IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Umeclidinium/vilanterol – Benefit assessment according to §35a Social Code Book V[1]

Extract

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Institute for Quality and Efficiency in Health Care
Im Mediapark 8 (KölnTurm)
50670 Cologne
Germany

Tel.: +49 (0)221 – 35685-0
Fax: +49 (0)221 – 35685-1
E-Mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice:

No advisor on medical and scientific questions was available for the present dossier assessment.

IQWiG employees involved in the dossier assessment[2]:

- Helmut Hörn
- Gertrud Egger
- Dorothea Gechter
- Andreas Gerber-Grote
- Charlotte Guddat
- Michaela Florina Kerekes
- Sarah Mostardt
- Katrin Nink
- Volker Vervölgyi
- Min Zhou

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[2] Due to legal data protection regulations, employees have the right not to be named.

Table of contents

List of tables[3]

Page

[3] 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
FCV	forced vital capacity
FEV_1	forced expiratory volume in one second
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)
ITT	intention to treat
LABA	long-acting beta-2-agonist
MMRC	Modified Medical Research Council
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SGRQ	St. George's Respiratory Questionnaire
SOBDA	Shortness of Breath with Daily Activities
TDI	Transition Dyspnoea Index

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 umeclidinium/vilanterol. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 14 July 2014.

Research question

The aim of this report is to assess the added benefit of umeclidinium/vilanterol as maintenance bronchodilator treatment for the relief of symptoms in adult patients with chronic obstructive pulmonary disease (COPD) in comparison with the appropriate comparator therapy (ACT).

For the benefit assessment, the following 2 research questions result from the G-BA's specification on the ACT.

Table 2: Research questions of the benefit assessment of umeclidinium/vilanterol

Research question	Therapeutic indication	ACT[a]
1	Adult patients with COPD grade II and adult patients with COPD grades ≥ III with < 2 exacerbations per year	LABA (formoterol, salmeterol) and/or LAMA (**tiotropium**)
2	Adult patients with COPD grades ≥ III with ≥ 2 exacerbations per year	LABA (formoterol, salmeterol) and/or LAMA (tiotropium) and additional ICS[b]

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: The company chose no comparator therapy for this subpopulation and claimed no added benefit because, from the company's point of view, no sufficient data were recorded.
ACT: appropriate comparator therapy; COPD: chronic obstructive pulmonary disease; G-BA: Federal Joint Committee; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist

The assessment was conducted in comparison with the ACT specified by the G-BA and based on patient-relevant outcomes and on randomized controlled trials (RCTs) with a minimum duration of 24 weeks.

This approach partially deviated from that of the company, which only chose an ACT for research question 1. It followed the specification of the G-BA and, from the options

mentioned, chose tiotropium as the comparator therapy. The company chose no comparator therapy for research question 2 and claimed no added benefit.

In its criteria for study inclusion, the company considered the requirement that intervention and comparator therapy can also be used in combination with inhaled corticosteroids (ICS). However, it did not consider the conditions for the use of ICS according to the ACT. Concomitant ICS treatment is not to be used in patients of research question 1, whereas patients of research question 2 are to receive concomitant ICS treatment. Deviating from the company, the criteria for ICS treatment specified by the G-BA were used in the present benefit assessment, and it is examined for the respective study whether the use of ICS concurred with the G-BA's specifications.

Supplementary research question

The company additionally presented an indirect comparison between umeclidinium/vilanterol and indacaterol/glycopyrronium. Deviating from the company, this comparison was not considered because indacaterol/glycopyrronium is no ACT.

Results

Study pool and patient populations

3 RCTs (DB2113360, DB2113374 and ZEP117115) were included for the direct comparison of umeclidinium/vilanterol with the ACT. All 3 studies investigated the comparison of daily inhalation of the fixed combination of 62.5 µg umeclidinium and 25 µg vilanterol versus 18 µg tiotropium. Patients were randomized in a ratio of 1:1. The study duration of all the studies was 24 weeks. Patients aged 40 years or older with confirmed COPD grade II to IV were enrolled. ICS treatment could be continued as concomitant treatment irrespective of the severity grade and the frequency of exacerbations of the patients. In most study participants with concomitant ICS treatment, this did not concur with the conditions specified by the ACT. Hence analyses based on the total populations of the 3 studies are unsuitable to derive the added benefit for one of the 2 research questions.

Since the dossier contained no separate analyses for the relevant subpopulation, the subgroup analyses of patients without concomitant ICS treatment were used as an approximation for patients of COPD grade II and patients of COPD grades ≥ III with < 2 exacerbations per year for answering research question 1. None of the analyses conducted by the company could be operationalized as an approximation for patients with COPD grades ≥ III and ≥ 2 exacerbations per year for answering research question 2.

The risk of bias at study level was rated as low for the 3 studies included.

Results for research question 1: patients with COPD grade II and patients with COPD grades ≥ III with < 2 exacerbations per year

For answering research question 1, evaluable analyses were only available for the outcomes "COPD symptoms" (Transition Dyspnoea Index [TDI]) and "health-related quality of life" (St. George's Respiratory Questionnaire [SGRQ]).

COPD symptoms (TDI)

The TDI is a questionnaire for the direct measurement of the change of dyspnoea in comparison with the baseline status.

Based on the meta-analysis of the results from the studies DB2113360 and DB2113374, there was no statistically significant difference between the treatment arms for the outcome "COPD symptoms" (TDI responder). Hence an added benefit of umeclidinium/vilanterol in comparison with the ACT tiotropium is not proven for this outcome.

Health-related quality of life (SGRQ)

The SGRQ is a self-reported instrument to measure health-related quality of life of patients with chronic respiratory diseases.

Neither the effect with a low risk of bias from the ZEP117115 study nor the overall effect resulting from the meta-analysis of all 3 studies was statistically significant for the outcome "health-related quality of life" (SGRQ responder). Hence an added benefit of umeclidinium/vilanterol in comparison with the ACT tiotropium is not proven for this outcome.

Outcomes without evaluable results

No relevant analyses were available for the following outcomes because the dossier contained no analyses for patients without concomitant ICS treatment: all-cause mortality, COPD symptoms (COPD Assessment Test [CAT]), COPD symptoms (Shortness of Breath with Daily Activities [SOBDA] questionnaire), moderate and severe exacerbations, serious adverse events (SAEs) and discontinuation due to adverse events (AEs). No added benefit or greater or lesser harm of umeclidinium/vilanterol in comparison with tiotropium is proven with regard to these outcomes.

Results for research question 2: patients with COPD grades ≥ III with ≥ 2 exacerbations per year

No analyses contained in the dossier could be used for answering research question 2. Hence an added benefit of umeclidinium/vilanterol in comparison with tiotropium + ICS is not proven for patients with COPD grades ≥ III and ≥ 2 exacerbations per year.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

On the basis of the results presented, the extent and probability of the added benefit of the drug umeclidinium/vilanterol compared with the ACT is assessed as follows.

