_1$ ≥0.100 litre.<br>[e] A decrease from baseline in SGRQ total score ≥4 was deemed the minimum clinically important difference.<br>[f] The method of randomisation used suggests allocation was concealed. |
| **Abbreviations:** CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FVC, forced vital capacity; $FEV_1$, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; SGRQ, St George's Respiratory Questionnaire (measuring health-related quality of life). | |

Table 7 Papi A et al. 2018 (TRIBUTE)

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|---|---|
| Study reference | Papi A, Vestbo J, Fabbri L et al. (2018) Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. Lancet 391: 1076–84 |
| Unique identifier | NCT02579850 |
| Study type | Randomised, parallel group, double blind, double dummy, active-controlled study. |

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|---|---|
| **Aim of the study** | Compared the efficacy and safety of single inhaler triple therapy with beclometasone dipropionate, formoterol fumarate, and glycopyrronium bromide with that of dual therapy with indacaterol maleate and glycopyrronium bromide in people with COPD with severe or very severe airflow limitation, symptoms despite treatment and a history of exacerbations. |
| **Study dates** | 29 May 2015 to 10 July 2017. |
| **Setting** | 187 sites in 17 countries: 37 primary care, 104 secondary care, 1 tertiary care and 45 specialist investigation units. |
| **Number of participants** | 1,532 participants were randomly assigned to treatment. |
| **Population** | Adults aged 40 years or older who were current or ex-smokers and had a diagnosis of COPD (72% male, 92% white, mean age 64 years, 45% current smokers and 55% ex-smokers, mean time since diagnosis 8 years, 85% with at least 1 concurrent disease). |
| **Inclusion criteria** | • Post-bronchodilator $FEV_1$ <50% predicted (mean 36%) and $FEV_1$/FVC ratio <0.7 (mean 0.4).<br>• At least 1 moderate or severe COPD exacerbation[a] in the previous 12 months (mean 1.2 exacerbations).<br>• Symptomatic, classified as a CAT total score of ≥10.<br>• Use for at least 2 months before screening of:<br>– an ICS plus a LABA (61%),<br>– an ICS plus a LAMA (4%),<br>– a LABA plus a LAMA (25%) or<br>– LAMA monotherapy (10%). |

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| **Exclusion criteria** | • Diagnosis of asthma, which needed corticosteroid treatment.<br>• Clinically significant cardiovascular conditions or laboratory abnormalities.<br>• Unstable concurrent disease that might have affected efficacy or safety (as judged by the investigator).<br>• Current triple therapy with an ICS, LABA and LAMA. |
| **Intervention(s)** | Beclometasone dipropionate 100 micrograms, formoterol fumarate 6 micrograms and glycopyrronium bromide 12.5 micrograms in a single pressurised metered dose inhaler (2 puffs twice daily) plus a dummy dry powder inhaler (1 puff daily) (n=764). |
| **Comparator(s)** | Indacaterol maleate 110 micrograms and glycopyrronium bromide 54 micrograms in a single dry powder inhaler (Breezhaler; 1 puff daily) plus a dummy pressurised metered dose inhaler (2 puffs twice daily) (n=768). |
| **Length of follow-up** | During a 2-week open-label run-in period, all participants had their maintenance therapy switched to indacaterol maleate plus glycopyrronium bromide.<br>After the run-in period, they were randomly assigned 1:1 to 1 of the 2 treatment groups for a 52-week treatment period (compliance 98.5%). |
| **Outcomes** | Primary outcome<br>• Moderate-to-severe COPD exacerbation[b] frequency over 52 weeks of treatment. |

| | | |
|---|---|---|
| | Secondary outcomes:[c]<br>• time to first moderate-to-severe COPD exacerbation<br>• time to first severe COPD exacerbation<br>• rate of severe and of moderate COPD exacerbations<br>• change from baseline in pre-dose $FEV_1$ at all treatment visits and averaged over the treatment period<br>• pre-dose $FEV_1$ response[d] at weeks 26 and 52<br>• change from baseline in SGRQ total score at all treatment visits and averaged over the treatment period<br>• SGRQ response[e] at weeks 26 and 52<br>• percentage of days without rescue medication use<br>• average number of puffs of rescue medication (salbutamol or terbutaline) per day. | |
| | Safety outcomes:<br>• treatment-emergent adverse events[f]<br>• treatment-related adverse events. | |
| **Source of funding** | Chiesi Farmaceutici SpA | |
| **Overall risk of bias/quality assessment** (CASP RCT checklist) | Did the trial address a clearly focused issue? | Yes |
| | Was the assignment of patients to treatments randomised? | Yes[g] |
| | Were patients, health workers and study personnel blinded? | Yes |
| | Were the groups similar at the start of the trial? | Yes |
| | Aside from the experimental intervention, were the groups treated equally? | Yes |
| | Were all of the patients who entered the trial properly accounted for at its conclusion? | Yes |

