

IQWiG Reports – Commission No. A16-02

Umeclidinium – Benefit assessment according to §35a Social Code Book V¹

Extract

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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
FEV1	forced expiratory volume in 1 second
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICS	inhaled corticosteroids
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
mMRC	modified Medical Research Council
PDE4	phosphodiesterase type 4
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SGRQ	St. George's Respiratory Questionnaire
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 umeclidinium. 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 29 January 2016.

Research question

The aim of this report is to assess the added benefit of umeclidinium bromide (umeclidinium for short) as maintenance bronchodilator treatment to relieve symptoms in adults with chronic obstructive pulmonary disease (COPD) in comparison with the appropriate comparator therapy (ACT).

From the G-BA’s specification of the ACT, the following 2 research questions resulted for the benefit assessment (Table 2):

Table 2: Research questions of the benefit assessment of umeclidinium

Research question	Therapeutic indication	ACT ^a
1	Adults with COPD from moderate severity ($50\% \leq \text{FEV1} < 80\%$ predicted) ^b	LABA and/or LAMA (tiotropium bromide)
2	Adults with COPD of higher severity ($30\% \leq \text{FEV1} < 50\%$ predicted or $\text{FEV1} < 30\%$ predicted or respiratory failure) with ≥ 2 exacerbations per year ^c	LABA and/or LAMA (tiotropium bromide) and additional ICS ^d

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: For better understandability, the term “adults with COPD grade II and adults with COPD grade \geq III with < 2 exacerbations per year” is used in the report.

c: For better understandability, the term “adults with COPD grade \geq III with ≥ 2 exacerbations per year” is used in the report.

d: The company did not investigate research question 2 because no sufficient number of patients with the corresponding severity grade were observed in the available study. The company therefore chose no ACT for research question 2.

ACT: appropriate comparator therapy; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; G-BA: Federal Joint Committee; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist

For research question 1, the assessment was conducted in comparison with tiotropium bromide (tiotropium for short). No data were available for research question 2.

Results for research question 1 (adults with COPD grade II and adults with COPD grade \geq III with < 2 exacerbations per year)

One relevant study of direct comparison (study 201316) was available for the benefit assessment.

Study characteristics

In study 201316, umeclidinium as intervention was compared with tiotropium as control. It was a double-blind, multicentre, parallel group randomized controlled trial (RCT). Patients aged 40 years or older with moderate to severe COPD (Global Initiative for Chronic Obstructive Lung Disease [GOLD] grades II and III) were enrolled. The company presented analyses based on a subpopulation of the study, in which patients were included who were receiving no long-term treatment with inhaled corticosteroids (ICS) and who were treated for 24 weeks. The patients included in these analyses were an adequate representation of the population relevant for research question 1 and were used for the benefit assessment.

Risk of bias

The risk of bias at study level was rated as low.

Results

The subpopulation relevant for research question 1 comprised adults with COPD grade II and adults with COPD grade III with < 2 exacerbations per year who were receiving no long-term treatment with ICS and were treated for 24 weeks. There were no data on patients with COPD grade IV with < 2 exacerbations per year, who were also relevant for research question 1.

Analyses for the relevant subpopulation at the time point of 24 weeks were available for the following outcomes:

- all-cause mortality
- COPD symptoms (COPD Assessment Test [CAT] responder)
- severe exacerbations
- health-related quality of life (St. George's Respiratory Questionnaire [SGRQ] responder)
- serious adverse events (SAEs)
- discontinuation due to adverse events (AEs)

There was no statistically significant difference between the treatment groups for any of these outcomes.

The outcome "COPD symptoms (Transition Dyspnoea Index [TDI] responder)" was no longer recorded at the time point of 24 weeks; there was no information on exacerbations (moderate and severe).

There was thus no hint of an added benefit of umeclidinium in comparison with tiotropium for any outcome. An added benefit of umeclidinium in comparison with the ACT for adults with COPD grade II and adults with COPD grade \geq III with < 2 exacerbations per year is therefore not proven.

Results for research question 2: adults with COPD grade \geq III with ≥ 2 exacerbations per year

No data were available for the assessment of the added benefit of umeclidinium for the treatment of adults with COPD grade \geq III with ≥ 2 exacerbations per year.

Extent and probability of added benefit, patient groups with therapeutically important added benefit⁴

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

Research question 1: adults with COPD grade II and adults with COPD grade \geq III with < 2 exacerbations per year

Overall, neither positive nor negative effects remained for adults with COPD grade II and adults with COPD grade III with < 2 exacerbations per year. An added benefit of umeclidinium in comparison with the ACT is not proven for these patients.

Research question 2: adults with COPD grade \geq III with ≥ 2 exacerbations per year

An added benefit of umeclidinium in comparison with the ACT is not proven for adults with COPD grade \geq III and ≥ 2 exacerbations per year.

Extent and probability of added benefit – summary

Table 3 presents a summary of the extent and probability of the added benefit of umeclidinium.

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). 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). For further details see [1,2].

