

# Chronic obstructive pulmonary disease: fluticasone furoate, umeclidinium and vilanterol (Trelegy)

## Evidence summary

Published: 14 June 2018

[nice.org.uk/guidance/es18](https://www.nice.org.uk/guidance/es18)

## Key points

The content of this evidence summary was up-to-date in June 2018. See [summaries of product characteristics](#) (SPC), [British national formulary](#) (BNF) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

**Regulatory status:** Fluticasone furoate/umeclidinium/vilanterol ([Trelegy](#), GlaxoSmithKline UK) received a [European marketing authorisation](#) in November 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 ([summary of product characteristics](#)).

## Overview

This evidence summary discusses 2 randomised controlled trials (RCTs) looking at the safety and efficacy of fluticasone furoate/umeclidinium/vilanterol (an ICS/LAMA and LABA combination inhaler) in people with COPD who were symptomatic despite regular maintenance treatment and who either had a history, or were at risk, of exacerbations.

Fluticasone furoate/umeclidinium/vilanterol ([Trelegy](#)) is licensed for maintenance treatment of adults with moderate-to severe COPD who are not adequately treated by a combination of an ICS and a LABA. Fluticasone furoate/umeclidinium/vilanterol has been shown to reduce the annual rate of moderate or severe exacerbations by 15% compared with fluticasone furoate/vilanterol. The NICE [COPD full guideline](#) considers 20% to be the minimum clinically important difference. There was no statistically significant difference between fluticasone furoate/umeclidinium/vilanterol and fluticasone furoate/vilanterol for the annual rate of severe COPD exacerbations. Compared with umeclidinium/vilanterol, fluticasone furoate/umeclidinium/vilanterol reduced the annual rate of moderate or severe exacerbations by 25% and the annual rate of severe exacerbations by 34%. However, 39% of the participants in the umeclidinium/vilanterol group were previously using an ICS, LABA and a LAMA and stopped ICS treatment upon randomisation. It is unclear whether or not this abrupt cessation of ICS treatment may have had an effect on exacerbation outcomes.

There were improvements in the St George's Respiratory Questionnaire total score ([SGRQ](#); a health-related quality of life score) with fluticasone furoate/umeclidinium/vilanterol compared with budesonide/formoterol after 24 weeks' treatment, however there was no difference between the 2 groups after 52 weeks' treatment. There were also improvements in SGRQ total score with fluticasone furoate/umeclidinium/vilanterol compared with both fluticasone furoate/vilanterol and umeclidinium/vilanterol although the differences were less than what is considered to be the minimum clinically important difference.

More participants had a clinically significant improvement in dyspnoea (defined as a Transitional Dyspnoea Index ([TDI](#)), focal score of at least a 1-unit increase) with fluticasone furoate/umeclidinium/vilanterol compared with fluticasone furoate/vilanterol (36% compared with 29% respectively).

There was an increase of 171 ml in change from baseline in trough forced expiratory volume in 1 second (FEV<sub>1</sub>) with fluticasone furoate/umeclidinium/vilanterol compared with budesonide/formoterol. However, the European Public Assessment Report ([EPAR](#)) highlighted that the results for the fluticasone furoate/umeclidinium/vilanterol group may be unduly flattering as people in the comparator group were undertreated for their degree of severity of COPD and may have benefited from additional treatment.

The EPAR stated that the safety profile of fluticasone furoate/umeclidinium/vilanterol was in line with the pharmacologic class of each component and with the dual combination products fluticasone furoate/vilanterol and umeclidinium/vilanterol, and no new safety signals emerged in the populations studied. However, the EPAR highlighted that pneumonia occurred more frequently

with fluticasone furoate/umeclidinium/vilanterol than with budesonide/formoterol. There was no difference between fluticasone furoate/umeclidinium/vilanterol and fluticasone furoate/vilanterol for risk of pneumonia. There was a statistically significant higher risk of pneumonia with fluticasone furoate/umeclidinium/vilanterol compared with umeclidinium/vilanterol. There were fewer all-cause mortality deaths in the fluticasone furoate/umeclidinium/vilanterol group than the umeclidinium/vilanterol group, although the overall number of deaths in the study was low.

It is not known from these studies how the efficacy and safety of fluticasone furoate/umeclidinium/vilanterol compares with other treatments for COPD such as other combinations of an ICS/LABA (alone or with a separate LAMA) or beclometasone/formoterol/glycopyrronium (Trimbow).

Fluticasone furoate/umeclidinium/vilanterol may be suitable for some people with moderate-to-severe COPD who have found triple therapy beneficial using more than 1 inhaler, who have difficulty using multiple inhalers and can use a dry powder inhaler.

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 [Lipson et al. 2018 \(IMPACT\)](#), there was a statistically significant 15% reduction in the annual rate of moderate or severe exacerbations with fluticasone furoate/umeclidinium/vilanterol compared with fluticasone furoate/vilanterol (0.91 compared with 1.07 per year, rate ratio [RR] 0.85, 95% [confidence interval](#) [CI] 0.80 to 0.90;  $p < 0.001$ ). There was a 25% reduction compared with umeclidinium/vilanterol (0.91 compared with 1.21, RR 0.75, 95% CI 0.70 to 0.81;  $p < 0.001$ , RCT, primary outcome,  $n = 10,355$ , 52 weeks).
- In Lipson et al. 2018, there was no statistically significant difference between fluticasone furoate/umeclidinium/vilanterol and fluticasone furoate/vilanterol for the annual rate of severe exacerbations (0.13 compared with 0.15 per year, RR 0.87, 95% CI 0.76 to 1.01;  $p = 0.06$ ) and a statistically significant 34% reduction compared with umeclidinium/vilanterol (0.13 compared with 0.19 per year, RR 0.66, 95% CI 0.56 to 0.78;  $p < 0.001$ ).
- In [Lipson et al. 2017 \(FULFIL\)](#), there was a statistically significant improvement in the change from baseline in SGRQ total score with fluticasone furoate/umeclidinium/vilanterol compared with budesonide/formoterol after 24 weeks treatment ( $-2.2$  units, 95% CI  $-3.5$  to  $-1.0$  units;  $p < 0.001$ ). However there was no statistically significant difference between the 2 groups after 52 weeks' treatment ( $-2.7$  units, 95% CI  $-5.5$  to  $0.2$  units;  $p = 0.065$ , RCT, co-primary outcome,  $n = 1,811$  and  $n = 430$  for 52-week data).
- In Lipson et al. 2018, there were statistically significant improvements in the change from baseline in SGRQ total score with fluticasone furoate/umeclidinium/vilanterol compared with both fluticasone furoate/vilanterol ( $-1.8$  units, 95% CI  $-2.4$  to  $-1.1$  units;  $p < 0.001$ ) and umeclidinium/vilanterol ( $-1.8$  units, 95% CI  $-2.6$  to  $-1.0$  units;  $p < 0.001$ ; secondary outcome). However, the differences between the groups were less than the 4 units' decrease considered to be the minimum clinically important difference.
- In Lipson et al. 2017, there was a statistically significant improvement in the change from baseline in trough forced expiratory volume in 1 second ( $FEV_1$ ) with fluticasone furoate/umeclidinium/vilanterol compared with budesonide/formoterol (142 ml compared with  $-29$  ml respectively; difference 171 ml, 95% CI 148 ml to 194 ml;  $p < 0.001$ , co-primary outcome).
- In Lipson et al. 2018, more participants had a clinically significant improvement in TDI focal score with fluticasone furoate/umeclidinium/vilanterol compared with fluticasone furoate/vilanterol (36% compared with 29% respectively, odds ratio 1.36; 95% CI 1.19 to 1.55,  $p < 0.001$ , RCT, additional outcome in a subset of participants,  $n = 5,058$ , 52 weeks).

## Safety

- The EPAR highlighted that pneumonia occurred more frequently in the fluticasone furoate/umeclidinium/vilanterol group than the budesonide/formoterol group in the Lipson et al. 2017 study (2.2% participants compared with 0.8% participants). The EPAR further added that the significance of this, if any, is uncertain as both groups contained an ICS and it is unknown if there are differences within the class for ICS propensity to cause pneumonia. The Medicines and Healthcare products Regulatory Agency issued a [Drug Safety Update](#) in October 2007 on the risk of pneumonia with inhaled corticosteroids. In Lipson et al. 2017 for the subset who continued treatment for 52 weeks the incidence of pneumonia was similar between the 2 groups (1.9% and 1.8%).
- There was no statistically significant difference between fluticasone furoate/umeclidinium/vilanterol and fluticasone furoate/vilanterol for the risk of pneumonia (hazard ratio [HR] 1.02, 95% CI 0.87 to 1.19; p=0.85). However, there was a statistically significant higher risk of pneumonia with fluticasone furoate/vilanterol/umeclidinium compared with umeclidinium/vilanterol (HR 1.53; 95% CI 1.22 to 1.92; p<0.001).
- According to the [SPC](#) the most commonly reported adverse reactions with fluticasone furoate/umeclidinium/vilanterol were nasopharyngitis (7%), headache (5%) and upper respiratory tract infection (2%).

## Patient factors

- It is not known from the studies whether the single triple-therapy inhaler has any advantages over triple therapy in separate inhalers in terms of patient factors such as preference, adherence to treatment and ease of use of devices.
- 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.
- Fluticasone furoate/umeclidinium/vilanterol is supplied in a dry powder inhaler (Ellipta inhaler) and cannot be used with a spacer. Beclometasone/formoterol/glycopyrronium (Trimbow) is supplied in a pressurised metered-dose inhaler and can be used with a spacer. Some people may prefer a particular inhaler device or be able to use one device better than another and some people are unable to use a spacer, others like to use one.
- Fluticasone furoate/umeclidinium/vilanterol is administered once daily and beclometasone/formoterol/glycopyrronium (Trimbow) is administered twice daily.

### Resource implications

- The acquisition cost of fluticasone furoate/umeclidinium/vilanterol (Trelegy) is less than that of other combinations of ICS/LABA plus LAMA in 2 inhalers.
- A 30-day supply of treatment with fluticasone furoate, umeclidinium and vilanterol costs £44.50 (excluding VAT) when the triple-therapy inhaler (Trelegy) is prescribed. This compares with £49.50 (excluding VAT) when fluticasone furoate and vilanterol are prescribed in a dual-therapy inhaler (Relvar Ellipta, fluticasone furoate/vilanterol 92/22 micrograms) together with umeclidinium in a single-therapy inhaler (Incruse Ellipta).
- Triple therapy with fluticasone furoate/umeclidinium/vilanterol (Trelegy) costs the same as triple therapy with beclometasone/formoterol/glycopyrronium (Trimbow).