| | | |
|---|---|---|
| | How large was the treatment effect? | See table 10 |
| | How precise was the estimate of the treatment effect? | See table 10 |
| | Can the results be applied in your context? (or to the local population) | Yes |
| | Were all clinically important outcomes considered? | Yes |
| | Are the benefits worth the harms and costs? | See key points |

| | |
|---|---|
| **Study limitations** | • The study included people with COPD with severe or very severe airflow limitation, symptoms despite treatment and a history of exacerbations and at least 1 moderate-to-severe exacerbation in the previous 12 months, who were symptomatic despite treatment. The results of the study may not apply to other populations with COPD.<br>• People who had asthma requiring treatment with corticosteroids, clinically significant cardiovascular conditions or laboratory abnormalities, or unstable concurrent disease were excluded from the study. The results of the study may not apply to these populations.<br>• 61% of participants formerly took an ICS/LABA and the results may not apply to those formerly using other treatments. In this study, 25% of people previously took a LABA/LAMA.<br>• It is not known from the study how the efficacy and safety of beclometasone/formoterol/glycopyrronium compares with treatments for COPD apart from indacaterol/glycopyrronium.<br>• It is also not known from the study whether the triple-therapy inhaler has any advantages in terms of patient factors such as adherence to treatment and ease of use of the device.<br>• The exacerbation rate seen during the study was lower than that seen before the study. This may have been because of regular follow up, improved compliance with treatment or more accurate identification of COPD exacerbations by investigators.<br>• The study may have had insufficient statistical power to detect differences between the groups for outcomes that occur relatively rarely; for example, severe exacerbations.<br>• The 2 groups received different LABAs, from different devices and in different dosing regimens. It is possible that these differences between the treatments could have affected the outcomes observed. |

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| **Comments** | [a] Defined as a sustained worsening of respiratory symptoms that required treatment with systemic corticosteroids, antibiotics or hospital admission, or any combination of these.<br>[b] Defined as a worsening of the person's respiratory symptoms that in the view of their healthcare provider required treatment with systemic corticosteroids, antibiotics, or hospital admission, or a combination of these. Severe exacerbations were defined as those requiring hospital admission or resulting in death.<br>[c] Not all of the secondary outcomes are discussed in this evidence summary. See the paper for more details.<br>[d] Change from baseline in pre-dose $FEV_1$ ≥0.100 litre.<br>[e] A decrease from baseline in SGRQ total score ≥4 was deemed the minimum clinically important difference.<br>[f] Defined as events starting on or after first intake of randomised study medication.<br>[g] The method of randomisation used suggests allocation was concealed. |
| **Abbreviations:** CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FVC, forced vital capacity; $FEV_1$, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; SGRQ, St George's Respiratory Questionnaire (measuring health-related quality of life). | |

## Results tables

### Table 8 Singh D et al. 2016 (TRILOGY)

| | Beclometasone/ formoterol/ glycopyrronium bromide (100/6/ 12.5 micrograms) | Beclometasone/ formoterol (100/ 6 micrograms) | **Analysis** |
|---|---|---|---|
| **n**[a] | 687 | 680 | |
| **Co-primary outcomes** | | | |

| | | | |
|---|---|---|---|
| Mean change from baseline in pre-dose (morning) $FEV_1$ at week 26 | 0.082 litre<br>(95% CI 0.062 litre to 0.102 litre) | 0.001 litre<br>(95% CI −0.019 litre to 0.021 litre) | Adjusted mean difference 0.081 litre<br>(95% CI 0.052 litre to 0.109 litre)<br>p<0.001 |
| Mean change from baseline in 2-hour post-dose $FEV_1$ at week 26 | 0.261 litre<br>(95% CI 0.240 litre to 0.283 litre) | 0.145 litre<br>(95% CI 0.123 litre to 0.166 litre) | Adjusted mean difference 0.117 litre<br>(95% CI 0.086 litre to 0.147 litre)<br>p<0.001 |
| TDI focal score (change in dyspnoea severity from baseline) at week 26 | 1.71<br>(95% CI 1.50 to 1.92) | 1.50<br>(95% CI 1.29 to 1.71) | Adjusted mean difference 0.21<br>(95% CI −0.08 to 0.51)<br>p=0.160<br>No statistically significant difference |
| **Selected secondary outcomes** | | | |
| Pre-dose $FEV_1$ response[b] at week 26 | 287/687 (42%) | 165/680 (24%) | OR 2.30<br>(95% CI 1.82 to 2.91)<br>p<0.001 |
| Pre-dose $FEV_1$ response[b] at week 52 | 259/687 (38%) | 158/680 (23%) | OR 2.06<br>(95% CI 1.62 to 2.62)<br>p<0.001 |