Table 3: Umeclidinium – extent and probability of added benefit

Therapeutic indication	ACT ^a	Extent and probability of added benefit
Adult patients with COPD from moderate severity ($50\% \leq \text{FEV1} < 80\%$ predicted) ^b	LABA and/or LAMA (tiotropium bromide)	Added benefit not proven
Adult patients with COPD of higher severity ($30\% \leq \text{FEV1} < 50\%$ predicted or $\text{FEV1} < 30\%$ predicted or respiratory failure) with ≥ 2 exacerbations per year ^c	LABA and/or LAMA (tiotropium bromide) and additional ICS ^d	Added benefit not proven
<p>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.</p> <p>b: For better understandability, the term "adults with COPD grade II and adults with COPD grade \geq III with < 2 exacerbations per year" is used in the report.</p> <p>c: For better understandability, the term "adults with COPD grade \geq III with ≥ 2 exacerbations per year" is used in the report.</p> <p>d: The company did not investigate research question 2 because no sufficient number of patients with the corresponding severity grade were observed in the available study. The company therefore chose no ACT for research question 2.</p> <p>ACT: appropriate comparator therapy; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; G-BA: Federal Joint Committee; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist</p>		

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 as maintenance bronchodilator treatment to relieve symptoms in adults with COPD in comparison with the ACT.

From the G-BA's specification of the ACT, the following 2 research questions resulted for the benefit assessment (Table 4):

Table 4: Research questions of the benefit assessment of umeclidinium

Research question	Therapeutic indication	ACT ^a
1	Adults with COPD from moderate severity ($50\% \leq \text{FEV1} < 80\%$ predicted) ^b	LABA and/or LAMA (tiotropium bromide)
2	Adults with COPD of higher severity ($30\% \leq \text{FEV1} < 50\%$ predicted or $\text{FEV1} < 30\%$ predicted or respiratory failure) with ≥ 2 exacerbations per year ^c	LABA and/or LAMA (tiotropium bromide) and additional ICS ^d
<p>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.</p> <p>b: For better understandability, the term "adults with COPD grade II and adults with COPD grade \geq III with < 2 exacerbations per year" is used in the report.</p> <p>c: For better understandability, the term "adults with COPD grade \geq III with ≥ 2 exacerbations per year" is used in the report.</p> <p>d: The company did not investigate research question 2 because no sufficient number of patients with the corresponding severity grade were observed in the available study. The company therefore chose no ACT for research question 2.</p> <p>ACT: appropriate comparator therapy; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; G-BA: Federal Joint Committee; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist</p>		

To improve presentation and readability, the following terms according to the spirometric classification of COPD severity according to the GOLD recommendations [3] are used for both research questions in the report:

- adults with COPD grade II and adults with COPD grade \geq III with < 2 exacerbations per year (research question 1)
- adults with COPD grade \geq III with ≥ 2 exacerbations per year (research question 2)

For research question 1, the company followed the G-BA's specification of the ACT and chose tiotropium. The company's choice of the comparator therapy was followed. The company did not consider research question 2 in the dossier.

The assessment was conducted based on patient-relevant outcomes and on 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 did not concur with inclusion criteria used by the company, which specified a minimum study duration of 12 weeks.

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

2.3.1 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 (status: 4 November 2015)
- bibliographical literature search on umeclidinium (last search on 2 November 2015)
- search in trial registries for studies on umeclidinium (last search on 5 November 2015)

To check the completeness of the study pool:

- search in trial registries for studies on umeclidinium (last search on 12 February 2016)

No additional relevant study was identified from the check.

2.3.1.1 Studies included

The study listed in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: umeclidinium + placebo vs. tiotropium + placebo

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study ^a (yes/no)	Third-party study (yes/no)
201316	No	Yes	No
a: Study for which the company was sponsor. RCT: randomized controlled trial; vs.: versus			

The study pool concurred with the one of the company. Deviating from the company, however, the benefit assessment was only based on the 24-week data of study 201316. The company additionally used data at the time point of 12 weeks.

Section 2.3.4 contains a reference list for the study included.

2.3.1.2 Study characteristics

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

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes ^a
201316	RCT, double-blind, parallel	Patients (≥ 40 years) with confirmed COPD ^b : <ul style="list-style-type: none"> FEV1/FVC $< 70\%$ and $30\% \leq \text{FEV1} \leq 70\%$ predicted (post salbutamol) at first visit current or former smokers with ≥ 10 pack years mMRC dyspnoea score ≥ 2 at the first visit 	Total population ^c : UMEC (N = 509) TIO (n = 508) Subpopulation ^d relevant for research question 1 ^e : UMEC (n = 39) TIO (n = 39)	Run-in: 7 to 14 days Treatment: <ul style="list-style-type: none"> total population: 12 weeks relevant subpopulation: 24 weeks^d Follow-up: 7 ± 2 days	99 study centres in Canada, Chile, Denmark, France, Germany, Italy, Romania, Russia, South Africa, South Korea, Ukraine, USA 9/2014–6/2015	Primary: FEV1 Secondary: COPD symptoms (TDI, CAT), exacerbations, health-related quality of life (SGRQ), AEs
<p>a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.</p> <p>b: Patients were stratified by participation or non-participation in 24-hour serial FEV1 measurements.</p> <p>c: The population is not relevant for the assessment and is not shown in the following tables.</p> <p>d: Only German study centres because the study duration was 24 weeks only in these centres.</p> <p>e: Research question 1 comprises adults with COPD grade II and adults with COPD grade \geq III with < 2 exacerbations per year without ICS use.</p> <p>AE: adverse event; CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; ICS: inhaled corticosteroids; mMRC: modified Medical Research Council; n: relevant subpopulation; N: number of randomized patients; RCT: randomized controlled trial; SGRQ: St. George's Respiratory Questionnaire; TDI: Transition Dyspnoea Index; TIO: tiotropium; UMEC: umeclidinium; vs.: versus</p>						

