IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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

Extract

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

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BDI	Baseline Dyspnoea Index
CI	confidence interval
COPD	chronic obstructive pulmonary disease
EQ-5D VAS	European Quality of Life-5 Dimensions visual analogue scale
E-RS	Exacerbation of Chronic Pulmonary Disease Tool Respiratory Symptoms
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)
ITT	intention to treat
PDE4	phosphodiesterase type 4
PGR	patient global rating
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SGRQ	St. George’s Respiratory Questionnaire
SMD	standardized mean difference
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 tiotropium/olodaterol. 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 13 August 2015.

Research question

The aim of the present report was to assess the added benefit of tiotropium/olodaterol as a maintenance bronchodilator treatment to relieve symptoms in adult patients 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 tiotropium/olodaterol

Research question	Therapeutic indication	Appropriate comparator therapy[a]
1	Adult patients with COPD from moderate severity (50% ≤ FEV1 < 80% predicted)[b]	LABA (formoterol or salmeterol) and/or LAMA (**tiotropium**)
2	Adult patients with COPD of higher severity (30% ≤ FEV1 < 50% predicted or FEV1 < 30% predicted or respiratory failure) with ≥ 2 exacerbations per year[c]	LABA (formoterol or salmeterol) and/or LAMA (**tiotropium**) and additional **ICS**

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 "patients with COPD grade II and patients with COPD grades ≥ III with < 2 exacerbations per year" is used in the report.
c: For better understandability, the term "patients with COPD grades ≥ III with ≥ 2 exacerbations per year" is used in the report.
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

From the options named by the G-BA, the company chose tiotropium for research question 1, and tiotropium and additional inhaled corticosteroids (ICS) for research question 2 as ACT. The assessment was conducted with the ACTs chosen by the company for the populations described in Table 2.

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

Results

Study pool and patient population

Two double-blind, multi-centre, randomized controlled approval studies (TONADO 1 and TONADO 2) were included for the direct comparison of tiotropium/olodaterol with the ACT. These were 5-arm studies with a randomization ratio of 1:1:1:1:1. The study duration of both studies was 52 weeks. Patients aged 40 years and older with moderate to very severe COPD, i.e. with spirometric Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades II to IV, were enrolled. Patients also had to have a smoking history of more than 10 pack years at enrolment. Both studies investigated the comparison of morning inhalation of the fixed combination of tiotropium and olodaterol in comparison with the individual components tiotropium or olodaterol. The study arms relevant for this assessment investigated a fixed combination of 5 µg tiotropium and 5 µg olodaterol compared with 5 µg tiotropium.

ICS treatment could be continued in both studies irrespective of the patient's disease severity and frequency of exacerbations. Consequently, the treatment did not comply with the conditions determined by the ACT. Analogous to the company's approach, subpopulations for both research questions were therefore used as the basis of the assessment.

Risk of bias

The risk of bias at study level was rated as low for both studies and for both research questions. The risk of bias at outcome level was also rated as low for most outcomes. The outcomes "health status" (patient global rating [PGR]) and health-related quality of life (St. George's Respiratory Questionnaire [SGRQ] responder)" were exceptions. For these outcomes, the risk of bias was rated as high for both research questions (PGR) and for research question 2 (SGRQ responder).

Subgroups and other effect modifiers

Deviating from the regular approach, only subgroup analyses in which the p-value of the interaction test was below the threshold value of 0.05 were considered in the present assessment. Moreover, this was interpreted as indication and not as proof of different subgroup effects. This approach was chosen because the company did not present the results from individual studies for the respective subgroups and only presented the overall estimator of the results.

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

The subpopulation of the studies TONADO 1 and TONADO 2 relevant for research question 1 included patients with COPD grade II and patients with COPD grades ≥ III with

< 2 exacerbations in the year before the start of the study who did not receive concomitant ICS treatment.

The following analyses were available for answering research question 1.

COPD symptoms (TDI responder)

The meta-analysis of the included studies showed no statistically significant difference between the treatment groups for the outcome "COPD symptoms (Transition Dyspnoea Index [TDI] responder)" at week 52. Moreover, there was an indication of an effect modification by the characteristic "sex". Under consideration of the subgroup data, there was an indication of an added benefit for women. For men, in contrast, there was no hint of an added benefit; an added benefit is therefore not proven for these patients.

Health-related quality of life (SGRQ responder)

The meta-analysis of the included studies showed no statistically significant difference between the treatment groups for the outcome "health-related quality of life (SGRQ responder)" at week 52. Moreover, there was an indication of an effect modification by the characteristic "sex". Under consideration of the subgroup data, there was an indication of an added benefit for women. For men, in contrast, there was no hint of an added benefit; an added benefit is therefore not proven for these patients.

Adverse events (discontinuation due to adverse events)

The meta-analysis of the included studies showed a statistically significant advantage of tiotropium/olodaterol over tiotropium for the outcome "discontinuation due to adverse events (AEs)". This was of only marginal effect size. Hence there was no hint of an added benefit for the outcome "discontinuation due to AEs". An added benefit for the outcome "discontinuation due to AEs" is therefore not proven.

Further outcomes

For the further outcomes investigated, the meta-analysis of the included studies showed no statistically significant difference between the treatment groups (mortality), important unexplained heterogeneity without effects in the same direction (severe exacerbations, serious AEs [SAEs]), or no data were available (health status, European Quality of Life-5 Dimensions visual analogue scale [EQ-5D VAS]) for research question 1. There were also no significant differences between the treatment groups for the outcomes "exacerbations" and "health status (PGR)". Indications of effect modifications were shown, but no hint of an added benefit resulted from them.

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

The subpopulation of the studies TONADO 1 and TONADO 2 relevant for research question 2 included patients with COPD grades III and IV with at least 2 exacerbations in the year before the start of the study who received concomitant ICS treatment.

The following analyses were available for answering research question 2.

Severe exacerbations

The meta-analysis of the included studies showed a statistically significant difference between the treatment groups to the disadvantage of tiotropium/olodaterol + ICS for the outcome "proportion of patients with severe exacerbations". This resulted in proof of lesser benefit of tiotropium/olodaterol + ICS in comparison with tiotropium + ICS.

Further outcomes

For the further outcomes investigated, the meta-analysis of the included studies showed no statistically significant difference between the treatment groups (mortality, COPD symptoms [TDI responder], exacerbations, health status [PGR], health-related quality of life [SGRQ responder], and AEs [SAEs]), important unexplained heterogeneity without effects in the same direction (AEs [discontinuation due to AEs]), or no data were available (health status [EQ-5D VAS]) for research question 2.

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 combination tiotropium/olodaterol versus 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 available results, a positive effect in the outcome categories "health-related quality of life (SGRQ responder)" and "non-serious/non-severe symptoms/late complications (TDI responder)", each with the same probability (indication) and the same extent (minor), was shown for the group of women in the overall consideration at outcome level. Hence there was an indication of a minor added benefit of tiotropium/olodaterol compared with tiotropium for women.

For men, the data presented showed neither positive nor negative effects; an added benefit of tiotropium/olodaterol in comparison with tiotropium for men is not proven.

[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].

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

On the basis of the results presented, there is a negative effect in the outcome category "serious/severe symptoms/late complications (severe exacerbations)" in the overall consideration at outcome level. This resulted in proof of lesser benefit of tiotropium/olodaterol + ICS in comparison with tiotropium + ICS.

Extent and probability of added benefit – summary

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

Table 3: Tiotropium/olodaterol – extent and probability of added benefit

Research question	**Therapeutic indication**	**Appropriate comparator therapy**[a]	**Subgroup**	**Extent and probability of added benefit**
1	Adult patients with COPD from moderate severity (50% ≤ FEV1 < 80% predicted)[b]	LABA (formoterol or salmeterol) and/or LAMA (**tiotropium**)	Women	Indication of minor added benefit
			Men	Added benefit not proven
2	Adult patients with COPD of higher severity (30% ≤ FEV1 < 50% predicted or FEV1 < 30% predicted or respiratory failure) with ≥ 2 exacerbations per year[c]	LABA (formoterol or salmeterol) and/or LAMA (**tiotropium**) and additional **ICS**	–	Proof of lesser benefit

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 "patients with COPD grade II and patients with COPD grades ≥ III with < 2 exacerbations per year" is used in the report.
c: For better understandability, the term "patients with COPD grades ≥ III with ≥ 2 exacerbations per year" is used in the report.

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

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 the present report was to assess the added benefit of tiotropium/olodaterol as a maintenance bronchodilator treatment to relieve symptoms in adult patients 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 tiotropium/olodaterol

Research question	Therapeutic indication	Appropriate comparator therapy[a]
1	Adult patients with COPD from moderate severity (50% ≤ FEV1 < 80% predicted)[b]	LABA (formoterol or salmeterol) and/or LAMA (**tiotropium**)
2	Adult patients with COPD of higher severity (30% ≤ FEV1 < 50% predicted or FEV1 < 30% predicted or respiratory failure) with ≥ 2 exacerbations per year[c]	LABA (formoterol or salmeterol) and/or LAMA (**tiotropium**) and additional **ICS**

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 "patients with COPD grade II and patients with COPD grades ≥ III with < 2 exacerbations per year" is used in the report.
c: For better understandability, the term "patients with COPD grades ≥ III with ≥ 2 exacerbations per year" is used in the report.
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 easier presentation and better readability, the following terms according to the spirometric classification of COPD severity according to the GOLD recommendations [3] are used for the 2 research questions in the report:

- adult patients with COPD grade II and patients with COPD grades ≥ III with < 2 exacerbations per year (research question 1)
- adult patients with COPD grades ≥ III with ≥ 2 exacerbations per year (research question 2)

From the options named by the G-BA, the company chose tiotropium for research question 1, and tiotropium and additional ICS for research question 2 as ACT. The assessment was conducted with the ACTs chosen by the company for the populations described in Table 4.

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 concurs with the company's approach.

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 tiotropium/olodaterol (status: 8 June 2015)
- bibliographical literature search on tiotropium/olodaterol (last search on 8 June 2015)
- search in trial registries for studies on tiotropium/olodaterol (last search on 5 June 2015)

To check the completeness of the study pool:

- search in trial registries for studies on tiotropium/olodaterol (last search on 20 August 2015)

No additional relevant study was identified from the check.

