IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Fluticasone furoate/umeclidinium/vilanterol (COPD) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment Fluticasonfuroat/Umeclidinium/Vilanterol *(COPD) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 May 2018). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CAT	COPD Assessment Test
COPD	chronic obstructive pulmonary disease
FEV_1	forced expiratory volume in 1 second
FF	fluticasone furoate
FF/UMEC/VI	fluticasone furoate/umeclidinium/vilanterol
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICS	inhaled corticosteroid
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LABA	long-acting beta-2 agonist
LAMA	long-acting muscarinic antagonist;
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SGRQ	St. George's Respiratory Questionnaire
SPC	Summary of Product Characteristics
TDI	Transition Dyspnoea Index
TDI-SAC	Transition Dyspnea Index – Self-administered computerized
UMEC	umeclidinium
VI	vilanterol

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug combination fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI), The assessment was based on a dossier compiled by the company. The dossier was sent to IQWiG on 27 February 2018.

Research question

The aim of the present report was to assess the added benefit of the fixed combination FF/UMEC/VI as maintenance treatment in comparison with the appropriate comparator therapy (ACT) in adults with moderate to severe chronic obstructive pulmonary disease (COPD) inadequately controlled with a combination of an inhaled corticosteroid (ICS) and a long-acting beta-2 agonist (LABA).

Table 2 shows the research question of the benefit assessment and the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of FF/UMEC/VI

Research question	Subindication	ACT[a]
1	Maintenance treatment in adults with moderate to severe COPD inadequately controlled with a combination of one ICS and one LABA[b]	Individual treatment optimization in accordance with physician's choice – under consideration of the previous therapy – with LABA and LAMA and ICS as the circumstanced require

a: Presentation of the ACT specified by the G-BA.
b: It is assumed that COPD was inadequately controlled with the previous therapy and the patients still had symptoms (including exacerbations) in patients for whom treatment with the drug combination FF/UMEC/VI was an option.
COPD: chronic obstructive pulmonary disease; FF: fluticasone furoate; G-BA: Federal Joint Committee; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; UMEC: umeclidinium; VI: vilanterol

The company followed the G-BA's specification of the ACT.

Assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of the added benefit.

Results

Study pool

The 200812 study was suitable to derive conclusions on the added benefit of FF/UMEC/VI using a subpopulation. In addition to the 200812 study included in the present benefit assessment, the company considered another RCT in its assessment (CTT116855; hereinafter referred to as IMPACT study). However, this study was unsuitable for an assessment of the added benefit of FF/UMEC/VI in comparison with the ACT (see below).

Study 200812

Study characteristics

The 200812 study was included in the benefit assessment. The 200812 study is a randomized, double-blind, controlled non-inferiority study on the comparison of the fixed triple combination FF/UMEC/VI with the free triple combination of FF/VI and UMEC (hereinafter referred to as FF/VI + UMEC) in patients aged 40 years and older with confirmed COPD with spirometric Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades II to IV (moderate to very severe). Included patients had to have received daily COPD maintenance treatment for at least 3 months before screening.

A total of 1055 patients were randomly assigned to treatment with the fixed (N = 527) or the free (N = 528) combination of FF, UMEC and VI in a ratio of 1:1.

Administration of the study medication was conducted once daily via inhalation according to the Summary of Product Characteristics (SPC). FF was applied in the approved dosage of 100 µg. To maintain blinding, patients in the study arm with the fixed triple combination FF/UMEC/VI additionally received inhaled placebo once daily. Short-term treatment (≤ 14 days) of the patients with systemic corticosteroids, antibiotics or, at the physician's discretion, with further COPD drugs was possible in case of exacerbations or pneumonia. Moreover, application of salbutamol as rescue medication was allowed over the entire treatment period.

The 200812 study comprised a 2-week run-in phase, in which COPD maintenance treatment before study inclusion was maintained, as well as a randomized treatment phase of 24 weeks. The patients were switched to the study medication at the start of the treatment phase. After planned or premature end of treatment, the patients underwent 7-day follow-up observation.

Primary outcome of the 200812 study was the change of the FEV_1 trough level after 24 weeks in comparison with the baseline value. Secondary patient-relevant outcomes were symptoms (exacerbation, Transition Dyspnoea Index [TDI]), health-related quality of life (recorded using the St. George's Respiratory Questionnaire [SGRQ]) and adverse events (AEs).

Relevant subpopulation

The 200812 study included patients who had been receiving daily COPD maintenance treatment for at least 3 months. FF/UMEC/VI is indicated for maintenance treatment in adults

with moderate to severe COPD inadequately controlled with a combination of ICS and LABA. The prior therapy of the patients included in the 200812 study is thus not restricted to the maintenance treatment with ICS + LABA comprised in the approval of FF/UMEC/VI. For this reason, the present benefit assessment only considered patients whose maintenance treatment before study inclusion comprised at least one ICS and one LABA. Moreover, only those patients were considered whose maintenance treatment comprised no long-acting muscarinic antagonists (LAMAs). This subpopulation comprised 147 patients in the FF/UMEC/VI arm and 142 patients in the FF/VI + UMEC arm.

Risk of bias at study and outcome level

The risk of bias at study and outcome level for the 200812 study was rated as low.

The IMPACT study was inadequate for the assessment of the added benefit

Inadequate treatment in the comparator arm UMEC/VI

The IMPACT study presented in addition by the company was unsuitable for assessing the added benefit of FF/UMEC/VI versus the ACT. The IMPACT study is a 52-week randomized, double-blind 3-arm study on the comparison of FF/UMEC/VI with the dual combinations FF/VI and UMEC/VI. The included patients had been receiving daily COPD maintenance treatment for at least 3 months.

In accordance with the therapeutic indication of FF/UMEC/VI, the company only considered patients whose maintenance treatment before study inclusion comprised at least one ICS and one LABA. Moreover, patients who had received simultaneous treatment with LAMA were excluded. Since treatment in the FF/VI arm does not correspond to the ACT, the company only considered the described subpopulation of the FF/UMEC/VI arm and the UMEC/VI arm.

According to the classification based on GOLD, most patients included in the IMPACT study were patients of group D. For this patient group with current ICS + LABA therapy, treatment escalation through additional administration of a LAMA was recommended in accordance with the treatment algorithm according to GOLD at ongoing symptoms as well as exacerbations. While this recommendation was implemented in the intervention arm with the administration of FF/UMEC/VI, ICS was abruptly stopped at the start of the study despite prior exacerbations in patients of the UMEC/VI arm. Therewith, switching to ICS-free study medication in the comparator arm resulted in a de-escalation of the treatment that had already been inadequate at this time point despite administration of ICS. However, abrupt discontinuation of ICS can favour exacerbations. Therewith, it is altogether doubtful whether the patients included in the comparator arm UMEC/VI of the IMPACT study received adequate treatment.