| | | | |
|---|---|---|---|
| TDI response[c] at week 26 | 394/687 (57%) | 352/680 (52%) | OR 1.28<br>(95% CI 1.03 to 1.59)<br>p=0.027 |
| TDI response[c] at week 52 | 370/687 (54%) | 354/680 (52%) | OR 1.09<br>(95% CI 0.88 to 1.36)<br>p=0.430 |
| SGRQ response[d] at week 26 | 321/687 (47%) | 246/680 (36%) | OR 1.52<br>(95% CI 1.21 to 1.91)<br>p<0.001 |
| SGRQ response[d] at week 52 | 297/687 (43%) | 244/680 (36%) | OR 1.33<br>(95% CI 1.06 to 1.66)<br>p=0.014 |
| Rate of moderate-to-severe COPD exacerbations[e] over 52 weeks | 0.41 | 0.53 | RR 0.77<br>(95% CI 0.65 to 0.92)<br>p=0.005 |
| Time to first moderate-to-severe COPD exacerbation[e] over 52 weeks | Not applicable | Not applicable | HR 0.80<br>(95% CI 0.67 to 0.97)<br>p=0.020 |
| Percentage of days without rescue medication use during weeks 5 to 12 | 6.23%<br>(95% CI 4.19% to 8.27%) | 3.18%<br>(95% CI 1.12% to 5.24%) | Adjusted mean difference 3.05%<br>(95% CI 0.15% to 5.95%)<br>p=0.039 |

| | | | |
|---|---|---|---|
| Change from baseline in average number of puffs per day of rescue salbutamol during weeks 13 to 26 | −0.21 puffs<br>(95% CI −0.32 puffs to −0.09 puffs) | −0.02 puffs<br>(95% CI −0.14 puffs to 0.10 puffs) | Adjusted mean difference −0.19 puffs<br>(95% CI −0.35 puffs to −0.02 puffs)<br>p=0.029 |
| **Safety and tolerability outcomes**[f] | | | |
| n[g] | 687 | 680 | |
| Treatment-emergent adverse events | 368/687 (54%) | 379/680 (56%) | 58% and 63% of these respectively were COPD-related |
| Serious treatment-emergent adverse events | 106/687 (15%) | 123/680 (18%) | |
| Treatment-emergent adverse events leading to discontinuation | 35/687 (5%) | 33/680 (5%) | |
| Treatment-emergent adverse events leading to death | 15/687 (2%) | 16/680 (2%) | |
| Treatment-emergent major adverse cardiovascular events[h] | 15/687 (2%) | 15/680 (2%) | |
| Treatment-related adverse events | 26/687 (4%) | 14/680 (2%) | Primarily oral candidiasis, muscle spasms and dry mouth |
| Serious treatment-related adverse events | 1/687 (<1%) | 0/680 (0%) | 1 person developed atrial fibrillation |

[a] The intention-to-treat population includes all randomly assigned participants who received at least 1 dose of study medication and had at least 1 post-baseline efficacy assessment.

[b] Change from baseline in pre-dose $FEV_1$ ≥0.100 litre.

[c] A TDI focal score of ≥1 was deemed the minimum clinically important difference.

[d] A decrease from baseline in SGRQ total score ≥4 was deemed the minimum clinically important difference.

[e] A COPD exacerbation was defined as a worsening of the person's respiratory symptoms that in the view of their healthcare provider required treatment with systemic corticosteroids, antibiotics, or hospital admission, or a combination of these. Severe exacerbations were those requiring hospital admission or resulting in death.

[f] Statistical analyses not reported.

[g] The safety population includes all randomly assigned participants who received at least 1 dose of study medication.

[h] Acute myocardial infarction, arrhythmias, cardiovascular death, heart failure and stroke.

**Abbreviations:** CI, confidence interval; $FEV_1$, forced expiratory volume in 1 second; HR, hazard ratio; OR, odds ratio; RR, rate ratio; SGRQ, St George's Respiratory Questionnaire (measuring health-related quality of life); TDI, Transition Dyspnoea Index.