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: tiotropium/olodaterol 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)
1237.5 (TONADO 1)	Yes	Yes	No
1237.6 (TONADO 2)	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 is identical for both research questions and corresponds to that of the company. Analogous to the company's approach, the analyses of subpopulations on both research questions were the basis of the assessment.

For better understandability, the studies 1237.5 (TONADO 1) and 1237.6 (TONADO 2) are referred to as "TONADO 1" and "TONADO 2" in the report.

Section 2.6 contains a reference list for the studies included.

2.3.2 Study characteristics

2.3.2.1 Characteristics of the studies and of the intervention

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

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
TONADO 1	RCT, double-blind, parallel	Patients (≥ 40 years) with COPD: ▪ FEV1/FVC < 70% und FEV1 < 80% predicted at first study visit ▪ spirometric grade II to IV according to GOLD ▪ current or former cigarette smokers with > 10 pack years	OLO 5 µg (N = 528)[b] TIO 2.5 µg (N = 525)[b] TIO 5 µg (N = 527) TIO 2.5 µg/OLO 5 µg (N = 522)[b] TIO 5 µg/OLO 5 µg (N = 522) Relevant subpopulation thereof: Research question 1[c] ▪ TIO 5 µg/OLO 5 µg (n = 229) ▪ TIO 5 µg (n = 264) Research question 2[d] ▪ TIO 5 µg/OLO 5 µg (n = 45) ▪ TIO 5 µg (n = 28)	▪ Screening: 2 weeks ▪ Treatment: 52 weeks ▪ Follow-up: 21 days after the last study medication	239 study centres in 25 countries: Argentina, Australia, Bulgaria, Canada, China, Czech Republic, Denmark, Estonia, Finland, France, Germany, Guatemala, Hungary, India, Italy, Japan, Korea, Mexico, Netherlands, New Zealand, Portugal, Russia, Slovenia, Turkey, USA 9/2011–9/2013	Primary: FEV1 AUC_{0-3h} response on day 169, trough FEV1 on day 170 Secondary: COPD symptoms, exacerbations, health-related quality of life, AEs
TONADO 2	RCT, double-blind, parallel	Patients (≥ 40 years) with COPD: ▪ FEV1/FVC < 70% und FEV1 < 80% predicted at first study visit ▪ spirometric grade II to IV according to GOLD ▪ current or former cigarette smokers with > 10 pack years	OLO 5 µg (N = 510)[b] TIO 2.5 µg (N = 507)[b] TIO 5 µg (N = 507) TIO 2.5 µg/OLO 5 µg (N = 508)[b] TIO 5 µg/OLO 5 µg (N = 507) Relevant subpopulation thereof: Research question 1[c] ▪ TIO 5 µg/OLO 5 µg (n = 243) ▪ TIO 5 µg (n = 252) Research question 2[d] ▪ TIO 5 µg/OLO 5 µg (n = 31) ▪ TIO 5 µg (n = 40)	▪ Screening: 2 weeks ▪ Treatment: 52 weeks ▪ Follow-up: 21 days after the last study medication	241 study centres in 24 countries: Austria, Belgium, Brazil, Canada, China, Columbia, Croatia, Germany, Hungary, India, Ireland, Japan, Norway, Romania, Russia, Serbia and Montenegro, Slovak Republic, South Africa, Spain, Sweden, Taiwan, Turkey, United Kingdom, USA 9/2011–11/2013	Primary: FEV1 AUC_{0-3h} response on day 169, trough FEV1 on day 170 Secondary: COPD symptoms, exacerbations, health-related quality of life, AEs

(continued)

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

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.
b: The arm is not relevant for the assessment and is not shown in the next tables.
c: Research question 1 comprises patients with COPD grade II and patients with higher grades with < 2 exacerbations in the previous year without concomitant ICS treatment.
d: Research question 2 comprises patients with COPD grade III or higher with ≥ 2 exacerbations in the previous year with concomitant ICS treatment.
AE: adverse event; AUC: area under the curve; ICS: inhaled corticosteroids; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity, GOLD: Global Initiative for Chronic Obstructive Lung Disease; N: number of randomized patients; n: relevant subpopulation; OLO: olodaterol; RCT: randomized controlled trial; TIO: tiotropium; vs.: versus

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

Study	Intervention	Comparison
TONADO 1	Tiotropium 5 µg/olodaterol 5 µg, once daily, in the morning, 2 puffs	Tiotropium 5 µg, once daily, in the morning, 2 puffs
	As-needed medication (rescue medication for acute exacerbations) ▪ salbutamol ▪ temporary dose increase or additional use of oral corticosteroids[a, b] ▪ temporary use of theophylline ▪ use of antibiotics **Concomitant medication allowed with restriction** ▫ ICS[b] ▫ oral or parenteral corticosteroids[a, b] ▫ (cardioselective) beta-blockers[b] ▫ mucolytics[b] (except bronchodilators) ▫ cromoglicic acid, nedocromil, antihistamines, leukotriene antagonists and methylxanthines[c] **Non-permitted concomitant medication:** ▪ Other COPD drugs had to be discontinued before the start of the study: ▫ anticholinergics and beta-2 sympathomimetics, both short-acting and long-acting (inhaled, intranasal, oral, patch) ▫ long- or short-acting combination therapy of anticholinergics and beta-2 sympathomimetics combined with ICS[d] ▫ PDE4 inhibitor (roflumilast) ▪ oxygen therapy (> 1 hour daily when incompatible with visits to the clinic)	
TONADO 2	Tiotropium 5 µg/olodaterol 5 µg, once daily, in the morning, 2 puffs	Tiotropium 5 µg, once daily, in the morning, 2 puffs
	As-needed medication (rescue medication for acute exacerbations) ▪ salbutamol ▪ temporary dose increase or additional use of oral corticosteroids[a, b] ▪ temporary use of theophylline ▪ use of antibiotics **Concomitant medication allowed with restriction** ▫ ICS[b] ▫ oral or parenteral corticosteroids[a, b] ▫ (cardioselective) beta-blockers[b] ▫ mucolytics[b] (except bronchodilators) ▫ cromoglicic acid, nedocromil, antihistamines, leukotriene antagonists and methylxanthines[c] **Non-permitted concomitant medication:** ▪ Other COPD drugs had to be discontinued before the start of the study: ▫ anticholinergics and beta-2 sympathomimetics, both short-acting and long-acting (inhaled, intranasal, oral, patch) ▫ long- or short-acting combination therapy of anticholinergics and beta-2 sympathomimetics combined with ICS[d] ▫ PDE4 inhibitor (roflumilast) ▪ oxygen therapy (> 1 hour daily when incompatible with visits to the clinic)	

a: Prednisone (or equivalent): ≤ 10 mg/day or ≤ 20 mg on any further day.
b: At a stable dose 6 weeks before the first visit.
c: Allowed if not prescribed for the therapeutic indication of asthma.
d: Change to ICS monotherapy in the wash-out phase.

ICS: inhaled corticosteroids; COPD: chronic obstructive pulmonary disease; PDE4 inhibitor: phosphodiesterase type 4 inhibitor; RCT: randomized controlled trial; vs.: versus

Both studies included (TONADO 1 and TONADO 2) were double-blind, multicentre, randomized controlled approval studies. The study duration of both studies was 52 weeks. Patients aged 40 years and older with moderate to very severe COPD, i.e. with spirometric GOLD grades II to IV, were enrolled. Patients also had to have a smoking history of more than 10 pack years at enrolment.

Both studies followed an identical protocol and were conducted in the same geographical regions, although partly in different countries, at the same time. They were 5-arm studies with a randomization ratio of 1:1:1:1:1. Both studies investigated the comparison of morning inhalation of the fixed combination of tiotropium and olodaterol in comparison with the individual components tiotropium or olodaterol. The study arms relevant for this assessment investigated a fixed combination of 5 µg tiotropium and 5 µg olodaterol compared with 5 µg tiotropium, i.e. each in the approved dosage. All other treatment arms are not relevant for this benefit assessment and were therefore not considered further.

In addition to the randomized study medication, the patients could treat their COPD with the short-acting beta-2 sympathomimetics salbutamol as rescue medication. In addition, the patients could continue any ongoing ICS treatment in the study. Treatment with oral and parenteral corticosteroids, cardioselective beta-blockers, mucolytics, cromoglicic acid, nedocromil, antihistamines, leukotriene antagonists and methylxanthines as concomitant treatment could be continued with restriction. Other COPD drugs, bronchodilators such as anticholinergics and beta-2 sympathomimetics as well as phosphodiesterase type 4 (PDE4) inhibitors had to be discontinued at the start of the study.

Hence ICS treatment could be continued in both studies irrespective of the patients' severity and frequency of exacerbations. Consequently, the treatment did not comply with the conditions determined by the ACT in a large proportion of the study participants. Analogous to the company's approach, subpopulations for both research questions were therefore used as the basis of the assessment (see Section 2.3.2.2).

2.3.2.2 Characteristics of the study population

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

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

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

Study Group	N	Age [years]	Sex [F/M]	Duration of COPD [years]	Smoking status [smoker/ ex-smoker][a]	Smoking [pack years]	Disease severity [COPD grade][b] n (%)			Study discontin-uations	Treatment discontin-uations[c]
		mean (SD)	%	mean (SD)	%	mean (SD)	II	III	IV	n (%)	n (%)
TONADO 1											
Tiotropium/ olodaterol	229	64 (9)	26/74	ND	42/59	46.3 (25.5)	144 (62.9)	64 (27.9)	21 (9.2)	ND	ND
Tiotropium	264	63 (9)	27/73	ND	43/57	45.7 (26.5)	156 (59.1)	74 (28.0)	34 (12.9)	ND	ND
TONADO 2											
Tiotropium/ olodaterol	243	63 (9)	31/69	ND	50/50	46.5 (24.7)	145 (59.7)	82 (33.7)	16 (6.6)	ND	ND
Tiotropium	252	64 (9)	29/71	ND	37/63	46.5 (25.8)	158 (62.7)	80 (31.7)	14 (5.6)	ND	ND

a: Deviation from 100% possible because of rounding.
b: The classification of spirometric COPD grades is based on 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% corresponds to GOLD IV.
c: The number of treatment discontinuations in the total population of the randomized patients was 56 (10.7%) for TIO/OLO and 72 (13.7%) patients for TIO in the TONADO 1 study; and 77 (15.2%) for TIO/OLO and 96 (18.9%) patients for TIO in the TONADO 2 study.