Regarding the ACT, the G-BA specified that individual treatment optimization was to comprise the substance classes LABA and LAMA, whereas ICS was only indicated as an adjunct, if appropriate. However, this only applies on condition that the individual treatment optimization takes place under consideration of the (inadequate) previous therapy. In the particular case, ongoing symptoms and the history of exacerbations of the subpopulation pretreated with

ICS + LABA suggest that at the start of the study there was the indication for an ICS + LABA + LAMA combination therapy at least for the major part of these patients. Since this was not implemented in the UMEC/VI arm, the IMPACT study was not used for the present benefit assessment.

Results of the study 200812

All-cause mortality

In the 200812 study, deaths were determined by the recording of adverse events. One death had occurred until week 24. There was no statistically significant difference between the treatment groups. Overall, this resulted in no hint of an added benefit of FF/UMEC/VI in comparison with FF/VI + UMEC; an added benefit is therefore not proven.

Morbidity – exacerbations

Exacerbations that occurred under the study medication, operationalized as moderate or severe exacerbations as well as severe exacerbations, were included in the present benefit assessment in the form of the annual exacerbation rates at week 24. The proportion of patients with event was presented as additional information. There was no statistically significant difference between the treatment arms for both operationalizations. Overall, this resulted in no hint of an added benefit of FF/UMEC/VI in comparison with FF/VI + UMEC for the outcome "exacerbations"; an added benefit is therefore not proven.

Morbidity –TDI-SAC

The mean change of the TDI Focal Score at week 24 vs. start of the study was used for the COPD symptom "dyspnoea" recorded using TDI-SAC. There was no statistically significant difference between the treatment arms for this outcome. This resulted in no hint of an added benefit of FF/UMEC/VI in comparison with FF/VI + UMEC; an added benefit is therefore not proven.

Health-related quality of life - SGRQ

Responder analyses of the SGRQ for an improvement ≥ 4 points at week 24 were used for "health-related quality of life". There was no statistically significant difference between the treatment arms. This resulted in no hint of an added benefit of FF/UMEC/VI in comparison with FF/VI + UMEC; an added benefit is therefore not proven.

Side effects – Serious adverse events

The present benefit assessment includes those nonfatal SAEs which comprise no exacerbation events. There was no statistically significant difference between the treatment groups at week 24. This resulted in no hint of greater or lesser harm from FF/UMEC/VI in comparison with FF/VI + UMEC for this outcome. Greater or lesser harm is therefore not proven for this outcome.

Side effects – discontinuation due to AEs

According to the outcome "SAEs", the present benefit assessment includes AEs resulting in the discontinuation of treatment which comprised no exacerbation events. There was no statistically significant difference between the treatment groups at week 24 for the outcome "discontinuation due to AEs". Hence, there was no hint of greater or lesser harm from FF/UMEC/VI in comparison with FF/VI + UMEC for this outcome. Greater or lesser harm is therefore not proven.

Side effects – specific AEs

Cardiovascular events

There were no usable data for the outcome "cardiovascular events". Hence, this resulted in no hint of greater or lesser harm from FF/UMEC/VI in comparison with FF/VI + UMEC. Greater or lesser harm is therefore not proven for this outcome.

Pneumonia

There was no statistically significant difference between the treatment groups for the outcome "pneumonia". Hence, this resulted in no hint of greater or lesser harm from FF/UMEC/VI in comparison with FF/VI + UMEC. Greater or lesser harm is therefore not proven for this outcome.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 presents a summary of the probability and extent of the added benefit of FF/UMEC/VI.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: FF/UMEC/VI – probability and extent of added benefit

Subindication	ACT[a]	Probability and extent of added benefit
Maintenance treatment in adults with moderate to severe COPD inadequately controlled with a combination of one ICS and one LABA[b]	Individual treatment optimization in accordance with physician's choice – under consideration of the previous therapy – with LABA and LAMA and possibly ICS	Added benefit not proven

a: Presentation of the ACT specified by the G-BA.
b: It is assumed that COPD was inadequately controlled with the previous therapy and the patients still had symptoms (including exacerbations) in patients for whom treatment with the drug combination FF/UMEC/VI was an option

ACT: appropriate comparator therapy; COPD: chronic obstructive pulmonary disease; FF: fluticasone furoate; G-BA: Federal Joint Committee; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; UMEC: umeclidinium; VI: vilanterol

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report was to assess the added benefit of the fixed combination of fluticasone furoate (FF), umeclidinium (UMEC) and vilanterol (VI) (hereinafter referred to as FF/UMEC/VI) as maintenance treatment in comparison with the ACT in adults with moderate to severe COPD inadequately controlled with a combination of inhaled corticosteroids (ICS) and a LABA.

Table 4 shows the research question of the benefit assessment and the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of FF/UMEC/VI

Research question	Subindication	ACT[a]
1	Maintenance treatment in adults with moderate to severe COPD inadequately controlled with a combination of one ICS and one LABA[b]	Individual treatment optimization in accordance with physician's choice – under consideration of the previous therapy – with LABA and LAMA and possibly ICS

a: Presentation of the ACT specified by the G-BA.
b: It is assumed that COPD was inadequately controlled with the previous therapy and the patients still had symptoms (including exacerbations) in patients for whom treatment with the drug combination FF/UMEC/VI was an option.

COPD: chronic obstructive pulmonary disease; FF: fluticasone furoate; G-BA: Federal Joint Committee; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; UMEC: umeclidinium; VI: vilanterol

The company followed the G-BA's specification of the ACT.

Assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on FF/UMEC/VI (status: 10 January 2018)
- bibliographical literature search on FF/UMEC/VI (last search on 5 December 2017)
- search in trial registries for studies on FF/UMEC/VI (last search on 04 December 2017)
- bibliographical literature search on the ACT (last search on 5 December 2017)
- search in trial registries for studies on the ACT (last search on 4 December 2017)

To check the completeness of the study pool:

- search in trial registries for studies on FF/UMEC/VI (last search on 14 March 2018)

The check identified no additional relevant study.

