

IQWiG Reports – Commission No. A14-45

# **Umeclidinium/vilanterol (Addendum to Commission A14-22)<sup>1</sup>**

## **Addendum**

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**List of abbreviations**

<b>Abbreviation</b>	<b>Meaning</b>
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 corticosteroid
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
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

## 1 Background

On 2 December 2014, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for Commission A14-22 (Umeclidinium/vilanterol – Benefit assessment according to §35a Social Code Book (SGB) V [1]).

In the commenting procedure on the assessment of umeclidinium/vilanterol, the pharmaceutical company (hereinafter abbreviated to “the company”) submitted supplementary information with its comment for the proof of added benefit to the G-BA [2] that went beyond the information in the dossier [3]. These were analyses on the studies DB2113360, DB2113374 and ZEP117115, in each case on the comparison of umeclidinium/vilanterol versus tiotropium. These studies were already contained in the company’s dossier and were included as relevant in the dossier assessment A14-22. In the dossier assessment, the subpopulations from the studies of patients without concomitant inhaled corticosteroid (ICS) treatment were considered to be relevant. However, the company only used the respective total populations for the assessment of the added benefit in the dossier. For the subpopulation of patients without concomitant ICS treatment, evaluable results were only available for the outcomes “health-related quality of life” (measured with the St. George’s Respiratory Questionnaire [SGRQ]) and “symptoms” (measured with the Transition Dyspnoea Index [TDI]). No conclusive balancing on the added benefit could be conducted on the basis of these data. With its comment, the company subsequently submitted the following analyses on patients without concomitant ICS treatment (research question 1 of the dossier assessment):

- analyses of further outcomes, particularly all-cause mortality, chronic obstructive pulmonary disease (COPD) symptoms (COPD Assessment Test [CAT]), COPD symptoms (Shortness of Breath with Daily Activities [SOBDA]), moderate and severe exacerbations, serious adverse events (SAEs), and discontinuation due to adverse events (AEs)
- subgroup analyses to investigate the following possible effect modifiers: age, sex, region, and severity grade of the disease (COPD grades according to the Global Initiative for Chronic Obstructive Lung Disease [GOLD] criteria)

The G-BA commissioned IQWiG with the assessment of these analyses submitted by the company in the commenting procedure under consideration of the information provided in the dossier. The data were to be assessed under the research question whether further conclusions on the added benefit are possible under consideration of the analyses on patients without additional ICS treatment submitted by the company in the written and oral commenting procedure.

The responsibility for the present assessment and the results of the assessment lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

### **1.1 Changes in Version 1.1**

The present Version 1.1 from 5 January 2015 replaces Version 1.0 of the Addendum from 11 December 2014. Compared with Version 1.0, Version 1.1 contains the following change: In the running text of Section 2.1.4, the outcomes “SAEs” and “discontinuation due to AEs” were interchanged with each other with regard to their results. This has been corrected accordingly.

The result of the assessment was not affected by this change.



## 2 Assessment

### 2.1 Results on added benefit

Since the dossier contained no information on patients with COPD grade II or patients with COPD grades  $\geq$  III and  $<$  2 exacerbations (research question 1), the subpopulation of patients without ICS treatment was used as an approximation for the dossier assessment [1]. As described in the dossier assessment, this approximation was subject to an increased uncertainty. The company did not solve this uncertainty in its comment so that the population of patients without concomitant ICS treatment had to be used also in the present addendum.

For this population, the dossier contained data for only 2 outcomes (see Chapter 1). Due to the lack of analyses, no final conclusion on the added benefit of umeclidinium/vilanterol in these patients could be drawn. Moreover, there were neither data on patient characteristics including comprehensive analyses of the frequency of exacerbation before the start of the study nor subgroup analyses for this subpopulation.

According to the commission by the G-BA, the following assessment of the data subsequently submitted only refers to research question 1 of the dossier assessment, the assessment of the added benefit of umeclidinium/vilanterol versus the appropriate comparator therapy (ACT) for patients with COPD grade II or patients with COPD grades  $\geq$  III and  $<$  2 exacerbations per year. The company presented no data in the dossier or in the analyses subsequently submitted for patients of research question 2 (patients with COPD grade  $\geq$  III and  $\geq$  2 exacerbations per year).