**Table 9 Vestbo J et al. 2017 (TRINITY)**

| | Fixed triple therapy: beclometasone/ formoterol/ glycopyrronium bromide (100/6/ 12.5 micrograms) | Tiotropium (18 micrograms) | Open triple therapy: beclometasone/ formoterol (100/ 6 micrograms) plus tiotropium (18 micrograms) | **Analysis** |
|---|---|---|---|---|
| **n**[a] | **1,077**[b] | **1,074**[c] | **538** | |
| **Primary outcome** | | | | |

| | | | | |
|---|---|---|---|---|
| Rate of moderate-to-severe COPD exacerbations[d] over 52 weeks | 0.46<br>(SD 0.41 to 0.51) | 0.57<br>(SD 0.52 to 0.63) | 0.45<br>(SD 0.39 to 0.52) | Primary outcome, fixed triple versus tiotropium:<br>RR 0.80<br>(95% CI 0.69 to 0.92)<br>p=0.0025<br>Secondary outcome, fixed triple versus open triple:<br>RR 1.01<br>(95% CI 0.85 to 1.21)<br>p=0.89<br>No statistically significant difference |
| **Selected secondary outcomes** | | | | |

| | | | | |
|---|---|---|---|---|
| Mean change from baseline in pre-dose $FEV_1$ at week 52 | 0.082 litre<br>(95% CI 0.065 litre to 0.100 litre) | 0.021 litre<br>(95% CI 0.003 litre to 0.039 litre) | 0.085 litre<br>(95% CI 0.061 litre to 0.110 litre) | Fixed triple versus tiotropium:<br>adjusted mean difference 0.061 litre<br>(95% CI 0.037 litre to 0.086 litre)<br>p<0.0001<br>Fixed triple versus open triple:<br>adjusted mean difference −0.003 litre<br>(95% CI −0.033 litre to 0.027 litre)<br>p=0.85<br>Non-inferior[e] |

| | | | | |
|---|---|---|---|---|
| Time to first moderate-to-severe COPD exacerbation[d] over 52 weeks | Not applicable | Not applicable | Not applicable | Fixed triple versus tiotropium:<br>HR 0.84<br>(95% CI 0.72 to 0.97)<br>p=0.0154<br>Fixed triple versus open triple:<br>HR 1.06<br>(95% CI 0.88 to 1.27)<br>p=0.57<br>No statistically significant difference |

| | | | | |
|---|---|---|---|---|
| Time to first severe COPD exacerbation[d] over 52 weeks | Not applicable | Not applicable | Not applicable | Fixed triple versus tiotropium:<br>HR 0.70<br>(95% CI 0.52 to 0.95)<br>p=0.0208<br>Fixed triple versus open triple:<br>HR 1.05<br>(95% CI 0.70 to 1.56)<br>p=0.82<br>No statistically significant difference |

| | | | | |
|---|---|---|---|---|
| Rate of moderate COPD exacerbations[d] over 52 weeks | 0.37<br>(SD 0.33 to 0.42) | 0.44<br>(SD 0.39 to 0.49) | 0.38<br>(SD 0.32 to 0.44) | Fixed triple versus tiotropium:<br>RR 0.84<br>(95% CI 0.71 to 0.98)<br>p=0.03<br>Fixed triple versus open triple:<br>RR 0.98<br>(95% CI 0.81 to 1.20)<br>p=0.87<br>No statistically significant difference |

| | | | | |
|---|---|---|---|---|
| Rate of severe COPD exacerbations[d] over 52 weeks | 0.07<br>(SD 0.05 to 0.09) | 0.10<br>(SD 0.08 to 0.12) | 0.06<br>(SD 0.04 to 0.08) | Fixed triple versus tiotropium:<br>RR 0.68<br>(95% CI 0.50 to 0.94)<br>p=0.0174<br>Fixed triple versus open triple:<br>RR 1.18<br>(95% CI 0.77 to 1.80)<br>p=0.45<br>No statistically significant difference |

| | | | | |
|---|---|---|---|---|
| Pre-dose $FEV_1$ response[f] at week 26 | 421/1,077 (39%) | 306/1,074 (28%) | 204/538 (38%) | Fixed triple versus tiotropium:<br>OR 1.61<br>(95% CI 1.34 to 1.93)<br>p<0.0001<br>Fixed triple versus open triple:<br>OR 1.04<br>(95% CI 0.84 to 1.30)<br>p=0.69<br>No statistically significant difference |

| | | | | |
|---|---|---|---|---|
| Pre-dose $FEV_1$ response[f] at week 52 | 408/1,077 (38%) | 295/1,074 (27%) | 210/538 (39%) | Fixed triple versus tiotropium:<br>OR 1.62<br>(95% CI 1.35 to 1.95)<br>p<0.0001<br>Fixed triple versus open triple:<br>OR 0.95<br>(95% CI 0.76 to 1.18)<br>p=0.63<br>No statistically significant difference |