2.3.1 Studies included

Study 200812 listed in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: FF/UMEC/VI vs. FF/VI + UMEC

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
200812	No	Yes	No

a: Study sponsored by the company.
FF: fluticasone furoate; RCT: randomized controlled trial; UMEC: umeclidinium; VI: vilanterol; vs.: versus

The 200812 study was suitable to derive conclusions on the added benefit of FF/UMEC/VI using a subpopulation. In addition to the 200812 study included in the present benefit assessment, the company considered another RCT in its assessment (CTT116855; hereinafter referred to as IMPACT study). However, this study was unsuitable for an assessment of the added benefit of FF/UMEC/VI versus the ACT (see below).

The company additionally presented an indirect comparison (based on RCTs) of FF/UMEC/VI with beclomethasone/formoterol/glycopyrronium, the further triple fixed combination approved in Germany [3]. However, the company did not use this adjusted indirect comparison for a derivation of the added benefit of FF/UMEC/VI, but presented it only as additional information. The indirect comparison presented by the company was not used for the present benefit assessment (for reasons, see Section 2.7.2.5 of the full dossier assessment).

Section 2.6 contains a reference list for the included study 200812.

The IMPACT study was inadequate for the assessment of the added benefit

The IMPACT study presented by the company was unsuitable for assessing the added benefit of FF/UMEC/VI versus the ACT. This is justified below.

Study design

The IMPACT study [4-10] is a randomized, double-blind, controlled 3-arm study on the comparison of FF/UMEC/VI with the dual combinations FF/VI and UMEC/VI. Patients aged ≥ 40 years with confirmed and symptomatic COPD and a smoking history of at least 10 pack years were included in the study. In addition, moderate and/or severe exacerbations had have to be documented within the last 12 months before screening. Moreover, the included patients had moderate to very severe airway obstruction (severity grades 2 to 4) according to GOLD [11] and had received daily COPD maintenance treatment for at least 3 months before study inclusion.

A total of 10367 patients were randomly assigned (in a ratio of 2:2:1) to inhalative treatment with FF/UMEC/VI (N = 4155), FF/VI (N = 4139) or UMEC/VI (N = 2073) (once daily each). The dosage was in compliance with the respective SPC [12-14], FF was applied in the dosage of 100 µg [13]. Short-term treatment (≤ 14 days) of the patients with systemic corticosteroids, antibiotics or, at the physician's discretion, with further COPD drugs was possible in case of exacerbations or pneumonia. Moreover, application of salbutamol as rescue medication was allowed over the entire treatment period with the study medication.

The IMPACT study comprised a 2-week run-in phase, in which the current COPD maintenance treatment was continued, as well as a randomized treatment phase of 52 weeks. The patients were switched to the study medication at the start of the treatment phase. End of treatment was followed by a 7-day follow-up observation phase. Further information on the study and intervention characteristics of the IMPACT study are presented in Appendix A of the full dossier assessment.

Subpopulation corresponding to the therapeutic indication of FF/UMEC/VI

In accordance with the therapeutic indication of FF/UMEC/VI, the company only considered the subpopulation of patients whose maintenance treatment before study inclusion comprised at least one ICS and one LABA (ICS + LABA). In doing so, the company excluded patients who received simultaneous treatment with a long-acting muscarinic antagonist (LAMA). Since

the FF/VI arm does not correspond to the ACT, the company only considered patients from the FF/UMEC/VI arm and the UMEC/VI arm comprised in the therapeutic indication. This subpopulation of the IMPACT study, referred to as "ITT-ICS+LABA population" by the company, comprised 1220 patients in the FF/UMEC/VI arm and 576 patients in the UMEC/VI arm. These also included 10% patients who received a xanthine and/or a phosphodiesterase (PDE) inhibitor in addition to ICS + LABA. As this proportion was only minor, the company's definition of the subpopulation is altogether acceptable for the present benefit assessment.

Inadequate treatment in the comparator arm UMEC/VI

On average, the patients of the subpopulation comprised in the therapeutic indication had strong symptoms with a COPD assessment test (CAT) score of about 20.0 at the start of the study [11]. Moreover, about 73% of the patients comprised in the considered subpopulation had ≥ 2 moderate exacerbations or ≥ 1 severe exacerbation (see also Appendix B, Table 23, of the full dossier assessment) in the year before study inclusion. According to the classification based on GOLD, most of the patients belonged to group D [11]. In accordance with the treatment algorithm according to GOLD, treatment escalation through additional administration of a LAMA was recommended for this patient group with current ICS + LABA therapy at ongoing symptoms and exacerbations. While this recommendation was implemented in the intervention arm with the administration of FF/UMEC/VI, ICS was abruptly stopped at the start of the study medication despite prior exacerbations in patients of the UMEC/VI arm. Therewith, switching to ICS-free study medication in the comparator arm resulted in a de-escalation of the treatment that had already been inadequate at this time point despite administration of ICS. Such abrupt discontinuation of ICS can favour exacerbations [15,16] and was also discussed with regard to the IMPACT study [17]. Therewith, it is altogether doubtful whether the patients included in the comparator arm UMEC/VI of the IMPACT study received adequate treatment.

Regarding the ACT, the G-BA specified that individual treatment optimization was to comprise the substance classes LABA and LAMA, whereas ICS was only indicated as an adjunct, if appropriate. However, this only applies on condition that individual treatment optimization takes place under consideration of the (inadequate) previous therapy. In the particular case, ongoing symptoms and the history of exacerbations of the subpopulation pretreated with ICS + LABA suggest, as described above, that there was the indication for an ICS + LABA + LAMA combination therapy at the start of the study at least for most of these patients.

Moreover, it remained at least unclear whether individual treatment optimization could be regarded as fully implemented in the comparator arm UMEC/VI of the IMPACT study by specifying the therapy to the use of certain drugs from the substance classes LABA and LAMA, since individual treatment optimization with LABA and LAMA principally comprises all drugs of the mentioned substance classes. In the IMPACT study, application of LABA and LAMA is limited to VI or UMEC. Moreover, switching from one substance within a drug class, for instance, due to intolerances or problems encountered in applying different inhalation systems can principally be understood as possible treatment optimization. However, since the IMPACT study is excluded for another reason, this limitation had no further consequences.

The results of the IMPACTG study are presented as supplementary information in Appendix C of the full dossier assessment.