#### 2.1.1 Characteristics of the study population

For the dossier assessment, only information on the respective total populations of the 3 studies included was available for the characteristics of the study populations. These are shown in Section 2.3.2.2 of the dossier assessment [1]. The characteristics of the study population of patients without concomitant ICS treatment were not presented in the comment either. This is particularly important because the proportion of patients with  $\geq$  2 exacerbations per year before inclusion in the study still remains unclear. Hence it can still not be estimated exactly whether the population of patients without concomitant ICS treatment is an adequate approximation of research question 1.

#### 2.1.2 Outcomes included

The list of outcomes included in the present assessment is presented in Section 2.4.1.1 of the dossier assessment [1]. This list again deviated from the one of the company, which – as already in Module 4 of the dossier – additionally included the outcomes “COPD symptoms (emergency treatment)” and “lung function (forced expiratory volume in 1 second [FEV1]”. The arguments presented with the company’s comment [2] also resulted in no deviating assessment of the relevance of the outcomes for the assessment.

Regarding the outcomes considered it is to be additionally noted that the data subsequently submitted by the company also contained no separate analyses on the outcomes “moderate exacerbations” and “severe exacerbations”, but only data for the composite outcome of moderate and severe exacerbations.

### **2.1.3 Risk of bias at outcome level**

The company neither conducted the assessment of the risk of bias at outcome level for the documents subsequently submitted, which is required by the dossier template, nor did it provide information on whether the assessment of the risk of bias on the basis of the total population, which it had provided in the dossier, also applied to the relevant subpopulation. Moreover, in comparison with the dossier, it additionally presented analyses on the outcomes “COPD symptoms (CAT)” and “COPD symptoms (SOBDA)”, for which therefore an assessment of the risk of bias for the total population and for the relevant subpopulation was lacking. Hence the presentation of the results for the individual outcomes did not meet the requirements for the dossier. An assessment of the probability of an added benefit for the individual outcomes on the basis of the information provided in the comment is not possible.

No Institute’s assessment of the outcome-specific risk of bias was conducted in the present situation. Since the meta-analysis showed no statistically significant difference between the treatment arms for any of the outcomes considered and no effects in the same direction (see Section 2.1.4), a final conclusion on the added benefit does not depend on the outcome-specific assessment of the risk of bias.

### **2.1.4 Results**

Table 1 summarizes the results on the comparison of umeclidinium/vilanterol versus tiotropium for patients without concomitant ICS treatment (research question 1). The most common AEs and SAEs are additionally presented in Appendix A (Table 5, Table 6, Table 7 and Table 8).

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

Outcome category outcome <sup>a</sup> study	UMEC/VI		TIO		UMEC/VI vs. TIO RR [95% CI]; p-value
	N	Patients with events n (%)	N	Patients with events n (%)	
<b>Mortality</b>					
All-cause mortality					
DB2113360	119	1 (< 1)	115	0	ND
DB2113374	114	1 (< 1)	100	1 (1)	0.88 [0.06; 13.84]; ND
ZEP117115	207	1 (< 1)	214	3 (1)	0.34 [0.04; 3.29]; ND
Total					0.73 [0.17; 3.24] <sup>b</sup> ; p = 0.682 <sup>c</sup>
<b>Morbidity</b>					
COPD symptoms (CAT responder <sup>d</sup> )					
DB2113360	101	52 (51)	91	50 (55)	0.94 [0.72; 1.22] <sup>e</sup> ; ND
DB2113374	87	43 (49)	88	41 (47)	1.06 [0.78; 1.44] <sup>e</sup> ; ND
ZEP117115			Outcome not recorded		
Total					0.99 [0.81; 1.21]; p = 0.905 <sup>c</sup>
COPD symptoms (SOBDA responder <sup>f</sup> )					
DB2113360	105	24 (23)	98	29 (30)	0.77 [0.48; 1.23] <sup>e</sup> ; ND
DB2113374	96	20 (21)	90	26 (29)	0.72 [0.43; 1.20] <sup>e</sup> ; ND
ZEP117115			Outcome not recorded		
Total					0.75 [0.53; 1.05] p = 0.098 <sup>c</sup>
Moderate exacerbations			No evaluable data available		
Severe exacerbations			No evaluable data available		
Moderate and severe exacerbations					
DB2113360	114	5 (4)	110	5 (5)	0.96 [0.29; 3.24] <sup>e</sup> p > 0.999 <sup>g</sup>
DB2113374	114	16 (14)	100	3 (3)	4.68 [1.40; 15.59] p = 0.005 <sup>g</sup>
ZEP117115	207	4 (2)	214	9 (4)	0.46 [0.14; 1.47] p = 0.218 <sup>g</sup>
Total			Heterogeneity <sup>cc</sup>		Q = 7.75; df = 2, p = 0.021, I <sup>2</sup> = 74.2%