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 randomized patients in the subpopulation; n: number of patients with event; ND: no data; OLO: olodaterol; RCT: randomized controlled trial; SD: standard deviation; TIO: tiotropium; vs.: versus

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

Study Severity[a] Group	N	COPD exacerbations in the year prior to screening n (%) 0	 1	 ≥ 2
TONADO 1 + TONADO 2				
GOLD II				
Tiotropium/olodaterol	289	204 (70.6[b])	56 (19.4[b])	29 (10.0[b])
Tiotropium	314	222 (70.7[b])	55 (17.5[b])	37 (11.8[b])
TONADO 1 + TONADO 2				
GOLD III				
Tiotropium/olodaterol	146	96 (65.8[b])	50 (34.2[b])	0 (0)
Tiotropium	154	105 (68.2[b])	49 (31.8[b])	0 (0)
TONADO 1 + TONADO 2				
GOLD IV				
Tiotropium/olodaterol	37	26 (70.3[b])	11 (29.7[b])	0 (0)
Tiotropium	48	34 (70.8[b])	14 (29.2[b])	0 (0)

a: Spirometric COPD severity is classified based on the FEV1: 50% ≤ FEV1 < 80% predicted corresponds to GOLD II, 30% ≤ FEV1 < 50% predicted corresponds to GOLD III, and FEV1 < 30% predicted corresponds to GOLD IV.
b: Institute's calculation.
COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; GOLD: Global Initiative for Chronic Obstructive Lung Disease; N: number of randomized patients in the subpopulation; n: number of patients with event; RCT: randomized controlled trial; vs.: versus

The subpopulations of the 2 relevant studies presented by the company for research question 1 included patients with COPD grade II without concomitant ICS treatment and patients with grades III and IV with fewer than 2 exacerbations in the previous year also without concomitant ICS treatment. The subpopulation presented by the company also includes 66 patients with COPD grade II and with 2 or more exacerbations in the previous year. They belong to the therapeutic indication of research question 1 specified by the G-BA and are therefore relevant for this research question.

The average age of the patients in this subpopulation in both studies was about 63 to 64 years; and more than 2 thirds of the patients were men. Depending on the study arm, a total of between 37% and 50% of the patients were current smokers with about 46 pack years on average. Regarding the distribution of the severity grades, the group with grade II was the largest group (about 60% of the patients). The proportion of patients with grade III was between 28% and 34%, depending on the study arm. Only a small proportion of the patients were very severely ill patients with grade IV. This proportion was between 6% and 13%, depending on the study arm. In total, the proportion of very severely ill patients with grade IV was somewhat larger in the TONADO 1 study than in the TONADO 2 study.

No differences relevant for the assessment were shown between the study arms for any of the patient characteristics for the subpopulation of research question 1.

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

Table 10 shows the patient characteristics in the relevant subpopulation of the studies included for research question 2.

Table 10: Characteristics of the study populations – RCT, direct comparison: tiotropium/olodaterol + ICS vs. tiotropium + ICS (research question 2)

Study Group	N	Age [years]	Sex [F/M]	Duration of COPD [years]	Smoking status [current smoker/ ex-smoker][a]	Smoking [pack years]	Disease severity [COPD grade][b] n (%)		Study discontin-uations	Treatment discontin-uations[c]
		mean (SD)	%	mean (SD)	%	mean (SD)	III	IV	n (%)	n (%)
TONADO 1										
Tiotropium/ olodaterol + ICS	45	64 (8)	33/67	ND	22/78	45.7 (22.4)	37 (82.2)	8 (17.8)	ND	ND
Tiotropium + ICS	28	66 (8)	32/68	ND	25/75	57.5 (43.6)	20 (71.4)	8 (28.6)	ND	ND
TONADO 2										
Tiotropium/ olodaterol + ICS	31	62 (8)	29/71	ND	29/71	40.6 (22.0)	23 (74.2)	8 (25.8)	ND	ND
Tiotropium + ICS	40	64 (9)	20/80	ND	33/68	45.3 (25.9)	21 (52.5)	19 (47.5)	ND	ND

a: Deviation from 100% possible because of rounding.
b: The classification of spirometric COPD grades is based on 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% corresponds to GOLD IV.
c: The number of treatment discontinuations in the total population of the randomized patients was 56 (10.7%) for TIO/OLO and 72 (13.7%) patients for TIO in the TONADO 1 study; and 77 (15.2%) for TIO/OLO and 96 (18.9%) patients for TIO in the TONADO 2 study.
COPD: chronic obstructive pulmonary disease; F: female; FEV1: forced expiratory volume in 1 second; GOLD: Global Initiative for Chronic Obstructive Lung Disease; ICS: inhaled corticosteroids; M: male; ND: no data; N: number of randomized patients in the subpopulation; n: number of patients with event; OLO: olodaterol; RCT: randomized controlled trial; SD: standard deviation; TIO: tiotropium; vs.: versus

The relevant subpopulation of the 2 studies included for research question 2 included only patients with COPD grade III and IV with 2 or more exacerbations in the year before the start of the study. All patients received concomitant ICS treatment.

According to the research question, this subpopulation included patients with grades III and IV; the proportion of patients with grade III was between 53% and 82%, depending on the study arm.

Overall, no differences relevant for the assessment were shown between the study arms for any of the patient characteristics for the subpopulation of research question 2.

2.3.2.2.3 Risk of bias at study level

Table 11 shows the risk of bias at study level under consideration of the subpopulation relevant for research question 1 and 2 respectively.

Table 11: Risk of bias at study level – RCT, direct comparison: tiotropium/olodaterol (+ ICS) vs. tiotropium (+ ICS)

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			
Research question 1: tiotropium/olodaterol vs. tiotropium[a]							
TONADO 1	Yes	Yes	Yes	Yes	Yes	Yes	Low
TONADO 2	Yes	Yes	Yes	Yes	Yes	Yes	Low
Research question 2: tiotropium/olodaterol + ICS vs. tiotropium + ICS[b]							
TONADO 1	Yes	Yes	Yes	Yes	Yes	Yes	Low
TONADO 2	Yes	Yes	Yes	Yes	Yes	Yes	Low

a: Research question 1 comprises patients with COPD grade II and patients with higher grades with < 2 exacerbations per year.
b: Research question 2 comprises patients with COPD grade III or higher with ≥ 2 exacerbations per year.
ICS: inhaled corticosteroids; RCT: randomized controlled trial; vs.: versus

For research questions 1 and 2, the risk of bias at study level was rated as low for both studies. This concurs with the company's assessment, which did not differentiate between the subpopulations of both research questions in the risk of bias at study level, however.

2.4 Results on added benefit

2.4.1 Outcomes included

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

- Mortality
  - all-cause mortality
- Morbidity
  - COPD symptoms (TDI)
  - exacerbations
  - severe exacerbations
  - health status (PGR)
  - health status (EQ-5D VAS)
- Health-related quality of life
  - health-related quality of life (SGRQ)
- Adverse events
  - SAEs
  - discontinuation due to AEs

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

Table 12 shows for which outcomes data were available in the included studies.

Table 12: Matrix of outcomes – RCT, direct comparison: tiotropium/olodaterol (+ ICS) vs. tiotropium (+ ICS)

Study	Outcomes								
	All-cause mortality	COPD symptoms (TDI)	Exacerbations	Severe exacerbations	Health status (PGR)	Health status (EQ-5D VAS)	Health-related quality of life (SGRQ)	SAEs	Discontinuation due to AEs
Research question 1: tiotropium/olodaterol vs. tiotropium[a]									
TONADO 1	Yes	Yes	Yes	Yes	Yes	No[b]	Yes	Yes	Yes
TONADO 2	Yes	Yes	Yes	Yes	Yes	No[b]	Yes	Yes	Yes
Research question 2: tiotropium/olodaterol + ICS vs. tiotropium + ICS[c]									
TONADO 1	Yes	Yes	Yes	Yes	Yes	No[b]	Yes	Yes	Yes
TONADO 2	Yes	Yes	Yes	Yes	Yes	No[b]	Yes	Yes	Yes

a: Research question 1 comprises patients with COPD grade II and patients with higher grades with < 2 exacerbations per year.
b: The outcome was recorded in the study, but no data are available.
c: Research question 2 comprises patients with COPD grade III or higher with ≥ 2 exacerbations per year with concomitant ICS treatment.

AE: adverse event; COPD: chronic obstructive pulmonary disease; EQ-5D: European Quality of Life-5 Dimensions; PGR: patient global rating; RCT: randomized controlled trial; SAE: serious adverse event; SGRQ: St. George's Respiratory Questionnaire; TDI: Transition Dyspnoea Index; VAS: visual analogue scale; vs.: versus

2.4.2 Risk of bias

Table 13 shows the risk of bias for the relevant outcomes.