2.3.2 Study characteristics

Table 6 and Table 7 describe the 200182 study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: FF/UMEC/VI vs. FF/VI + UMEC

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
200812	RCT, double-blind, parallel	Adults (≥ 40 years) with confirmed COPD: $FEV_1/FVC < 0.70$ (post-salbutamol) at screening post-bronchodilator $FEV_1 < 50\%$ predicted at screening and ≥ 1 documented moderate[b] or severe[c] exacerbation within the last 12 months before screening **or** post-bronchodilator $FEV_1 \geq 50\%$ to < 80% predicted at screening and ≥ 2 documented moderate[b] exacerbations or ≥ 1 documented severe[c] exacerbation within the last 12 months before screening daily COPD maintenance-treatment ≥ 3 months CAT score ≥ 10 current or former[d] smokers with ≥ 10 pack years	total population: FF/UMEC/VI + placebo (N = 527) FF/VI + UMEC (N = 528) relevant subpopulation thereof[e]: FF/UMEC/VI + placebo (n = 147) FF/VI + UMEC (n = 142)	Run-in[f]: 2 weeks Treatment: 24 weeks Follow-up: 1 week	126 centres in Argentina, Australia, Germany, France, Italy, Japan, Mexico, Poland, Romania, Russia, Spain, South Korea 06/2016–05/2017	primary: change of the FEV_1 trough level at week 24 secondary: morbidity, health-related quality of life, AEs

(continued)

Table 6: Characteristics of the study included – RCT, direct comparison: FF/UMEC/VI vs. FF/VI + UMEC (continued)

a: Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes exclusively include information on relevant available outcomes for this benefit assessment.
b: According to the study protocol, deterioration of the COPD symptoms requiring treatment with oral/systemic corticosteroids and/or antibiotics presents a moderate exacerbation.
c: According to the study protocol, deterioration of the COPD symptoms requiring hospitalization of a patient to hospital presents a severe exacerbation.
d: Patients who had stopped smoking ≥ 6 months before screening were classified as former smokers.
e: Pretreatment with ICS + LABA.
f: Patients received their ongoing COPD medication until randomization. This medication was discontinued at the start of the study medication. Moreover, application of salbutamol as rescue medication was allowed over the entire study duration.

AE: adverse event; CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; FF: fluticasone furoate; FVC: forced vital capacity; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; n: relevant subpopulation; N: number of randomized patients; RCT: randomized controlled trial; UMEC: umeclidinium; VI: vilanterol; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: FF/UMEC/VI vs. FF/VI + UMEC

Study	Intervention	Comparison
200812	FF/UMEC/VI 100 µg/62.5 µg/25 µg once daily, in the morning + Placebo once daily, in the morning	FF/VI 100 µg/25 µg once daily, in the morning + UMEC 62.5 µg once daily, in the morning
	Rescue medication: ▪ salbutamol[a] **Pretreatment:** **allowed:** ▪ ICS, LABA, LAMA, SABA, SAMA ▪ Xanthines ▪ Oxygen ▪ Mucolytics ▪ PDE-4 inhibitors ▪ Leukotriene receptor antagonists ▪ Systemic corticosteroids, depot corticosteroids ▪ Antiinfectives ▪ Nedocromil or cromoglicic acid ▪ Other COPD medication **not allowed:** ▪ continuous long-term treatment with antibiotics ≥ 30 days before screening ▪ systemic, oral and parenteral corticosteroids ≥ 30 before screening ▪ every other study medication ≥ 30 days or 5 half-lives before screening **Concomitant treatment permitted:** ▪ oral or injectable corticosteroids ≤ 14 days for short-term treatment of COPD exacerbations or pneumonia ▪ antibiotics ≤ 14 days for short-term treatment of COPD exacerbations or pneumonia as well as acute infections ▪ any COPD drugs ≤ 14 days for short-term treatment of moderate/severe exacerbations or pneumonia, if medically required ▪ mucolytics (e.g. acetyl cysteine) ▪ long-term treatment with oxygen ≤ 3 l/min flow rate ▪ vaccinations (e.g. influenza, pneumonia, herpes zoster) ▪ systemic and ophthalmologic beta blockers (to be used with precaution) ▪ treatment for smoking cessation ▪ antitussive drugs ▪ positive airway pressure in sleep apnoea	

a: No application ≥ 4 hours before spirometry.

COPD: chronic obstructive pulmonary disease; FF: fluticasone furoate; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; PDE-4: phosphodiesterase-4; RCT: randomized controlled trial; SABA: short-acting beta-2 sympathomimetic; SAMA: short-acting muscarinic antagonist; UMEC: umeclidinium; vs.: versus; VI: vilanterol

Study design

The 200812 study is a randomized, double-blind, controlled non-inferiority study on the comparison of the fixed triple combination FF/UMEC/VI with the free triple combination of FF/VI and UMEC (hereinafter referred to as FF/VI + UMEC). Patients aged 40 years or older with confirmed COPD with spirometric GOLD grades II to IV (moderate to very severe) were to be included, who had received daily COPD maintenance therapy at least 3 months before screening. Moreover, patients had to have a smoking history of at least 10 pack years as well as a CAT score ≥ 10 regarding the symptoms. Further inclusion criteria of the study were documented moderate or severe exacerbations within the last 12 months before study inclusion. According to the study protocol, deterioration of the COPD symptoms requiring treatment with oral/systemic corticosteroids and/or antibiotics was defined to be a moderate exacerbation. In cases of severe exacerbations, deterioration of the COPD symptoms resulted in the hospitalization of the patient.

A total of 1055 patients were randomly assigned to treatment with the fixed (N = 527) or the free (N = 528) combination of FF, UMEC and VI in a ratio of 1:1. Randomization was stratified by number of long-acting bronchodilators during the run-in phase (0; 1; 2).

Administration of the study medication was conducted once daily via inhalation according to the SPC [12,13,18]. FF was applied in the approved dosage of 100 µg [13]. Dosage of the individual substances was identical in both study arms. To maintain blinding, patients in the study arm with the fixed triple combination FF/UMEC/VI additionally received inhaled placebo once daily. Short-term treatment (≤ 14 days) of the patients with systemic corticosteroids, antibiotics or, at the physician's discretion, with further COPD drugs was possible in case of exacerbations or pneumonia. Moreover, application of salbutamol as rescue medication was allowed over the entire treatment period.

The 200812 study comprised a 2-week run-in phase, in which COPD maintenance treatment before study inclusion was maintained, as well as a randomized treatment phase of 24 weeks. The patients were switched to the study medication at the start of the treatment phase. After planned or premature end of treatment, the patients underwent 7-day follow-up observation (follow-up observation period).