Costs taken from the [Drug Tariff](#) and [MIMS](#), May 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<sub>1</sub>) is 50% predicted or more: either a long-acting beta-2 agonist (LABA) or a long-acting muscarinic antagonist (LAMA)
  - if FEV<sub>1</sub> is less than 50% predicted: either a LABA with an inhaled corticosteroid (ICS) in a combination inhaler, or a LAMA.

- In people with stable COPD and an FEV<sub>1</sub> 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<sub>1</sub>.
- 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<sub>1</sub>.
- 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, the guideline is to be updated (expected publication date November 2018).

This evidence summary discusses the best available evidence for the safety and efficacy of the triple combination inhaler containing fluticasone furoate (ICS), umeclidinium (LAMA) and vilanterol (LABA; [Trelegy](#)).

## Product overview

### *Mode of action*

Trelegy (GlaxoSmithKline UK) contains fluticasone furoate, umeclidinium bromide and vilanterol (as trifenate) and is, therefore, a combination of an inhaled corticosteroid (ICS), long-acting muscarinic receptor antagonist (LAMA) and long-acting beta-2 agonist (LABA). Following oral inhalation, umeclidinium and vilanterol act locally on airways to produce bronchodilation by separate mechanisms and fluticasone furoate reduces inflammation ([summary of product characteristics](#)).

## *Regulatory status*

Fluticasone furoate/umeclidinium/vilanterol received a European marketing authorisation in November 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 single inhalation of fluticasone furoate/umeclidinium/vilanterol provides a delivered dose (the dose leaving the mouthpiece) of 92 micrograms fluticasone furoate, 65 micrograms umeclidinium bromide (equivalent to 55 micrograms of umeclidinium) and 22 micrograms vilanterol (as trifenate). Each pre-dispensed dose contains 100 micrograms fluticasone furoate, 74.2 micrograms umeclidinium bromide (equivalent to 62.5 micrograms umeclidinium) and 25 micrograms vilanterol (as trifenate).

The recommended (and maximum) dose of fluticasone furoate/umeclidinium/vilanterol is 1 inhalation daily.

## *Cost*

A fluticasone furoate/umeclidinium/vilanterol dry powder inhaler costs £44.50 and provides 30 inhalations (30 days' treatment; cost [excluding VAT] from [MIMS](#), May 2018).

## *Evidence review*

A literature search was conducted which identified 121 references (see [search strategy](#) for full details). These references were screened using their titles and abstracts and 2 references were obtained and assessed for relevance.

One randomised controlled trial (RCT) on the safety and efficacy of fluticasone furoate/umeclidinium/vilanterol was identified from the search ([Lipson DA et al. 2017 \[FULFIL\]](#)) and included in this evidence summary. One further RCT was published after the searches were undertaken and has also been included ([Lipson DA et al. 2018 \[IMPACT\]](#)). A summary of these studies is shown in table 2 (see [evidence tables](#) for full details).

A cost-utilisation study based on the FULFIL study was also identified from the search ([Ismaila AS et al. 2017](#)) and has been summarised briefly in this evidence summary (see [estimated impact for the NHS](#) for more details).

**Table 2 Summary of included studies**

Study	Population	Intervention and comparison	Primary outcomes
-------	------------	-----------------------------	------------------

<p><u>Lipson DA et. al 2017 (FULFIL)</u> RCT conducted at 200 study centres globally (with no centres in the UK).</p>	<p>1,811 adults aged 40 years or older with COPD and an:</p> <ul style="list-style-type: none"> <li>• FEV<sub>1</sub> &lt; 50% and CAT score ≥ 10 or</li> <li>• FEV<sub>1</sub> ≥ 50% to &lt; 80% and CAT score ≥ 10 and either ≥ 2 moderate exacerbations in the past year or ≥ 1 severe exacerbation in past year.</li> </ul> <p>Participants also had to have been receiving daily maintenance therapy for COPD for at least 3 months.</p> <p>A subset of the first 430 participants to enter the study and consent to longer-term treatment remained on their allocated study treatment for up to 52 weeks.</p>	<p>Triple therapy with fluticasone furoate 100 micrograms, umeclidinium 62.5 micrograms and vilanterol 25 micrograms in a single inhaler (Ellipta device) once a day (n=911) versus</p> <p>Dual therapy with budesonide 400 micrograms and formoterol 12 micrograms in a single inhaler (Turbohaler) twice a day (n=899).</p>	<p>Co-primary outcomes (assessed at week 24):</p> <ul style="list-style-type: none"> <li>• change from baseline in trough FEV<sub>1</sub></li> <li>• change from baseline in SGRQ total score.</li> </ul>
---	---	---	---

<p><a href="#">Lipson DA et al. 2018 (IMPACT)</a> RCT Multicentre study conducted in 37 countries including the UK.</p>	<p>10,355 adults aged 40 years or older with COPD and:</p> <ul style="list-style-type: none"> <li>• FEV<sub>1</sub> &lt;50% and CAT score ≥10 and a history of at least 1 moderate or severe exacerbation in the previous year or</li> <li>• FEV<sub>1</sub> ≥ 50% to &lt; 80% and a CAT score ≥10 at least 2 moderate or 1 severe exacerbation in the previous year.</li> </ul>	<p>The 2 co-primary treatment comparisons were:</p> <ul style="list-style-type: none"> <li>• triple therapy with fluticasone furoate 100 micrograms, umeclidinium 62.5 micrograms and vilanterol 25 micrograms in a single inhaler once a day (n=4,151) versus dual therapy with umeclidinium 62.5 micrograms and vilanterol 25 micrograms in a single inhaler once a day (n=2,070) and</li> <li>• the fluticasone furoate/umeclidinium/vilanterol group (n=4,151) versus dual therapy with fluticasone furoate 100 micrograms and vilanterol 25 micrograms in a single inhaler once a day (n=4,134).</li> </ul> <p>All treatments were given in an Ellipta device.</p>	<p>Annual rate of moderate or severe COPD exacerbations<sup>a</sup> (on-treatment).</p>
---	--	---	---

Abbreviations: CAT, [COPD Assessment Test](#) (assesses all aspects of the impact of COPD on a scale of 0 to 40, higher scores indicate more symptoms); COPD, chronic obstructive pulmonary disease; FEV<sub>1</sub>, forced expiratory volume in 1 second; [GOLD](#), Global Initiative for COPD; RCT, randomised controlled trial; [SGRQ](#), [St George's Respiratory Questionnaire](#) (measuring health-related quality of life).

<sup>a</sup> A moderate exacerbation was defined as an exacerbation leading to treatment with antibiotics or systemic corticosteroids. A severe exacerbation required hospitalisation or resulted in death.

## Clinical effectiveness

An overview of the results for clinical effectiveness can be found in the [results tables](#).

The [European public assessment report](#) (EPAR) for fluticasone furoate/umeclidinium/vilanterol states that there is a lack of evidence to claim a step-up indication from a long-acting muscarinic antagonist (LAMA) and LABA combination regime due to the absence of a LAMA plus LABA

combination as a comparator in the main phase III study ([Lipson et al. 2017](#)) considered for the license application.

## Exacerbations of COPD

In the IMPACT study ([Lipson et al. 2018](#)) there was a statistically significant 15% reduction in the annual rate of moderate or severe exacerbations (primary outcome) with fluticasone furoate/umeclidinium/vilanterol compared with fluticasone furoate/vilanterol (0.91 per year compared with 1.07 per year, rate ratio 0.85, 95% [confidence interval](#) [CI] 0.80 to 0.90;  $p < 0.001$ ). Although this is a statistically significant reduction, it is less than the 20% relative risk reduction for COPD exacerbations that the [NICE COPD full guideline](#) considers to be the minimum clinically important difference. There was also a statistically significant 25% reduction in the annual rate of on-treatment moderate or severe exacerbations with fluticasone furoate/umeclidinium/vilanterol compared with umeclidinium/vilanterol (0.91 per year compared with 1.21 per year, rate ratio 0.75, 95% CI 0.70 to 0.81;  $p < 0.001$ ), however the upper 95% CI crosses the minimum clinically important difference of 20%. The study included a 2-week run-in period prior to randomisation where participants continued using their current COPD medication; 39% of the participants in the umeclidinium/vilanterol group were previously using an ICS, LABA and a LAMA. It is unclear whether or not this abrupt cessation of ICS treatment in the umeclidinium/vilanterol group may have had an effect on exacerbation outcomes. In the fluticasone furoate/vilanterol group, 38% of participants were also using an ICS, LABA and LAMA prior to randomisation and so they will have also had a step down in treatment.

[Lipson et al. 2018](#) included several secondary outcomes on exacerbations. In line with the results for the annual rates of moderate or severe exacerbations, there was a statistically significant reduction in the time to first on-treatment moderate or severe exacerbation with fluticasone furoate/umeclidinium/vilanterol compared with both fluticasone furoate/vilanterol and umeclidinium/vilanterol (see table 7 for results). There was a statistically significant 34% reduction in the annual rate of on-treatment severe exacerbations with fluticasone furoate/umeclidinium/vilanterol compared with umeclidinium/vilanterol (0.13 per year compared with 0.19 per year, rate ratio 0.66, 95% CI 0.56 to 0.78;  $p < 0.001$ ). However, there was no statistically significant difference for this outcome for the triple-therapy regime compared with fluticasone furoate/vilanterol (0.13 per year compared with 0.15 per year, rate ratio 0.87, 95% CI 0.76 to 1.01;  $p = 0.06$ ).