Table 13: Risk of bias at study and outcome level – RCT, direct comparison: tiotropium/olodaterol (+ ICS) vs. tiotropium (+ ICS)

Study	Study level	Outcomes								
		All-cause mortality	COPD symptoms (TDI)	Exacerbations	Severe exacerbations	Health status (PGR)	Health status (EQ-5D VAS)	Health-related quality of life (SGRQ)	SAEs	Discontinuation due to AEs
Research question 1: tiotropium/olodaterol vs. tiotropium[a]										
TONADO 1	L	L	L	L	L	H[b]	-[c]	L	L	L
TONADO 2	L	L	L	L	L	H[b]	-[c]	L	L	L
Research question 2: tiotropium/olodaterol + ICS vs. tiotropium + ICS[d]										
TONADO 1	L	L	L	L	L	H[b, e]	-[c]	H[e]	L	L
TONADO 2	L	L	L	L	L	H[b]	-[c]	H[e]	L	L

a: Research question 1 comprises patients with COPD grade II and patients with higher grades with < 2 exacerbations per year without concomitant ICS treatment.
b: Selective reporting.
c: The outcome was recorded in the study, but no data are available.
d: Research question 2 comprises patients with COPD grade III or higher with ≥ 2 exacerbations per year with concomitant ICS treatment.
e: Difference between the groups for the proportion of patients not considered in the analysis > 5 percentage points.
AE: adverse event; COPD: chronic obstructive pulmonary disease; EQ-5D: European Quality of Life-5 Dimensions; H: high; ICS: inhaled corticosteroids; L: low; PGR: patient global rating; RCT: randomized controlled trial; SAE: serious adverse event; SGRQ: St. George's Respiratory Questionnaire; TDI: Transition Dyspnoea Index; VAS: visual analogue scale; vs.: versus

The risk of bias for the outcome "health status (PGR)" was rated as high for both research questions, and the risk of bias for health-related quality of life (SGRQ) was rated as high for research question 2 (see Section 2.7.2.4.2 of the full dossier assessment). From the 2 outcomes on health status (EQ-5D VAS, PGR), only data for the outcome "health status (PGR)" were available for both research questions; selective reporting of these outcomes can therefore not be excluded. In research question 2, the aspect "adequate implementation of the intention to treat (ITT) principle" was not implemented for the outcomes "health status (PGR)" and "health-related quality of life (SGRQ)". For both outcomes, the proportions of patients who were not considered were relevantly different between the treatment groups.

The assessment of the risk of bias at outcome level partly deviates from the company's assessment, which rated the risk of bias as low for all outcomes.

2.4.3 Results

Methods for information synthesis

Since the present research questions deal with the maintenance treatment of a chronic disease, analyses over a longer period of time are more suitable to draw conclusions on long-term effects (see Section 2.7.2.1 of the full dossier assessment). Analyses at week 52 were therefore used for all outcomes in the present assessment. This deviates from the company's approach, which presented analyses at the time points week 24 or week 52 or at both time points, depending on the outcome. For the outcomes "TDI responder" and "SGRQ responder", for example, it used only results at week 24.

Meta-analyses

In the statistical analyses conducted by the company, the study was included in the models as factor, which corresponds to a meta-analysis with fixed effects based on individual patient data. This approach was not accepted. According to the methods of IQWiG, the use of fixed effects is only envisaged in justified cases when there is evidence of sufficiently homogeneous effects [1]. The company provided no information that justified the use of a meta-analysis with fixed effects. Moreover, it did not present a formal description of the handling of possible heterogeneity (see Section 2.4.2). In the present benefit assessment, the results for all outcomes were therefore recalculated in a meta-analysis with random effects with data at week 52. A continuity correction was required for the relative risk and the corresponding confidence interval (CI) in cases where no events occurred in the treatment arm. The continuity correction was 0.5. The assessment of the added benefit was based on the data from this new calculation. The forest plots of meta-analyses calculated by the Institute can be found in Appendix B of the full dossier assessment.

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

Table 14 and Table 15 summarize the results on the comparison of tiotropium/olodaterol compared with tiotropium in patients with COPD grade II and patients with COPD grades III and IV with fewer than 2 exacerbations per year. All overall effects of the company were replaced by the Institute's calculations. The analysis at week 52 was used for research question 1.

Table 14: Results (dichotomous outcomes) – RCT, direct comparison: tiotropium/olodaterol vs. tiotropium (research question 1)

Outcome category Outcome Study	Tiotropium/ olodaterol		Tiotropium		Tiotropium/olodaterol vs. tiotropium
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Mortality					
All-cause mortality					
TONADO 1	229	4 (1.7)	264	3 (1.1)	1.54 [0.35; 6.80]; 0.571
TONADO 2	243	3 (1.2)	252	4 (1.6)	0.78 [0.18; 3.44]; 0.740
Total					1.09 [0.38; 3.13]; 0.868[a]
Morbidity					
COPD symptoms (TDI responder)[b]					
TONADO 1	223	122 (54.7[c])	248	131 (52.8[c])	1.04 [0.88; 1.23][d]; ND
TONADO 2	233	129 (55.4[c])	236	111 (47.0[c])	1.18 [0.99; 1.41][d]; ND
Total					1.10 [0.98; 1.25]; 0.116[a]
Exacerbations[e]					
TONADO 1	229	45 (19.7)	264	60 (22.7)	0.86 [0.61; 1.22][a]; ND
TONADO 2	243	46 (18.9)	252	52 (20.6)	0.92 [0.64; 1.31][a]; ND
Total					0.89 [0.69; 1.14]; 0.354[a]
Severe exacerbations					
TONADO 1	229	6 (2.6)	264	11 (4.2)	0.63 [0.24; 1.67][a]; ND
TONADO 2	243	11 (4.5)	252	5 (2.0)	2.28 [0.80; 6.47][a]; ND
Total					Heterogeneity: Q = 3.12; df = 1; p = 0.077; I^2 = 68%[a]
Health-related quality of life					
SGRQ responder[f]					
TONADO 1	221	119 (53.8[c])	247	123 (49.8[c])	1.08 [0.91; 1.29][d]; ND
TONADO 2	228	120 (52.6[c])	233	116 (49.8[c])	1.06 [0.89; 1.26][d]; ND
Total					1.07 [0.95; 1.21]; 0.282[a]
Adverse events					
AEs					
TONADO 1	229	163 (71.2)	264	179 (67.8)	
TONADO 2	243	168 (69.1)	252	185 (73.4)	
SAEs					
TONADO 1	229	21 (9.2)	264	39 (14.8)	0.62 [0.38; 1.02]; ND
TONADO 2	243	36 (14.8)	252	39 (15.5)	0.96 [0.63; 1.45]; ND
Total					Heterogeneity: Q = 1.70; df = 1; p = 0.192; I^2 = 41.3%[a]
Discontinuation due to AEs					
TONADO 1	229	8 (3.5)	264	18 (6.8)	0.51 [0.23; 1.16]; ND
TONADO 2	243	16 (6.6)	252	27 (10.7)	0.61 [0.34; 1.11]; ND
Total					0.58 [0.36; 0.93]; 0.024[a]

(continued)

Table 14: Results (dichotomous outcomes) – RCT, direct comparison: tiotropium/olodaterol vs. tiotropium (research question 1) (continued)

a: Institute's calculation; meta-analysis with random effects according to DerSimonian and Laird.
b: Patients with TDI total score ≥ 1 point.
c: Institute's calculation.
d: Calculated from GLM.
e: Includes moderate and severe exacerbations.
f: Patients with a reduction in the SGRQ total score of ≥ 4 points.
AE: adverse event; CI: confidence interval; COPD: chronic obstructive pulmonary disease; GLM: generalized linear model; 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; TDI: Transition Dyspnoea Index; vs.: versus

Table 15: Results (continuous outcomes) – RCT, direct comparison: tiotropium/olodaterol vs. tiotropium (research question 1)

Outcome category **Outcome** **Study**	**Tiotropium/olodaterol**		**Tiotropium**		**Tiotropium/ olodaterol vs. tiotropium**
	N[a]	**Value at end of study mean[b] (SE)**	**N[a]**	**Value at end of study mean[b] (SE)**	**MD [95% CI][b]; p-value**
Morbidity					
Health status (PGR)[c]					
TONADO 1	226	2.98 (0.07)	257	3.05 (0.07)	-0.08 [-0.26; 0.11]; ND
TONADO 2	237	2.89 (0.07)	242	3.20 (0.07)	-0.30 [-0.49; -0.11]; ND
Total			Heterogeneity: Q = 2.64; df = 1; p = 0.104; I^2 = 62.2%[d]		
Health status (EQ-5D VAS)					
TONADO 1	No data available				
TONADO 2					

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: MMRM analysis of the FAS population.
c: PGR indicates the health status on a scale from 1 (much better) to 4 (no change) to 7 (much worse).
d: Institute's calculation; meta-analysis with random effects according to DerSimonian and Laird.
CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; FAS: full analysis set; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; ND: no data; PGR: patient global rating; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale; vs.: versus

Mortality

The meta-analysis of the included studies showed no statistically significant difference between the treatment groups for the outcome "all-cause mortality". This resulted in no hint of an added benefit of tiotropium/olodaterol in comparison with tiotropium; an added benefit for all-cause mortality is therefore not proven.

This concurs with the company's assessment.

Morbidity

COPD symptoms (TDI responder)

The meta-analysis of the included studies showed no statistically significant difference between the treatment groups for the outcome "COPD symptoms (TDI responder)" at week 52. Moreover, there was an indication of an effect modification by the characteristic "sex". Consequently, it was necessary to consider the results separately for men and women. The subgroup analyses, the corresponding interpretation of results and overview of the evidence can be found in Section 2.4.4.1. Under consideration of the subgroup data, there was an indication of an added benefit for women. For men, in contrast, there was no hint of an added benefit; an added benefit is therefore not proven for these patients.

This assessment deviates from that of the company, which derived no added benefit on the basis of the responder analysis at week 24.

Exacerbations

The meta-analysis of the included studies showed no statistically significant difference between the treatment groups for the outcome "proportion of patients with exacerbations (moderate and severe)". The assessment of the subgroup characteristics resulted in an indication of an effect modification regarding the characteristic "COPD grade" (see Section 2.4.4.1). However, this resulted in no hint of an added benefit of tiotropium/olodaterol in comparison with tiotropium for the subgroups; an added benefit for exacerbations is therefore not proven.

This assessment deviates from that of the company. Based on the analysis of the annual rate of moderate and severe exacerbations at week 24, the company identified proof of an effect modification by the characteristic "severity grade" and derived an indication of an added benefit for patients with grade II from this.

The results on the outcome "annual rate of moderate and severe exacerbations" presented as additional information can be found in Appendix A of the full dossier assessment.

Severe exacerbations

The meta-analysis of the included studies showed important unexplained heterogeneity without effects in the same direction for the outcome "proportion of patients with severe exacerbations". This resulted in no hint of an added benefit of tiotropium/olodaterol in comparison with tiotropium; an added benefit is therefore not proven.