Primary outcome of the 200812 study was the change of the FEV_1 trough level after 24 weeks in comparison with the baseline value. Secondary patient-relevant outcomes were symptoms (exacerbation, TDI), health-related quality of life (recorded using the SGRQ) and AEs.

Relevant subpopulation

The 200812 study included patients who had been receiving daily COPD maintenance treatment for at least 3 months. FF/UMEC/VI is indicated for maintenance treatment in adults with moderate to severe COPD inadequately controlled with a combination of ICS and LABA [12]. The prior therapy of the patients included in the 200812 study is thus not restricted to the maintenance treatment with ICS und LABA comprised in the approval of FF/UMEC/VI. For

this reason, the present benefit assessment only considered patients whose maintenance treatment before study inclusion comprised at least one ICS and one LABA, which is analogous to the company's approach. Moreover, only those patients were considered whose maintenance treatment comprised no LAMA. This subpopulation of the 200812 study referred to as "ITT-ICS+LABA population" by the company, comprised 147 patients in the FF/UMEC/VI arm and 142 patients in the FF/VI + UMEC arm.

Implementation of the ACT

In the 200812 study, the fixed triple combination was compared with the free triple combination of FF, UMEC and VI. On the basis of the specification of the ACT, this comparison is possible. However, it must be noted that the ACT cannot be considered as fully implemented by specifying the therapy to the use of certain drugs from the substance classes LABA, LAMA and ICS. It is unclear whether the used drugs FF, UMEC and VI presented the individual treatment optimization for all patients. Individual treatment optimization with LABA, LAMA and possibly ICS principally comprises all drugs of the mentioned substance classes. Moreover, switching from one substance within a drug class, for instance, due to intolerances or problems encountered in applying different inhalation systems can principally be understood as possible treatment optimization. Therefore, a conclusion on the added benefit of FF/UMEC/VI can only be made with regard to the used drug combination FF/VI + UMEC.

Patient characteristics

Table 8 shows the characteristics of the patients in the relevant subpopulation of the study included.

Table 8: Characteristics of the study population – RCT, direct comparison: FF/UMEC/VI vs. FF/VI + UMEC

Study Characteristics Category	**FF/UMEC/VI**	**FF/VI + UMEC**
200812	N[a] = 147	N[a] = 142
Age [years], mean (SD)	65 (8)	63 (10)
Sex [F/M], %	34/66	33/67
Duration of COPD [years], mean (SD)	ND	ND
Smoking status [smoker/former smoker], %	36/64	37/63
Smoking [pack years], mean (SD)	39.8 (23.8)	42.4 (29.2)
COPD grade [according to GOLD], n (%)		
Grade 1 (mild; $FEV_1 \geq 80\%$ target)	0 (0)	0 (0)
Grade 2 (moderate; $FEV_1 \geq 50\%$ to < 80% target)	53 (36)	61 (43)
Grade 3 (severe; $FEV_1 \geq 30\%$ to < 50% target)	66 (45)	55 (39)
Grade 4 (very severe; $FEV_1 < 30\%$ target)	26 (18)	20 (14)
Unknown	2 (1)	6 (4)
Exacerbations[b], n (%)		
< 2 moderate and no severe exacerbation	57 (39)	49 (35)
≥ 2 moderate or ≥ 1 severe exacerbation	90 (61)	93 (65)
CAT score, mean (SD)	20.1 (5.8)	19.4 (5.1)
BMI [kg/m^2], mean (SD)	27.0 (4.6)	27.1 (5.1)
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)	ND	ND

a: Number of randomized patients in the relevant subpopulation (pretreatment with ICS + LABA).
b: Within the last 12 months before screening.
BMI: body mass index; CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; f: female; FEV_1: forced expiratory volume in 1 second; FF: fluticasone furoate; GOLD: Global Initiative for Chronic Obstructive Lung Disease; m: male; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; UMEC: umeclidinium; vs.: versus; VI: vilanterol

The patient characteristics were sufficiently balanced between the treatment arms of the 200812 study.

The mean age of the patients was about 64 years, and the majority were male. These were mostly ex-smokers; the number of the pack years was slightly lower in the intervention arm than in the comparator arm.

The COPD grade according to GOLD chiefly comprised severity grades 2 and 3 in both study arms with only minor differences between the study arms and the severity grades.

In the year before study inclusion, exacerbations had occurred in all patients, approx. 60% of the patients had ≥ 2 moderate exacerbations or ≥ 1 severe exacerbation.

There was no information on treatment and study discontinuations for the relevant sub-population.

Risk of bias at study level

Table 9 shows the risk of bias at study level.

Table 9: Risk of bias at study level – RCT, direct comparison: FF/UMEC/VI vs. FF/VI + UMEC

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
200812	Yes	Yes	Yes	Yes	Yes	Yes	Low

FF: fluticasone furoate; RCT: randomized controlled trial; UMEC: umeclidinium; VI: vilanterol; vs.: versus

The risk of bias at study level for study 200812 was rated as low. This concurs with the company's assessment.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - All-cause mortality
- Morbidity
  - Exacerbations
  - Symptoms, recorded using the TDI-SAC
- Health-related quality of life
  - measured using the St. George`s Respiratory Questionnaire (SGRQ)
- Side effects
  - SAEs
  - Discontinuation due to AEs
  - Cardiovascular events

- Pneumonia
- if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.7.2.4.3 of the full dossier assessment).

Table 10 shows for which outcomes data were available for the relevant subpopulation of the study included.

Table 10: Matrix of the outcomes – RCT, direct comparison: FF/UMEC/VI vs. FF/VI + UMEC

Study	Outcomes							
	All-cause mortality	Exacerbations	TDI Focal Score	Health-related quality of life (SGRQ)	SAEs[a]	Discontinuation due to AEs	Cardiovascular events[b]	Pneumonia (PT)
200812	Yes[c]	Yes	Yes	Yes	Yes	Yes	No[d]	Yes

a: Only separate analyses are available on fatal and nonfatal SAEs. Nonfatal SAEs that occurred under treatment were used as SAEs.
b:Group of the following SMQs (MedDRA coding, version 20.0): Cardiac Arrhythmia (composed of several SMQs referred to as "Sub-SMQs" by the company), cardiac failure (SMQ), ischaemic heart disease (SMQ), hypertension (SMQ), CNS bleedings and cerebrovascular conditions (SMQ).
c: Determined by the recording of AEs.
d: Operationalization comprises several SMQs; it is unclear whether all events that occurred are patient-relevant.