(continued)

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

Outcome category outcome <sup>a</sup> study	UMEC/VI		TIO		UMEC/VI vs. TIO RR [95% CI]; p-value
	N	Patients with events n (%)	N	Patients with events n (%)	
<b>Adverse events</b>					
SAEs					
DB2113360	119	3 (3)	115	6 (5)	0.48 [0.12; 1.89]; p = 0.292 <sup>b</sup>
DB2113374	114	11 (10)	100	4 (4)	2.41 [0.79; 7.34]; p = 0.113 <sup>b</sup>
ZEP117115	207	7 (3)	214	8 (4)	0.90 [0.33; 2.45]; p = 0.862 <sup>b</sup>
Total				Heterogeneity <sup>c</sup>	Q = 3.47; df = 2, p = 0.177; I <sup>2</sup> = 42.3%
Discontinuation due to adverse events					
DB2113360	119	5 (4)	115	4 (3)	1.21 [0.33; 4.39]; p > 0.999
DB2113374	114	11 (10)	100	3 (3)	3.22 [0.92; 11.20]; p = 0.057
ZEP117115	207	7 (3)	214	5 (2)	1.45 [0.47; 4.49]; p = 0.570
Total					1.77 [0.88; 3.57]; p = 0.112
a: Only for the outcomes with results subsequently submitted. The results of the outcomes “COPD symptoms (TDI)” and “health-related quality of life (SGRQ)” can be found in Section 2.4.1.3 of the dossier assessment [1].					
b: Peto odds ratio; Institute’s calculation of effect estimate and CI.					
c: Institute’s calculation from meta-analysis.					
d: Patients with a reduction in total score $\geq 2$ .					
e: Institute’s calculation, asymptotic.					
f: Patients with a reduction in total score $\geq 0.2$ .					
g: Institute’s calculation, unconditional exact test (CSZ method according to [4]).					
AE: adverse event; CAT: COPD Assessment Test; CI: confidence interval; COPD: chronic obstructive pulmonary disease; CSZ: convexity, symmetry, z score; N: number of analysed patients; n: number of patients with event; ND: no data; 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 and morbidity

There was no statistically significant result at the level of the meta-analysis for any of the outcomes on mortality and morbidity included. There was a heterogeneous situation without effects in the same direction for the composite outcome “moderate and severe exacerbations”. Hence an added benefit of umeclidinium/vilanterol in comparison with the ACT tiotropium is not proven for these outcomes.

**Adverse events**

There was important heterogeneity without effects in the same direction for the outcome “SAEs”; for the outcome “discontinuation due to AEs”, there was no statistically significant difference between the treatment arms on the basis of the meta-analysis. Hence greater or lesser harm from umeclidinium/vilanterol in comparison with the ACT tiotropium is not proven for these outcomes.

The company additionally presented analyses on the most common AEs and SAEs with the comments (see Appendix A). These were examined in the addendum on whether there were notable differences between the treatment groups. No specific AEs were identified.

**2.1.5 Subgroups and other effect modifiers**

In its supplementary analyses for the comment, the company presented subgroup analyses to investigate the following possible effect modifiers: age, sex, region, and severity grade of the disease (COPD grades according to the GOLD criteria), in each case based on the individual studies however. However, a meta-analytical calculation of the p-values of the interactions is necessary to identify effect modifications. The subgroup analyses were therefore not evaluable in the framework of the addendum and they are neither presented nor further commented on.

**2.2 Extent and probability of added benefit****2.2.1 Assessment of added benefit at outcome level**

For research question 1, the data presented in Section 2.4 of the dossier assessment A14-22 and in Section 2.1 of the present addendum 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 2).

Table 2: Extent of added benefit at outcome level: umeclidinium/vilanterol vs. tiotropium (research question 1)