Research question 1: patients with COPD grade II and patients with COPD grades ≥ III with < 2 exacerbations per year

On the basis of the results presented, there are neither positive nor negative effects for adult patients with COPD grade II or of COPD grades ≥ III with < 2 exacerbations per year.

Overall, evaluable results for the benefit assessment were only available for 2 outcomes. Because of the lack of evaluable results on the remaining outcomes of mortality and morbidity and particularly of all outcomes on AEs, overall, greater harm from umeclidinium/vilanterol cannot be excluded either. Hence no conclusive balancing on the added benefit is possible irrespective of the results of the 2 outcomes presented.

In summary, an added benefit of umeclidinium/vilanterol is not proven for adult patients with COPD grade II or with COPD grades ≥ III with < 2 exacerbations per year.

Research question 2: patients with COPD grades ≥ III with ≥ 2 exacerbations per year

No analyses contained in the dossier could be used for answering research question 2. Hence an added benefit of umeclidinium/vilanterol in comparison with tiotropium + ICS is not proven for patients with COPD grades ≥ III and ≥ 2 exacerbations per year.

Extent and probability of added benefit – summary

The result of the assessment of the added benefit of umeclidinium/vilanterol in comparison with the ACT is summarized in Table 3.

[4] 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), see [1]. 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, no added benefit, or less benefit), see [2].

Table 3: Umeclidinium/vilanterol – extent and probability of added benefit

Research question	**Therapeutic indication**	**ACT**[a]	**Extent and probability of added benefit**
1	Adult patients with COPD grade II and adult patients with COPD grades ≥ III with < 2 exacerbations per year	LABA (formoterol, salmeterol) and/or LAMA (**tiotropium**)	Added benefit not proven
2	Adult patients with COPD grades ≥ III with ≥ 2 exacerbations per year	LABA (formoterol, salmeterol) and/or LAMA (tiotropium) and additional ICS[b]	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: The company chose no comparator therapy for this subpopulation and claimed no added benefit because, from the company's point of view, no sufficient data were recorded.
ACT: appropriate comparator therapy; COPD: chronic obstructive pulmonary disease; G-BA: Federal Joint Committee; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist

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

2.2 Research question

The aim of this report is to assess the added benefit of umeclidinium/vilanterol as maintenance bronchodilator treatment for the relief of symptoms in adult patients with COPD in comparison with the ACT.

For the benefit assessment, the following 2 research questions result from the G-BA's specification on the ACT.

Table 4: Research questions of the benefit assessment of umeclidinium/vilanterol

Research question	Therapeutic indication	ACT[a]
1	Adult patients with COPD grade II and adult patients with COPD grades ≥ III with < 2 exacerbations per year	LABA (formoterol, salmeterol) and/or LAMA (**tiotropium**)
2	Adult patients with COPD grades ≥ III with ≥ 2 exacerbations per year	LABA (formoterol, salmeterol) and/or LAMA (tiotropium) and additional ICS[b]

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: The company chose no comparator therapy for this subpopulation and claimed no added benefit because, from the company's point of view, no sufficient data were recorded.
ACT: appropriate comparator therapy; COPD: chronic obstructive pulmonary disease; G-BA: Federal Joint Committee; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist

The assessment was conducted in comparison with the ACT specified by the G-BA and based on patient-relevant outcomes and on RCTs with a minimum duration of 24 weeks. This approach partially deviated from that of the company.

The company only chose an ACT for research question 1. It followed the specification of the G-BA and, from the options mentioned, chose tiotropium as the comparator therapy. The company chose no comparator therapy for research question 2 and claimed no added benefit.

Use of ICS

In its criteria for study inclusion, the company considered the requirement that intervention and comparator therapy can also be used in combination with ICS. However, it did not consider the conditions for the use of ICS according to the appropriate comparator therapy (COPD grades[5] ≥ III with ≥ 2 exacerbations per year). Concomitant ICS treatment is not to be used in patients of research question 1, whereas patients of research question 2 are to receive concomitant ICS treatment. Deviating from the company, the criteria for ICS treatment specified by the G-BA were used in the present benefit assessment, and it is examined for the respective study whether the use of ICS concurred with the G-BA's specifications (see Section 2.7.2.1 of the full dossier assessment).

[5] The spirometric classification of COPD severity grades is based on the forced expiratory volume in one second (FEV_1): $FEV_1 \geq 80\%$ is grade I, $50\% \leq FEV_1 < 80\ \%$ is grade II, $30\% \leq FEV_1 < 50\%$ is grade III, $FEV_1 < 30\%$ is grade IV [3].

Supplementary research question

The company additionally presented an indirect comparison between umeclidinium/vilanterol and indacaterol/glycopyrronium. Deviating from the company, this comparison was not considered because indacaterol/glycopyrronium is no ACT.

Further information about the research question can be found in Module 3, Section 3.1, and Module 4, Section 4.2.1 of the dossier, and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

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 umeclidinium/vilanterol (studies completed up to 18 April 2014)
- bibliographical literature search on umeclidinium/vilanterol (last search on 19 April 2014)
- search in trial registries for studies on umeclidinium/vilanterol (last search on 19 April 2014)

To check the completeness of the study pool:

- search in trial registries for studies on umeclidinium/vilanterol (last search on 1 August 2014)

No additional relevant study was identified from the check.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.

2.3.1 Studies included

The studies listed in the following table were included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: umeclidinium/vilanterol vs. tiotropium

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
DB2113360	Yes	Yes	No
DB2113374	Yes	Yes	No
ZEP117115	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. RCT: randomized controlled trial; vs.: versus			

The study pool concurred with the study pool of the company. However, the company used the 3 studies for the assessment only for answering research question 1, taking into account the total population of the 3 studies. However, only the subpopulation of patients with COPD grade II and of patients of COPD grades ≥ III with < 2 exacerbations per year is relevant for answering research question 1. Since the dossier contained no results for this subpopulation, the subpopulation of patients without concomitant ICS treatment was used as an approximation for answering research question 1 (see Section 2.3.2.2.1).

No relevant analyses were available for research question 2, also not from subgroup analyses (see Section 2.3.2 and Sections 2.7.2.4.1 and 2.7.2.4.3 of the full dossier assessment).

Section 2.6 contains a reference list for the studies included.

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier, and in Sections 2.7.2.3.1 and 2.7.2.3.2 of the full dossier assessment.

2.3.2 Study characteristics

2.3.2.1 Characteristics of the studies and of the interventions

Table 6 and Table 7 describe the studies used for the benefit assessment.