[Lipson et al. 2018](#) also included a secondary outcome on the annual rate of on-treatment moderate or severe exacerbations in participants with a blood eosinophil count greater than or equal to 150 cells per millilitre at baseline. This was 0.95 per year (95% CI 0.90 to 1.01 per year) in the fluticasone furoate/umeclidinium/vilanterol group, 1.08 per year (95% CI 1.02 to 1.14 per year) in

the fluticasone furoate/vilanterol group and 1.39 per year (95% CI 1.29 to 1.51 per year) in the umeclidinium/vilanterol group. For participants with an eosinophil level less than 150 cells per millilitre at baseline, the annual rate of moderate or severe exacerbations was 0.85 (95% CI 0.80 to 0.91) with fluticasone furoate/umeclidinium/vilanterol, 1.06 (95% CI 0.99 to 1.14) with fluticasone furoate/vilanterol and 0.97 (95% CI 0.88 to 1.07) with umeclidinium/vilanterol. No between-group statistical comparisons were provided in the paper for this outcome.

In the FULFIL study (Lipson et al. 2017) the number of moderate and severe COPD exacerbations over the 24-week treatment period was low (95/911 [10%] in the fluticasone furoate/umeclidinium/vilanterol group and 126/899 [14%] in the budesonide/formoterol group). At week 24 the mean annualised rate of moderate and severe exacerbations was 0.22 in the fluticasone furoate/umeclidinium/vilanterol group and 0.34 in the budesonide/formoterol group (rate ratio 0.65, 95% CI 0.49 to 0.86;  $p=0.002$ ). The EPAR for fluticasone furoate/umeclidinium/vilanterol highlighted that as COPD exacerbations are highly seasonal anything less than a 12 month study is considered sub-optimal to measure exacerbation rates. However, a subgroup of 430 participants continued treatment for up to 52 weeks, in this subgroup the mean annualised rate of moderate and severe exacerbations was 0.20 and 0.36 in the fluticasone furoate/umeclidinium/vilanterol and budesonide/formoterol groups respectively (rate ratio 0.56, 95% CI 0.37 to 0.85%;  $p=0.006$ ).

## Health-related quality of life

A co-primary outcome in the FULFIL study (Lipson et al. 2017) was change from baseline in the St George's Respiratory Questionnaire total score (SGRQ: which measures health-related quality of life). The difference between the fluticasone furoate/umeclidinium/vilanterol group and the budesonide/formoterol group for this outcome was  $-2.2$  units (95% CI  $-3.5$  to  $-1.0$  units;  $p<0.001$ ). This is less than the 4 units decrease in SGRQ total score considered to be the minimum clinically important difference in the study. The study included a secondary outcome on the proportion of participants with at least a 4-unit decrease in SGRQ total score from baseline after 24 weeks' treatment. This was seen in a statistically significant higher percentage of participants in the fluticasone furoate/umeclidinium/vilanterol group compared with the budesonide/formoterol group (50% and 41% respectively, odds ratio 1.41, 95% CI 1.16 to 1.70;  $p<0.001$ ).

For the subset of 430 participants who continued treatment up to week 52, there was no statistically significant difference between the 2 treatment groups for mean change from baseline to week 52 in SGRQ total score, which was  $-4.6$  units in the fluticasone furoate/umeclidinium/vilanterol group compared with  $-1.9$  units in the budesonide/formoterol group (between group difference:  $-2.7$  units, 95% CI  $-5.5$  to 0.2 units;  $p=0.065$ ).

Lipson et al. 2018 included mean change from baseline in SGRQ total score at week 52 as a secondary outcome. At week 52 the mean change in SGRQ was –5.5 units in the fluticasone furoate/umeclidinium/vilanterol group and –3.7 units in both the fluticasone furoate/vilanterol and umeclidinium/vilanterol groups. A statistically significant difference was shown between fluticasone furoate/umeclidinium/vilanterol and the 2 dual-therapy groups, however this difference of –1.8 units is less than the –4 units in SGRQ total score considered to be the minimum clinically important difference. However, more participants had a clinically significant improvement from baseline in SGRQ total score with fluticasone furoate/umeclidinium/vilanterol compared with both fluticasone furoate/vilanterol and umeclidinium/vilanterol (42% compared with 34% in both groups, see table 7 for results).

## Lung function

Lipson et al. 2017 found that participants who had triple therapy with fluticasone furoate/umeclidinium/vilanterol had a 171 ml greater change from baseline in trough FEV<sub>1</sub> at week 24 (a co-primary outcome) compared with dual therapy with budesonide/formoterol (142 ml compared with –29 ml respectively; difference 171 ml 95% CI 148 ml to 194 ml; p<0.001). In the study, an increase from baseline in trough FEV<sub>1</sub> of at least 100 ml was considered the minimum clinically important difference. In the fluticasone furoate/umeclidinium/vilanterol group the increase from baseline in trough FEV<sub>1</sub> was 142 ml. However, in the comparator budesonide/formoterol group there was a decrease in trough FEV<sub>1</sub> of –29 ml from baseline. Prior to randomisation, 28% of the budesonide/formoterol group were using an ICS, LABA and a LAMA and so would have had a step down in therapy. Therefore some participants in the comparator group may have been undertreated for their severity of COPD compared to participants in the fluticasone furoate/umeclidinium/vilanterol group. The EPAR for fluticasone furoate/umeclidinium/vilanterol highlighted that in the study the results for the treatment group may be unduly flattering as the comparator group were undertreated for their degree of severity of COPD and may have benefited from additional treatment.

Lipson et al. 2017 included a secondary outcome on the proportion of participants with at least a 100-ml increase in trough FEV<sub>1</sub> from baseline after 24 weeks' treatment. In the fluticasone furoate/umeclidinium/vilanterol group this proportion was 50% compared with 21% in the budesonide/formoterol group (odds ratio 4.03, 95% CI 3.27 to 4.97; p<0.001).

A subset of 430 participants continued on their allocated study treatment for up to 52 weeks. For this group the mean change from baseline to week 52 for trough FEV<sub>1</sub> was 126 ml in the fluticasone furoate/umeclidinium/vilanterol group (n=210) and –59 ml in the budesonide/formoterol group (n=220; between group difference: 179 ml, 95% CI 131 ml to 226 ml; p<0.001).

## Additional outcomes

A secondary outcome in Lipson et al. 2017, was change from baseline in [Evaluating Respiratory Symptoms in COPD total score](#) (a scale used to measure the effect of treatment on the severity of respiratory symptoms in stable COPD). The study reported that there were statistically significant reductions from baseline for this outcome measure with fluticasone furoate/umeclidinium/vilanterol compared with budesonide/formoterol. However, the data provided in the study paper for this outcome was limited.

Time to death from any cause was included in Lipson et al. 2018 as a pre-specified additional outcome. There were 50/4,151 (1.20%) on-treatment deaths in the fluticasone furoate/umeclidinium/vilanterol group, 49/4,134 (1.19%) in the fluticasone furoate/vilanterol group and 39/2,070 (1.88%) in the umeclidinium/vilanterol group. The [hazard ratio](#) (HR) for on-treatment all-cause mortality for fluticasone furoate/umeclidinium/vilanterol compared with umeclidinium/vilanterol was 0.58 (95% CI 0.38 to 0.88; unadjusted  $p=0.01$ ). However, the overall number of deaths in the study was low. In addition the study included multiple pre-specified additional outcomes and treatment comparisons for these additional outcomes were not corrected for multiplicity.

In Lipson et al. 2018 an additional outcome assessed dyspnoea in a subset of participants ( $n=5,058$ ). Dyspnoea was measured using the [Transitional Dyspnoea Index](#) (TDI), which measures change in dyspnoea severity from baseline. A TDI focal score of at least 1 unit is considered to be the minimum clinically important difference. Within the subset, a greater proportion of participants had at least a 1 unit increase in TDI focal score in the fluticasone furoate/umeclidinium/vilanterol group compared with either dual-therapy group; 36% in the triple-therapy group compared with 29% in the fluticasone furoate/vilanterol group and 30% in the umeclidinium/vilanterol group. The odds ratio for at least a 1 unit increase in TDI focal score (response) versus non-response for fluticasone furoate/umeclidinium/vilanterol compared with fluticasone furoate/vilanterol was 1.36 (95% CI 1.19 to 1.55,  $p<0.001$ ). For triple therapy compared with umeclidinium/vilanterol (this was not a pre-specified comparison for this outcome) it was 1.33 (95% CI 1.13 to 1.57,  $p<0.001$ ).

## Safety and tolerability

The [EPAR](#) stated that the safety profile of fluticasone furoate/umeclidinium/vilanterol in the supporting clinical studies was in line with the pharmacologic class of each component and with the dual combination products fluticasone furoate/vilanterol and umeclidinium/vilanterol, and no new safety signals emerged in the populations studied. However, the EPAR did highlight that it was

important to note a signal in respect of pneumonia, which occurred more frequently in the fluticasone furoate/umeclidinium/vilanterol group than the budesonide/formoterol group in the [Lipson et al. 2017](#) study. The EPAR further added that the significance of this, if any, is uncertain as both groups contained an inhaled corticosteroid (ICS) and it is unknown if there are differences within the class for ICS propensity to cause pneumonia. The MHRA issued a [Drug Safety Update](#) in October 2007 on the risk of pneumonia with inhaled corticosteroids. The MHRA advised that healthcare professionals should remain vigilant for the development of pneumonia and other infections of the lower respiratory tract in people with COPD who are treated with ICS because the clinical features of such infections and exacerbations frequently overlap. The MHRA advised that anyone with severe COPD who has had pneumonia during treatment with ICS should have their treatment reconsidered.

There are several special warnings and precautions for use in the summary of product characteristics (SPC) for fluticasone furoate/umeclidinium/vilanterol ([Trelegy](#)). The SPC includes warnings on deterioration of disease, paradoxical bronchospasm, cardiovascular effects, use in people with hepatic impairment and in people with co-existing conditions, systemic corticosteroid effects, hypokalaemia, hyperglycaemia, visual disturbances, anticholinergic activity and pneumonia. According to the SPC the most commonly reported adverse reactions with fluticasone furoate/umeclidinium/vilanterol were nasopharyngitis (7%), headache (5%) and upper respiratory tract infection (2%).