<b>Outcome category outcome</b>	<b>Umeclidinium/vilanterol vs. tiotropium proportions of events effect estimate [95% CI] p-value probability<sup>a</sup></b>	<b>Derivation of extent</b>
<b>Mortality</b>		
All-cause mortality	UMEC/VI: < 1% TIO: 0% to 1% <sup>b</sup> POR: 0.73 [0.17; 3.24] <sup>c</sup> p = 0.682 <sup>c</sup>	Added benefit not proven
<b>Morbidity</b>		
COPD symptoms (TDI responder) <sup>d</sup>	UMEC/VI: 56% to 64% <sup>b</sup> TIO: 56% to 57% <sup>b</sup> RR: 1.06 [0.89; 1.25] <sup>c</sup> p = 0.522 <sup>c</sup>	Added benefit not proven
COPD symptoms (CAT responder)	UMEC/VI: 49% to 51% <sup>b</sup> TIO: 47% to 55% <sup>b</sup> RR: 0.99 [0.81; 1.21] <sup>c</sup> p = 0.905 <sup>c</sup>	Added benefit not proven
COPD symptoms (SOBDA responder)	UMEC/VI: 21% to 23% <sup>b</sup> TIO: 29% to 30% <sup>b</sup> RR: 0.75 [0.53; 1.05] <sup>c</sup> p = 0.098 <sup>c</sup>	Added benefit not proven
Moderate exacerbations	No evaluable data available	Added benefit not proven
Severe exacerbations	No evaluable data available	Added benefit not proven
Composite outcome: moderate and severe exacerbations	Heterogeneity of the results; no effects in the same direction	Added benefit not proven
<b>Health-related quality of life</b>		
Health-related quality of life (SGRQ responder) <sup>d</sup>	UMEC/VI: 45% to 59% <sup>b</sup> TIO: 45% to 56% <sup>b</sup> RR: 1.06 [0.92; 1.23] <sup>c</sup> p = 0.430 <sup>c</sup>	Added benefit not proven
<b>Adverse events</b>		
SAEs	Heterogeneity of the results; no effects in the same direction	Greater/lesser harm not proven
Discontinuation due to AEs	UMEC/VI: 3% to 10% <sup>b</sup> TIO: 2% to 3% <sup>b</sup> RR: 1.77 [0.88; 3.57] p = 0.112	Greater/lesser harm not proven

(continued)

Table 2: Extent of added benefit at outcome level: umeclidinium/vilanterol vs. tiotropium (research question 1) (continued)

<p>a: Probability provided if statistically significant differences were present.  b: Minimum and maximum proportions of events in each treatment arm in the studies included.  c: Institute's calculation from meta-analysis.  d: The data were taken from the dossier assessment [1].</p> <p>AE: adverse event; CAT: COPD Assessment Test; CI: confidence interval; COPD: chronic obstructive pulmonary disease; POR: Peto odds ratio; 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</p>
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### 2.2.2 Overall conclusion on added benefit

Table 3 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 3: Positive and negative effects from the assessment of umeclidinium/vilanterol compared with tiotropium (research question 1)

Positive effects	Negative effects
—	—

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  $\geq$  III with  $< 2$  exacerbations per year.

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

### 2.2.3 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 4.

Table 4: Umeclidinium/vilanterol: extent and probability of added benefit

Research question	Therapeutic indication	ACT <sup>a</sup>	Extent and probability of added benefit
1	Adult patients with COPD grade II and adult patients with COPD grades $\geq$ III with < 2 exacerbations per year	LABA (formoterol, salmeterol) and/or LAMA ( <b>tiotropium</b> )	Added benefit not proven
2	Adult patients with COPD grades $\geq$ III with $\geq$ 2 exacerbations per year	LABA (formoterol, salmeterol) and/or LAMA (tiotropium) and additional ICS <sup>b</sup>	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: 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.</p> <p>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</p>			

The documents subsequently submitted did not change the overall conclusion on the added benefit in comparison with the dossier assessment [1].

This result deviates from that of the company, which derived proof of a minor added benefit on the basis of the subpopulation of patients without concomitant ICS treatment in the 3 studies included.

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

### **Additional comments on the analyses subsequently submitted**

In the oral hearing on umeclidinium/vilanterol, the company stated that it had not been possible for the company to present the data for the relevant subpopulation already in the dossier. The time between the decision for the drug combination indacaterol/glycopyrronium on 8 May 2014 – from which information on the relevant subpopulations for the similar situation of assessment regarding umeclidinium/vilanterol could be inferred – and the dossier template for umeclidinium/vilanterol was too short to produce new analyses, the company claimed. Due to the documentation of the date in the output documents of the analysis software, it was clear from the analyses presented in the comment [2] that some of the analyses had already been conducted starting from May 2012. For example, all analyses on the relevant subpopulation (without concomitant ICS treatment) on AEs (AEs, SAEs, and discontinuation due to AEs) were performed in the period between 29 November 2013 and 18 March 2014. Hence the question arises why it was not possible for the company to provide relevant analyses for the assessment of the harm of umeclidinium/vilanterol versus tiotropium already with the dossier [3].