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

Study	Intervention	Comparison
201316	<p>UMEC 62.5 µg administered once daily with the Ellipta inhaler in one inhalation</p> <p>+</p> <p>placebo administered once daily with the HandiHaler inhaler in 2 subsequent inhalations</p>	<p>TIO 18 µg administered once daily with the HandiHaler inhaler in 2 subsequent inhalations</p> <p>+</p> <p>placebo administered once daily with the Ellipta inhaler in one inhalation</p>
<p>Rescue medication (use as needed)</p> <ul style="list-style-type: none"> ▪ salbutamol^a <p>Allowed concomitant medication/treatment</p> <ul style="list-style-type: none"> ▪ mucolytics ▪ antibiotics for short-term treatment (≤ 14 days) of acute infections including COPD exacerbations ▪ systemic corticosteroids for short-term treatment (≤ 14 consecutive days) of COPD exacerbations ▪ oxygen use as needed^b ▪ pulmonary rehabilitation programme in the maintenance phase ▪ treatment for smoking cessation ▪ CPAP ventilation in sleep apnoea ▪ local corticosteroid injections ▪ oral muscarinic antagonists for the treatment of overactive bladder <p>Non-permitted concomitant medication/treatment</p> <ul style="list-style-type: none"> ▪ systemic, oral, parenteral^c or depot corticosteroids ▪ antibiotics for > 14 days ▪ initiation or discontinuation of ICS treatment ▪ long-term oxygen therapy for > 12 hours/day ▪ regular daily nebulized therapy with salbutamol ▪ initiation of pulmonary rehabilitation within 4 weeks before the first visit ▪ other COPD drugs had to be discontinued before the start of the study: <ul style="list-style-type: none"> ▫ LABA/ICS combinations ▫ ICS > 1000 µg/day fluticasone or equivalent ▫ PDE4 inhibitors ▫ inhaled LABAs ▫ LAMAs and LAMA/LABA combinations ▫ theophylline ▫ oral beta-2 sympathomimetics ▫ inhaled short-acting beta-2 sympathomimetics and anticholinergics as well as combinations of both drug classes 		
<p>a: If discontinued at least 4 hours before spirometry.</p> <p>b: ≤ 12 hours/day.</p> <p>c: Except for treatment of COPD exacerbations ≤ 14 days.</p> <p>CPAP: continuous positive airway pressure; COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; PDE4: phosphodiesterase type 4; RCT: randomized controlled trial; TIO: tiotropium; UMEC: umeclidinium; vs.: versus</p>		

The included study 201316 was a double-blind, multicentre, parallel group RCT. In the study, umeclidinium as intervention was compared with tiotropium as control. The study was conducted in 99 centres worldwide. In the study, 509 patients were randomized to the umeclidinium arm, and 508 patients to the tiotropium arm. The inclusion criteria comprised patients aged 40 years or older with moderate to very severe COPD (GOLD grades II to IV).

Patients with a forced expiratory volume in 1 second (FEV1) $\leq 70\%$ were included in study 201316; according to the GOLD criteria, moderate COPD (GOLD grade II) is defined as $50\% \leq \text{FEV1} < 80\%$ predicted, however. Hence conclusions could only be drawn for patients with $\text{FEV1} \leq 70\%$. Furthermore, patients had to have a smoking history of at least 10 pack years as well as a dyspnoea score of ≥ 2 on the modified Medical Research Council (mMRC) dyspnoea scale at enrolment.

Patients in the umeclidinium arm received 62.5 µg umeclidinium once daily with the Ellipta inhaler in one inhalation. Patients in the tiotropium arm received 18 µg tiotropium once daily with the HandiHaler inhaler in 2 subsequent inhalations. Since the 2 inhalers for umeclidinium and tiotropium differ in their appearance and application, the study was conducted in a double-dummy design.

In addition to the study medication, all patients could use the short-acting beta-2 sympathomimetic salbutamol as rescue medication. In addition, they could continue any ongoing treatment with an ICS at a constant dosage (≤ 1000 µg/day fluticasone or equivalent) over the total study duration. Treatment with ICS did not concur with the G-BA's specifications of the ACT for patients of research question 1. The benefit assessment was therefore conducted on the basis of a subpopulation who was not receiving long-term ICS medication (see below).