| | | | | |
|---|---|---|---|---|
| SGRQ response[g] at week 26 | 508/1,077 (47%) | 438/1,074 (41%) | 276/538 (51%) | Fixed triple versus tiotropium:<br>OR 1.32<br>(95% CI 1.10 to 1.57)<br>p=0.0024<br>Fixed triple versus open triple:<br>OR 0.81<br>(95% CI 0.65 to 1.00)<br>p=0.0486 |

| | | | | |
|---|---|---|---|---|
| SGRQ response[g] at week 52 | 494/1,077 (46%) | 423/1,074 (39%) | 254/538 (47%) | Fixed triple versus tiotropium:<br>OR 1.33<br>(95% CI 1.11 to 1.59)<br>p=0.0019<br>Fixed triple versus open triple:<br>OR 0.91<br>(95% CI 0.73 to 1.13)<br>p=0.37<br>No statistically significant difference |

| | | | | |
|---|---|---|---|---|
| Percentage of days without rescue medication use during weeks 41 to 52 | 12.89%<br>(95% CI 10.77% to 15.01%) | 4.11%<br>(95% CI 1.94% to 6.29%) | 14.13%<br>(95% CI 11.12% to 17.14%) | Fixed triple versus tiotropium:<br>adjusted mean difference 8.78%<br>(95% CI 5.74% to 11.81%)<br>p<0.0001<br>Fixed triple versus open triple:<br>adjusted mean difference −1.24%<br>(95% CI −4.92% to 2.44%)<br>p=0.510<br>No statistically significant difference |

| | | | | |
|---|---|---|---|---|
| Change from baseline in average number of puffs per day of rescue salbutamol during weeks 41 to 52 | −0.42 puffs<br>(95% CI −0.53 puffs to −0.30 puffs) | 0.20 puffs<br>(95% CI 0.08 puffs to 0.32 puffs) | −0.46 puffs<br>(95% CI −0.63 puffs to −0.30 puffs) | Fixed triple versus tiotropium:<br>adjusted mean difference −0.61 puffs<br>(95% CI −0.78 puffs to −0.44 puffs)<br>p<0.0001<br>Fixed triple versus open triple:<br>adjusted mean difference 0.05 puffs<br>(95% CI −0.16 puffs to 0.25 puffs)<br>p=0.649<br>No statistically significant difference |
| **Safety and tolerability outcomes** | | | | |
| n[h] | 1,077[b] | 1,076[c,i] | 537[i] | |

| | | | | |
|---|---|---|---|---|
| Treatment-emergent adverse events | 594/1,077 (55%) | 622/1,076 (58%) | 309/537 (58%) | 59%,62% and 54% of these respectively were COPD-related |
| Serious treatment-emergent adverse events | 140/1,077 (13%) | 164/1,076 (15%) | 68/537 (13%) | |
| Treatment-emergent adverse events leading to discontinuation | 33/1,077 (3%) | 62/1,076 (6%) | 15/537 (3%) | |
| Treatment-emergent adverse events leading to death | 20/1,077 (2%) | 29/1,076 (3%) | 8/537 (1%) | |
| Treatment-emergent major adverse cardiovascular events[j] | 20/1,077 (2%) | 23/1,076 (2%) | 7/537 (1%) | |
| Treatment-related adverse events | 25/1,077 (2%) | 33/1,076 (3%) | 27/537 (5%) | Primarily dry mouth, muscle spasms, dysphonia and oral candidiasis |
| Serious treatment-related adverse events | 0/1,077 (0%) | 1/1,076 (<1%) | 0/537 (0%) | 1 person developed angina pectoris |

[a] The intention-to-treat population includes all randomly assigned participants who received at least 1 dose of study medication and had at least 1 post-baseline efficacy assessment.

[b] 1 person in the fixed triple-therapy group was randomised in error and did not receive the allocated therapy.

[c] 1 person in the tiotropium group received the first dose of study medication, but withdrew consent before providing any post-baseline data, and is included in the safety population but not the efficacy population.

[d] A COPD exacerbation was defined as a worsening of the person's respiratory symptoms that in the view of their healthcare provider required treatment with systemic corticosteroids, antibiotics, or hospital admission, or a combination of these. Severe exacerbations were those requiring hospital admission or resulting in death.