### 3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen.

Umeclidinium/Vilanterol: Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; A14-22 [online]. 13 October 2014 [accessed: 16 October 2014]. (IQWiG-Berichte; Volume 248).

URL: [https://www.iqwig.de/download/A14-22\\_Umeclidinium-Vilanterol\\_Nutzenbewertung-35a-SGB-V.pdf](https://www.iqwig.de/download/A14-22_Umeclidinium-Vilanterol_Nutzenbewertung-35a-SGB-V.pdf).

2. GlaxoSmithKline. Stellungnahme zum IQWiG-Bericht Nr. 248: Umeclidinium/Vilanterol; Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A14-22. [Soon available under: <https://www.g-ba.de/informationen/nutzenbewertung/124/#tab/beschluesse> in the document "Zusammenfassende Dokumentation"].

3. GlaxoSmithKline. Umeclidinium / Vilanterol (Anoro): Dossier zur Nutzenbewertung gemäß § 35a SGB V; Modul 4A; COPD; medizinischer Nutzen und medizinischer Zusatznutzen, Patientengruppen mit therapeutisch bedeutsamem Zusatznutzen [online]. 10 July 2014 [accessed: 12 November 2014]. URL: <https://www.g-ba.de/informationen/nutzenbewertung/124/>.

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.

**Appendix A – Additional results on adverse events**Table 5: Common AEs ( $\geq 3\%$  patients with  $\geq 1$  event in at least one study arm) – RCT, direct comparison: umeclidinium/vilanterol vs. tiotropium (research question 1), study DB2113360

SOC PT	Patients with at least one event n (%)	
	UMEC/VI N = 119	TIO N = 115
Overall rate	52 (44)	42 (37)
Infections and infestations	20 (17)	29 (25)
nasopharyngitis	9 (8)	8 (7)
upper respiratory tract infections	4 (3)	5 (4)
sinusitis	3 (3)	3 (3)
urinary tract infection	0	3 (3)
Respiratory, thoracic and mediastinal disorders	13 (11)	10 (9)
cough	5 (4)	2 (2)
Nervous system disorders	12 (10)	4 (3)
headache	11 (9)	3 (3)
General disorders and administration site conditions	11 (9) <sup>a</sup>	3 (3) <sup>a</sup>
Gastrointestinal disorders	9 (8)	9 (8)
toothache	4 (3)	1 (< 1)
Musculoskeletal and connective tissue disorders	9 (8)	4 (3)
back pain	5 (4)	2 (2)
Cardiac disorders	6 (5) <sup>a</sup>	0
Injury, poisoning and procedural complications	5 (4) <sup>a</sup>	5 (4) <sup>a</sup>
Investigations	4 (3)	4 (3)
blood pressure increased	3 (3)	0
Eye disorders	4 (3)	1 (< 1)
conjunctivitis	3 (3)	0
Psychiatric disorders	4 (3) <sup>a</sup>	0
Skin and subcutaneous tissue disorders	3 (3) <sup>a</sup>	0
Vascular disorders	2 (2)	3 (3) <sup>a</sup>
In descending order according to frequency in the UMEC/VI arm.		
a: The respective event occurred in < 3% of the patients at the PT level.		
AE: adverse event; N: number of patients in the analyses; n: number of patients with event; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; TIO: tiotropium; UMEC: umeclidinium; VI: vilanterol; vs.: versus		

Table 6: Common AEs ( $\geq 3\%$  patients with  $\geq 1$  event in at least one study arm) – RCT, direct comparison: umeclidinium/vilanterol vs. tiotropium (research question 1), study DB2113374