In [Lipson et al. 2018](#) the incidence of any on-treatment adverse events was 70% in the fluticasone furoate/umeclidinium/vilanterol group compared with 68% and 69% respectively in the fluticasone furoate/vilanterol and umeclidinium/vilanterol groups. The most common adverse events were viral upper respiratory tract infection and COPD-related adverse events. Adverse events leading to permanent discontinuation of the study medicines or withdrawal from the study occurred in 6% of participants in the fluticasone furoate/umeclidinium/vilanterol group compared with 8% and 9% respectively in the fluticasone furoate/vilanterol and umeclidinium/vilanterol groups. On-treatment serious adverse events occurred in 22% of participants in the fluticasone furoate/umeclidinium/vilanterol group compared with 21% and 23% respectively in the fluticasone furoate/vilanterol and umeclidinium/vilanterol groups. The most frequent on-treatment serious adverse events were COPD-related adverse events (which occurred in 11% of participants in the fluticasone furoate/vilanterol/umeclidinium and fluticasone furoate/vilanterol groups and 13% of participants in the umeclidinium/vilanterol group) and pneumonia (which occurred in 4% of participants in the fluticasone furoate/vilanterol/umeclidinium and fluticasone furoate/vilanterol groups and 3% of participants in the umeclidinium/vilanterol group, not all cases of pneumonia were classed as a serious adverse event). There were 3 (less than 1% of participants) on-treatment medicines-related fatal adverse events in both the fluticasone furoate/vilanterol/umeclidinium and

fluticasone furoate/vilanterol groups and 1 (less than 1% of participants) in the umeclidinium/vilanterol group.

In Lipson et al. 2018, cardiovascular effects occurred in 11% of participants in the fluticasone furoate/vilanterol/umeclidinium and umeclidinium/vilanterol groups and 10% of participants in the fluticasone furoate/vilanterol group. Local steroid effects were more common in the fluticasone furoate/vilanterol/umeclidinium and fluticasone furoate/vilanterol groups (8% and 7% respectively) compared with the umeclidinium/vilanterol group (5%), however no statistical analysis was conducted. However, the incidence of decreased bone mineral density and associated fractures was the same in all 3 groups (2% in each group). Lower respiratory tract infections (excluding pneumonia) had the same frequency of incidence in all 3 groups (5% in each group). However, there was a higher incidence of pneumonia in the fluticasone furoate/vilanterol/umeclidinium and fluticasone furoate/vilanterol groups (8% and 7% respectively) compared with the umeclidinium/vilanterol group (5%). There was a statistically significant higher risk of pneumonia in the fluticasone furoate/vilanterol/umeclidinium group compared with the umeclidinium/vilanterol group (HR for time to first event 1.53; 95% confidence interval [CI] 1.22 to 1.92;  $p < 0.001$ ). However, there was no statistically significant difference between the fluticasone furoate/vilanterol/umeclidinium and fluticasone furoate/vilanterol groups for the risk of pneumonia (HR 1.02, 95% CI 0.87 to 1.19;  $p = 0.85$ ). The rate of pneumonia per 1,000 patient years was 95.8 in the fluticasone furoate/umeclidinium/vilanterol group compared with 96.6 in the fluticasone furoate/vilanterol group and 61.2 in the umeclidinium/vilanterol group.

In Lipson et al. 2017, the incidence of on-treatment adverse events up-to week 24 was 38.9% in the fluticasone furoate/vilanterol/umeclidinium group and 37.7% in the budesonide/formoterol group. The most common adverse events were nasopharyngitis (7% and 5% in the fluticasone furoate/vilanterol/umeclidinium and budesonide/formoterol groups respectively) and headache (5% and 6% in the fluticasone furoate/vilanterol/umeclidinium and budesonide/formoterol groups respectively). The incidence of on-treatment serious adverse events up-to week 24 was 5.4% in the fluticasone furoate/vilanterol/umeclidinium group and 5.7% in the budesonide/formoterol group. The most common on-treatment serious adverse events were COPD exacerbation (1.3% in the fluticasone furoate/vilanterol/umeclidinium group and 2.3% in the budesonide/formoterol group) and pneumonia (1.0% and 0.3% in the furoate/vilanterol/umeclidinium and budesonide/formoterol groups respectively, not all cases of pneumonia were classed as a serious adverse event). As stated in the EPAR, pneumonia occurred more frequently in the fluticasone furoate/umeclidinium/vilanterol group than the budesonide/formoterol group; 20/911 cases (2.2%) and 7/899 cases (0.8%) respectively in the intention to treat population up to week 24. In the subset who continued treatment up to week 52, incidences of pneumonia were similar between the 2 groups (4/210 cases [1.9%] compared with 4/220 cases [1.8%] respectively).

There were 12 on-treatment deaths in the study (6 in each treatment group). None of the deaths were considered to be medicines-related. For the subset of 430 participants who continued treatment up to week 52, the most common adverse events were also nasopharyngitis and headache. In this smaller subgroup COPD worsening occurred in 2% of participants in the fluticasone furoate/vilanterol/umeclidinium group compared with 10% in the budesonide/formoterol group. However, in the intention-to-treat population up to week 24 the incidence was similar in both groups (2% and 3% in the fluticasone furoate/vilanterol/umeclidinium and budesonide/formoterol groups respectively). The incidence of on-treatment serious adverse events in the subset who continued treatment up to week 52 was 10.0% and 12.7% in the fluticasone furoate/vilanterol/umeclidinium and budesonide/formoterol groups respectively.

In Lipson et al. 2017, cardiovascular events occurred in 4.3% of participants in the fluticasone furoate/vilanterol/umeclidinium group and 5.2% in the budesonide/formoterol group in the intention-to-treat population up to week 24 and in 8.6% and 10.0% respectively for the subset who continued treatment up to week 52. The incidence of major cardiovascular events was 0.4% and 0.8% in the fluticasone furoate/vilanterol/umeclidinium and budesonide/formoterol groups respectively up to week 24. In the subset who continued treatment up to week 52 the incidence of major cardiovascular events was higher in the fluticasone furoate/vilanterol/umeclidinium group than the budesonide/formoterol group (2.4% compared with 0.9%).

An overview of the results for safety and tolerability can be found in [results tables](#).

## *Evidence strengths and limitations*

The FULFIL study ([Lipson DA et al. 2017](#)) was the key RCTs for licensing fluticasone furoate/umeclidinium/vilanterol. This study compared fluticasone furoate/umeclidinium/vilanterol with budesonide/formoterol.

Fluticasone furoate/umeclidinium/vilanterol ([Trelegy](#)) is only licensed for maintenance treatment of adults with moderate-to-severe COPD who are not adequately treated by a combination of an ICS and a LABA. The EPAR states that there is a lack of evidence to claim a step-up indication from a LAMA and LABA combination regime due to the absence of a LAMA plus LABA combination as a comparator in the main study considered for the license application.

The IMPACT study ([Lipson DA et al. 2018](#)) compared fluticasone furoate/umeclidinium/vilanterol with fluticasone furoate/vilanterol and umeclidinium/vilanterol.

Lipson et al. 2018 included people with COPD who were symptomatic despite regular maintenance treatment and with a history of exacerbations; 64% of participants had GOLD grade 3 or 4 (severe or very severe) COPD and in the previous year 45% of the population had 1 moderate or severe COPD exacerbation, 43% had 2 and 11% had 3 or more. Lipson et al. 2017 included people with advanced COPD who were symptomatic despite regular maintenance treatment, however they had fewer moderate or severe exacerbations in the previous year than participants in Lipson et al. 2018 (35% of participants had none and 37% had 2 or more). On study entry, in Lipson et al. 2018, 38% were using triple therapy, 29% were using ICS/LABA combinations and 9% were using LAMA/LABA combinations. In Lipson et al. 2017, these percentages were 28%, 29% and 10% respectively. Treatment groups appeared balanced in both studies for factors such as age, sex, smoking status, cardiovascular risk factors and history of exacerbations.

Both studies excluded people with a current diagnosis of asthma or other significant respiratory disorder, with pneumonia that had not resolved within 14 days of screening or a respiratory tract infection that had not resolved within 7 days of screening. Lipson et al. 2017 also excluded people with a severe COPD exacerbation that had not resolved within 14 days of screening. It is unclear if the results of these studies apply to populations other than those recruited; for example, people with mild-to-moderate COPD or those with other concomitant respiratory disorders. Both studies excluded people with asthma. However, the IMPACT study, included people with an FEV<sub>1</sub> between 50% and 80% and at least 2 moderate or 1 severe exacerbation in the previous year. Specialists who commented on this evidence summary highlighted that COPD exacerbations increase with disease severity. Therefore this group with moderate COPD and frequent exacerbations may have included people with asthmatic features (without a confirmed diagnosis of asthma) who would be more sensitive to ICS treatment.

Lipson et al. 2018 was a large study with an important patient orientated primary outcome on moderate or severe exacerbation rates conducted over 52 weeks. For participants on fluticasone furoate/umeclidinium/vilanterol there was a 25% reduction in exacerbation rates compared with umeclidinium/vilanterol. However, the study included a 2-week run-in period prior to randomisation where participants continued using their current COPD medication; 39% of the participants in the umeclidinium/vilanterol group were previously using an ICS, LABA and a LAMA and so therefore will have stopped ICS treatment upon randomisation. It is unclear whether or not this abrupt cessation of ICS treatment in the umeclidinium/vilanterol group may have had an effect on exacerbation outcomes. There was a 15% reduction in exacerbation rates with fluticasone furoate/umeclidinium/vilanterol compared with fluticasone furoate/vilanterol, however this is less than the 20% relative risk reduction considered to be the minimum clinically important difference in the [NICE COPD full guideline](#).

Lipson et al. 2017 focused on non-exacerbation outcomes and the proportion of participants with moderate or severe COPD exacerbations in the overall population over the course of the 24-week study was low (10% of participants in the fluticasone furoate/umeclidinium/vilanterol group and 14% in the budesonide/formoterol group). Improvements in lung function and health-related quality of life were seen with fluticasone furoate/umeclidinium/vilanterol compared with budesonide/formoterol. However, again as in Lipson et al. 2018, participants continued on their current treatment during a 2 week run-in period; 28% of the budesonide/formoterol group were using an ICS, LABA and a LAMA and so would have had a step down in therapy upon randomisation to study treatment. It was also highlighted in the EPAR that participants in the budesonide/formoterol group were undertreated for their degree of severity of COPD and may have benefited from additional treatment.

Both studies were randomised, double-blinded and the method of randomisation used suggests that [allocation was concealed](#). Lipson et al. 2018 was a multicentre study conducted in 37 countries, including the UK. Lipson et al. 2017 was conducted at 200 study centres globally, however this did not include any centres in the UK.