[e] The upper limit of the 95% CI was less than the pre-specified margin of −0.050 litre; therefore, fixed triple therapy was shown to be non-inferior to open triple therapy. Non-inferiority was confirmed in a per-protocol analysis.

[f] Change from baseline in pre-dose $FEV_1$ ≥0.100 litre.

[g] A decrease from baseline in SGRQ total score ≥4 was deemed the minimum clinically important difference.

[h] The safety population includes all randomly assigned participants who received at least 1 dose of study medication. Statistical analyses not reported.

[i] 1 person in the open triple-therapy group received only tiotropium and was included in the tiotropium arm for the safety analyses.

[j] Acute myocardial infarction, arrhythmias, cardiovascular death, heart failure, and stroke.

**Abbreviations:** CI, confidence interval; $FEV_1$, forced expiratory volume in 1 second; HR, hazard ratio; OR, odds ratio; RR, rate ratio; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire (measuring health-related quality of life).

**Table 10 Papi A et al. 2018 (TRIBUTE)**

| | Beclometasone/ formoterol/ glycopyrronium bromide (100/6/ 12.5 micrograms) | Indacaterol/ glycopyrronium bromide (110/ 63 micrograms) | **Analysis** |
|---|---|---|---|
| **n[a]** | **764** | **768** | |

| | | | |
|---|---|---|---|
| **Primary outcome** | | | |
| Rate of moderate-to-severe COPD exacerbations[b] over 52 weeks | 0.50<br>(95% CI 0.45 to 0.57) | 0.59<br>(95% CI 0.53 to 0.67) | RR 0.85<br>(95% CI 0.72 to 0.99)<br>p=0.043 |
| **Selected secondary outcomes** | | | |
| Rate of moderate COPD exacerbations[b] over 52 weeks | 0.41<br>(95% CI 0.36 to 0.47) | 0.47<br>(95% CI 0.41 to 0.54) | RR 0.87<br>(95% CI 0.72 to 1.04)<br>p=0.118<br>No statistically significant difference |
| Rate of severe COPD exacerbations[b] over 52 weeks | 0.07<br>(95% CI 0.06 to 0.10) | 0.09<br>(95% CI 0.07 to 0.12) | RR 0.79<br>(95% CI 0.55 to 1.13)<br>p=0.189<br>No statistically significant difference |
| Time to first moderate-to-severe COPD exacerbation[b] over 52 weeks | Not applicable | Not applicable | HR 0.90<br>(95% CI 0.76 to 1.06)<br>p=0.219<br>No statistically significant difference |
| Time to first severe COPD exacerbation[b] over 52 weeks | Not applicable | Not applicable | HR 0.86<br>(95% CI 0.61 to 1.22)<br>p=0.405<br>No statistically significant difference |
| Mean change from baseline in pre-dose $FEV_1$ over 52 weeks | Not reported | Not reported | Adjusted mean difference 0.022 litre<br>p<0.05 |

| | | | |
|---|---|---|---|
| Pre-dose $FEV_1$ response[c] at week 26 | 176/764 (23%) | 156/768 (20%) | OR 1.18<br>(95% CI 0.92 to 1.50)<br>p=0.194<br>No statistically significant difference |
| Pre-dose $FEV_1$ response[c] at week 52 | 145/764 (19%) | 125/768 (16%) | OR 1.19<br>(95% CI 0.91 to 1.55)<br>p=0.198<br>No statistically significant difference |
| SGRQ response[d] at week 26 | 310/764 (41%) | 292/768 (38%) | OR 1.13<br>(95% CI 0.92 to 1.40)<br>p=0.255<br>No statistically significant difference |
| SGRQ response[d] at week 52 | 311/764 (41%) | 279/768 (36%) | OR 1.22<br>(95% CI 0.99 to 1.51)<br>p=0.068<br>No statistically significant difference |
| Percentage of days without rescue medication use over 52 weeks | 8.31%<br>(95% CI 6.24% to 10.37%) | 9.66%<br>(95% CI 7.60% to 11.73%) | Adjusted mean difference 1.36%<br>(95% CI −1.56% to 4.28%)<br>p=0.361<br>No statistically significant difference |