Table 6: Characteristics of the studies included – RCT, direct comparison: umeclidinium/vilanterol vs. tiotropium

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
DB2113360	Randomized, double-blind, parallel, multicentre, clinical phase 3 study	Adults (≥ 40 years) with confirmed COPD ▪ current or former cigarette smokers with ≥ 10 pack years ▪ $FEV_1/FVC < 0.70$ ▪ $FEV_1 \leq 70\%$ of predicted normal values (post-salbutamol) ▪ dyspnoea score of ≥ 2 on the MMRC dyspnoea scale	UMEC/VI 125/25 µg (N = 216)[b] UMEC/VI 62.5/25 µg (N = 212) VI 25 µg (N = 209)[b] TIO 18 µg (N = 209) subpopulation relevant for research question 1[c]: ▪ UMEC/VI 62.5/25 µg (n = 119) ▪ TIO (n = 115)	Run-in: 7–10 days treatment phase: 24 weeks follow-up: 7 ± 2 days	91 centres in Germany, Italy, Mexico, Peru, Poland, Romania, Russian Federation, Ukraine, United States 3/2011–4/2012	Primary outcome: FEV_1 secondary outcomes: health-related quality of life, COPD symptoms, exacerbations, AEs
DB2113374	Randomized, double-blind, parallel, multicentre, clinical phase 3 study	Adults (≥ 40 years) with confirmed COPD ▪ current or former cigarette smokers with ≥ 10 pack years ▪ $FEV_1/FVC < 0.70$ ▪ $FEV_1 \leq 70\%$ of predicted normal values (post-salbutamol) ▪ dyspnoea score of ≥ 2 on the MMRC dyspnoea scale	UMEC/VI 125/25 µg (N = 217)[b] UMEC/VI 62.5/25 µg (N = 218) UMEC (125 µg): N = 222[b] TIO 18 µg (N = 215) subpopulation relevant for research question 1[c]: ▪ UMEC/VI 62.5/25 µg (n = 114) ▪ TIO (n = 100)	Run-in: 7–10 days treatment phase: 24 weeks follow-up: 7 ± 2 days	95 centres in: Argentina, Australia, Canada, Chile, Germany, Mexico, Romania, South Africa, South Korea, United States 3/2011–4/2012	Primary outcome: FEV_1 secondary outcomes: health-related quality of life, COPD symptoms, exacerbations, AEs

(continued)

Table 6: Characteristics of the studies included – RCT, direct comparison: umeclidinium/vilanterol vs. tiotropium (continued)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ZEP117115	Randomized, double-blind, parallel, multicentre, clinical phase 3 study	Adults (≥ 40 years) with confirmed COPD ▪ current or former cigarette smokers with ≥ 10 pack years ▪ FEV_1/FVC < 0.70 ▪ FEV_1 ≤ 70% of predicted normal values (post-salbutamol) ▪ dyspnoea score of ≥ 2 on the MMRC dyspnoea scale	UMEC/VI 62.5/25 µg (N = 454) TIO 18 µg (N = 451) subpopulation relevant for research question 1[c]: ▪ UMEC/VI 62.5/25 µg (n = 207) ▪ TIO (n = 214)	Wash-out phase of ≤ 12 weeks before visit 1[d] run-in: 7–10 days treatment phase: 24 weeks follow-up: 7 ± 2 days	71 centres in Bulgaria, Canada, Germany, Hungary, Romania, Russian Federation, Spain, United States 1/2013–10/2013	Primary outcome: FEV_1 secondary outcomes: health-related quality of life, exacerbations, AEs

a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes exclusively contain information on the relevant available outcomes for this benefit assessment.
b: The arm is not relevant for the assessment and is no longer shown in the following tables.
c: Research question 1 comprises patients with COPD grade II and patients with COPD grades ≥ III with < 2 exacerbations per year (without use of ICS). As an approximation, patients without use of ICS were used as relevant subpopulation.
d: The patients were included in the study at visit 0. Drugs that had to be washed out were discontinued between visit 0 and visit 1.

AE: adverse event; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; MMRC: Modified Medical Research Council; N: number of randomized patients; n: number of patients in the relevant subpopulation; RCT: randomized controlled trial; TIO: tiotropium; UMEC: umeclidinium; VI: vilanterol; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison: umeclidinium/vilanterol vs. tiotropium

Study	Intervention	Comparison	Concomitant medication
DB2113360	UMEC/VI 62.5/25 µg once daily + placebo for tiotropium each inhaled	Tiotropium 18 µg once daily + placebo for UMEC/VI each inhaled	▪ salbutamol (inhaled rescue medication) ▪ ICS treatment up to a dose of fluticasone 1000 µg/day or equivalent was allowed at a stable dose (if ongoing for ≥ 30 days before visit 1). ICS/LABA combination therapy had to be discontinued ≥ 30 days before visit 1, or had to be switched to ICS monotherapy ≥ 48 hours before visit 1. Non-permitted concomitant medication: ▪ Other COPD drugs (e.g. LABA and LAMA) as well as antibiotics for the treatment of lower respiratory tract infection and corticosteroids (depot, systemic, oral, or parenteral) had to be discontinued within certain periods of ≤ 12 weeks before visit 1.
DB2113374	UMEC/VI 62.5/25 µg once daily + placebo for tiotropium each inhaled	Tiotropium 18 µg once daily + placebo for UMEC/VI each inhaled	▪ salbutamol (inhaled rescue medication) ▪ ICS treatment up to a dose of fluticasone 1000 µg/day or equivalent was allowed at a stable dose (if ongoing for ≥ 30 days before visit 1). ICS/LABA combination therapy had to be discontinued ≥ 30 days before visit 1, or had to be switched to ICS monotherapy ≥ 48 hours before visit 1. Non-permitted concomitant medication: ▪ Other COPD drugs (e.g. LABA and LAMA) as well as antibiotics for the treatment of lower respiratory tract infection and corticosteroids (depot, systemic, oral, or parenteral) had to be discontinued within certain periods of ≤ 12 weeks before visit 1.
ZEP117115	UMEC/VI 62.5/25 µg once daily + placebo for tiotropium each inhaled	Tiotropium 18 µg once daily + placebo for UMEC/VI each inhaled	▪ salbutamol (inhaled rescue medication) ▪ ICS treatment up to a dose of fluticasone 1000 µg/day or equivalent was allowed at a stable dose (if ongoing for ≥ 30 days before visit 1). ICS/LABA combination therapy had to be discontinued ≥ 30 days before visit 1, or had to be switched to ICS monotherapy ≥ 48 hours before visit 1. Non-permitted concomitant medication: ▪ Other COPD drugs (e.g. LABA and LAMA) as well as antibiotics for the treatment of lower respiratory tract infection and corticosteroids (depot, systemic, oral, or parenteral) had to be discontinued within certain periods of ≤ 12 weeks before visit 1.

COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; RCT: randomized controlled trial; UMEC/VI: umeclidinium/vilanterol; vs.: versus

The 3 studies included (DB2113360, DB2113374 und ZEP117115) were double-blind, multicentre, randomized, controlled approval studies. The study duration of all the studies was 24 weeks. Patients aged 40 years or older with confirmed COPD were enrolled. At baseline, patients had to have a smoking history of at least 10 pack years and a forced expiratory volume in one second (FEV_1) of ≤ 70%, a post-bronchodilator ratio of FEV_1 and forced vital capacity (FCV) of < 0.7, as well as a symptom burden score of ≥ 2 on the Modified Medical Research Council (MMRC) dyspnoea scale.