It is not known from these studies how the efficacy and safety of fluticasone furoate/umeclidinium/vilanterol compares with treatments for COPD apart from fluticasone furoate/vilanterol, budesonide/formoterol or umeclidinium/vilanterol, such as other combinations of an ICS/LABA (alone or with a separate LAMA) or a different LABA/LAMA combination.

These studies also provide no information on whether the triple-therapy inhaler has any advantages over using an ICS/LABA with a separate LAMA 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 fluticasone furoate/umeclidinium/vilanterol (dry powder) inhaler ([Trelegy](#)) was the second triple-therapy combination inhaler licensed for chronic obstructive pulmonary disease (COPD) in the UK. The first was a beclometasone/formoterol/glycopyrronium (metered-dose) inhaler ([Trimbow](#)), which is the subject of a [separate evidence summary](#).

Four dual-therapy long-acting muscarinic antagonist (LAMA)/long-acting beta-2 agonist (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 inhaled corticosteroid (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 furoate/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 indicated 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](#))
- 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](#))
- 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 alternative brands 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 fluticasone furoate/umeclidinium/vilanterol metered-dose inhaler ([Trelegy](#)). 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 <sup>a,b</sup>	30-day cost excluding VAT
<b>Single-component LABAs</b>		
Formoterol 12 micrograms (Formoterol Easyhaler)	1 puff twice daily	£11.87 <sup>c,d</sup>
Indacaterol 150 micrograms and 300 micrograms (Onbrez Breezhaler)	1 puff daily	£32.19 <sup>c</sup>
Olodaterol 2.5 micrograms (Striverdi Respimat)	2 puffs once daily	£26.35 <sup>c</sup>
Salmeterol 50 micrograms (Serevent Accuhaler)	1 puff twice daily	£35.11 <sup>c,d</sup>
<b>Single-component LAMAs</b>		

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

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

<sup>a</sup> Doses taken from the relevant [summary of product characteristics](#).

<sup>b</sup> The doses shown do not represent the full range that can be used and they do not imply therapeutic equivalence.

<sup>c</sup> Costs taken from the [Drug Tariff](#) (May 2018). All costs include the inhaler device.

<sup>d</sup> Lowest cost dry powder formulations selected; other brands and formulations are available.

<sup>e</sup> Costs taken from [MIMS](#) (May 2018). All costs include the inhaler device.

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

		30-day cost excluding VAT <sup>a</sup>
<b>Combination ICS/LABA inhaler plus a separate LAMA inhaler</b>		
Beclometasone/formoterol 100/6 micrograms (Fostair <sup>b</sup> or Fostair NEXThaler)	Acclidinium 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)	Acclidinium 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
<b>Triple ICS/LABA/LAMA inhalers</b>		
	Beclometasone/formoterol/glycopyrronium 87/5/9 micrograms (Trimbow) <sup>b</sup>	£44.50
	Fluticasone furoate/vilanterol/umeclidinium 92/55/22 micrograms (Trelegy)	£44.50
<p>Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist.</p> <p><sup>a</sup> Costs taken from the <a href="#">Drug Tariff</a> (May 2018) or <a href="#">MIMS</a> (May 2018). Lowest cost dry powder formulations selected unless footnoted otherwise; other brands and formulations are available. All costs include the inhaler device. See <a href="#">table 3</a> for more details.</p> <p><sup>b</sup> Pressurised metered-dose inhaler.</p>		

A 30-day supply of combination therapy with fluticasone furoate/umeclidinium/vilanterol costs £44.50 (excluding VAT) when the triple-therapy inhaler (Trelegy) is prescribed. It is the same price as the beclometasone/formoterol/glycopyrronium triple-therapy inhaler (Trimbow). This compares with £49.50 (excluding VAT) when fluticasone furoate and vilanterol are prescribed in a dual-therapy inhaler (Relvar Ellipta, fluticasone furoate/vilanterol 92/22 micrograms) together with umeclidinium in a single-therapy inhaler (Incruse Ellipta).

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 £45.00 to about £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 around £6.00 to £160 per year when these products are used (based on using 12 inhalers per year). 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.

[Ismaila AS et al. 2017](#) assessed the healthcare resource utilisation data and associated costs from the FULFIL study ([Lipson et al. 2017](#)). Based on the intention-to-treat population, annualised total non-medicine costs were lower in the group who received fluticasone furoate/umeclidinium/vilanterol compared with budesonide/formoterol (£653.80 per participant versus £763.32 per participant). However, the total annualised cost (non-medicine and medicine costs) was higher with fluticasone furoate/umeclidinium/vilanterol compared with budesonide/formoterol (£1,289.35 per participant versus £1,267.45 per participant). Based on the subset of 430 participants who completed 52 weeks treatment, annualised non-medicine costs were £749.22 per participant with

fluticasone furoate/umeclidinium/vilanterol compared with £988.03 with budesonide/formoterol. The annualised cost (non-medicine and medicine costs) was £1,376.95 for fluticasone furoate/umeclidinium/vilanterol compared with £1,470.18 with budesonide/formoterol.

### *Current or estimated usage*

It is not possible to provide estimated usage of the fluticasone furoate/umeclidinium/vilanterol triple-therapy inhaler based on the available data. This is because it is not 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 a triple-therapy regimen. The majority of people who were initially using triple therapy stepped down to a LABA/ICS (25%) or LAMA (31%) during the 2-year follow-up ([Wurst et al. 2014](#)). However, the study included a relatively small number of people, 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 offered to people who remain breathless or have exacerbations despite using an ICS/LABA (add a LAMA) and considered for people who remain breathless or have exacerbations despite using a LAMA (add an ICS/LABA), irrespective of forced expiratory volume in 1 second (FEV<sub>1</sub>). (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.

Fluticasone furoate/umeclidinium/vilanterol ([Trelegy](#)) is licensed for maintenance treatment of adults with moderate-to-severe COPD who are not adequately treated by a combination of an ICS and a LABA. At the time of publication, it is not licensed to be used in people not adequately treated by a combination of a LABA and LAMA. Fluticasone furoate/umeclidinium/vilanterol has been shown to reduce the annual rate of on-treatment moderate or severe exacerbations compared with fluticasone furoate/vilanterol. Although this reduction was less than the 20% relative risk reduction for COPD exacerbations that the [NICE COPD full guideline](#) considers to be the minimum clinically important difference. There was no statistically significant difference between fluticasone

furoate/umeclidinium/vilanterol and fluticasone furoate/vilanterol for the annual rate of severe COPD exacerbations. There was a reduction in the annualised rate of moderate and severe exacerbations with fluticasone furoate/umeclidinium/vilanterol group compared with budesonide/formoterol group. There were improvements in health-related quality of life scores (as measured by St George's Respiratory Questionnaire total score, [SGRQ](#)) with fluticasone furoate/umeclidinium/vilanterol compared with budesonide/formoterol after 24 weeks' treatment but there was no difference between the 2 groups after 52 weeks' treatment. More participants had a clinically significant improvement in SGRQ total score with fluticasone furoate/umeclidinium/vilanterol compared with both fluticasone furoate/vilanterol and umeclidinium/vilanterol. More participants had a clinically significant improvement in dyspnoea (as measured by the [Transitional Dyspnoea Index](#)) with fluticasone furoate/umeclidinium/vilanterol compared with fluticasone furoate/vilanterol in the subset of participants that this outcome was assessed in.

The [EPAR](#) stated that the safety profile of fluticasone furoate/umeclidinium/vilanterol in the supporting clinical studies was in line with the pharmacologic class of each component and with the dual combination products fluticasone furoate/vilanterol and umeclidinium/vilanterol, and no new safety signals emerged in the populations studied. However, the EPAR did highlight that it was important to note a signal in respect of pneumonia which occurred more frequently with fluticasone furoate/umeclidinium/vilanterol than with budesonide/formoterol in one of the studies. The EPAR further added that the significance of this, if any, is uncertain as both groups contained an ICS and it is unknown if there are differences within the class for ICS propensity to cause pneumonia.

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

Some people may prefer a particular inhaler device or be able to use 1 device better than another. Some people with COPD are unable to use a spacer, others like to use one. Fluticasone furoate/umeclidinium/vilanterol is supplied in a dry powder inhaler and cannot be used with a spacer. Beclometasone/formoterol/glycopyrronium is supplied in a pressurised metered-dose inhaler and can be used with a spacer. Fluticasone furoate/umeclidinium/vilanterol is administered once daily and beclometasone/formoterol/glycopyrronium is administered twice 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.

However, triple therapy in a single inhaler lacks flexibility and makes it difficult to amend the individual medicines if treatment needs changing for any reason.

Fluticasone furoate/umeclidinium/vilanterol may be suitable for some people with moderate-to-severe COPD who have found triple therapy beneficial using more than 1 inhaler, can use a dry powder inhaler, 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 fluticasone furoate/umeclidinium/vilanterol.

## 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 fluticasone furoate/umeclidinium/vilanterol 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 101), which has been incorporated into a [NICE pathway](#). This guideline is currently being [updated](#) (expected publication date November 2018).

### **References**

Ismaila AS, Birk R, Shah D et al. (2017) [Once-daily triple therapy in patients with advanced COPD: healthcare resource utilization data and associated costs from the FULFIL trial](#). *Advances in Therapy* 34: 2163–72

Lipson DA, Barnacle H, Birk R et al. (2017) [FULFIL Trial: Once-daily triple therapy in patients with chronic obstructive pulmonary disease](#). *American Journal of Respiratory and Critical Care Medicine* 196(4): 438–46

Lipson DA, Barnhart F, Brealey N et al. (2018) [Once-daily single inhaler triple therapy versus dual therapy in patients with COPD](#). *New England Journal of Medicine* DOI: 10.1056/NEJMoa1713901

Pascoe SJ, Lipson DA, Locantore N et al. (2016) [A phase III randomised controlled trial of single-dose triple therapy in COPD: the IMPACT protocol](#). *European Respiratory Journal* 48:320-30

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

## Evidence tables

*Table 5 Lipson DA et al. 2018 (IMPACT)*

<b>Study reference</b>	Lipson DA, Barnhart F, Brealey N et al. (2018) <a href="#">Once-daily single inhaler triple therapy versus dual therapy in patients with COPD</a> <i>New England Journal of Medicine</i> DOI: 10.1056/NEJMoa1713901 and Pascoe SJ, Lipson DA, Locantore N et al. (2016) <a href="#">A phase III randomised controlled trial of single-dose triple therapy in COPD: the IMPACT protocol</a> <i>European Respiratory Journal</i> 48: 320–30.
<b>Unique identifier</b>	<a href="#">NCT02164513</a> .
<b>Study type</b>	Randomised, double-blind, parallel-group study.
<b>Aim of the study</b>	To evaluate the effects of 52 weeks' treatment with a once-daily combination of fluticasone furoate/umeclidinium/vilanterol compared with fluticasone furoate/umeclidinium or umeclidinium/vilanterol on the rate of moderate or severe COPD exacerbations.
<b>Study dates</b>	June 2014 to July 2017.
<b>Setting</b>	Multicentre study conducted in 37 countries, including the UK.
<b>Number of participants</b>	10,367 participants randomised to treatment and 10,355 included in the intention-to-treat population.