| | | | |
|---|---|---|---|
| Change from baseline in average number of puffs per day of rescue salbutamol or terbutaline over 52 weeks | −0.29 puffs (95% CI −0.40 puffs to −0.18 puffs) | −0.24 puffs (95% CI −0.35 puffs to −0.13 puffs) | Adjusted mean difference −0.05 puffs (95% CI −0.20 puffs to −0.10 puffs) p=0.517 No statistically significant difference |
| **Safety and tolerability outcomes**[e] | | | |
| n[f] | 764 | 768 | |
| Treatment-emergent adverse events | 490/764 (64%) | 516/768 (67%) | 56% of these were COPD-related in both groups |
| Serious treatment-emergent adverse events | 117/764 (15%) | 130/768 (17%) | |
| Treatment-emergent adverse events leading to discontinuation | 37/764 (5%) | 47/768 (6%) | |
| Treatment-emergent adverse events leading to death | 16/764 (2%) | 21/768 (3%) | |
| Treatment-related adverse events | 43/764 (6%) | 37/768 (5%) | Primarily oral candidiasis, dry mouth and cough |
| Serious treatment-related adverse events | 1/764 (<1%) | 1/768 (<1%) | 1 person developed dysuria in the triple-therapy group and 1 person developed atrial fibrillation in the dual-therapy group |

[a] The intention-to-treat population includes all randomly assigned participants who received at least 1 dose of study medication and had at least 1 post-baseline efficacy assessment.

[b] Defined as a worsening of the person's respiratory symptoms that in the view of their healthcare provider required treatment with systemic corticosteroids, antibiotics, or hospital admission, or a combination of these. Severe exacerbations were defined as those requiring hospital admission or resulting in death.

[c] Change from baseline in pre-dose $FEV_1$ ≥0.100 litre.

[d] A decrease from baseline in SGRQ total score ≥4 was deemed the minimum clinically important difference.

[e] Statistical analyses not reported.

[f] The safety population includes all randomly assigned participants who received at least 1 dose of study medication.

**Abbreviations:** CI, confidence interval; $FEV_1$, forced expiratory volume in 1 second; HR, hazard ratio; OR, odds ratio; RR, rate ratio; SGRQ, St George's Respiratory Questionnaire (measuring health-related quality of life).

## Excluded studies

| Study reference | Reason for exclusion |
|---|---|
| Gosden TB, Dhanjal J, Arper D et al. (2017) Assessing the cost effectiveness of a new, first-in-class triple fixed dose combination therapy for COPD patients. Value in Health 20(9): A647 | Abstract only |
| Gosden TB, Dhanjal J, Arper D et al. (2017) Budget impact of a new, first-in-class triple fixed dose combination therapy for COPD patients. Value in Health 20(9): A641 | Abstract only |

## Terms used in this evidence summary

Baseline Dyspnoea Index (BDI): a validated 24-item questionnaire to rate the severity of dyspnoea at a single time point. It is administered by an investigator and measures 3 components relating to dyspnoea in activities of daily living (functional impairment, magnitude of task and magnitude of effort). Each category is rated on a 5-point scale ranging from 0 (very severe) to 4 (no impairment) giving a total score ranging from 0 to 12, with a lower score indicating more severe dyspnoea.

St George's Respiratory Questionnaire (SGRQ): a validated 50-item questionnaire developed to measure health status (quality of life) in people with diseases of airways obstruction such as COPD. It is self-administered and scores are subsequently calculated for 3 domains (symptoms, activity and psychosocial impact) as well as a total score. A score of 100 represents worst possible health status and 0 indicates best possible health status. A minimum change in score of 4 units is considered to be clinically important.

Transition Dyspnoea Index (TDI): measures changes in dyspnoea severity from the baseline as established by the BDI. The 3 components (functional impairment, magnitude of task and magnitude of effort) are each rated on a 7-point scale ranging from −3 (major deterioration) to +3 (major improvement), giving a total score from −9 to +9, with a lower score indicating more deterioration in dyspnoea. A TDI focal score of ≥1 is considered to be clinically important.

## Search strategy

**Database: Medline**

Platform: Ovid

Version: 1946 to present with daily update

Search date: 19/12/2017

Number of results retrieved: 6

Search strategy:

Database: Ovid MEDLINE(R) 1946 to Present with Daily Update

Search Strategy:

---

1 (trimbow or chf5993 or chf 5993).tw. (2)

2 Beclomethasone/ (3085)

3 (beclomethason* or beklomethason* or Beclometason* or beklometason*or qvar or clenil or "asmabec clickhaler").tw. (2955)

4 2 or 3 (3873)

5 Formoterol Fumarate/ (1660)

6 (formoterol* or eformoterol or "BD-40A" or "CGP-25827A" or "YM-08316" or oxis).tw. (2017)

7 5 or 6 (2243)

8 Glycopyrrolate/ (972)

9 (glycopyrronium or glycopyrrolate or sialanar).tw. (1130)

10 8 or 9 (1330)

11 4 and 7 and 10 (6)

12 1 or 11 (6)