All 3 studies investigated the comparison of daily inhalation of the fixed combination of 62.5 µg umeclidinium and 25 µg vilanterol versus 18 µg tiotropium. Patients were randomized in a ratio of 1:1. The studies DB2113360 and DB2113374 had four study arms, and additionally included a treatment arm with daily inhalation of the fixed combination at an unapproved dosage of 125 µg umeclidinium and 25 µg vilanterol, as well as a treatment arm with daily inhalation of 25 µg vilanterol (study DB2113360) or 125 µg umeclidinium (study DB2113374). The additional treatment arms are not relevant for the benefit assessment and are not considered further.

In addition to the randomized study medication, the patients could treat their COPD with the short-acting LABA salbutamol as rescue medication. ICS treatment could be continued as concomitant treatment irrespective of the severity grade and the frequency of exacerbations of the patients if this treatment had been ongoing for at least 30 days before visit 1 at a stable dose of no more than 1000 µg/day fluticasone or equivalent.

Since in the 3 studies included the population of patients of COPD grade II only comprised patients with an FEV_1 of 50% to < 70%, on this basis, conclusions on the added benefit can only be drawn for these patients. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification, COPD grade II is already present at an FEV_1 < 80%.

2.3.2.2 Characteristics of the study populations

Table 8, Table 9, Table 10 and Table 11 show the characteristics of the patients in the studies included for the total populations. The characteristics of the patients in the studies included were not presented in the dossier for the 2 relevant subpopulations.

All conclusions drawn on patient characteristics only apply to the total populations in the 3 studies included. It remains unclear on the basis of the available information whether they can be transferred to the relevant subpopulations.

Table 8: Characteristics of the study populations – RCT, direct comparison: umeclidinium/vilanterol vs. tiotropium (total study populations)

Study group	N	Age [years] mean (SD)	Sex [F/M] %	Smoking status current smoker/ ex-smoker) n (%)	Pack years mean (SD)	Use of ICS yes/no n (%)	Treatment discon-tinuations n (%)
DB2113360							
UMEC/VI	212	63 (9)	30/70	98 (46)/114 (54)	44.8 (27.7)	93 (44)/119 (56)	31 (15)
TIO	208	63 (9)	33/67	99 (48)/109 (52)	41.9 (24.4)	93 (45)/115 (55)	31 (15)
DB2113374							
UMEC/VI	217	65 (9)	35/65	92 (42)/125 (58)	47.8 (26.1)	103 (47)/114 (53)	54 (25)
TIO	215	65 (8)	29/71	102 (47)/113 (53)	54.0 (31.6)	115 (53)/100 (47)	39 (18)
ZEP117115							
UMEC/VI	454	62 (8)	32/68	270 (59)/184 (41)	44.1 (24.4)	247 (54)/207 (46)	53 (12)
TIO	451	63 (9)	33/67	243 (54)/208 (46)	44.4 (25.0)	237 (53)/214 (47)	63 (14)

F: female; ICS: inhaled corticosteroid; M: male; N: number of randomized patients who received at least one dose of their allocated study medication; n: number of patients with event; RCT: randomized controlled trial; SD: standard deviation; TIO: tiotropium; UMEC: umeclidinium; VI: vilanterol; vs.: versus

Table 9: Characteristics of the study populations: duration of COPD – RCT, direct comparison: umeclidinium/vilanterol vs. tiotropium (total study populations)

Study group	N	COPD duration in years n (%)						
		< 1	≥ 1 to < 5	≥ 5 to < 10	≥ 10 to <15	≥ 15 to <20	≥ 20 to < 25	≥ 25
DB2113360								
UMEC/VI	212	20 (9)	75 (35)	63 (30)	30 (14)	11 (5)	8 (4)	5 (2)
TIO	208	20 (10)	79 (38)	54 (26)	34 (16)	14 (7)	6 (3)	1 (< 1)
DB2113374								
UMEC/VI	217	28 (13)	80 (37)	53 (24)	37 (17)	10 (5)	3 (1)	6 (3)
TIO	215	16 (7)	83 (39)	65 (30)	34 (16)	12 (6)	3 (1)	2 (< 1)
ZEP117115								
UMEC/VI	454	21 (5)	160 (35)	153 (34)	90 (20)	11 (2)	9 (2)	10 (2)
TIO	451	17 (4)	149 (33)	152 (34)	81 (18)	27 (6)	15 (3)	10 (2)

COPD: chronic obstructive pulmonary disease; N: number of randomized patients who received at least one dose of their allocated study medication; n: number of patients with event; RCT: randomized controlled trial; TIO: tiotropium; UMEC: umeclidinium; VI: vilanterol; vs.: versus

Table 10: Characteristics of the study populations: disease severity – RCT, direct comparison: umeclidinium/vilanterol vs. tiotropium (total study populations)

Study group	N	Disease severity (COPD grades)[a] n (%)			
		I	II	III	IV
DB2113360					
UMEC/VI	212	0 (0)	104 (49)	85 (40)	22 (10)
TIO	208	0 (0)	96 (47)	87 (42)	23 (11)
DB2113374					
UMEC/VI	217	0 (0)	106 (49)	83 (38)	27 (13)
TIO	215	0 (0)	103 (48)	83 (39)	28 (13)
ZEP117115					
UMEC/VI	454	0 (0)	185 (41)	207 (46)	62 (14)
TIO	451	0 (0)	190 (42)	206 (46)	55 (12)

a: The spirometric classification of COPD severity grades is based on the FEV_1: $FEV_1 \geq 80\%$ is grade I, $50\% \leq FEV_1 < 80\%$ is grade II, $30\% \leq FEV_1 < 50\%$ is grade III, $FEV_1 < 30\%$ is grade IV [3].

COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in one second; N: number of randomized patients who received at least one dose of their allocated study medication; n: number of patients with event; RCT: randomized controlled trial; TIO: tiotropium; UMEC: umeclidinium; VI: vilanterol; vs.: versus

Table 11: Characteristics of the study populations: exacerbations – RCT, direct comparison: umeclidinium/vilanterol vs. tiotropium (total study populations)

Study group	N	COPD exacerbations in the last 12 months before screening (visit 1) n (%)			
		0	1	2	> 2
Treatment with oral/systemic corticosteroids and/or antibiotics, but no hospitalization required					
DB2113360					
UMEC/VI	212	148 (70)	50 (24)	13 (6)	1 (< 1)
TIO	208	138 (66)	52 (25)	14 (7)	4 (2)
DB2113374					
UMEC/VI	217	157 (72)	41 (19)	11 (5)	8 (4)
TIO	215	149 (69)	43 (20)	10 (5)	13 (6)
ZEP117115					
UMEC/VI	454	384 (85)	58 (13)	11 (2)	1 (< 1)
TIO	451	371 (82)	66 (15)	9 (2)	5 (1)
Required hospitalization					
DB2113360					
UMEC/VI	212	181 (85)	29 (14)	2 (< 1)	0 (0)
TIO	208	169 (81)	32 (15)	7 (3)	0 (0)
DB2113374					
UMEC/VI	217	208 (96)	8 (4)	1 (< 1)	0 (0)
TIO	215	201 (93)	14 (7)	0 (0)	0 (0)
ZEP117115					
UMEC/VI	454	420 (93)	33 (7)	1 (< 1)	0 (0)
TIO	451	423 (94)	27 (6)	1 (< 1)	0 (0)