<b>Population</b>	Adults aged 40 years or older with symptomatic COPD and a history of exacerbations. Average age 65 years; 34% female; 65% former smokers <sup>a</sup> ; average percent predicted FEV <sub>1</sub> 45.5%; 64% had GOLD grade 3 or 4 (severe or very severe) COPD and in the previous year 45% of the population had 1 moderate or severe COPD exacerbation, 43% had 2 and 11% had 3 or more. At screening 38% of participants were using an ICS, LABA and a LAMA; 29% were using an ICS and a LABA and 9% were using a LABA and a LAMA.
<b>Inclusion criteria</b>	<p>Adults aged 40 years or older with COPD and a <u>CAT</u> score <math>\geq 10</math> with either:</p> <ul style="list-style-type: none"> <li>• FEV<sub>1</sub> &lt; 50% and a history of at least one moderate or severe exacerbation in the previous year or</li> <li>• FEV<sub>1</sub> <math>\geq 50\%</math> to &lt; 80% and at least 2 moderate or one severe exacerbation in the previous year.</li> </ul> <p>Participants also had to have been receiving daily maintenance therapy for COPD for at least 3 months. All participants were required to have at least a 10 pack-year smoking history.</p>
<b>Exclusion criteria</b>	<ul style="list-style-type: none"> <li>• Current diagnosis of asthma or other respiratory disorder.</li> <li>• Current pneumonia that had not resolved within the 14 days prior to screening.</li> <li>• Current respiratory tract infection that had not resolved within the 7 days prior to screening.</li> <li>• COPD caused by alpha-1-antitrypsin deficiency and either unable to withhold salbutamol treatment for 4 hours prior to spirometry testing or with a moderate or severe COPD exacerbation that had not resolved within the 14 days prior to screening and 30 days or less since the last dose of oral or systemic corticosteroids.</li> </ul>
<b>Intervention(s)</b>	Triple therapy with fluticasone furoate 100 micrograms, umeclidinium 62.5 micrograms and vilanterol 25 micrograms in a single inhaler (Ellipta device) once a day (n=4,151).

<b>Comparator(s)</b>	Dual therapy with umeclidinium 62.5 micrograms and vilanterol 25 micrograms in a single inhaler once a day (n=2,070) and dual therapy with fluticasone furoate 100 micrograms and vilanterol 25 micrograms in a single inhaler once a day (n=4,134). Both comparators were given in an Ellipta device.
<b>Length of follow-up</b>	Two-week run-in period during which medication at screening was continued unchanged. After the run-in period, participants were randomly assigned 2:2:1 to 1 of the 3 treatment groups for a 52 week treatment period followed by a 1 week follow-up period.
<b>Outcomes</b>	<p>Primary outcome: annual rate of on-treatment moderate or severe exacerbations<sup>b</sup>. The 2 co-primary treatment comparisons were:</p> <ul style="list-style-type: none"> <li>• fluticasone furoate/umeclidinium/vilanterol versus umeclidinium/vilanterol, and</li> <li>• fluticasone furoate/umeclidinium/vilanterol versus fluticasone furoate/vilanterol.</li> </ul> <p>Secondary outcomes included<sup>c</sup>:</p> <ul style="list-style-type: none"> <li>• time to first on-treatment moderate or severe exacerbation</li> <li>• annual rate of on-treatment severe exacerbations</li> <li>• annual rate of on-treatment moderate or severe exacerbations comparing fluticasone furoate/umeclidinium/vilanterol with umeclidinium/vilanterol in the subset of participants with a blood eosinophil count 150 cells per millilitre.</li> <li>• change from baseline in SGRQ total score at week 52 comparing fluticasone furoate/umeclidinium/vilanterol with fluticasone furoate/vilanterol.</li> </ul> <p>The study also included multiple pre-specified protocol-defined other endpoints including on-treatment all-cause mortality and <a href="#">transitional dyspnoea index</a> focal score comparing fluticasone furoate/umeclidinium/vilanterol with fluticasone furoate/vilanterol.</p>

	Safety outcomes included incidence of adverse events, serious adverse events, pneumonia and supporting radiography, cardiovascular events, bone fractures and other adverse events of special interest (pre-specified adverse events associated with ICS, LAMA or LABA use).	
<b>Source of funding</b>	GlaxoSmithKline.	
<b>Overall risk of bias/quality assessment (CASP RCT checklist)</b>	Did the trial address a clearly focused issue?	Yes
	Was the assignment of patients to treatments randomised?	Yes <sup>d</sup>
	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 <a href="#">table 7</a>
	How precise was the estimate of the treatment effect?	See <a href="#">table 7</a>
	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 <a href="#">key points</a>

<p><b>Study limitations</b></p>	<ul style="list-style-type: none"> <li>• The study included people with COPD who were symptomatic despite regular maintenance treatment and with a history of exacerbations. The results of the study may not apply to other populations with COPD.</li> <li>• 39% of the participants in the umeclidinium/vilanterol group were using an ICS, LABA and LAMA prior to randomisation. It is unclear if the abrupt cessation of ICS treatment may have had an effect on exacerbation outcomes. Thirty-eight percent of participants in the fluticasone furoate/vilanterol group were also using an ICS, LABA and LAMA prior to randomisation and so will have also had a step down in treatment.</li> <li>• It is not known from the study how the efficacy and safety of fluticasone furoate/umeclidinium/vilanterol compares with treatments for COPD apart from fluticasone furoate/vilanterol and umeclidinium/vilanterol, such as other combinations of ICS/LABA (alone or with a separate LAMA) or a different LABA/LAMA combination.</li> <li>• It is also not known from the study whether the triple-therapy inhaler has any advantages over using an ICS/LABA with a separate LAMA in terms of patient factors such as adherence to treatment and ease of use of the device.</li> </ul>
<p><b>Comments</b></p>	<p><sup>a</sup> Former smokers were defined as having stopped smoking for at least 6 months prior to screening.</p> <p><sup>b</sup> Participants completed an electronic diary each morning to record their symptoms and were advised to contact their study investigator if symptoms suggestive of an exacerbation worsened over 2 consecutive days. The investigator confirmed whether or not it was an exacerbation. A moderate exacerbation was defined as an exacerbation that required treatment with antibiotics or systemic corticosteroids. A severe exacerbation was defined as an exacerbation that required hospital treatment or resulted in death. On-treatment exacerbations included exacerbations that occurred during treatment plus 1 day after the last dose was administered.</p> <p><sup>c</sup> Multiplicity across key secondary endpoints were controlled using a hierarchical, closed testing procedure.</p> <p><sup>d</sup> Participants were randomised using a computerised system. The method of randomisation used suggests <u>allocation was concealed</u>.</p>

Abbreviations: CAT, COPD Assessment Test, assesses all aspects of the impact of COPD on a scale of 0 to 40, higher scores indicate more symptoms; COPD, chronic obstructive pulmonary disease; FEV<sub>1</sub>, 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 6 Lipson DA et al. 2017 (FULFIL)*

<b>Study reference</b>	Lipson DA, Barnacle H, Birk R et al. (2017) <u>FULFIL Trial: Once-daily triple therapy in patients with chronic obstructive pulmonary disease</u> . <i>American Journal of Respiratory and Critical Care Medicine</i> 196(4): 438–46.
<b>Unique identifier</b>	<u>NCT02345161</u>
<b>Study type</b>	Randomised, double-blind, parallel-group study.
<b>Aim of the study</b>	Compared the efficacy and safety of a once-daily triple-therapy single inhaler (fluticasone/umeclidinium/vilanterol) with twice-daily dual therapy (budesonide/formoterol) in adults with advanced, symptomatic COPD, who were at risk of exacerbations.
<b>Study dates</b>	January 2015 to April 2016
<b>Setting</b>	200 study centres globally (with no centres in the UK)
<b>Number of participants</b>	1,811 participants randomised to study treatment; 1,810 participants were included in the intention-to-treat population with assessment of outcomes at week 24. A subset of the first 430 participants to enter the study and consent to longer-term treatment remained on their allocated study treatment for up to 52 weeks. Results from the subset who had extended treatment up-to week 52 are not provided in the results table but are briefly discussed in the main sections on clinical effectiveness and safety and tolerability.
<b>Population</b>	Adults aged 40 years or older with advanced, symptomatic COPD at risk of exacerbations. Average age 63.9 years; 26% female; 44% current smokers; average percent predicted FEV <sub>1</sub> 45.3%; 35% had no moderate or severe exacerbations in previous 12 months, 28% had 1 and 37% had at least 2. Prior to randomisation, 28% of the population were using an ICS, LABA and LAMA, 29% were using an ICS and a LABA and 10% were using a LABA plus a LAMA.