**Database: Medline in-process**

Platform: Ovid

Version: December 18 2017

Search date: 19/12/2017

Number of results retrieved: 6

Search strategy:

---

1 (trimbow or chf5993 or chf 5993).tw. (1)

2 Beclomethasone/ (0)

3 (beclomethason* or beklomethason* or Beclometason* or beklometason*or qvar or clenil or "asmabec clickhaler").tw. (128)

4 2 or 3 (128)

5 Formoterol Fumarate/ (0)

6 (formoterol* or eformoterol or "BD-40A" or "CGP-25827A" or "YM-08316" or oxis).tw. (185)

7 5 or 6 (185)

8 Glycopyrrolate/ (0)

9 (glycopyrronium or glycopyrrolate or sialanar).tw. (145)

10 8 or 9 (145)

11 4 and 7 and 10 (6)

12 1 or 11 (6)

**Database: Medline epubs ahead of print**

Platform: Ovid

Version December 18 2017

Search date: 19/12/2017

Number of results retrieved: 0

Search strategy: as above

**Database: Embase**

Platform: Ovid

Version: 1974 to 2017 December 18

Search date: 19/12/2017

Number of results retrieved: 52

Search strategy:

Database: Embase <1974 to 2017 December 18>

Search Strategy:

---

1 (trimbow or chf5993 or chf 5993).tw. (11)

2 beclometasone dipropionate plus formoterol fumarate plus glycopyrronium bromide/ (25)

3 1 or 2 (26)

4 beclometasone dipropionate/ or beclometasone/ (13881)

5 (beclomethason* or beklomethason* or Beclometason* or beklometason* or qvar or clenil or "asmabec clickhaler").tw. (4441)

6 4 or 5 (14250)

7 formoterol fumarate/ or formoterol/ (6098)

8 (formoterol* or eformoterol or "BD-40A" or "CGP-25827A" or "YM-08316").tw. (3521)

9 7 or 8 (7068)

10 Glycopyrrolate/ (618)

11 (glycopyrronium or glycopyrrolate or sialanar).tw. (1795)

12 10 or 11 (2177)

13 6 and 9 and 12 (37)

14 3 or 13 (52)

**Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); DARE; CENTRAL; HTA database; NHS EED**

Platform: Wiley

Version:

CDSR – 12 of 12 December 2017

DARE – 2 of 4, April 2015 (legacy database) 0

CENTRAL – 11 of 12 November 2017

HTA – 4 of 4 October 2016

NHS EED – 2 of 4, April 2015 (legacy database) 0

Search date:

Number of results retrieved: CDSR 0; DARE 0 CENTRAL 26; HTA 0; NHS EED.0 Search strategy:

Search Name:

Date Run: 19/12/17 14:29:14.349

Description:

ID Search Hits

#1 trimbow.or chf5993 or chf 5993:ti,ab,kw (Word variations have been searched) 3

#2 MeSH descriptor: [Beclomethasone] explode all trees 952

#3 beclomethason* or beklomethason* or Beclometason* or beklometason* or qvar or clenil or "asmabec clickhaler":ti,ab,kw (Word variations have been searched) 2323

#4 #2 or #3 2323

#5 MeSH descriptor: [Formoterol Fumarate] explode all trees 645

#6 formoterol* or eformoterol or "BD-40A" or "CGP-25827A" or "YM-08316" or oxis:ti,ab,kw (Word variations have been searched) 2292

#7 #5 or #6 2292

#8 MeSH descriptor: [Glycopyrrolate] explode all trees 267

#9 glycopyrronium or glycopyrrolate or sialanar:ti,ab,kw (Word variations have been searched) 1259

#10 #8 or #9 1259

#11 #4 and #7 and #10 26

#12 #1 or #11 26

## Development of this evidence summary

The evidence summary: process guide (2017) sets out the process NICE uses to select topics for evidence summaries and details how the summaries are developed, quality assured and approved for publication.

### *Expert advisers*

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## *Declarations of interest*

Peter Calverley receives payments from Boehringer Ingelheim for advice on clinical trial design and conduct, and speaking at meetings. He has also received an honorarium from GSK for work on a study.

Anastasios Lekkas: no relevant interests declared.

Sarah Scrivener: no relevant interests declared.

Jadwiga Wedzicha has received research grants for her institution from GSK, Astra Zeneca, Novartis and Boehringer Ingelheim.

**About this evidence summary**

Evidence summaries provide a summary of the best available published evidence for selected new medicines, unlicensed medicines or off-label use of licensed medicines.

The summaries assess the strengths and weaknesses of the best available evidence to inform health professionals and commissioners' decision-making.

**This summary is not NICE guidance.**

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