This concurs with the assessment of the company, which arrived at a similar result on the basis of the analysis of annual rates of severe exacerbations.

The results on the outcome "annual rate of severe exacerbations" presented as additional information can be found in Appendix A of the full dossier assessment.

Health status (PGR)

The meta-analysis of the included studies showed important unexplained heterogeneity without effects in the same direction for the outcome "health status (PGR)". Moreover, there was an indication of an effect modification by the characteristic "sex". The subgroup analyses, the corresponding interpretation of results and overview of the evidence can be found in Section 2.4.4.1. Under consideration of the subgroup data, there was no hint of an added benefit for women or for men. An added benefit is therefore not proven for the outcome "health status (PGR)".

This concurs with the company's assessment.

Health status (EQ-5D VAS)

Although the outcome "health status (EQ-5D VAS)" was recorded according to the study protocol, no analyses were available. This resulted in no hint of an added benefit of tiotropium/olodaterol in comparison with tiotropium; an added benefit for health status (EQ-5D VAS) is therefore not proven.

Health-related quality of life

SGRQ responder

The meta-analysis of the included studies showed no statistically significant difference between the treatment groups for the outcome "SGRQ responder" at week 52. Moreover, there was an indication of an effect modification by the characteristic "sex". Consequently, it was necessary to consider the results separately for men and women. The subgroup analyses, the corresponding interpretation of results and overview of the evidence can be found in Section 2.4.4.1. Under consideration of the subgroup data, there was an indication of an added benefit for women. For men, in contrast, there was no hint of an added benefit; an added benefit is therefore not proven for these patients.

This assessment deviates from that of the company. Based on the analyses at week 24, the company derived an indication of an added benefit of tiotropium/olodaterol versus tiotropium for the total population.

Adverse events

Serious adverse events and discontinuation due to adverse events

The meta-analysis of the included studies showed important unexplained heterogeneity without effects in the same direction for the outcome "SAEs". The meta-analysis of the included studies showed a statistically significant advantage of tiotropium/olodaterol over tiotropium for the outcome "discontinuation due to AEs". This was of only marginal effect size (see Section 2.5.1). In each case this resulted in no hint of an added benefit of

tiotropium/olodaterol compared with tiotropium. An added benefit for the outcomes “SAEs” and “discontinuation due to AEs” is therefore not proven.

This deviates from the company’s assessment for the outcome “discontinuation due to AEs”. The company claimed an indication of an added benefit of tiotropium/olodaterol compared with tiotropium here.

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

Table 16 and Table 17 summarize the results on the comparison of tiotropium/olodaterol compared with tiotropium in patients with COPD grades III and IV with 2 or more exacerbations per year. The analyses at the time point 52 weeks were used for research question 1.

Table 16: Results (dichotomous outcomes) – RCT, direct comparison: tiotropium/olodaterol + ICS vs. tiotropium + ICS (research question 2)

Outcome category Outcome Study	Tiotropium/ olodaterol + ICS		Tiotropium + ICS		Tiotropium/olodaterol + ICS vs. tiotropium + ICS
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Mortality					
All-cause mortality					
TONADO 1	45	1 (2.2)	28	2 (7.1)	0.31 [0.03; 3.27]; 0.331
TONADO 2	31	1 (3.2)	40	0 (0)	3.84 [0.16; 91.24]; ND
Total					0.87 [0.08; 9.87]; 0.909[a]
Morbidity					
COPD symptoms (TDI responder)[b]					
TONADO 1	44	25 (56.8[c])	26	10 (38.5[c])	1.48 [0.85; 2.56][d]; ND
TONADO 2	28	17 (60.7[c])	38	21 (55.3[c])	1.10 [0.73; 1.66][d]; ND
Total					1.22 [0.88; 1.70]; 0.231[a]
Exacerbations[e]					
TONADO 1	45	23 (51.1)	28	12 (42.9)	1.19 [0.71; 1.99][a]; ND
TONADO 2	31	18 (58.1)	40	22 (55.0)	1.06 [0.70; 1.59][a]; ND
Total					1.11 [0.80; 1.53]; 0.535[a]
Severe exacerbations					
TONADO 1	45	8 (17.8)	28	0 (0)	10.72 [0.64; 178.74][a]; ND
TONADO 2	31	6 (19.4)	40	3 (7.5)	2.58 [0.70; 9.51][a]; ND
Total					3.32 [1.02; 10.84]; 0.047[a]
Health-related quality of life					
SGRQ responder[f]					
TONADO 1	43	20 (46.5[c])	24	11 (45.8[c])	1.02 [0.59; 1.74][d]; ND
TONADO 2	30	11 (36.7[c])	36	18 (50.0[c])	0.73 [0.41; 1.3][d]; ND
Total					0.87 [0.59; 1.29]; 0.497[a]
Adverse events					
AEs					
TONADO 1	45	35 (77.8)	28	24 (85.7)	–
TONADO 2	31	30 (96.8)	40	35 (87.5)	–
SAEs					
TONADO 1	45	12 (26.7)	28	9 (32.1)	0.83 [0.40; 1.71]; ND
TONADO 2	31	9 (29.0)	40	7 (17.5)	1.66 [0.70; 3.96]; ND
Total					1.12 [0.57; 2.21]; 0.735[a]
Discontinuation due to AEs					
TONADO 1	45	7 (15.6)	28	5 (17.9)	0.87 [0.31; 2.48]; ND
TONADO 2	31	5 (16.1)	40	2 (5.0)	3.23 [0.67; 15.53]; ND
Total					Heterogeneity: Q = 1.87; df = 1; p = 0.172; I^2 = 46.5%[a]

(continued)

Table 16: Results (dichotomous outcomes) – RCT, direct comparison: tiotropium/olodaterol + ICS vs. tiotropium + ICS (research question 2) (continued)

a: Institute's calculation; meta-analysis with random effects according to DerSimonian and Laird.
b: Patients with TDI total score ≥ 1 point.
c: Institute's calculation.
d: Calculated from GLM.
e: Includes moderate and severe exacerbations.
f: Patients with a reduction in the SGRQ total score of ≥ 4 points.

AE: adverse event; CI: confidence interval; COPD: chronic obstructive pulmonary disease; GLM: generalized linear model; ICS: inhaled corticosteroids; 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; TDI: Transition Dyspnoea Index; vs.: versus

Table 17: Results (continuous outcomes) – RCT, direct comparison: tiotropium/olodaterol + ICS vs. tiotropium + ICS (research question 2)

Outcome category **Outcome** **Study**	**Tiotropium/olodaterol + ICS**		**Tiotropium + ICS**		**Tiotropium/ olodaterol + ICS vs. tiotropium + ICS**
	N[a]	**Value at end of study mean[b] (SE)**	**N[a]**	**Value at end of study mean[b] (SE)**	**MD [95% CI][b]; p-value**
Morbidity					
Health status (PGR)[c]					
TONADO 1	45	3.35 (0.18)	26	3.42 (0.24)	-0.07 [-0.65; 0.52]; ND
TONADO 2	30	3.05 (0.26)	40	3.18 (0.20)	-0.13 [-0.72; 0.46]; ND
Total					-0.10 [-0.52; 0.32]; 0.638[d]
Health status (EQ-5D VAS)					
TONADO 1	No data available				
TONADO 2					

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: MMRM analysis of the FAS population.
c: PGR indicates the health status on a scale from 1 (much better) to 4 (no change) to 7 (much worse).
d: Institute's calculation; meta-analysis with random effects according to DerSimonian and Laird.

CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; FAS: full analysis set; ICS: inhaled corticosteroids; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; ND: no data; PGR: patient global rating; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale; vs.: versus

The company presented results and subgroup analyses on research question 2, but derived no added benefit for this subpopulation. Hence the deviation from the company's assessment is not described in the following reporting of results. The company justified its approach with the insufficient possibility to allocate the patients to research question 2 (see Section 2.7.2.1 of the full dossier assessment).

Mortality

The meta-analysis of the included studies showed no statistically significant difference between the treatment groups for the outcome "all-cause mortality". This resulted in no hint of an added benefit of tiotropium/olodaterol + ICS in comparison with tiotropium + ICS; an added benefit for all-cause mortality is therefore not proven.

Morbidity

COPD symptoms (TDI responder)

The meta-analysis of the included studies showed no statistically significant difference between the treatment groups for the outcome "COPD symptoms (TDI responder)" at week 52. This resulted in no hint of an added benefit of tiotropium/olodaterol + ICS in comparison with tiotropium + ICS; an added benefit for the outcome "COPD symptoms (TDI responder)" is therefore not proven.

Exacerbations

The meta-analysis of the included studies showed no statistically significant difference between the treatment groups for the outcome "proportion of patients with exacerbations (moderate and severe)". This resulted in no hint of an added benefit of tiotropium/olodaterol + ICS in comparison with tiotropium + ICS; an added benefit for the outcome "exacerbations" is therefore not proven.

The results on the outcome "annual rate of moderate and severe exacerbations" presented as additional information can be found in Appendix A of the full dossier assessment.

Severe exacerbations

The meta-analysis of the included studies showed a statistically significant difference between the treatment groups to the disadvantage of tiotropium/olodaterol + ICS for the outcome "proportion of patients with severe exacerbations". This resulted in proof of lesser benefit of tiotropium/olodaterol + ICS in comparison with tiotropium + ICS.

The results on the outcome "annual rate of severe exacerbations" presented as additional information can be found in Appendix A of the full dossier assessment.

Health status (PGR)

The meta-analysis of the included studies showed no relevant difference between the treatment groups for the outcome "health status (PGR)". This resulted in no hint of an added benefit of tiotropium/olodaterol + ICS in comparison with tiotropium + ICS; an added benefit for health status (PGR) is therefore not proven.

Health status (EQ-5D VAS)

Although the outcome "health status (EQ-5D VAS)" was recorded according to the study protocol, no analyses were available. This resulted in no hint of an added benefit of

tiotropium/olodaterol in comparison with tiotropium; an added benefit for health status (EQ-5D VAS) is therefore not proven.