COPD: chronic obstructive pulmonary disease; N: number of randomized patients who received at least one dose of their allocated study medication; n: number of patients with event; RCT: randomized controlled trial; TIO: tiotropium; UMEC: umeclidinium; VI: vilanterol; vs.: versus

In the 3 studies included, the mean age of the patients was approximately 63 years, and just over 2/3 of the patients were men. About half of the study participants were current cigarette smokers at study inclusion. Their proportion was highest in the ZEP117115 study. About half of the patients received concomitant ICS treatment at study inclusion. Their proportion was also highest in the ZEP117115 study.

The majority of the patients had had their COPD for between ≥ 1 and < 10 years at study inclusion. The proportion of patients with a disease duration of < 1 year was lowest in the ZEP117115 study and highest in the DB2113374 study. The proportion of patients of COPD grade IV was low (10% to 14%) in the 3 studies. In the ZEP117115 study, the proportion of patients of COPD grade II was about 7 percentage points lower, and the proportion of patients of COPD grade III was about 5 and 7 percentage points higher than in the 2 other studies.

The available data on the history of exacerbations in the year before the start of the study are presented in Table 11. The results of the patients with exacerbations who required treatment with oral/systemic corticosteroids and/or antibiotics, but no hospitalization were separated from the results of the patients with exacerbations who required hospitalization. The proportion of patients with < 2 and ≥ 2 exacerbations in the year before the start of the study therefore remained unclear. Hence relevant information on the classification of the populations is not available for the 2 research questions (see Sections 2.3.2.2.1 and 2.3.2.2.2).

Overall, no relevant differences in patient characteristics that are relevant for the assessment were shown between the study arms.

The number of patients who discontinued treatment was 15% in the umeclidinium/vilanterol and in the tiotropium arm of the DB2113360 study, and 12% in the umeclidinium/vilanterol arm and 14% in the tiotropium arm of the ZEP117115 study. In the DB2113374 study, 25% of the patients discontinued treatment in the umeclidinium/vilanterol arm and 18% in the tiotropium arm.

2.3.2.2.1 Research question 1: patients with COPD grade II and patients with COPD grades ≥ III with < 2 exacerbations per year

According to the specifications of the G-BA's ACT, concomitant ICS treatment is not indicated for patients of COPD grade II and patients of COPD grades ≥ III with < 2 exacerbations per year. The studies as a whole are not relevant for research question 1 because patients with concomitant ICS treatment and ≥ 2 exacerbations per year before the start of the study were also enrolled in the 3 studies included. The dossier contained no separate analyses comprising patients of COPD grade II and patients of COPD grades ≥ III with no more than one exacerbation in the previous year – in each case without concomitant ICS treatment, although processing the data accordingly would have been possible for the company using the individual patient data. For this reason it was checked whether there were subgroup analyses in the company's dossier that present an adequate approximation to the relevant subpopulation. The subgroup of patients without concomitant ICS treatment can be regarded as such a sufficient approximation for research question 1, and was therefore used for answering research question 1 in the present benefit assessment. Even though no complete information on these patients' history of exacerbations was available, under plausible assumptions it can be assumed that a relevant proportion of the patients without concomitant ICS treatment (≥ 80%) had fewer than 2 exacerbations in the year before the start of the study. Nonetheless, this approximation is subject to an increased uncertainty, which is to be taken into account when assessing the certainty of results. Moreover, results for the subgroup were only available for individual outcomes.

Further information on the operationalization of the relevant subpopulation can be found in Section 2.7.2.4.1 of the full dossier assessment.

This approach deviates from that of the company, which derived the added benefit for patients of COPD grade II and patients of COPD grades ≥ III with < 2 exacerbations per year (research question 1) on the basis of the total populations of the 3 studies included.

2.3.2.2.2 Research question 2: patients with COPD grades ≥ III with ≥ 2 exacerbations per year

According to the specification of the ACT, patients of COPD grades ≥ III with ≥ 2 exacerbations per year are to be treated with concomitant ICS treatment (research question 2).

Since no separate analyses for the relevant subpopulation of patients with COPD grades ≥ III with ≥ 2 exacerbations per year and concomitant ICS treatment were available in the dossier and these data could also not be inferred from the information provided in the dossier, it was checked whether the subpopulation of patients with concomitant ICS treatment and COPD grades ≥ III can be used as an approximation for the relevant subpopulation. However, this subpopulation is unsuitable because based on the available information on the frequency of exacerbations it is highly unlikely that a relevant proportion (≥ 80%) of these patients had at least 2 exacerbations in the previous year. Hence the dossier contained no evaluable results for this research question. This concurs with the company's assessment, which also derived no added benefit for this subpopulation because, from the company's point of view, no sufficient number of data was recorded for this research question.

Ultimately however, it would have been possible for the company to explain how many patients who fulfilled the criteria of research question 2 were included in the 3 studies using the individual patient data including data on exacerbations.

2.3.2.3 Risk of bias at study level

Table 12 shows the risk of bias at study level.

Table 12: Risk of bias at study level – RCT, direct comparison: umeclidinium/vilanterol vs. tiotropium

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
DB2113360	Yes	Yes	Yes	Yes	Yes	Yes	Low
DB2113374	Yes	Yes	Yes	Yes	Yes	Yes	Low
ZEP117115	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level was rated as low for the 3 studies included. This concurs with the company's assessment.

Further information on study design, study populations and the risk of bias at study level can be found in Module 4, Sections 4.3.1.2.1, 4.3.1.2.2 and 4.3.2.1.2, and in Appendix 4-F of the dossier, and in Sections 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment.

2.4 Results on added benefit

2.4.1 Research question 1: patients with COPD grade II and patients with COPD grades ≥ III with < 2 exacerbations per year

2.4.1.1 Outcomes included

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

- Mortality
  - all-cause mortality
- Morbidity
  - COPD symptoms
    - TDI
    - CAT
    - SOBDA
  - moderate and severe exacerbations
- Health-related quality of life
  - SGRQ
- Adverse events
  - SAEs
  - treatment discontinuation due to AEs

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

Further information on the choice of outcomes can be found in Module 4, Sections 4.2.5.2, 4.3.1.3 and 4.3.2.1.3 of the dossier, and in Sections 2.7.2.2 and 2.7.2.4.3 of the full dossier assessment.

Table 13 shows for which outcomes evaluable data were available in the dossier.