<p><b>Inclusion criteria</b></p>	<ul style="list-style-type: none"> <li>• Diagnosis of COPD and: FEV<sub>1</sub> &lt;50% and <u>CAT</u> score ≥10 or FEV<sub>1</sub> ≥ 50% to &lt;80% and CAT score ≥10 and either ≥2 moderate exacerbations in the past year or ≥1 severe exacerbation in past year.</li> <li>• Receiving daily maintenance therapy for COPD for at least 3 months.</li> </ul>
<p><b>Exclusion criteria</b></p>	<ul style="list-style-type: none"> <li>• Current diagnosis of asthma or other significant respiratory disorder.</li> <li>• Lung resection within 12 months of screening or other clinically significant diseases.</li> <li>• Current pneumonia or severe COPD exacerbation that had not resolved within 14 days of screening.</li> <li>• Current respiratory tract infection that had not resolved within 7 days of screening.</li> <li>• COPD caused by alpha-1-antitrypsin deficiency.</li> <li>• People with an abnormal chest X-ray or an abnormal and clinically significant ECG.</li> </ul>
<p><b>Intervention(s)</b></p>	<p>Fluticasone furoate 100 micrograms, umeclidinium 62.5 micrograms and vilanterol 25 micrograms in a single inhaler (Ellipta device) once a day (n=911)</p>
<p><b>Comparator(s)</b></p>	<p>Budesonide 400 micrograms and formoterol 12 micrograms in a single inhaler (Turbohaler) twice a day (n=899).</p>
<p><b>Length of follow-up</b></p>	<p>Two-week run-in period during which medication at screening was continued unchanged. After the run-in period, participants were randomly assigned to 1 of the 2 treatment groups for a 24-week treatment period. A subset of the study population were included in an extended study phase where they received treatment for up to 52 weeks.</p>
<p><b>Outcomes</b></p>	<p>Co-primary outcomes (assessed at week 24):</p> <ul style="list-style-type: none"> <li>• change from baseline in trough FEV<sub>1</sub></li> <li>• change from baseline in SGRQ total score</li> </ul>

	<p>Secondary outcomes included:</p> <ul style="list-style-type: none"> <li>• proportion of participants with at least a 100 ml increase in trough FEV<sub>1</sub> from baseline after 24 weeks treatment<sup>a</sup></li> <li>• proportion of participants with at least a 4 unit decrease in SGRQ total score from baseline after 24 weeks treatment<sup>b,c</sup></li> <li>• change from baseline in <u>Evaluating Respiratory Symptoms in COPD score</u> over 24 weeks and proportion of responders<sup>d</sup>.</li> </ul> <p>• Safety assessments were conducted up to week 24 in the intention-to-treat population and up to week 52 in the extension population. Safety assessments included the incidence of adverse events, serious adverse events, pneumonia and supporting radiography, cardiovascular events and bone fractures.</p>	
<p><b>Source of funding</b></p>	<p>GlaxoSmithKline</p>	
<p><b>Overall risk of bias/quality assessment (CASP RCT checklist)</b></p>	<p>Did the trial address a clearly focused issue?</p>	<p>Yes</p>
	<p>Was the assignment of patients to treatments randomised?</p>	<p>Yes<sup>e</sup></p>
	<p>Were patients, health workers and study personnel blinded?</p>	<p>Yes</p>
	<p>Were the groups similar at the start of the trial?</p>	<p>Yes</p>
	<p>Aside from the experimental intervention, were the groups treated equally?</p>	<p>Yes</p>
	<p>Were all of the patients who entered the trial properly accounted for at its conclusion?</p>	<p>Yes</p>
	<p>How large was the treatment effect?</p>	<p>See <a href="#">table 8</a></p>
	<p>How precise was the estimate of the treatment effect?</p>	<p>See <a href="#">table 8</a></p>
	<p>Can the results be applied in your context? (or to the local population)</p>	<p>Yes</p>
	<p>Were all clinically important outcomes considered?</p>	<p>Yes</p>

	Are the benefits worth the harms and costs?	See <a href="#">key points</a>
<b>Study limitations</b>	<ul style="list-style-type: none"> <li>• The study included people with advanced COPD who were symptomatic despite regular maintenance treatment and at risk of exacerbations. The results of the study may not apply to other populations with COPD.</li> <li>• Prior to randomisation, 28% of the budesonide/formoterol group were using an ICS, LABA and a LAMA and so would have had a step down in therapy. Therefore some participants in the comparator group may have been untreated for their severity of COPD compared to participants in the fluticasone furoate/umeclidinium/vilanterol group.</li> <li>• The co-primary outcomes of the study were non-exacerbation outcomes and the proportion of participants with moderate or severe COPD exacerbations<sup>f</sup> in the overall population over the course of the 24 week study was low (10% of participants in the fluticasone furoate/umeclidinium/vilanterol group and 14% in the budesonide/formoterol group).</li> <li>• It is not known from the study how the efficacy and safety of fluticasone furoate/umeclidinium/vilanterol compares with treatments for COPD apart from budesonide/formoterol, such as other combinations of ICS/LABA (alone or with a separate LAMA) or a LABA/LAMA.</li> <li>• It is also not known from the study whether the triple-therapy inhaler has any advantages over using an ICS/LABA with a separate LAMA in terms of patient factors such as adherence to treatment and ease of use of the device.</li> </ul>	

<b>Comments</b>	<p><sup>a</sup> An increase from baseline in trough FEV<sub>1</sub> ≥100 ml was deemed the minimum clinically important difference.</p> <p><sup>b</sup> A decrease from baseline in SGRQ total score ≥4 was deemed the minimum clinically important difference.</p> <p><sup>c</sup> SGRQ was completed using a patient-held e-diary at day 1 and at weeks 4 and 24.</p> <p><sup>d</sup> Evaluating Respiratory Symptoms in COPD score questionnaire completed each evening using the e-diary.</p> <p><sup>e</sup> Randomised using an interactive voice recognition system stratified by smoking status. The method of randomisation used suggests <u>allocation was concealed</u>.</p> <p><sup>f</sup> A moderate exacerbation was defined as having worsening symptoms of COPD that required treatment with oral/systemic corticosteroids or antibiotics. A severe exacerbation was defined as worsening symptoms of COPD that required treatment with in-patient hospitalisation.</p>
-----------------	--

Abbreviations: CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FEV<sub>1</sub>, forced expiratory volume in 1 second; GOLD, Global Initiative for COPD; 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 7 Lipson DA et al. 2018 (IMPACT)*

	Triple therapy: fluticasone furoate/ umeclidinium/ vilanterol (100/62.5/25 micrograms) once a day.	Dual therapy: fluticasone furoate /vilanterol (100/25 micrograms).	Dual therapy: umeclidinium/ vilanterol (62.5/25 micrograms).	<b>Analysis</b>
<b>n<sup>a</sup></b>	<b>4,151</b>	<b>4,134</b>	<b>2,070</b>	
<b>Primary outcome</b>				

Annual rate of on-treatment moderate or severe exacerbations <sup>b,c</sup>	0.91 per year.	1.07 per year.	1.21 per year.	FF/UMEC/VI compared with FF/VI: RR 0.85, 15% difference (95% CI 0.80 to 0.90; $p < 0.001$ ) FF/UMEC/VI compared with UMEC/VI: RR 0.75, 25% difference (95% CI 0.70 to 0.81; $p < 0.001$ ).
<b>Selected secondary and additional outcomes</b>				
Time to first on-treatment moderate or severe exacerbation <sup>b,c</sup> .	No data provided in paper.	No data provided in paper.	No data provided in paper.	FF/UMEC/VI compared with FF/VI: HR 0.85 (95% CI 0.80 to 0.91; $p < 0.001$ ). FF/UMEC/VI compared with UMEC/VI: HR 0.84 (95% CI 0.78 to 0.91; $p < 0.001$ ).

Annual rate of on-treatment severe exacerbations <sup>b,c</sup> .	0.13 per year.	0.15 per year.	0.19 per year.	FF/UMEC/VI compared with FF/VI: RR 0.87 (95% CI 0.76 to 1.01; p=0.06, no statistically significant difference between the 2 groups). FF/UMEC/VI compared with UMEC/VI: RR 0.66, 34% difference (95% CI 0.56 to 0.78; p<0.001).
Annual rate of on-treatment moderate or severe exacerbations in participants with a blood eosinophil count greater than or equal to 150 cells per millilitre at baseline <sup>d</sup> .	0.95 per year (95% CI 0.90 to 1.01 per year).	1.08 per year (95% CI 1.02 to 1.14 per year).	1.39 per year (95% CI 1.29 to 1.51 per year).	No statistical analysis provided.
Mean change from baseline in SGRQ total score at week 52 <sup>e,f</sup> .	-5.5 units (95% CI -5.9 to -5.0 units).	-3.7 units (95% CI -4.2 to -3.2 units).	-3.7 units (95% CI -4.4 to -3.0 units).	FF/UMEC/VI compared with FF/VI: difference -1.8 units (95% CI -2.4 to -1.1 units; p<0.001). FF/UMEC/VI compared with UMEC/VI: difference -1.8 units (95% CI -2.6 to -1.0 units; p<0.001) <sup>g</sup> .

Proportion of participants with at least a 4 unit decrease in SGRQ total score from baseline after 52 weeks treatment.	1,723/4,151 (42%).	1,390/4,134 (34%).	696/2,070 (34%).	FF/UMEC/VI compared with FF/VI: OR 1.41 (95% CI 1.29 to 1.55; p<0.001). FF/UMEC/VI compared with UMEC/VI: OR 1.41 (95% CI 1.26 to 1.57; p<0.001).
On-treatment all-cause mortality <sup>h</sup> .	50/4,151 (1.20%) on-treatment deaths.	49/4,134 (1.19%) on-treatment deaths.	39/2,070 (1.88%) on-treatment deaths.	FF/UMEC/VI compared with UMEC/VI on-treatment all-cause mortality HR 0.58 (95% CI 0.38 to 0.88; unadjusted p=0.01).
<b>Safety and tolerability outcomes</b>				
<b>n</b>	<b>4,151</b>	<b>4,134</b>	<b>2,070</b>	No statistical analysis provided.
On-treatment adverse events.	2,897/4,151 (70%)	2,800/4,134 (68%)	1,429/2,070 (69%)	
On-treatment drug related adverse events.	478/4,151 (12%)	492/4,134 (12%)	214/2,070 (10%)	
On-treatment adverse events leading to discontinuation of study treatment or withdrawal from study.	252/4,151 (6%)	327/4,134 (8%)	187/2,070 (9%)	
On-treatment serious adverse events <sup>i</sup> .	895/4,151 (22%)	850/4,134 (21%)	470/2,070 (23%)	
Anticholinergic syndrome.	184/4,151 (4%)	140/4,134 (3%)	70/2,070 (3%)	

Cardiovascular effects.	450/4,151 (11%)	430/4,134 (10%)	224/2,070 (11%)	
Decreased bone mineral density and associated fractures.	98/4,151 (2%)	85/4,134 (2%)	37/2,070 (2%)	
Local steroid effects.	337/4,151 (8%)	301/4,134 (7%)	108/2,070 (5%)	
LRTI excluding pneumonia.	200/4,151 (5%)	199/4,134 (5%)	108/2,070 (5%)	
Pneumonia <sup>c</sup> .	317/4,151 (8%)	292/4,134 (7%)	97/2,070 (5%)	FF/UMEC/VI compared with FF/VI for time to first event: no statistically significant difference, HR 1.02, 95% CI 0.87 to 1.19; p=0.85. FF/UMEC/VI compared with UMEC/VI for time to first event: HR 1.53, 95% CI 1.22 to 1.92; p<0.001.