Health-related quality of life

SGRQ responder

The meta-analysis of the included studies showed no statistically significant difference between the treatment groups for the outcome "health-related quality of life (SGRQ responder)" at week 52. This resulted in no hint of an added benefit of tiotropium/olodaterol + ICS in comparison with tiotropium + ICS; an added benefit for the outcome "health-related quality of life (SGRQ responder)" is therefore not proven.

Adverse events

Serious adverse events and discontinuation due to adverse events

The meta-analysis of the included studies showed no statistically significant difference between the treatment groups for the outcome "SAEs". The meta-analysis of the included studies showed important unexplained heterogeneity without effects in the same direction for the outcome "discontinuation due to AEs". This resulted in no hint of an added benefit of tiotropium/olodaterol + ICS in comparison with tiotropium + ICS for the outcomes "SAEs" and "discontinuation due to AEs"; an added benefit is therefore not proven.

2.4.4 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 modifications.

Subgroup analyses for the following characteristics were considered:

- sex
- age group (< 65, ≥ 65 to < 75 and ≥ 75)
- COPD grade (GOLD II, GOLD III and GOLD IV)
- ethnicity (white and non-white)
- region (East Asia, Eastern Europe, Western Europe, Latin America, North America, India, Australia/New Zealand/South Africa)

Apart from COPD grade, these subgroup characteristics had been defined a priori for the outcome "lung function" in the study protocol.

As described in Section 2.7.2.2 of the full dossier assessment, the company's subgroup analysis was conducted on the basis of composite data of both studies using a meta-analysis with fixed effects. Since the company did not show the homogeneity of the 2 studies, this is no adequate approach, however. Deviating from the company's approach, the interaction p-values and overall effects were recalculated in a meta-analysis with random effects. The forest

plots of the calculated meta-analyses can be found in Appendix B of the full dossier assessment.

As described in Section 2.7.2.2 of the full dossier assessment, the company did not present the results from individual studies for the respective subgroups and only presented the overall estimator of the results. It can therefore not be assessed whether the results within the subgroups are homogeneous. To account for the resulting uncertainty of results, the regular approach was deviated from [1]. In the present assessment, the condition for an indication of differing subgroup effects is met when the interaction p-value is below the threshold value of 0.05. The result of the total population is also taken into account in the interpretation of the results and the determination of the certainty of conclusions.

In the present assessment, only the results on subgroups and outcomes with at least indications (in the present assessment $p < 0.05$) of an interaction between treatment effect and subgroup characteristic and with statistically significant results in at least one subgroup are presented.

The company identified proof of a statistically significant interaction when $p < 0.05$ and indications when the p-value ≥ 0.05 and < 0.2.

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

Table 18 to Table 21 present the relevant results on subgroups in patients with COPD grade II and patients with COPD grade III and IV with fewer than 2 exacerbations per year.

Table 18: Subgroups (COPD symptoms [TDI responder]) – RCT, direct comparison: tiotropium/olodaterol vs. tiotropium (research question 1)

Outcome Characteristic	Tiotropium/olodaterol		Tiotropium		Tiotropium/olodaterol vs. tiotropium	
Study Subgroup	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]	p-value
COPD symptoms (TDI responder)[a]						
Sex						
TONADO 1						
Men	ND	ND	ND	ND	ND	ND
Women	ND	ND	ND	ND	ND	ND
TONADO 2						
Men	ND	ND	ND	ND	ND	ND
Women	ND	ND	ND	ND	ND	ND
Total					Interaction:	0.004[b]
Men	323	169 (52.3)	353	188 (53.3)	0.98 [0.85; 1.13][b]	0.808[b]
Women	133	82 (61.7)	131	54 (41.2)	1.50 [1.17; 1.91][b]	0.001[b]

a: Patients with TDI total score ≥ 1 point.
b: Institute's calculation; meta-analysis with random effects according to DerSimonian and Laird.
CI: confidence interval; COPD: chronic obstructive pulmonary disease; N: number of analysed patients; n: number of patients with event; ND: no data; RCT: randomized controlled trial; RR: relative risk; TDI: Transition Dyspnoea Index; vs.: versus

Table 19: Subgroups (exacerbations [moderate and severe]) – RCT, direct comparison: tiotropium/olodaterol vs. tiotropium (research question 1)

Outcome Characteristic Study Subgroup	Tiotropium/olodaterol		Tiotropium		Tiotropium/olodaterol vs. tiotropium	
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]	p-value
Exacerbations[a]						
Severity						
TONADO 1						
GOLD II	ND	ND	ND	ND	ND	ND
GOLD III	ND	ND	ND	ND	ND	ND
GOLD IV	ND	ND	ND	ND	ND	ND
TONADO 2						
GOLD II	ND	ND	ND	ND	ND	ND
GOLD III	ND	ND	ND	ND	ND	ND
GOLD IV	ND	ND	ND	ND	ND	ND
Total					Interaction:	0.002[b]
GOLD II	289	42 (14.5)	314	70 (22.3)	0.65 [0.46; 0.92][b]	0.016[b]
GOLD III	146	44 (30.1)	154	29 (18.8)	1.60 [1.06; 2.41][b]	0.025[b]
GOLD IV	37	5 (13.5)	48	13 (27.1)	0.50 [0.20; 1.27][b]	0.146[b]

a: Includes moderate and severe exacerbations.
b: Institute's calculation; meta-analysis with random effects according to DerSimonian and Laird.
CI: confidence interval; GOLD: Global Initiative for Chronic Obstructive Lung Disease; N: number of analysed patients; n: number of patients with (at least one) event; ND: no data; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Table 20: Subgroups (health status [PGR]) – RCT, direct comparison: tiotropium/olodaterol vs. tiotropium (research question 1)

Outcome Characteristic Study Subgroup	Tiotropium/olodaterol		Tiotropium		Tiotropium/olodaterol vs. tiotropium
	N[a]	Value at end of study mean[b] (SE)	N[a]	Value at end of study mean[b] (SE)	MD [95% CI]; p-value
Health status (PGR)[c]					
Sex					
TONADO 1					
Men	ND	ND	ND	ND	ND
Women	ND	ND	ND	ND	ND
TONADO 2					
Men	ND	ND	ND	ND	ND
Women	ND	ND	ND	ND	ND
Total				Interaction:	p = 0.001[b]
Men	329	3.01 (0.06)	364	3.05 (0.05)	-0.04 [-0.19; 0.11]; 0.601[b]
Women	134	2.76 (0.10)	135	3.32 (0.10)	−0.56 [−0.84; −0.28]; < 0.001[b] Hedges' g: −0.48 [−0.72; −0.24][d]

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: Institute's calculation; meta-analysis with random effects according to DerSimonian and Laird.
c: PGR indicates the health status on a scale from 1 (much better) to 4 (no change) to 7 (much worse).
d: Institute's calculation based on the changes at the end of the study (mean values and standard errors) of the MMRM.

CI: confidence interval; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; ND: no data; PGR: patient global rating; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; vs.: versus

Table 21: Subgroups (health-related quality of life [SGRQ responder]) – RCT, direct comparison: tiotropium/olodaterol vs. tiotropium (research question 1)

Outcome Characteristic Study Subgroup	Tiotropium/olodaterol		Tiotropium		Tiotropium/olodaterol vs. tiotropium	
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]	p-value
SGRQ responder[a]						
Sex						
TONADO 1						
Men	ND	ND	ND	ND	ND	ND
Women	ND	ND	ND	ND	ND	ND
TONADO 2						
Men	ND	ND	ND	ND	ND	ND
Women	ND	ND	ND	ND	ND	ND
Total					Interaction:	0.014[b]
Men	318	160 (50.3)	352	183 (52.0)	0.97 [0.83; 1.12][b]	0.665[b]
Women	131	79 (60.3)	128	56 (43.8)	1.38 [1.08; 1.75][b]	0.009[b]

a: Patients with a reduction in the SGRQ total score of ≥ 4 points.
b: Institute's calculation; meta-analysis with random effects according to DerSimonian and Laird.
CI: confidence interval; N: number of analysed patients; n: number of patients with event; ND: no data; RCT: randomized controlled trial; RR: relative risk; SGRQ: St. George's Respiratory Questionnaire; vs.: versus

Morbidity

COPD symptoms (TDI responder)

The subgroup analysis on the outcome "COPD symptoms (TDI responder)" showed an indication of an effect modification regarding the characteristic "sex". The result of the meta-analysis showed a statistically significant effect in favour of tiotropium/olodaterol for women. Overall there is an indication of added benefit for women. For men, in contrast, there was no hint of an added benefit; an added benefit is therefore not proven for these patients.

This assessment deviates from that of the company, which derived no indication of effect modification on the basis of the analysis of the TDI responders at week 24.

Exacerbations

There was an indication of an effect modification regarding the characteristic "severity" for the outcome "exacerbations (moderate and severe)" in the subgroup analysis. The subgroup analysis showed statistically significant effects for patients with COPD grade II and III. These were of different direction of effect. An advantage of tiotropium/olodaterol was shown for patients with severity grade II, and an advantage of tiotropium was shown for patients with severity grade III. In each case, the extent of the effect in this non-serious/non-severe outcome was no more than marginal. This resulted in no hint of an added benefit for patients with COPD grade II and in no hint of lesser benefit for patients with COPD grade III. An added

benefit or lesser benefit for the outcome "exacerbations (moderate and severe)" is therefore not proven.

This assessment deviates from that of the company. On the basis of the analysis of annual rates of moderate and severe exacerbations, the company identified in each case an indication of effect modification by the characteristic "age" and proof by the characteristic "severity". Overall, the company derived proof of an added benefit for the outcome "annual rate of moderate and severe exacerbations" only for patients with COPD grade II.

Health status (PGR)

The subgroup analysis on the outcome "health status (PGR)" showed an indication of an effect modification regarding the characteristic "sex". The result of the subgroup analysis showed a statistically significant difference in favour of tiotropium/olodaterol for women. In men, in contrast, no statistically significant effect was shown.