Table 13: Matrix of outcomes – RCT, direct comparison: umeclidinium/vilanterol vs. tiotropium (research question 1)

Study	Outcomes							
	All-cause mortality	COPD symptoms (TDI)	COPD symptoms (CAT)	COPD symptoms (SOBDA)	Moderate and severe exacerbations	Health-related quality of life (SGRQ)	SAEs	Discontinuation due to AEs
DB2113360	No[a]	Yes	No[a]	No[a]	No[a]	Yes	No[a]	No[a]
DB2113374	No[a]	Yes	No[a]	No[a]	No[a]	Yes	No[a]	No[a]
ZEP117115	No[a]	No[b]	No[b]	No[b]	No[a]	Yes	No[a]	No[a]

a: The dossier contained no evaluable data. See Section 2.3.2 and Sections 2.7.2.4.1 and 2.7.2.4.3 of the full dossier assessment for reasons.
b: The outcome was not recorded in the study.
AE: adverse event; CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; RCT: randomized controlled trial; SAE: serious adverse event; SGRQ: St. George's Respiratory Questionnaire; SOBDA: Shortness of Breath with Daily Activities; TDI: Transition Dyspnoea Index; vs.: versus

2.4.1.2 Risk of bias

Table 14 shows the risk of bias for the outcomes presented in Table 13.

Table 14: Risk of bias at study and outcome level – RCT, direct comparison: umeclidinium/vilanterol vs. tiotropium (research question 1)

Study	Study level	Outcomes							
		All-cause mortality	COPD symptoms (TDI)	COPD symptoms (CAT)	COPD symptoms (SOBDA)	Moderate and severe exacerbations	Health-related quality of life (SGRQ)	SAEs	Discontinuation due to AEs
DB2113360	L	–[a]	H[b]	–[a]	–[a]	–[a]	H[b]	–[a]	–[a]
DB2113374	L	–[a]	H[b]	–[a]	–[a]	–[a]	H[b]	–[a]	–[a]
ZEP117115	L	–[a]	–[c]	–[c]	–[c]	–[a]	L	–[a]	–[a]

a: The dossier contained no evaluable data. See Section 2.3.2 and Sections 2.7.2.4.1 and 2.7.2.4.3 of the full dossier assessment for reasons.
b: Due to the inadequate implementation of the ITT principle.
c: The outcome was not recorded in the study.
AE: adverse event; CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; H: high; L: low; RCT: randomized controlled trial; SAE: serious adverse event; SGRQ: St. George's Respiratory Questionnaire; SOBDA: Shortness of Breath with Daily Activities; TDI: Transition Dyspnoea Index; vs.: versus

The risk of bias at outcome level was only assessed for the 2 outcomes for which evaluable data were available.

The results for the outcome "COPD symptoms" (TDI) available from the studies DB2113360 and DB2113374 were rated as having a high risk of bias because of an inadequate implementation of the intention-to-treat (ITT) principle. The assessment concurs with that of the company.

The risk of bias of the results on the outcome "health-related quality of life" (SGRQ) was rated as high for the studies DB2113360 and DB2113374. As was the case for the outcome "COPD symptoms" (TDI), the reason was an inadequate implementation of the ITT principle. The results from the ZEP117115 study were considered to have a low risk of bias. These assessments concur with those of the company presented in the running text.

Further information on the risk of bias at outcome level can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3, and in Appendix 4-F of the dossier and in Section 2.7.2.4.2 of the full dossier assessment.

2.4.1.3 Results

The results of the comparison of umeclidinium/vilanterol and tiotropium for patients with COPD grade II and patients with COPD grades ≥ III and < 2 exacerbations per year (research

question 1) are summarized in Table 15. The results were taken from the subgroup analyses of patients without concomitant ICS treatment and, where necessary, supplemented by the Institute's calculations.

The company did not present the subgroup analyses by concomitant ICS treatment for all patient-relevant outcomes. Hence evaluable data were only available for the patient-relevant outcomes "COPD symptoms" (TDI responder) and "health-related quality of life" (SGRQ responder).

Table 15: Results (dichotomous outcomes) – RCT, direct comparison: umeclidinium/vilanterol vs. tiotropium (research question 1)

Outcome category **outcome** **study**	**UMEC/VI**		**TIO**		**UMEC/VI vs. TIO**
	N	**Patients with events n (%)**	**N**	**Patients with events n (%)**	**RR [95% CI]; p-value**
Mortality					
All-cause mortality	No evaluable data available				
Morbidity					
COPD symptoms (TDI responder[a])					
DB2113360	108	60 (56)	102	58 (57)	0.98 [0.77; 1.24][b]
DB2113374	99	63 (64)	93	52 (56)	1.14 [0.90; 1.44][b]
ZEP117115	Outcome not recorded				
Total					1.06 [0.89; 1.25]; 0.522[c]
COPD symptoms (CAT)	No evaluable data available				
COPD symptoms (SOBDA)	No evaluable data available				
Moderate and severe exacerbations	No evaluable data available				
Health-related quality of life					
SGRQ responder[d]					
DB2113360	106	48 (45)	95	48 (51)	0.90 [0.67; 1.20][b]
DB2113374	97	57 (59)	89	50 (56)	1.05 [0.82; 1.34][b]
ZEP117115	203	106 (52)	204	91 (45)	1.17 [0.96; 1.43][b]
Total					1.06 [0.92; 1.23]; 0.430[c]
Adverse events					
SAEs	No evaluable data available				
Discontinuation due to AEs	No evaluable data available				

a: Patients with a focal score ≥ 1.
b: Institute's calculation of effect estimate and CI (asymptotic).
c: Institute's calculation from meta-analysis.
d: Patients with a reduction in total score ≥ 4.

AE: adverse event; CAT: COPD Assessment Test; CI: confidence interval; COPD: chronic obstructive pulmonary disease; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SGRQ: St. George's Respiratory Questionnaire; SOBDA: Shortness of Breath with Daily Activities; TDI: Transition Dyspnoea Index; TIO: tiotropium; UMEC: umeclidinium; VI: vilanterol; vs.: versus

Mortality

The dossier contained no evaluable data for the outcome "mortality". Hence an added benefit of umeclidinium/vilanterol in comparison with the ACT tiotropium is not proven for this outcome.

This concurs with the assessment of the company, which derived no added benefit using mortality on the basis of the meta-analyses of the total study populations.

Morbidity

COPD symptoms (TDI responder)

Based on the meta-analysis of the results from the studies DB2113360 and DB2113374, there was no statistically significant difference between the treatment arms for the outcome "COPD symptoms" (TDI responder). Hence an added benefit of umeclidinium/vilanterol in comparison with the ACT tiotropium is not proven for this outcome.

This concurs with the assessment of the company, which also derived no added benefit for the outcome "COPD symptoms" (TDI responder) on the basis of the meta-analysis of the total study populations in the studies DB2113360 and DB2113374.

COPD symptoms (CAT)

The dossier contained no evaluable data for the outcome "COPD symptoms" (CAT). Hence an added benefit of umeclidinium/vilanterol in comparison with the ACT tiotropium is not proven for this outcome.