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; FF, fluticasone furoate; HR, hazard ratio; ITT, intention to treat; LRTI, lower respiratory tract infection; RR, rate ratio; SGRQ, St George's Respiratory Questionnaire (measuring health-related quality of life); UMEC, umeclidinium; VI, vilanterol.

<sup>a</sup> ITT population, defined as all participants randomised to treatment, excluded those who were randomised in error who did not receive a dose of study medication, 10,367 participants were randomised to treatment and 10,355 were included in the ITT population. Twelve participants were randomised in error and did not receive study medication.

<sup>b</sup> A moderate exacerbation was defined as an exacerbation that required treatment with antibiotics or systemic corticosteroids. A severe exacerbation was defined as an exacerbation that required hospital treatment or resulted in death.

<sup>c</sup> All participants with suspected pneumonia or a moderate or severe COPD exacerbation had a chest radiograph.

<sup>d</sup> Number of participants with a blood eosinophil count greater than or equal to 150 cells per millilitre not provided in paper. Forty-three percent of participants were reported to have a baseline blood eosinophil level of less than 150 cells per millilitre.

<sup>e</sup> A decrease from baseline in SGRQ total score  $\geq 4$  was deemed the minimum clinically important difference.

<sup>f</sup> Outcome on SGRQ total score change from baseline based on data from 3,318 participants in the FF/UMEC/VI group, 3,026 in the FF/VI group and 1,470 in the UMEC/VI group.

<sup>g</sup> The comparison of FF/UMEC/VI with UMEC/VI for change from baseline in SGRQ total score was not a secondary outcome but was a protocol-defined other endpoint. Treatment comparisons for these other endpoints were not corrected for multiplicity.

<sup>h</sup> On-treatment all-cause mortality was not a secondary outcome but a pre-specified protocol-defined other endpoint. Treatment comparisons for these other endpoints were not corrected for multiplicity.

<sup>i</sup> The most frequent on-treatment serious adverse events were COPD-related adverse events (11% of participants in the fluticasone furoate/vilanterol/umeclidinium and fluticasone furoate/vilanterol groups and 13% of participants in the umeclidinium/vilanterol group) and pneumonia (4% of participants in the fluticasone furoate/vilanterol/umeclidinium and fluticasone furoate/vilanterol groups and 3% of participants in the umeclidinium/vilanterol group).

**Table 8 Lipson DA et al. 2017 (FULFIL)**

	Triple therapy: fluticasone furoate/ umeclidinium/ vilanterol (100/62.5/25 micrograms) once a day.	Dual therapy: budesonide/ formoterol (400/12 micrograms) twice a day.	Analysis
n <sup>a</sup>	911	899	
<b>Co-primary outcomes</b>			
LS mean change from baseline in trough FEV <sub>1</sub> at week 24.	142 ml (95% CI 126 ml to 158 ml).	-29 ml (95% CI -46 ml to -13 ml).	Difference: 171 ml (95% CI 148 ml to 194 ml; p<0.001).
LS mean change from baseline in SGRQ total score at week 24 <sup>b</sup>	-6.6 units (95% CI -7.4 to -5.7 units).	-4.3 units (95% CI -5.2 to -3.4 units).	Difference: -2.2 units (95% CI -3.5 to -1.0 units; p<0.001).
<b>Selected secondary outcomes</b>			
Proportion of participants with at least a 100 ml increase in trough FEV <sub>1</sub> from baseline after 24 weeks treatment <sup>c</sup> .	50% (453/907)	21% (184/892)	OR: 4.03 (95% CI 3.27 to 4.97; p<0.001)
Proportion of participants with at least a 4 unit decrease in SGRQ total score from baseline after 24 weeks treatment <sup>d</sup> .	50% (448/904)	41% (368/893)	OR: 1.41 (95% CI 1.16 to 1.70; p<0.001)
<b>Safety and tolerability outcomes up to week 24</b>			
n	911	899	

On-treatment adverse events <sup>e</sup> .	38.9% (number of participants not provided).	37.7% (number of participants not provided).	No statistical analysis was provided for any of the safety outcomes.
On-treatment serious adverse events <sup>f</sup> .	5.4% (number of participants not provided).	5.7% (number of participants not provided).	
On-treatment deaths.	6/911 (0.7%)	6/899 (0.7%)	
Major cardiovascular events.	0.4% (number of participants not provided)	0.8% (number of participants not provided)	
Cardiovascular effects.	39/911 (4.3%)	47/899 (5.2%)	
Pneumonia.	20/911 (2.2%)	7/899 (0.8%)	
Local steroid effects.	19/911 (2.1%)	24/899 (2.7%)	
Decreased bone mineral density.	4/911 (0.4%)	6/899 (0.7%)	
Ocular effects.	1/911 (0.1%)	4/899 (0.4%)	

Abbreviations: CI, confidence interval; FEV<sub>1</sub>, forced expiratory volume in 1 second; ITT, intention to treat; LS, least squares; OR, odds ratio; SGRQ, St George's Respiratory Questionnaire (measuring health-related quality of life).

<sup>a</sup> ITT population, defined as all participants randomised to treatment, excluded those who were randomised in error who did not receive a dose of study medication, 1,811 participants were randomised to treatment and 1,810 were included in the ITT population.

<sup>b</sup> Co-primary outcomes were reported to have been conducted in the ITT population. However, number of participants reported for this outcome were 846 in the fluticasone furoate/umeclidinium/vilanterol group and 791 in the budesonide/formoterol group.

<sup>c</sup> An increase from baseline in trough FEV<sub>1</sub>  $\geq$  100 ml was deemed the minimum clinically important difference.

<sup>d</sup> A decrease from baseline in SGRQ total score  $\geq$ 4 was deemed the minimum clinically important difference.

<sup>e</sup> The most common adverse events were nasopharyngitis (7% and 5% in the fluticasone furoate/vilanterol/umeclidinium and budesonide/formoterol groups respectively) and headache (5% and 6% in the fluticasone furoate/vilanterol/umeclidinium and budesonide/formoterol groups respectively).

<sup>f</sup> The most common on-treatment serious adverse events were COPD exacerbation (1.3% in the fluticasone furoate/vilanterol/umeclidinium group and 2.3% in the budesonide/formoterol group) and pneumonia (1.0% and 0.3% in the furoate/vilanterol/umeclidinium and budesonide/formoterol groups respectively).

## Excluded studies

No studies obtained and assessed for relevance to this evidence summary were subsequently excluded.

## 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.

COPD Assessment Test (CAT): a patient-completed questionnaire assessing all aspects of the impact of COPD (cough, sputum, breathlessness, chest tightness, confidence, activity, sleep and

energy levels). There are 8 questions on a 0 to 5 point scale (with a score of 0 on the scale as no symptoms or impact on daily life and 5 on the scale as the worst symptoms and impact on daily life).

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  $\geq 1$  is considered to be clinically important.

## Search strategy

Database: Medline ALL segments

Platform: Ovid

Version: 1946 to December 13, 2017

Search date: 15th December 2017

Number of results retrieved: 29

Search strategy:

1 trelegy.ti,ab. (0)

2 vilanterol.ti,ab. (291)

3 GSK642444.ti,ab. (0)

4 "642444".ti,ab. (3)

5 or/2-4 (294)

6 Fluticasone/ (2822)

7 fluticasone.ti,ab. (3802)

8 fluticason.ti,ab. (15)

9 or/6-8 (4445)

10 umeclidinium.ti,ab. (176)

11 GSK573719.ti,ab. (9)

12 "573719".ti,ab. (0)

13 or/10-12 (177)

14 1 or (5 and 9 and 13) (29)

Database: Embase

Platform: Ovid

Version: 1974 to 2017 December 13

Search date: 15th December 2017

Number of results retrieved: 65

Search strategy:

1 trelegy.ti,ab. (0)

2 vilanterol/ (418)

3 vilanterol.ti,ab. (456)

4 GSK642444.ti,ab. (0)

5 "642444".ti,ab. (4)

6 or/2-5 (656)

7 Fluticasone/ (7416)

8 fluticasone furoate/ (692)

9 fluticasone.ti,ab. (5994)

10 fluticason.ti,ab. (43)

11 or/7-10 (11573)

12 umeclidinium/ (334)

13 umeclidinium.ti,ab. (254)

14 GSK573719.ti,ab. (27)

15 "573719".ti,ab. (1)

16 or/12-15 (417)

17 1 or (6 and 11 and 16) (85)

18 17 (85)

19 limit 18 to english language (83)

20 19 (83)

21 limit 20 to conference abstract status (18)

22 19 not 21 (65)

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)

CENTRAL – 11 of 12, November 2017

HTA – 4 of 4, October 2016

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

Search date:

Number of results retrieved: CDSR – 0; DARE – 0; CENTRAL – 27; HTA – 0; NHS EED – 0.

Search strategy:

ID Search

#1 trelegy:ti,ab

#2 vilanterol:ti,ab

#3 GSK642444:ti,ab

#4 "642444":ti,ab

#5 {or #2-#4}

#6 [mh ^fluticasone]

#7 fluticasone:ti,ab

#8 fluticason:ti,ab

#9 {or #6-#8}

#10 umeclidinium:ti,ab

#11 GSK573719:ti,ab

#12 "573719":ti,ab

#13 {or #10-#12}

#14 #1 or (#5 and #9 and #13)

## 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*

Professor Peter Calverley, Professor of Respiratory Medicine, University of Liverpool.

Dr Anastasios Lekkas, Consultant Respiratory Physician, University Hospital Southampton NHS Foundation Trust.

Dr Sarah Scrivener, Consultant Respiratory Physician, Portsmouth Hospitals NHS Trust.

Professor Jadwiga Wedzicha, Professor of Respiratory Medicine, Imperial College London.

### *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.**

ISBN 978-1-4731-2974-0