The standardized mean difference (SMD) in the form of Hedges' g was considered to additionally check the relevance of the results in women. The 95% CI of the SMD for women was completely below the irrelevance threshold of -0.2. There was an increased uncertainty for this outcome due to the high risk of bias and the heterogeneity between the studies TONADO 1 and TONADO 2 at the level of the total population (see Table 11 and Section 2.7.2.4.2 of the full dossier assessment). Although the 95% CI was below the irrelevance threshold, a marginal effect for this outcome of the category "non-serious/non-severe symptoms/late complications" cannot be excluded. Hence there was no hint of an added benefit also for women; an added benefit is not proven for women or men.

The company arrived at a similar result on the basis of its analyses. It also identified a statistically significant advantage of tiotropium/olodaterol in women, but derived no added benefit for women for the outcome "health status (PGR)" because of the medical-biological rationale that it considered to be missing.

Health-related quality of life

SGRQ responder

The subgroup analysis on the outcome "health-related quality of life (SGRQ responder)" resulted in an indication of interaction regarding the characteristic "sex". The result of the subgroup analysis in the meta-analysis showed a statistically significant effect for women. No statistically significant effect was identified for men. Overall this resulted in an indication of added benefit for women. For men, in contrast, there was no hint of an added benefit; an added benefit is therefore not proven for these patients.

This deviates from the company's assessment, which derived an indication of an added benefit for the outcome "health-related quality of life (SGRQ responder)" on the basis of the results of the total subpopulation at week 24.

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

There was no effect modification by the characteristics considered for any of the outcomes included.

Although the company presented the data in Module 4 A of the dossier, it derived no added benefit for the total subpopulation or for individual subgroups (see Section 2.7.2.4.1 of the full dossier assessment).

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit of tiotropium/olodaterol 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 Evaluation of added benefit at outcome level

The data presented in Section 2.4 for research question 1 resulted in the following assessments for tiotropium/olodaterol in comparison with the ACT (tiotropium):

- an indication of an added benefit regarding COPD symptoms (TDI responder) for women
- an indication of an added benefit regarding health-related quality of life (SGRQ responder) for women

Determination of the outcome category for the outcome "TDI responder"

An assessment of the outcome category of the TDI depends on the patients' initial situation, particularly on the severity of their symptoms or dyspnoea. For this purpose, the data of the responders would be required in addition to the average baseline values of the total subpopulation relevant for research question 1. Then it could have been investigated whether, in an extreme scenario, responders only included patients of a certain symptom severity grade. However, the company did not present a stratified analysis of TDI responders by baseline value. Hence only the baseline data of the entire subpopulation could be used for the assessment. The corresponding patients of both studies (TONADO 1 and TONADO 2) had a mean Baseline Dyspnoea Index (BDI) with a minimum value of 6.7 and a maximum value of 7.0, depending on the study arm. This value represents the shortage of breath of the patients at

the start of the study, the change of which is measured with the TDI. No other data were available that could have supported the assessment of the severity of symptoms at baseline.

In a previous assessment on the same therapeutic indication (A15-06), based on the BDI values and the subscale on breathlessness of the Exacerbation of Chronic Pulmonary Disease Tool Respiratory Symptoms (E-RS), a BDI of 5.7 to 6.9 was assessed as moderate limitation of the patients [4]. Since the mean baseline values in the present assessment were in a similar range, the results of the outcome "TDI" were allocated to the outcome category "non-serious/non-severe symptoms/late complications".

Determination of the outcome category for the outcome "discontinuation due to AEs"

The assessment of the outcome category of "discontinuations due to AEs" depends on the severity of the AEs that led to discontinuation. However, there was no information on the proportion of SAEs from the discontinuations for the relevant subpopulations. With respect to the total study population, the proportion of SAEs from the discontinuations due to AEs was 42.7% for the tiotropium/olodaterol arm, and 39.4% for the tiotropium arm. Hence the proportion of SAEs from the AEs leading to discontinuation was below 50%. The results of the outcome "discontinuation due to AEs" were allocated to the outcome category "non-serious/non-severe symptoms/late complications".

The extent of the respective added benefit at outcome level was estimated from these results (see Table 22). In the overall assessment, it was investigated whether different conclusions on the extent of added benefit arise for the individual patient groups.

Table 22: Extent of added benefit at outcome level: tiotropium/olodaterol vs. tiotropium (research question 1: adult patients with COPD grade II and adult patients with COPD grade III and IV with < 2 exacerbations per year)

Outcome category **Outcome** **Characteristic**	**Tiotropium/olodaterol vs. tiotropium** **Proportion of events[a] or mean** **Effect estimate [95% CI]** **p-value** **Probability[b]**	**Derivation of extent[c]**
Mortality		
All-cause mortality	TIO/OLO: 1.2% to 1.7% TIO: 1.1% to 1.6% RR: 1.09 [0.38; 3.13] p = 0.868	Lesser benefit/added benefit not proven
Morbidity		
COPD symptoms (TDI responder)	TIO/OLO: 54.7% to 55.4% TIO: 47.0% to 52.8% RR: 1.10 [0.98; 1.25] p = 0.116	
Men	TIO/OLO: 52.3% TIO: 53.3% RR: 0.98 [0.85; 1.13] p = 0.808	Lesser benefit/added benefit not proven
Women	TIO/OLO: 61.7% TIO: 41.2% RR: 1.50 [1.17; 1.91] RR: 0.67 [0.52; 0.85][d] p = 0.001 probability: "indication"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit, extent: "minor"
Exacerbations	TIO/OLO: 18.9% to 19.7% TIO: 20.6% to 22.7% RR: 0.89 [0.69; 1.14] p = 0.354	Lesser benefit/added benefit not proven
Severe exacerbations	Heterogeneous results without effects in the same direction[e]	Lesser benefit/added benefit not proven
Health status PGR[f]	Heterogeneous results without effects in the same direction[e]	
Men	TIO/OLO: 3.01 TIO: 3.05 MD: -0.04 [-0.19; 0.11] p = 0.601	Lesser benefit/added benefit not proven
Women	TIO/OLO: 2.76 TIO: 3.32 MD: -0.56 [-0.84; -0.28] SMD: -0.48 [-0.72; -0.24] p < 0.001	Lesser benefit/added benefit not proven[g]
Health status EQ-5D VAS	No data available	

(continued)

Table 22: Extent of added benefit at outcome level: tiotropium/olodaterol vs. tiotropium (research question 1: adult patients with COPD grade II and adult patients with COPD grade III and IV with < 2 exacerbations per year) (continued)

Outcome category **Outcome** **Characteristic**	**Tiotropium/olodaterol vs. tiotropium** **Proportion of events[a] or mean** **Effect estimate [95% CI]** **p-value** **Probability[b]**	**Derivation of extent[c]**
Health-related quality of life		
SGRQ responder	TIO/OLO: 52.6% to 53.8% TIO: 49.8% to 49.8% RR: 1.07 [0.95; 1.21] p = 0.282	
Men	TIO/OLO: 50.3% TIO: 52.0% RR: 0.97 [0.83; 1.12] p = 0.665	Lesser benefit/added benefit not proven
Women	TIO/OLO: 60.3% TIO: 43.8% RR: 1.38 [1.08; 1.75] RR: 0.72 [0.57; 0.93][d] p = 0.009 probability: "indication"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
Adverse events		
SAEs	Heterogeneous results without effects in the same direction[e]	Greater/lesser harm not proven
Discontinuation due to AEs	TIO/OLO: 3.5% to 6.6% TIO: 6.8% to 10.7% RR: 0.58 [0.36; 0.93] p = 0.024	Greater/lesser harm not proven

a: Minimum and maximum proportions of events in each treatment arm in the included studies.
b: Probability given if statistically significant differences are present.
c: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
d: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
e: No common effect estimate provided due to heterogeneous data.
f: PGR indicates the health status on a scale from 1 (much better) to 4 (no change) to 7 (much worse).
g: A marginal effect cannot be excluded; an added benefit is not derived.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; COPD: chronic obstructive pulmonary disease; EQ-5D: European Quality of Life-5 Dimensions; MD: mean difference; ND: no data; OLO: olodaterol; PGR: patient global rating; RR: relative risk; SAE: serious adverse event; SGRQ: St. George's Respiratory Questionnaire; SMD: standardized mean difference; TDI: Transition Dyspnoea Index; TIO: tiotropium; VAS: visual analogue scale; vs.: versus

2.5.1.2 Overall conclusion on added benefit

The results showed a relevant effect modification by sex for 2 outcomes. Hereinafter, the overall conclusion on the added benefit is presented separately for women and men.

Women

Table 23 summarizes the results for women that were considered in the overall conclusion on added benefit.

Table 23: Women: positive and negative effects from the assessment of tiotropium/olodaterol compared with tiotropium (research question 1)

Positive effects	Negative effects
Indication of added benefit – extent "minor" (non-serious/non-severe symptoms/late complications: TDI responder)	–
indication of added benefit – extent: "minor" (quality of life: SGRQ responder)	–
SGRQ: St. George's Respiratory Questionnaire; TDI: Transition Dyspnoea Index	

On the basis of the available results, a positive effect in the outcome categories "health-related quality of life (SGRQ responder)" and "non-serious/non-severe symptoms/late complications COPD symptoms (TDI responder)", each with the same probability (indication) and the same extent (minor), was shown for the group of women in the overall consideration at outcome level.

In summary, there is an indication of a minor added benefit of tiotropium/olodaterol compared with tiotropium for women.

Men

Table 24 summarizes the results for men that were considered in the overall conclusion on added benefit.

Table 24: Men: positive and negative effects from the assessment of tiotropium/olodaterol compared with tiotropium (research question 1)

Positive effects	Negative effects
–	–

On the basis of the available results, neither positive nor negative effects were shown in the group of men in the overall consideration.

In summary, an added benefit of tiotropium/olodaterol in comparison with tiotropium for men is not proven.