COPD exacerbations could be treated with antibiotics and systemic corticosteroids for a short period of time (≤ 14 days). Longer treatment of the patients with these drugs was not allowed. Patients had to discontinue other COPD drugs before the start of the study. These drugs included long- and short-acting bronchodilators with and without combination with an ICS, ICS with a dosage of > 1000 µg/fluticasone or equivalent, phosphodiesterase type 4 (PDE4) inhibitors and theophylline.

FEV1 was the primary outcome of the study. Patient-relevant outcomes were COPD symptoms, health-related quality of life and AEs.

The planned study duration was originally 12 weeks. Before inclusion of the first patients, an extension of the study duration to 24 weeks was introduced for all patients included in Germany with an amendment to the protocol. The subpopulation of patients who were receiving no long-term medication with ICS and were treated for 24 weeks was relevant for the benefit assessment. This subpopulation comprised 39 patients each in the umeclidinium arm and in the tiotropium arm. They were only patients treated in Germany. The company

submitted analyses based on this relevant subpopulation of study 201316. The patients included in these analyses were an adequate representation of the population relevant for research question 1 and were used for the benefit assessment.

Table 8 and Table 9 show the available patient characteristics in the relevant subpopulation in the study included for research question 1.

Table 8: Characteristics of the study populations – RCT, direct comparison: umeclidinium + placebo vs. tiotropium + placebo (research question 1)

Study Group	N ^a	Age [≤ 65 years/> 65 years] n (%)	Sex [F/M] %	Duration of COPD [years] mean (SD)	Smoking status [current smoker/ ex-smoker] %	Smoking [pack years] mean (SD)	Disease severity [COPD grade] ^b n (%)		Treat- ment discon- tinuation n (%)	Study discon- tinuation n (%)
							I ^c – II	III – IV ^d		
201316										
UMEC	39	26 (67)/13 (33)	36/64	ND	ND	ND	24 (62)	15 (38)	ND ^e	ND ^f
TIO	39	26 (67)/13 (33)	51/49	ND	ND	ND	23 (59)	16 (41)	ND ^e	ND ^f
a: Number of randomized patients. b: COPD grades are classified according to the GOLD [3] criteria using the FEV1: FEV1 ≥ 80% predicted corresponds to GOLD I, 50% ≤ FEV1 < 80% predicted corresponds to GOLD II, 30% ≤ FEV1 < 50% predicted corresponds to GOLD III, and FEV1 < 30% predicted or FEV1 < 50% predicted with respiratory failure corresponds to GOLD IV. c: No patients with GOLD I were included. d: No patients with GOLD IV were included. e: Only data on discontinuations due to AEs were available for the relevant subpopulation. It remains unclear whether there were further treatment discontinuations. f: There were no data on the relevant subpopulation. In the total German study arm, 7 patients (13%) discontinued the study in the UMEC arm, and 5 patients (9%) discontinued the study in the TIO arm. COPD: chronic obstructive pulmonary disease; F: female; FEV1: forced expiratory volume in 1 second; GOLD: Global Initiative for Chronic Obstructive Lung Disease; M: male; n: number of patients with event; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; TIO: tiotropium; UMEC: umeclidinium; vs.: versus										

Table 9: Characteristics of the study population (exacerbations in the year before screening by COPD grade) – RCT, direct comparison: umeclidinium + placebo vs. tiotropium + placebo (research question 1)

Study Group	N ^a	COPD grade ^b II		COPD grade ^b III	
		< 2 exacerbations n (%)	≥ 2 exacerbations n (%)	< 2 exacerbations n (%)	≥ 2 exacerbations n (%)
201316					
UMEC	39	23 (59)	1 (3)	15 (38)	0 (0)
TIO	39	22 (56)	1 (3)	16 (41)	0 (0)
a: Number of randomized patients. b: COPD grades are classified according to the GOLD [3] criteria using the FEV1: 50% ≤ FEV1 < 80% predicted corresponds to GOLD II, 30% ≤ FEV1 < 50% predicted corresponds to GOLD III. COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; GOLD: Global Initiative for Chronic Obstructive Lung Disease; n: number of patients with event; N: number of randomized patients; RCT: randomized controlled trial; TIO: tiotropium; UMEC: umeclidinium; vs.: versus					

The distribution of the patient characteristics was largely balanced between the study arms. However, there were more men than women in the umeclidinium arm, whereas the relation was balanced in the tiotropium arm. More than half of the patients in both study arms were 65 years or younger. Regarding COPD grade, patients with COPD grade II and < 2 exacerbations per year were the largest group in both study arms.

There were no data for the subpopulation for the characteristics of duration of COPD, smoking status at the start of the study and smoking (pack years). The dossier provided no information on the number of patients in the subpopulation who discontinued treatment or the study.

Since no patients with COPD grade IV were treated in study 201316, the subpopulation eventually contained patients with COPD grade II and COPD grade III and < 2 exacerbations per year. Hence there were no data on patients with COPD grade IV and < 2 exacerbations per year, who were also comprised by therapeutic indication of research question 1.