AE: adverse event; FF: fluticasone furoate; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SMQ: Standardized MedDRA Query; SGRQ: St. George`s Respiratory Questionnaire; SAE: serious adverse event; TDI: Transition Dyspnea Index; UMEC: umeclidinium; VI: vilanterol; vs.: versus

2.4.2 Risk of bias

Table 11 describes the risk of bias for the relevant outcomes.

Table 11: Risk of bias at study and outcome level – RCT, direct comparison: FF/UMEC/VI vs. FF/VI + UMEC

Study		Outcomes							
	Study level	All-cause mortality	Exacerbations	TDI Focal Score	Health-related quality of life (SGRQ)	SAEs[a]	Discontinuation due to AEs	Cardiovascular events	Pneumonia (PT)
200812	N	N[b]	N	N	N	N	N	-[c]	N

a: Only separate analyses are available on fatal and nonfatal SAEs. Nonfatal SAEs that occurred under treatment were used as SAEs.
b: Determined by the recording of AEs.
c: Operationalization comprises several SMQs; it is unclear whether all events that occurred are patient-relevant.
AE: adverse event; FF: fluticasone furoate; L: low; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SGRQ: St. George`s Respiratory Questionnaire; TDI: Transition Dyspnea Index; UMEC: umeclidinium; VI: vilanterol; vs.: versus

The risk of bias for all relevant outcomes was rated as low. This concurs with the company's assessment.

2.4.3 Results

Table 12, Table 13 and Table 14 summarize f the results on the comparison of FF/UMEC/VI with FF/VI + UMEC in adults with moderate to severe COPD inadequately controlled with a combination of one ICS and one LABA. Where necessary, calculations conducted by the Institute were provided in addition to the data from the company's dossier.

Table 12: Results (mortality, health-related quality of life and side effects) – RCT, direct comparison: FF/UMEC/VI vs. FF/VI + UMEC

Study Outcome category Outcome	FF/UMEC/VI N	FF/UMEC/VI Patients with event n (%)	FF/VI + UMEC N	FF/VI + UMEC Patients with event n (%)	FF/UMEC/VI vs. FF/VI + UMEC RR [95% CI]; p-value
200812					
Mortality					
All-cause mortality[a]	147	1 (0.7)	142	0 (0)	2.90 [0.12; 70.57][b] 0.515[c]
Health-related quality of life					
SGRQ responder[d]	147	81 (55)	142	80 (56)	0.98 [0.80; 1.20][b] 0.860[c]
Side effects					
AEs (additional information)[e]	147	63 (42.9)	142	55 (38.7)	-
SAEs (nonfatal)[f]	147	5 (3.4)	142	4 (2.8)	1.21 [0.33; 4.41]; 0.831[c]
Discontinuation due to AEs (without exacerbations)	147	2 (1.4)	142	0 (0)	4.83 [0.23; 99.76]; 0.211[c]
Cardiovascular events	No usable data				
Pneumonia	147	2 (1.4)	142	1 (0.7)	1.93 [0.18; 21.07]; 0.683[c]

a: Determined by the recording of AEs.
b: Institute's calculation of effect (in case of 0 events in one study arm with correction factor of 0.5 in both study arms) and CI (asymptotic).
c: Unconditional exact test (CSZ method according to [19]).
d: Patients with an SGRQ total score of 4 units below the baseline value or less were defined as responders. Reduction of the SGRQ total score indicates an improvement of the quality of life.
e: Under treatment.
f: Under treatment without exacerbation events.

AE: adverse event; CI: confidence interval; FF: fluticasone furoate; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SGRQ: St. George`s Respiratory Questionnaire; UMEC: umeclidinium; VI: vilanterol; vs.: versus

Table 13: Results (morbidity: exacerbations) - RCT, direct comparison: FF/UMEC/VI vs. FF/VI + UMEC

Study Outcome category	FF/UMEC/VI		FF/VI + UMEC		FF/UMEC/VI vs. FF/VI + UMEC
Outcome	**N**	**Annual exacerbation rate: [95% CI]**	**N**	**Annual exacerbation rate: [95% CI]**	**Rate ratio [95% CI]; p-value[a]**
200812					
Morbidity					
Annual exacerbation rate					
moderate or severe exacerbations	145	0.40 [ND]	136	0.47 [ND]	0.85 [0.52; 1.40]; 0.529
severe exacerbations	145	0.0 [ND]	136	0.0 [ND]	0.31 [0.03; 3.76]; 0.357
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value**
Exacerbations (additional information)					
moderate or severe exacerbations	147	29 (20)	142	27 (19)	1.04 [0.65; 1.66]; 0.900[b]
severe exacerbations	147	1 (< 1)	142	2 (1)	0.48 [0.04; 5.27]; 0.600[b]

a: Negative binomial model adjusted for exacerbations in the year before study participation, geographical region and FEV_1 % predicted on day 1.

b: Institute's calculation, unconditional exact test (CSZ method according to [19]).

CI: confidence interval; FEV_1: forced expiratory volume in 1 second; FF: fluticasone furoate; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; RR: relative risk; UMEC: umeclidinium; VI: vilanterol; vs.: versus

Table 14: Results (morbidity: TDI) - RCT, direct comparison: FF/UMEC/VI vs. FF/VI + UMEC

Study Outcome category	FF/UMEC/VI			FF/VI + UMEC			FF/UMEC/VI vs. FF/VI + UMEC
Outcome	N[a]	Values at study start[b] mean (SD)	Change at end of study mean (SD)	N[a]	Values at study start[b] mean (SD)	Change at end of study mean (SD)	MD [95% CI]; p-value
200812							
Morbidity							
TDI Focal Score[c]	140	6.3 (1.86)	3.05 (3.09)	136	6.5 (1.78)	3.15 (3.00)	−0.11 [−0.83; 0.62]; 0.771[d]

a: Number of patients considered in the analysis for the calculation of the effect; the values at the start of the study may be based on other patient numbers.
b: Referred to as BDI.
c: The TDI-SAC was used in the study:
d: Institute's calculation: t-test.

BDI: Baseline Dyspnea Index; CI: confidence interval; FF: fluticasone furoate; MD: mean difference; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; TDI-SAC: Transition Dyspnea Index – Self-administered computerized; UMEC: umeclidinium; VI: vilanterol; vs.: versus

Based on the available data, at most indications, e.g. of an added benefit, can be determined for all outcomes. The assessment of the added benefit at outcome level deviates from that of the company. The company derived the added benefit at outcome level based on the data of the IMPACT study, which, however, is not assessed as relevant for the present benefit assessment (see Section 2.3.1). From the company's point of view, the study 200812 shows the non-inferiority of the fixed triple combination FF/UMEC/VI in comparison with the free triple combination FF/VI + UMEC, since no statistically significant differences were shown between the treatment arms.