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

2.5.2.1 Evaluation of added benefit at outcome level

The data presented in Section 2.4 for research question 2 resulted in the following assessments for tiotropium/olodaterol in comparison with the ACT (tiotropium):

- proof of lesser benefit regarding severe exacerbations

Table 25: Extent of added benefit at outcome level: tiotropium/olodaterol (+ ICS) vs. tiotropium + ICS (research question 2)

Outcome category **Outcome** **Characteristic**	**Tiotropium/olodaterol vs. tiotropium** **Proportion of events[a] or mean** **Effect estimate [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Mortality		
All-cause mortality	TIO/OLO: 2.2% to 3.2% TIO: 0% to 7.1% RR: 0.87 [0.08; 9.87] p = 0.909	Lesser benefit/added benefit not proven
Morbidity		
COPD symptoms (TDI responder)	TIO/OLO: 56.8% to 60.7% TIO: 38.5% to 55.3% RR: 1.22 [0.88; 1.70] p = 0.231	Lesser benefit/added benefit not proven
Exacerbations	TIO/OLO: 51.1% to 58.1% TIO: 42.9% to 55.0% RR: 1.11 [0.80; 1.53] p = 0.535	Lesser benefit/added benefit not proven
Severe exacerbations	TIO/OLO: 17.8% to 19.4% TIO: 0% to 7.5% RR: 3.32 [1.02; 10.84] RR: 0.30 [0.09; 0.98][d] p = 0.047 probability: “proof”	Outcome category: serious/severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit, extent: “minor”
Health status PGR[e]	TIO/OLO: 3.05 to 3.35 TIO: 3.18 to 3.42 MD: -0.10 [-0.52; 0.32] p = 0.638	Lesser benefit/added benefit not proven
Health status EQ5D VAS	No data available	
Health-related quality of life		
SGRQ responder	TIO/OLO: 36.7% to 46.5% TIO: 45.8% to 50.0% RR: 0.87 [0.59; 1.29] p = 0.497	Lesser benefit/added benefit not proven
Adverse events		
SAEs	TIO/OLO: 26.7% to 29.0% TIO: 17.5% to 32.1% RR: 1.12 [0.57; 2.21] p = 0.735	Greater/lesser harm not proven
Discontinuation due to AEs	Heterogeneous results without effects in the same direction[f]	Greater/lesser harm not proven

(continued)

Table 25: Extent of added benefit at outcome level: tiotropium/olodaterol (+ ICS) vs. tiotropium + ICS (research question 2) (continued)

a: Minimum and maximum proportions of events in each treatment arm in the included studies.
b: Probability given if statistically significant differences are present.
c: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
d: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
e: PGR indicates the health status on a scale from 1 (much better) to 4 (no change) to 7 (much worse).
f: No common effect estimate can be provided due to heterogeneous data.
AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; COPD: chronic obstructive pulmonary disease; EQ-5D: European Quality of Life-5 Dimensions; MD: mean difference; ND: no data; OLO: olodaterol; PGR: patient global rating; RR: relative risk; SAE: serious adverse event; SGRQ: St. George's Respiratory Questionnaire; TDI: Transition Dyspnoea Index; TIO: tiotropium; VAS: visual analogue scale; vs.: versus

2.5.2.2 Overall conclusion on added benefit

Table 26 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 26: Positive and negative effects from the assessment of tiotropium/olodaterol compared with tiotropium (research question 2)

Positive effects	Negative effects
–	Proof of lesser benefit – extent: "minor" (serious/severe symptoms/late complications: severe exacerbations)

On the basis of the results presented, there is a negative effect in the outcome category "serious/severe symptoms/late complications (severe exacerbations)" in the overall consideration at outcome level.

In summary, this resulted in proof of lesser benefit of tiotropium/olodaterol + ICS in comparison with tiotropium + ICS.

2.5.3 Extent and probability of added benefit – summary

The result of the assessment of the added benefit of tiotropium/olodaterol in comparison with the ACT tiotropium is summarized in Table 27.

Table 27: Tiotropium/olodaterol – extent and probability of added benefit

Research question	Therapeutic indication	Appropriate comparator therapy[a]	Subgroup	Extent and probability of added benefit
1	Adult patients with COPD from moderate severity (50% ≤ FEV1 < 80% predicted)[b]	LABA (formoterol or salmeterol) and/or LAMA (**tiotropium**)	Women	Indication of a minor added benefit
			Men	Added benefit not proven
2	Adult patients with COPD of higher severity (30% ≤ FEV1 < 50% predicted or FEV1 < 30% predicted or respiratory failure) with ≥ 2 exacerbations per year[c]	LABA (formoterol or salmeterol) and/or LAMA (**tiotropium**) and additional **ICS**	–	Proof of lesser benefit

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 "patients with COPD grade II and patients with COPD grades ≥ III with < 2 exacerbations per year" is used in the report.
c: For better understandability, the term "patients with COPD grades ≥ III with ≥ 2 exacerbations per year" is used in the report.
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

The overall assessment deviates from that of the company. Based on its analyses for patients in subpopulation 1, the company derived an indication of considerable added benefit, which it inferred from an improvement in quality of life and prevention of AEs.

The company derived no added benefit for subpopulation 2 (see Section 2.7.2.4.1 of the full dossier assessment).

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

2.6 List of included studies

Studie BI 1237.5 (TONADO 1)

Boehringer Ingelheim. Combined analysis of efficacy data obtained in the twin studies 1237.5 and 1237.6: randomised, double-blind, parallel group studies to assess the efficacy and safety of 52 weeks of once daily treatment of orally inhaled tiotropium + olodaterol fixed dose combination (2.5 µg /5 µg; 5 µg / 5 µg) (delivered by the Respimat Inhaler) compared with the individual components (2.5 µg and 5 µg tiotropium, 5 µg olodaterol) (delivered by the Respimat Inhaler) in patients with Chronic Obstructive Pulmonary Disease (COPD) [TOnadoTM 1 and TOnadoTM 2]; study 1237.9991 (1237.5 and 1237.6 combined); clinical trial report [unpublished].

Boehringer Ingelheim. A randomised, double-blind, parallel group study to assess the efficacy and safety of 52 weeks of once daily treatment of orally inhaled tiotropium + olodaterol fixed dose combination (2.5 µg / 5 µg; 5 µg /5 µg) (delivered by the Respimat Inhaler) compared with the individual components (2.5 µg and 5 µg tiotropium, 5 µg olodaterol) (delivered by the Respimat Inhaler) in patients with Chronic Obstructive Pulmonary Disease (COPD) [TOnado 1]: study 1237.5; clinical trial report [unpublished].

Boehringer Ingelheim. A randomised, double-blind, parallel group study to assess the efficacy and safety of 52 weeks of once daily treatment of orally inhaled tiotropium + olodaterol fixed dose combination (2.5 µg / 5 µg; 5 µg / 5 µg) (delivered by the Respimat Inhaler) compared with the individual components (2.5 µg and 5 µg tiotropium, 5 µg olodaterol) (delivered by the Respimat Inhaler) in patients with Chronic Obstructive Pulmonary Disease (COPD) [online]. In: EU Clinical Trials Register. [Accessed: 17 February 2015]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2009-010668-40.

Boehringer Ingelheim. Tiotropium + olodaterol fixed dose combination (FDC) versus tiotropium and olodaterol in Chronic Obstructive Pulmonary Disease (COPD): full text view [online]. In: ClinicalTrials.gov. 19 June 2015 [accessed: 19 October 2015]. URL: http://ClinicalTrials.gov/show/NCT01431274.

Boehringer Ingelheim. Tiotropium + olodaterol fixed dose combination (FDC) versus tiotropium and olodaterol in Chronic Obstructive Pulmonary Disease (COPD): study results [online]. In: ClinicalTrials.gov. 19 June 2015 [accessed: 26 October 2015]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01431274.

Buhl R, Maltais F, Abrahams R, Bjermer L, Derom E, Ferguson G et al. Tiotropium and olodaterol fixed-dose combination versus mono-components in COPD (GOLD 2-4). Eur Respir J 2015; 45(4): 969-979.

Studie BI 1237.6 (TONADO 2)

Boehringer Ingelheim. Combined analysis of efficacy data obtained in the twin studies 1237.5 and 1237.6: randomised, double-blind, parallel group studies to assess the efficacy and safety of 52 weeks of once daily treatment of orally inhaled tiotropium + olodaterol fixed dose combination (2.5 µg /5 µg; 5 µg / 5 µg) (delivered by the Respimat Inhaler) compared with the individual components (2.5 µg and 5 µg tiotropium, 5 µg olodaterol) (delivered by the Respimat Inhaler) in patients with Chronic Obstructive Pulmonary Disease (COPD) [TOnadoTM 1 and TOnadoTM 2]; study 1237.9991 (1237.5 and 1237.6 combined); clinical trial report [unpublished].

Boehringer Ingelheim. A randomised, double-blind, parallel group study to assess the efficacy and safety of 52 weeks of once daily treatment of orally inhaled tiotropium + olodaterol fixed dose combination (2.5 µg / 5 µg; 5 µg /5 µg) (delivered by the Respimat Inhaler) compared with the individual components (2.5 µg and 5 µg tiotropium, 5 µg olodaterol) (delivered by the Respimat Inhaler) in patients with Chronic Obstructive Pulmonary Disease (COPD) [TOnado 2]: study 1237.6; clinical trial report [unpublished].

Boehringer Ingelheim. A randomised, double-blind, parallel group study to assess the efficacy and safety of 52 weeks of once daily treatment of orally inhaled tiotropium + olodaterol fixed dose combination (2.5 µg / 5 µg; 5 µg / 5 µg) (delivered by the Respimat Inhaler) compared with the individual components (2.5 µg and 5 µg tiotropium, 5 µg olodaterol) (delivered by the Respimat Inhaler) in patients with Chronic Obstructive Pulmonary Disease (COPD) [TOnadoTM 2] [online]. In: EU Clinical Trials Register. [Accessed: 17 February 2015]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2009-010669-22.

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Boehringer Ingelheim. Tiotropium + olodaterol fixed dose combination (FDC) versus tiotropium and olodaterol in Chronic Obstructive Pulmonary Disease (COPD): study results [online]. In: ClinicalTrials.gov. 19 June 2015 [accessed: 26 October 2015]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01431287.

Buhl R, Maltais F, Abrahams R, Bjermer L, Derom E, Ferguson G et al. Tiotropium and olodaterol fixed-dose combination versus mono-components in COPD (GOLD 2-4). Eur Respir J 2015; 45(4): 969-979.

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Please see full dossier assessment for full reference list.

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