Table 10 shows the risk of bias at study level.

Table 10: Risk of bias at study level – RCT, direct comparison: umeclidinium + placebo vs. tiotropium + placebo (research question 1)

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			
201316	Yes	Yes	Yes ^a	Yes ^a	Yes	Yes	Low
a: Blinding of tiotropium was not completely ensured. This was considered in the assessment of the risk of bias at outcome level (see Section 2.3.2.2 and Section 2.6.2.4.2 of the full dossier assessment).							
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level for study 201316 was rated as low. This concurs with the company's assessment.

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.6.2.4.3 of the full dossier assessment):

- Mortality
 - all-cause mortality
- Morbidity
 - COPD symptoms (TDI)
 - COPD symptoms (CAT)
 - exacerbations
 - severe exacerbations
- Health-related quality of life
 - health-related quality of life (SGRQ)
- Side effects
 - SAEs
 - discontinuation due to AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in Module 4 A (see Section 2.6.2.4.3 of the full dossier assessment).

Table 11 shows for which outcomes data were available in the study included.

Table 11: Matrix of outcomes – RCT, direct comparison: umeclidinium + placebo vs. tiotropium + placebo (research question 1)

Study	Outcomes							
	All-cause mortality	COPD symptoms (TDI)	COPD symptoms (CAT)	Exacerbations ^b	Severe exacerbations	Health-related quality of life (SGRQ)	SAEs	Discontinuation due to AEs
201316	Yes	No ^a	Yes	No ^c	Yes	Yes	Yes	Yes
a: Outcome not recorded for the relevant subpopulation at the time point of 24 weeks. b: Includes moderate and severe exacerbations. c: No data; analysis of exacerbations only separated by severity grade. 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; TDI: Transition Dyspnoea Index; vs.: versus								

2.3.2.2 Risk of bias

Table 12 shows the risk of bias for the relevant outcomes.

Table 12: Risk of bias at study and outcome level – RCT, direct comparison: umeclidinium + placebo vs. tiotropium + placebo (research question 1)

Study	Study level	Outcomes							
		All-cause mortality	COPD symptoms (TDI)	COPD symptoms (CAT)	Exacerbations ^b	Severe exacerbations	Health-related quality of life (SGRQ)	SAEs	Discontinuation due to AEs
201316	L	L	- ^a	H	- ^c	L	H	L	H
a: Outcome not recorded for the relevant subpopulation at the time point of 24 weeks. b: Includes moderate and severe exacerbations. c: No data; analysis of exacerbations only separated by severity grade. 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; TDI: Transition Dyspnoea Index; vs.: versus									

Blinding of tiotropium was not completely ensured in study 201316 because the logo was printed on the tiotropium capsules, but not on the placebo capsules. Accordingly, the risk of bias for the patient-reported outcomes “COPD symptoms (CAT)”, “health-related quality of life (SGRQ)” and the outcome “discontinuation due to AEs” was rated as high (see Section 2.6.2.4.2 of the full dossier assessment). In contrast to this, the company rated the risk of bias as low.

The risk of bias for the outcomes “overall survival” and “severe exacerbations” and “SAEs” was rated as low. This concurs with the company’s assessment.

Since there were no data for the 2 outcomes “COPD symptoms (TDI)” and “exacerbations (moderate and severe)” (see Section 2.6.2.4.3 of the full dossier assessment), the risk of bias was not assessed.

2.3.2.3 Results

Due to the minimum study duration of 6 months, only the results of the subpopulation of the patients who were receiving no long-term ICS medication and who were treated for 24 weeks are presented below for all outcomes. This deviates from the company’s approach, which additionally presented the results of the total population and of the subpopulation without long-term ICS medication after 12 weeks.

Table 13 summarizes the results on the comparison of umeclidinium + placebo with tiotropium + placebo in patients with COPD. Where necessary, the data from the company’s dossier were supplemented by the Institute’s calculations.

Table 13: Results (dichotomous outcomes) – RCT, direct comparison: umeclidinium + placebo vs. tiotropium + placebo, 24 weeks (research question 1)