SOC PT	Patients with at least one event n (%)	
	UMEC/VI N = 114	TIO N = 100
Overall rate	62 (54)	50 (50)
Infections and infestations	29 (25)	26 (26)
nasopharyngitis	7 (6)	9 (9)
lower respiratory tract infections	6 (5)	1 (1)
upper respiratory tract infections	5 (4)	5 (5)
urinary tract infection	1 (< 1)	3 (3)
influenza	1 (< 1)	3 (3)
Nervous system disorders	13 (11)	12 (12)
headache	11 (10)	7 (7)
Gastrointestinal disorders	13 (11)	13 (13)
vomiting	3 (3)	0
Musculoskeletal and connective tissue disorders	12 (11)	7 (7)
back pain	4 (4)	2 (2)
neck pain	4 (4)	0
pain in extremity	3 (3)	1 (1)
Respiratory, thoracic and mediastinal disorders	11 (10)	12 (12)
COPD	4 (4)	1 (1)
productive cough	3 (3)	0
cough	1 (< 1)	5 (5)
General disorders and administration site conditions	5 (4) <sup>a</sup>	2 (2)
Psychiatric disorders	4 (4)	3 (3)
insomnia	3 (3)	3 (3)
Cardiac disorders	4 (4)	1 (1)
ventricular extrasystoles	3 (3)	0
Injury, poisoning and procedural complications	3 (3) <sup>a</sup>	3 (3) <sup>a</sup>
Investigations	2 (2)	4 (4) <sup>a</sup>
Vascular disorders	2 (2)	3 (3) <sup>a</sup>
Skin and subcutaneous tissue disorders	1 (< 1)	3 (3) <sup>a</sup>

In descending order according to frequency in the UMEC/VI arm.  
a: The respective event occurred in < 3% of the patients at the PT level.  
AE: adverse event; COPD: chronic obstructive lung disease; N: number of patients in the analyses; n: number of patients with event; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; TIO: tiotropium; UMEC: umeclidinium; VI: vilanterol; vs.: versus

Table 7: Common AEs ( $\geq 3\%$  patients with  $\geq 1$  event in at least one study arm) – RCT, direct comparison: umeclidinium/vilanterol vs. tiotropium (research question 1), study ZEP117115

SOC PT	Patients with at least one event n (%)	
	UMEC/VI N = 207	TIO N = 214
Overall rate	88 (43)	92 (43)
Infections and infestations	30 (14)	40 (19)
nasopharyngitis	14 (7)	15 (7)
Gastrointestinal disorders	19 (9) <sup>a</sup>	19 (9) <sup>a</sup>
Nervous system disorders	18 (9)	20 (9)
headache	13 (6)	14 (7)
Musculoskeletal and connective tissue disorders	17 (8)	16 (7)
back pain	2 (< 1)	6 (3)
Respiratory, thoracic and mediastinal disorders	16 (8)	14 (7)
cough	6 (3)	7 (3)
Injury, poisoning and procedural complications	8 (4) <sup>a</sup>	10 (5) <sup>a</sup>
General disorders and administration site conditions	6 (3) <sup>a</sup>	7 (3) <sup>a</sup>
Metabolism and nutrition disorders	6 (3) <sup>a</sup>	4 (2)
Vascular disorders	6 (3) <sup>a</sup>	3 (1)
Psychiatric disorders	2 (< 1)	7 (3) <sup>a</sup>

In descending order according to frequency in the UMEC/VI arm.  
a: The respective event occurred in < 3% of the patients at the PT level.  
AE: adverse event; N: number of patients in the analyses; n: number of patients with event; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; TIO: tiotropium; UMEC: umeclidinium; VI: vilanterol; vs.: versus

Table 8: Common SAEs ( $\geq 1\%$  patients with  $\geq 1$  event in at least one study arm) – RCT, direct comparison: umeclidinium/vilanterol vs. tiotropium (research question 1)

Study SOC PT	Patients with at least one event n (%)	
	UMEC/VI	TIO
<b>Study DB2113360</b>	<b>N = 119</b>	<b>N = 115</b>
Overall rate	3 (3)	6 (5)
Respiratory, thoracic and mediastinal disorders	2 (2)	1 (< 1)
COPD	2 (2)	1 (< 1)
Infections and infestations	0	2 (2) <sup>a</sup>
<b>Study DB2113374</b>	<b>N = 114</b>	<b>N = 100</b>
Overall rate	11 (10)	4 (4)
Infections and infestations	6 (5)	1 (1)
influenza	0	1 (1)
Respiratory, thoracic and mediastinal disorders	4 (4)	2 (2)
COPD	4 (4)	1 (1)
respiratory arrest	0	1 (1)
Nervous system disorders	1 (< 1)	1 (1)
syncope	0	1 (1)
<b>Study ZEP117115</b>	<b>N = 207</b>	<b>N = 214</b>
Overall rate	7 (3) <sup>a</sup>	8 (4) <sup>a</sup>
In descending order according to frequency in the UMEC/VI arm.		
a: The respective event occurred in < 1 % of the patients at the SOC or PT level.		
COPD: chronic obstructive pulmonary disease; N: number of patients in the analyses; n: number of patients with event; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; TIO: tiotropium; UMEC: umeclidinium; VI: vilanterol; vs.: versus		