Mortality

All-cause mortality

In the 200812 study, deaths were determined by the recording of adverse events. One death had occurred until week 24. There was no statistically significant difference between the treatment groups. Overall, this resulted in no hint of an added benefit of FF/UMEC/VI in comparison with FF/VI + UMEC; an added benefit is therefore not proven.

Morbidity

Exacerbations

Exacerbations that occurred under the study medication, operationalized as moderate or severe exacerbations as well as severe exacerbations, were included in the present benefit assessment in the form of the annual exacerbation rates at week 24. The proportion of patients with event was presented as additional information. There was no statistically significant difference

between the treatment arms for both operationalizations. Overall, this resulted in no hint of an added benefit of FF/UMEC/VI in comparison with FF/VI + UMEC for the outcome "exacerbations"; an added benefit is therefore not proven.

Transition Dyspnea Index – Self-administered computerized (TDI-SAC)

The mean change of the TDI Focal Score at week 24 vs. start of the study was used for the COPD symptom "dyspnoea" recorded using TDI-SAC. The results of the responder analyses presented by the company for the derivation of the added benefit are presented as additional information in Appendix D of the full dossier assessment. There was no statistically significant difference between the treatment arms for this outcome. This resulted in no hint of an added benefit of FF/UMEC/VI in comparison with FF/VI + UMEC; an added benefit is therefore not proven.

Health-related quality of life

SGRQ

Responder analyses of the SGRQ for an improvement ≥ 4 points at week 24 were used for "health-related quality of life". There was no statistically significant difference between the treatment arms. This resulted in no hint of an added benefit of FF/UMEC/VI in comparison with FF/VI + UMEC; an added benefit is therefore not proven.

Side effects

SAEs

Analyses on SAEs comprising both fatal and nonfatal SAEs are not available for the relevant subpopulation. Hence, the present benefit assessment considered the nonfatal SAEs - fatal SAEs were recorded under "all-cause mortality". Moreover, those SAEs were included which comprised no exacerbation events. In the present benefit assessment, exacerbations were used as separate morbidity outcome. There was no statistically significant difference between the treatment groups at week 24. This resulted in no hint of greater or lesser harm from FF/UMEC/VI in comparison with FF/VI + UMEC for this outcome. Greater or lesser harm is therefore not proven for this outcome.

Discontinuation due to AEs

According to the outcome "SAEs", the present benefit assessment includes AEs resulting in the discontinuation of treatment, which comprised no exacerbation events. There was no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". Hence, there was no hint of greater or lesser harm from FF/UMEC/VI in comparison with FF/VI + UMEC for this outcome. Greater or lesser harm is therefore not proven.

Specific AEs

Cardiovascular events

There were no usable data for the outcome "cardiovascular events". For reasons, see Section 2.7.2.4.3 of the full dossier assessment. Hence, this resulted in no hint of greater or lesser harm from FF/UMEC/VI in comparison with FF/VI + UMEC. Greater or lesser harm is therefore not proven for this outcome.

Pneumonia

There was no statistically significant difference between the treatment groups for the outcome "pneumonia". Hence, this resulted in no hint of greater or lesser harm from FF/UMEC/VI in comparison with FF/VI + UMEC. Greater or lesser harm is therefore not proven for this outcome.

2.4.4 Subgroups and other effect modifiers

The following effect modifiers were considered in the benefit assessment (see Section 2.7.2.4.3 of the full dossier assessment):

- Age (< 65 years / ≥ 65 years)
- Sex (female / male)
- Region (Europe / rest of the world)
- History of exacerbations in the last 12 months before screening (< 2 moderate and no severe exacerbations / ≥ 2 moderate or ≥ 1 severe exacerbation)
- FEV_1 at screening (< 50% / ≥ 50%)
- Smoking status (smoker / ex-smoker)

However, the company did not consider the effect modifiers "FEV_1 at screening" and "smoking status" and accordingly presented no subgroup analyses. The impact of these effect modifiers on the results of the 200812 study was unclear, since Institute's calculations were not possible on the basis of the available data.

Subgroup analyses for the relevant subpopulation on the outcome "TDI-SAC" are not available for the change of the TDI Focal Score at week 24 vs. start of the study used for the present benefit assessment. An assessment of the impact exerted by the mentioned effect modifiers on the results of the TDI Focal Score was not possible on the basis of the available data.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

Altogether, no relevant effect modifications were observed for the considered subgroup characteristics. This concurs with the approach of the company insofar as it also observed no relevant effect modifications on the basis of subgroup characteristics it considered.

2.5 Probability and extent of added benefit

The derivation of probability and extent of the added benefit at outcome level is presented below. The various outcome categories and the effect sizes were taken into account. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4.3 (see Table 15).

Table 15: Extent of added benefit at outcome level: FF/UMEC/VI vs. FF/VI + UMEC

Outcome category **Outcome**	**FF/UMEC/VI vs. FF/VI + UMEC proportion of events (%) or MD or annual rate** **Effect estimate [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality[c]	0.7% vs. 0% RR: 2.90 [0.12; 70.57] p = 0.515	Lesser benefit/added benefit not proven
Morbidity		
Moderate or severe exacerbations (annual rate)	0.40 vs. 0.47 rate ratio: 0.85 [0.52; 1.40] p = 0.529	Lesser benefit/added benefit not proven
Severe exacerbations (annual rate)	0.0 vs. 0.0 rate ratio: 0.31 [0.03; 3.76] p = 0.357	Lesser benefit/added benefit not proven
TDI Focal Score[d]	3.05 vs. 3.15 MD: −0.11 [−0.83; 0.62] p = 0.771	Lesser benefit/added benefit not proven
Health-related quality of life		
SGRQ responder[e]	55% vs. 56% RR: 0.98 [0.80; 1.20] p = 0.860	Lesser benefit/added benefit not proven
Side effects		
SAEs (nonfatal)[f]	3.4% vs. 2.8% RR: 1.21 [0.33; 4.41] p = 0.831	Greater/lesser harm not proven
Discontinuation due to AEs (without exacerbations)	1.4% vs. 0% RR: 4.83 [0.23; 99.76] p = 0.211	Greater/lesser harm not proven
Cardiovascular events	No usable data	Greater/lesser harm not proven
Pneumonia	1.4% vs. 0.7% RR: 1.93 [0.18; 21.07] p = 0.683	Greater/lesser harm not proven

a: Probability provided if a statistically significant and relevant effect is present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Determined by the recording of AEs.
d: The TDI-SAC version was used in the study.
e: Patients with an SGRQ total score of 4 units below the baseline value or less were defined as responders. Reduction of the SGRQ total score indicates an improvement of the quality of life.
f: Only separate analyses are available on fatal and nonfatal SAEs. Nonfatal SAEs that occurred under treatment were used as SAEs.