Study Outcome category Outcome	UMEC + placebo		TIO + placebo		UMEC + placebo vs. TIO + placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value ^a
201316					
Mortality					
All-cause mortality	39	0 (0)	39	0 (0)	NC
Morbidity					
COPD symptoms					
TDI responder			Not recorded at the time point of 24 weeks		
CAT responder ^b	39	20 (51)	39	16 (41)	1.25 [0.77; 2.03]; 0.528
Exacerbations ^c				No data ^d	
Severe exacerbations	39	2 (5)	39	0 (0)	5.00 [0.25; 100.89] ^e ; 0.208
Health-related quality of life					
SGRQ responder ^f	39	15 (38)	39	19 (49)	0.79 [0.47; 1.32]; 0.528
Side effects					
AEs	39	22 (56)	39	19 (49)	--
SAEs ^g	39	2 (5)	39	0 (0)	5.00 [0.25; 100.89] ^e ; 0.208
Discontinuation due to AEs ^h	39	1 (3)	39	1 (3)	1.00 [0.06; 15.43] ⁱ ; > 0.999
<p>a: Institute's calculation, unconditional exact test (CSZ method according to [4]).</p> <p>b: Patients with a reduction of the CAT score by ≥ 2 points (reduction of the score indicates improvement).</p> <p>c: Includes moderate and severe exacerbations.</p> <p>d: It can be inferred from the available information that 7 to 9 patients in the UMEC arm had an event for the outcome "exacerbations (moderate and severe)", in contrast to 6 patients in the TIO arm. No statistically significant result was shown for 7 vs. 6 patients or for 9 vs. 6 patients.</p> <p>e: Institute's calculation with continuity correction.</p> <p>f: Patients with a reduction of the SGRQ score by ≥ 4 points (reduction of the score indicates improvement).</p> <p>g: The analysis of the SAEs was conducted separately for fatal and non-fatal; no fatal SAEs occurred. Exacerbations were also considered in the recording of the SAEs. 2 of the total of 4 patients with SAEs in the UMEC arm only had the SAE "exacerbation". These patients were not included in the analysis of the SAEs.</p> <p>h: Exacerbations were also considered in the recording of the discontinuations due to AEs. One of the 2 patients in the UMEC arm discontinued the study due to an exacerbation. This patient was not included in the analysis of discontinuations due to AEs.</p> <p>i: Institute's calculation.</p> <p>AE: adverse event; CAT: COPD Assessment Test; CI: confidence interval; COPD: chronic obstructive pulmonary disease; CSZ: convexity, symmetry, z score; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculated; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SGRQ: St. George's Respiratory Questionnaire; TDI: Transition Dyspnoea Index; TIO: tiotropium; UMEC: umeclidinium; vs.: versus</p>					

Mortality

In study 201316, no deaths occurred in the relevant subpopulation. This resulted in no hint of an added benefit of umeclidinium in comparison with tiotropium; an added benefit for the outcome “all-cause mortality” is therefore not proven.

This concurs with the company’s assessment.

Morbidity***COPD symptoms (TDI responder)***

The outcome “COPD symptoms (TDI responder)” was no longer recorded at the time point of 24 weeks. Hence there was no hint of an added benefit of umeclidinium in comparison with tiotropium; an added benefit for the outcome “COPD symptoms (TDI responder)” is therefore not proven.

This concurs with the company’s assessment.

COPD symptoms (CAT responder)

No statistically significant difference was shown between the treatment groups for the outcome “COPD symptoms (CAT responder)”. There was no hint of an added benefit of umeclidinium in comparison with tiotropium; an added benefit for the outcome “COPD symptoms (CAT responder)” is therefore not proven.

This deviates from the company’s assessment, which used the 12-week data of the subpopulation without longterm ICS medication and derived an indication of an added benefit.

Exacerbations

No analyses were available for the outcome “exacerbations (moderate and severe)”. There was no hint of an added benefit of umeclidinium in comparison with tiotropium; an added benefit for the outcome “exacerbations (moderate and severe)” is therefore not proven.

The company did not present this outcome.

Severe exacerbations

No statistically significant difference was shown between the treatment groups for the outcome “severe exacerbations”. This resulted in no hint of an added benefit of umeclidinium in comparison with tiotropium; an added benefit for the outcome “severe exacerbations” is therefore not proven.

This concurs with the company’s assessment.

Health-related quality of life***SGRQ responder***

There was no statistically significant difference between the treatment groups for the outcome “SGRQ responder”. This resulted in no hint of an added benefit of umeclidinium in comparison with tiotropium; an added benefit for the outcome “SGRQ responder” is therefore not proven.

This concurs with the company’s assessment.

Side effects

The company’s dossier contained no information on the most common AEs, SAEs or discontinuations due to AEs for the relevant subpopulation of study 201316.

Serious adverse events and discontinuation due to adverse events

No statistically significant difference between the treatment groups was shown for the outcomes “SAEs” and “discontinuation due to AEs”. This resulted in no hint of greater or lesser harm of umeclidinium in comparison with tiotropium; an added benefit for the outcomes “SAEs” and “discontinuation due to AEs” is therefore not proven. This concurs with the company’s assessment.

2.3.2.4 Subgroups and other effect modifiers

For selected characteristics, the respective subgroups were investigated for the presence of heterogeneous treatment effects in order to identify possible effect modifiers. The following subgroup characteristics were considered as relevant:

- age (≤ 65 years/ > 65 years)
- sex (men/women)
- COPD grade ($\leq \text{II}/\geq \text{III}$)
- History of exacerbations ($0/1/\geq 2$)

For the characteristics “age”, “sex” and “COPD grade”, suitable subgroup analyses were available for the time point of 24 weeks or could be calculated by the Institute. No data were available on the characteristic “history of exacerbations”.

Only the results on subgroups and outcomes were to be presented in which there were at least indications of an interaction between treatment effect and subgroup characteristic. The prerequisite for proof of an effect modification is a statistically significant interaction with a p-value < 0.05 . A p-value ≥ 0.05 and < 0.2 provides an indication of an effect modification. Furthermore, subgroups were not to be shown if there were no statistically significant and relevant results in the total population or in one of the subgroups.