The company presented no results for this outcome in Module 4 of the dossier because the ITT principle was not adequately implemented from the company's point of view.

COPD symptoms (SOBDA)

The dossier contained no evaluable data for the outcome "COPD symptoms" (SOBDA). Hence an added benefit of umeclidinium/vilanterol in comparison with the ACT tiotropium is not proven for this outcome.

The company did not include this outcome in Module 4 of the dossier.

Moderate and severe exacerbations

The dossier contained no evaluable data for any of the 2 outcomes "moderate and severe exacerbations". Hence an added benefit of umeclidinium/vilanterol in comparison with the ACT tiotropium is not proven for these outcomes.

This deviates from the assessment of the company, which derived no added benefit for the composite outcome "moderate and severe exacerbations" on the basis of the total populations of the studies DB2113360 and DB2113374, and which claimed an indication of minor added benefit on the basis of the total population of the ZEP117115 study.

Health-related quality of life

Health-related quality of life (SGRQ responder)

Neither the effect with a low risk of bias from the ZEP117115 study nor the overall effect resulting from the meta-analysis of all 3 studies was statistically significant for the outcome "health-related quality of life" (SGRQ responder). Hence an added benefit of umeclidinium/vilanterol in comparison with the ACT tiotropium is not proven for this outcome.

This concurs with the assessment of the company, which also derived no added benefit for the outcome "health-related quality of life" (SGRQ responder) on the basis of the meta-analysis of the total study populations.

Adverse events

Serious adverse events

The dossier contained no evaluable data for the outcome "SAEs". Hence greater or lesser harm from umeclidinium/vilanterol in comparison with the ACT tiotropium is not proven for this outcome.

This concurs with the assessment of the company, which also derived no greater or lesser harm for the outcome "SAEs" on the basis of the total study populations.

Discontinuation due to adverse events

The dossier contained no evaluable data for the outcome "discontinuation due to AEs". Hence greater or lesser harm from umeclidinium/vilanterol in comparison with the ACT tiotropium is not proven for this outcome.

This concurs with the assessment of the company, which also derived no greater or lesser harm for the outcome "discontinuation due to AEs" on the basis of the meta-analyses of the total study populations.

Further information on the outcome results can be found in Module 4, Sections 4.3.1.3 and 4.3.2.1.3 of the dossier, and in 2.7.2.4.3 of the full dossier assessment.

2.4.1.4 Subgroups and other effect modifiers

The dossier contained subgroup analyses for the investigation of an effect modification in the total populations of the studies for the following characteristics: smoking status, reversibility of obstruction to salbutamol, age, sex, region, severity, ICS use, and the combined characteristics "severity and ICS use". The latter 2 subgroup analyses, among other things, were only presented for the patient-relevant outcomes "COPD symptoms" (TDI responder) and "health-related quality of life" (SGRQ responder).

The subgroup analyses conducted by the company to investigate an effect modification in the total populations of the studies were not relevant for the benefit assessment because the

benefit assessment was based on the subgroup of patients without concomitant ICS treatment. Because of this, evaluable subgroup analyses were only available for the characteristic "severity" and only for the patient-relevant outcomes "COPD symptoms" (TDI responder) and "health-related quality of life" (SGRQ responder).

Cochran's Q-test for interactions was used to investigate whether there were different effects in the 2 subgroup analyses by severity (COPD grade II versus COPD grades ≥ III) in the subpopulation without concomitant ICS treatment. There was no proof or indication of an effect modification by severity (COPD grade II versus COPD grades ≥ III) for any of the outcomes mentioned above. The results are therefore not presented.

Further information on the subgroup results can be found in Module 4, Sections 4.3.1.3.2 and 4.3.2.1.3.2 of the dossier, and in Section 2.7.2.4.3 of the full dossier assessment.

2.4.2 Research question 2: patients with COPD grades ≥ III and with ≥ 2 exacerbations per year

The company presented no relevant data for patients of COPD grades ≥ III with ≥ 2 exacerbations, and no adequate subpopulations for research question 2 could be operationalized on the basis of the data presented in the dossier (see Section 2.3.2.2.2).

An added benefit of umeclidinium/vilanterol in comparison with the ACT is not proven for the subpopulation of patients with COPD grades ≥ III with ≥ 2 exacerbations per year.

This result concurs with that of the company, which chose no comparator therapy for this research question and claimed no added benefit because, from the company's point of view, too few of these patients had been included in the 3 studies.

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit for each subquestion is presented below at outcome level, taking into account the different outcome categories and effect sizes. 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 Research question 1: patients with COPD grade II and patients with COPD grades ≥ III with < 2 exacerbations per year

2.5.1.1 Assessment of added benefit at outcome level

The data presented in Section 2.4 resulted in no added benefit at outcome level for umeclidinium/vilanterol versus tiotropium. Accordingly, no extent of added benefit at outcome level can be derived (see Table 16).

Table 16: Extent of added benefit at outcome level: umeclidinium/vilanterol vs. tiotropium (research question 1)

Outcome category **outcome**	**Umeclidinium/vilanterol vs. tiotropium** **proportions of events** **effect estimate [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	No evaluable data available	Added benefit not proven
Morbidity		
COPD symptoms (TDI responder)	UMEC/VI: 56% to 64%[c] TIO: 56% to 57%[c] RR: 1.06 [0.89; 1.25][d] p = 0.522[d]	Added benefit not proven
COPD symptoms (CAT)	No evaluable data available	Added benefit not proven
COPD symptoms (SOBDA)	No evaluable data available	Added benefit not proven
Moderate and severe exacerbations	No evaluable data available	Added benefit not proven
Health-related quality of life		
Health-related quality of life (SGRQ responder)	UMEC/VI: 45% to 59%[c] TIO: 45% to 56%[c] RR: 1.06 [0.92; 1.23][d] p = 0.430[d]	Added benefit not proven
Adverse events		
SAEs	No evaluable data available	Greater/lesser harm not proven
Discontinuation due to AEs	No evaluable data available	Greater/lesser harm not proven

a: Probability provided if statistically significant differences were present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Minimum and maximum proportions of events in each treatment arm in the studies included.
d: Institute's calculation from meta-analysis.

AE: adverse event; CAT: COPD Assessment Test; CI: confidence interval; CI_u: upper limit of CI; COPD: chronic obstructive pulmonary disease; RR: relative risk; SAE: serious adverse event; SGRQ: St. George's Respiratory Questionnaire; SOBDA: Shortness of Breath with Daily Activities; TDI: Transition Dyspnoea Index; TIO: tiotropium; UMEC: umeclidinium; VI: vilanterol; vs.: versus

2.5.1.2 Overall conclusion on added benefit

Table 17 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 17: Positive and negative effects from the assessment of umeclidinium/vilanterol compared with tiotropium (research question 1)

Positive effects	**Negative effects**
—	—
Due to the missing analyses for the majority of patient-relevant outcomes, particularly of all outcomes on AEs, no conclusive balancing on the added benefit is possible.	