AE: adverse event; FF: fluticasone furoate; CI: confidence interval; MD: mean difference; RR: relative risk; SAE: serious adverse event; SGRQ: St. George`s Respiratory Questionnaire; TDI: Transition Dyspnea Index; UMEC: umeclidinium; VI: vilanterol; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 16 summarizes the results considered in the overall conclusion on the extent of the added benefit.

Table 16: Positive and negative effects from the assessment of FF/UMEC/VI in comparison with FF/VI + UMEC

Positive effects	**Negative effects**
-	-
FF: fluticasone furoate; UMEC: umeclidinium; VI: vilanterol	

Overall, there were neither positive nor negative effects of FF/UMEC/VI in comparison with FF/VI + UMEC.

In summary, an added benefit of FF/UMEC/VI in comparison with FF/VI + UMEC is not proven for adult patients with moderate to severe COPD inadequately controlled with a combination of one ICS and one LABA who still have symptoms (including exacerbations) despite their ongoing therapy.

The result of the assessment of the added benefit of FF/UMEC/VI in comparison with the ACT is summarized in Table 17.

Table 17: FF/UMEC/VI – probability and extent of added benefit

Subindication	**ACT**[a]	**Probability and extent of added benefit**
Maintenance treatment in adults with moderate to severe COPD inadequately controlled with a combination of one ICS and one LABA[b]	Individual treatment optimization in accordance with physician's choice – under consideration of the previous therapy – with LABA and LAMA and possibly ICS	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. b: It is assumed that COPD in patients for whom treatment with the drug combination FF/UMEC/VI was an option was inadequately controlled with the previous therapy and the patients still had symptoms (including exacerbations). ACT: appropriate comparator therapy; COPD: chronic obstructive pulmonary disease; FF: fluticasone furoate; G-BA: Federal Joint Committee; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; UMEC: umeclidinium; VI: vilanterol		

The assessment described above deviates from that of the company, which derived an indication of major added benefit based on the results of the study 200812 and the IMPACT study.

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.6 List of included studies

Bremner PR, Birk R, Brealey N, Ismaila AS, Zhu CQ, Lipson DA. Single-inhaler fluticasone furoate/umeclidinium/vilanterol versus fluticasone furoate/vilanterol plus umeclidinium using two inhalers for chronic obstructive pulmonary disease: a randomized non-inferiority study. Respir Res 2018; 19: 19.

GlaxoSmithKline. Comparative study of fluticasone furoate(FF)/umeclidinium bromide (UMEC)/ vilanterol (VI) closed therapy versus FF/VI plus UMEC open therapy in subjects with chronic obstructive pulmonary disease (COPD): study details [online]. In: ClinicalTrials.gov. 31.01.2018 [Accessed: 19.03.2018]. URL: https://ClinicalTrials.gov/show/NCT02729051.

GlaxoSmithKline. A phase IIIb, 24-week randomised, double-blind study to compare 'closed' triple therapy (FF/UMEC/VI) with 'open' triple therapy (FF/VI + UMEC), in subjects with chronic obstructive pulmonary disease (COPD) [online]. In: EU Clinical Trials Register. [Accessed: 19.03.2018]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-005212-14.

GlaxoSmithKline. A phase IIIb, 24-week randomized, double-blind study to compare ‘closed’ triple therapy (FF/UMEC/VI) with ‘open’ triple therapy (FF/VI+UMEC), in subjects with chronic obstructive pulmonary disease (COPD): study 200812; protocol amendment 3 [unpublished]. 2016.

GlaxoSmithKline. A phase IIIb, 24-week randomised, double-blind study to compare ‘closed’ triple therapy (FF/UMEC/VI) with 'open' triple therapy (FF/VI + UMEC), in subjects with chronic obstructive pulmonary disease (COPD); study 200812; Zusatzanalysen [unpublished]. 2017.

GlaxoSmithKline. A phase IIIb, 24-week randomised, double-blind study to compare ‘closed’ triple therapy (FF/UMEC/VI) with 'open' triple therapy (FF/VI + UMEC), in subjects with chronic obstructive pulmonary disease (COPD): study 200812; reporting and analysis plan [unpublished]. 2017.

GlaxoSmithKline. A phase IIIb, 24-week randomized, double-blind study to compare ‘closed’ triple therapy (FF/UMEC/VI) with ‘open triple’ therapy (FF/VI+UMEC), in subjects with chronic obstructive pulmonary disease (COPD): study 200812; clinical study report [unpublished]. 2017.

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Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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4. GlaxoSmithKline. A study comparing the efficacy, safety and tolerability of fixed dose combination (FDC) of FF/UMEC/VI with the FDC of FF/VI and UMEC/VI; administered once-daily via a Dry Powder Inhaler (DPI) in subjects with chronic obstructive pulmonary disease (COPD): study details [online]. In: ClinicalTrials.gov. 23.03.2018 [Accessed: 13.04.2018]. URL: https://www.clinicaltrials.gov/ct2/show/NCT02164513.

5. GlaxoSmithKline Research & Development. A phase III, 52 week, randomized, double-blind, 3-arm parallel group study, comparing the efficacy, safety and tolerability of the fixed dose triple combination fluticasone furoate/ umeclidinium/vilanterol, with the fixed dose dual combinations of fluticasone furoate/vilanterol and umeclidinium/vilanterol, all administered once-daily in the morning via a dry powder inhaler in subjects with chronic obstructive pulmonary disease [online]. In: EU Clinical Trials Register. 04.12.2017 [Accessed: 13.04.2018]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=2013-003075-35.

6. GlaxoSmithKline. A phase III, 52 week, randomized, double-blind, 3-arm parallel group study, comparing the efficacy, safety and tolerability of the fixed dose triple combination FF/UMEC/VI with the fixed dose dual combinations of FF/VI and UMEC/VI, all administered once-daily in the morning via a dry powder inhaler in subjects with chronic obstructive pulmonary disease: study CTT116855; reporting and analysis plan [unpublished]. 2017.

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