No statistically significant result was shown in the benefit assessment for any of the subgroups investigated. The subgroup results are therefore not presented.

2.3.3 Extent and probability of added benefit

The derivation of extent and probability of added benefit for research question 1 at outcome level is shown below, taking into account the various 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.

2.3.3.1 Assessment of added benefit at outcome level

Based on the data presented in Section 2.3.2, there was overall no statistically significant difference of umeclidinium in comparison with the ACT tiotropium between the treatment groups for any outcome. The extent of the respective added benefit at outcome level was estimated from these results (see Table 14).

Table 14: Extent of added benefit at outcome level: umeclidinium + placebo vs. tiotropium + placebo (research question 1)

Outcome category Outcome	UMEC + placebo vs. TIO + placebo Proportion of events Effect estimate [95% CI] p-value	Derivation of extent
Mortality		
All-cause mortality	0% vs. 0%	Lesser benefit/added benefit not proven
Morbidity		
TDI responder	Not recorded at the time point of 24 weeks	Lesser benefit/added benefit not proven
CAT responder	51% vs. 41% RR: 1.25 [0.77; 2.03] p = 0.528	Lesser benefit/added benefit not proven
Exacerbations	No data	Lesser benefit/added benefit not proven
Severe exacerbations	5% vs. 0% RR: 5.00 [0.25; 100.89] p = 0.208	Lesser benefit/added benefit not proven
Health-related quality of life		
SGRQ responder	38% vs. 49% RR: 0.79 [0.47; 1.32] p = 0.528	Lesser benefit/added benefit not proven
Side effects		
SAEs	5% vs. 0% RR: 5.00 [0.25; 100.89] p = 0.208	Greater/lesser harm not proven
Discontinuation due to AEs	3% vs. 3% RR: 1.00 [0.06; 15.43] p = 0.999	Greater/lesser harm not proven
AE: adverse event; CAT: COPD Assessment Test; CI: confidence interval; COPD: chronic obstructive pulmonary disease; RR: relative risk; SAE: serious adverse event; SGRQ: St. George's Respiratory Questionnaire; TDI: Transition Dyspnoea Index; TIO: tiotropium; UMEC: umeclidinium; vs.: versus		

2.3.3.2 Overall conclusion on added benefit

Neither positive nor negative effects remained from the assessment of umeclidinium in comparison with the ACT.

In summary, an added benefit of umeclidinium in comparison with the ACT tiotropium for adults with COPD grade II and adults with COPD grade \geq III with < 2 exacerbations per year is not proven.

This deviates from the company's approach, which derived an indication of a minor added benefit for the total population of research question 1 on the basis of the 12-week data on the outcome COPD symptoms.

2.3.4 List of included studies

201316

GlaxoSmithKline. A 12-week study to evaluate the efficacy and safety of umeclidinium compared with tiotropium in subjects with chronic obstructive pulmonary disease: full text view [online]. In: ClinicalTrials.gov. 11.01.2016 [accessed: 16.02.1016]. URL: <https://ClinicalTrials.gov/show/NCT02207829>.

GlaxoSmithKline. A 12-week study to evaluate the efficacy and safety of umeclidinium compared with tiotropium in subjects with chronic obstructive pulmonary disease: study results [online]. In: ClinicalTrials.gov. 11.01.2016 [accessed: 16.02.1016]. URL: <https://clinicaltrials.gov/ct2/show/results/NCT02207829>.

GlaxoSmithKline. A randomized, blinded, double-dummy, parallel-group study to evaluate the efficacy and safety of umeclidinium (UMEC) 62.5 mcg compared with tiotropium 18 mcg in subjects with chronic obstructive pulmonary disease (COPD): study 201316; clinical study report [unpublished]. 2015.

GlaxoSmithKline. A randomized, blinded, double-dummy, parallel-group study to evaluate the efficacy and safety of umeclidinium (UMEC) 62.5 mcg compared with tiotropium 18 mcg in subjects with chronic obstructive pulmonary disease (COPD): study 201316; protocol summary [online]. In: GSK Clinical Study Register. 22.10.2015 [accessed: 16.11.2015]. URL: <http://www.gsk-clinicalstudyregister.com/study/201316#ps>.

GlaxoSmithKline. A randomized, blinded, double-dummy, parallel-group study to evaluate the efficacy and safety of umeclidinium (UMEC) 62.5 mcg compared with tiotropium 18 mcg in subjects with chronic obstructive pulmonary disease (COPD): study 201316; reporting and analysis plan for 201316 German value dossier [unpublished]. 2015.

GlaxoSmithKline. A randomized, blinded, double-dummy, parallel-group study to evaluate the efficacy and safety of umeclidinium (UMEC) 62.5 mcg compared with tiotropium 18 mcg in subjects with chronic obstructive pulmonary disease (COPD): study 201316; result summary [online]. In: GSK Clinical Study Register. 20.10.2015 [accessed: 16.11.2015]. URL: <http://www.gsk-clinicalstudyregister.com/files2/gsk-201316-clinical-study-result-summary.pdf>.