On the basis of the results presented, there are neither positive nor negative effects for adult patients with COPD grade II or of COPD grades ≥ III with < 2 exacerbations per year.

Overall, evaluable results for the benefit assessment were only available for 2 outcomes. Because of the lack of evaluable results on the remaining outcomes of mortality and morbidity and particularly of all outcomes on AEs, overall, greater harm from umeclidinium/vilanterol cannot be excluded either. Hence no conclusive balancing on the added benefit is possible irrespective of the results of the 2 outcomes presented.

In summary, an added benefit of umeclidinium/vilanterol is not proven for adult patients with COPD grade II or with COPD grades ≥ III with < 2 exacerbations per year.

Additional uncertainty

The derivation of the added benefit is accompanied by the additional uncertainty resulting from the unclear classification of patients to the research questions. The dossier contained no results for the relevant subpopulation of research question 1 consisting of patients of COPD grade II and of patients of COPD grades ≥ III with < 2 exacerbations per year. The analysis of patients without concomitant ICS treatment had therefore to be used as an approximation.

It remained unclear in this approximation, however, how large the proportion of patients with ≥ 2 exacerbations in the year before the start of the study, which is not relevant for the research question, was in the subpopulation of patients without concomitant ICS treatment. Even though the approximation was based on a plausible assumption, it can still not be excluded that a relevant proportion of patients did not concur with the research question. This additional uncertainty would have to be considered in the assessment of the certainty of results if a balancing of the added benefit was possible.

2.5.2 Research question 2: patients with COPD grades ≥ III and with ≥ 2 exacerbations per year

Since the dossier contained no evaluable data for the subpopulation of patients with COPD grades ≥ III with ≥ 2 exacerbations per year, an added benefit of umeclidinium/vilanterol in comparison with the ACT is not proven for this subpopulation.

2.5.3 Extent and probability of added benefit – summary

The result of the assessment of the added benefit of umeclidinium/vilanterol in comparison with the ACT is summarized in Table 18.

Table 18: Umeclidinium/vilanterol: extent and probability of added benefit

Research question	Therapeutic indication	ACT[a]	Extent and probability of added benefit
1	Adult patients with COPD grade II and adult patients with COPD grades ≥ III with < 2 exacerbations per year	LABA (formoterol, salmeterol) and/or LAMA (**tiotropium**)	Added benefit not proven
2	Adult patients with COPD grades ≥ III with ≥ 2 exacerbations per year	LABA (formoterol, salmeterol) and/or LAMA (tiotropium) and additional ICS[b]	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: The company chose no comparator therapy for this subpopulation and claimed no added benefit because, from the company's point of view, no sufficient data were recorded.
ACT: appropriate comparator therapy; COPD: chronic obstructive pulmonary disease; G-BA: Federal Joint Committee; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist

An added benefit is not proven for adult patients with COPD grade II or of COPD grades ≥ III with < 2 exacerbations per year. This result deviates from that of the company, which derived proof of a minor added benefit on the basis of the total populations in the 3 studies included.

An added benefit is not proven for adult patients with COPD grades ≥ III with ≥ 2 exacerbations per year because the dossier contained no evaluable results. This result concurs with that of the company, which chose no comparator therapy for this research question and claimed no added benefit.

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

Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier, and in Section 2.7.2.8 of the full dossier assessment.

2.6 List of included studies

Study DB2113360

GlaxoSmithKline. A multicenter trial comparing the efficacy and safety of GSK573719/GW642444 with GW642444 and with tiotropium over 24 weeks in subjects with COPD: study DB2113360; clinical study report [unpublished]. 2012.

GlaxoSmithKline. 24-week trial comparing GSK573719/GW642444 with GW642444 and with tiotropium in chronic obstructive pulmonary disease: study results [online]. In: Clinicaltrials.gov. 19 December 2013 [accessed: 12 May 2014]. URL: http://clinicaltrials.gov/ct2/show/results/NCT01316900.

GlaxoSmithKline Research & Development. DB2113360: a multicenter trial comparing the efficacy and safety of GSK573719/GW642444 with GW642444 and with tiotropium over 24 weeks in subjects with COPD [online]. In: EU Clinical Trials Register. [Accessed: 12 May 2014]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=2010-021800-72.

Study DB2113374

GlaxoSmithKline. A multicenter trial comparing the efficacy and safety of GSK573719/GW642444 with GSK573719 and with tiotropium over 24 weeks in subjects with COPD: study DB2113374; clinical study report [unpublished]. 2012.

GlaxoSmithKline. 24-week trial comparing GSK573719/GW642444 with GSK573719 and with tiotropium in chronic obstructive pulmonary disease: study results [online]. In: Clinicaltrials.gov. 9 January 2014 [accessed: 12 May 2014]. URL: http://www.clinicaltrials.gov/ct2/show/results/NCT01316913.

GlaxoSmithKline Research & Development. A multicenter trial comparing the efficacy and safety of GSK573719/GW642444 with GSK573719 with tiotropium over 24 weeks in subjects with COPD [online]. In: EU Clinical Trials Register. [Accessed: 12 May 2014]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=2010-021802-39.

Study ZEP117115

GlaxoSmithKline. A multicenter trial comparing the efficacy and safety of umeclidinium/vilanterol 62.5/25 mcg once daily with tiotropium 18 mcg once daily over 24 weeks in subjects with chronic obstructive pulmonary disease (COPD): study ZEP117115; clinical study report [unpublished]. 2013.

GlaxoSmithKline. The purpose of this study is to evaluate the spirometric effect (Trough FEV1) of umeclidinium/vilanterol 62.5/25 Mcg once daily compared with tiotriopium 18 Mcg once daily over a 24-week treatment period in subjects with COPD: full text view [online]. In: Clinicaltrials.gov. 7 November 2013 [accessed: 12 May 2014]. URL: http://www.clinicaltrials.gov/ct2/show/study/NCT01777334.

GlaxoSmithKline Research & Development Limited. A multicenter trial comparing the efficacy and safety of umeclidinium/vilanterol 62.5/25 mcg once daily with tiotropium 18 mcg once daily over 24 weeks in subjects with chronic obstructive pulmonar disease (COPD) [online]. In: EU Clinical Trials Register. [Accessed: 12 May 2014]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=2012-003973-24.

References for English extract

Please see full dossier assessment for full reference list.

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2. Institute for Quality and Efficiency in Health Care. Ticagrelor: benefit assessment according to §35a Social Code Book V; extract; commission no. A11-02 [online]. 29 September 2011 [accessed: 5 May 2012]. URL: https://www.iqwig.de/download/A11-02_Extract_of_dossier_assessment_Ticagrelor.pdf.

3. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease [online]. 2014 [accessed: 27 January 2014]. URL: http://www.goldcopd.org/uploads/users/files/GOLD_Report_2014_Jun11.pdf.

The full report (German version) is published under https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/a14-22-umeclidinium/vilanterol-nutzenbewertung-gemass-35a-sgb-v-dossierbewertung.6248.html.