GlaxoSmithKline. A randomized, blinded, double-dummy, parallel-group study to evaluate the efficacy and safety of umeclidinium (UMEC) 62.5 mcg compared with tiotropium 18 mcg in subjects with chronic obstructive pulmonary disease (COPD): study 201316; Zusatzanalysen [unpublished]. 2015.

GlaxoSmithKline. A randomized, blinded, double-dummy, parallel-group, study to evaluate the efficacy and safety of umeclidinium (UMEC) 62.5 mcg compared with tiotropium 18 mcg in subjects with chronic obstructive pulmonary disease (COPD) (German extension): study 201316; clinical study report [unpublished]. 2015.

GlaxoSmithKline Research & Development. A randomized, blinded, double-dummy, parallel-group study to evaluate the efficacy and safety of umeclidinium (UMEC) 62.5 mcg compared with tiotropium 18 mcg in subjects with chronic obstructive pulmonary disease (COPD) [online]. In: EU Clinical Trials Register. [Accessed: 16.02.1016]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-000884-42.

2.4 Research question 2: adults with COPD grades \geq III with \geq 2 exacerbations per year

2.4.1 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 (status: 4 November 2015)
- bibliographical literature search on umeclidinium (last search on 2 November 2015)
- search in trial registries for studies on umeclidinium (last search on 5 November 2015)

To check the completeness of the study pool:

- search in trial registries for studies on umeclidinium (last search on 12 February 2016)

No additional relevant study was identified from the check.

From the steps of information retrieval mentioned, the company identified study 201316 (see Section 2.3.1.1). In this study, only 1 patient with COPD grade \geq III and \geq 2 exacerbations per year was included who, concurring with the G-BA's specification on the ACT was treated with tiotropium and an ICS and whose treatment duration was 24 weeks. Due to this low number of patients, the company did not assess the added benefit for research question 2.

In summary, the company therefore presented no suitable studies in the dossier to investigate the added benefit of umeclidinium in comparison with the ACT for adults with COPD grade \geq III and \geq 2 exacerbations per year.

2.4.2 Results on added benefit

No data were available for the assessment of the added benefit of umeclidinium for the treatment of adults with COPD grade \geq III and \geq 2 exacerbations per year. Hence there was no hint of an added benefit of umeclidinium in comparison with the ACT. An added benefit is therefore not proven.

2.4.3 Extent and probability of added benefit

Since the company presented no data for the assessment of the added benefit of umeclidinium in adults with COPD grade \geq III and \geq 2 exacerbations per year, an added benefit of umeclidinium is not proven.

2.4.4 List of included studies

Not applicable as no studies were included in the benefit assessment.

2.5 Extent and probability of added benefit – summary

The result of the assessment of the added benefit of umeclidinium in comparison with the ACT is summarized in Table 15.

Table 15: Umeclidinium – extent and probability of added benefit

Therapeutic indication	ACT ^a	Extent and probability of added benefit
Adult patients with COPD from moderate severity ($50\% \leq \text{FEV1} < 80\%$ predicted) ^b	LABA and/or LAMA (tiotropium bromide)	Added benefit not proven
Adult patients with COPD of higher severity ($30\% \leq \text{FEV1} < 50\%$ predicted or $\text{FEV1} < 30\%$ predicted or respiratory failure) with ≥ 2 exacerbations per year ^c	LABA and/or LAMA (tiotropium bromide) and additional ICS ^d	Added benefit not proven
<p>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.</p> <p>b: For better understandability, the term "adults with COPD grade II and adults with COPD grade \geq III with < 2 exacerbations per year" is used in the report.</p> <p>c: For better understandability, the term "adults with COPD grade \geq III with ≥ 2 exacerbations per year" is used in the report.</p> <p>d: The company did not investigate research question 2 because no sufficient number of patients with the corresponding severity grade were observed in the available study. The company therefore chose no ACT for research question 2.</p> <p>ACT: appropriate comparator therapy; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; G-BA: Federal Joint Committee; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist</p>		

In summary, an added benefit of umeclidinium for the treatment of COPD is neither proven for research question 1 (adults with COPD grade II and adults with COPD grade \geq III with < 2 exacerbations per year) nor for research question 2 (adults with COPD grade \geq III with ≥ 2 exacerbations per year).

This deviates from the company's approach, which derived an indication of a minor added benefit for patients of research question 1. The company did not consider research question 2.

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

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General Methods: version 4.2 [online]. 22.04.2015 [accessed: 01.03.2016]. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-2.pdf.
2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. *Biom J* 2015; 58(1): 43-58
3. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic pulmonary disease (updated 2016) [online]. 2016 [accessed: 03.02.2016]. URL: <http://www.goldcopd.org/guidelines-global-strategy-for-diagnosis-management.html>.
4. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. *Computat Stat Data Anal* 1994; 17(5): 555-574.

The full report (German version) is published under <https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/a16-02-umeclidinium-nutzenbewertung-gemaess-35a-sgb-v.7227.html>.