IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A13-40

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Indacaterol/Glycopyrronium – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 12 February 2014). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Indacaterol/glycopyrronium – Benefit assessment according to §35a Social Code Book V

Commissioning agency:
Federal Joint Committee

Commission awarded on:
6 November 2013

Internal Commission No.:
A13-40

Address of publisher:
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Keywords: indacaterol, glycopyrrolate, pulmonary disease – chronic obstructive, benefit assessment

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BDI	Baseline Dyspnoea Index
CAT	COPD Assessment Test
COPD	chronic obstructive pulmonary disease
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
ICS	inhaled corticosteroids
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
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 indacaterol/glycopyrronium. 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 6 November 2013.

Research question

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

The G-BA specified the following ACT:

- The treatment of stable COPD of the severity stages "moderate" (stage II), "severe" (stage III) and "very severe" (stage IV) was conducted according to the recommendations of the most recently effective version of the German National Care Guideline COPD [4]. Long-acting beta-2 agonists (formoterol, salmeterol) and/or tiotropium are recommended for long-term drug treatment from stage II.
- In COPD stage III/IV with more than 2 exacerbations per year, inhaled corticosteroids (ICS) should be used in addition.

The company followed the specification of the G-BA and, from the options mentioned, chose formoterol in combination with tiotropium as the ACT. However, it did not consider the conditions for ICS use named above in the study inclusion.

Deviating from this, the criteria for ICS treatment specified by the G-BA were used in the present benefit assessment. The assessment for patients with COPD stages II to IV was conducted based on patient-relevant outcomes. Only direct comparative randomized controlled trials (RCTs) with a minimum duration of 6 months were included in the assessment.

Results

Study pool

One study (QUANTIFY – QVA149ADE01) was available for the direct comparison of indacaterol/glycopyrronium with tiotropium plus formoterol. This was a randomized

[4] The validity of the German National Care Guideline COPD has expired. It is under revision.

controlled 6-month study, which was conducted in Germany outside the approval process. 934 patients with COPD stage II and III were enrolled. Any ongoing ICS treatment was continued in the study. Apart from a few exceptions, the study participants with ICS treatment did not receive this treatment according to the conditions specified by the ACT. These patients, which constituted 41% of the study participants, were therefore excluded from the assessment. Hence there were no relevant data for patients who fulfilled the G-BA specifications for ICS treatment (at least COPD stage III and more than 2 exacerbations per year) and for patients with stage IV. The risk of bias at study level and for all included outcomes was rated as low.

Mortality

There was no statistically significant difference between the treatment groups in the relevant subpopulation of the QUANTIFY study for the outcome "all-cause mortality". Hence an added benefit of indacaterol/glycopyrronium in comparison with the ACT is not proven for this outcome.

Morbidity

Transition Dyspnoea Index

The outcome "Transition Dyspnoea Index (TDI)" is a questionnaire for the direct measurement of the change of dyspnoea in comparison with the baseline status. There was a statistically significant difference between the treatment groups in favour of indacaterol/glycopyrronium in the relevant subpopulation of the QUANTIFY study (without ICS treatment) for this outcome. There was an indication of an interaction with regards to severity. Whereas in patients with COPD stage III, there was a statistically significant difference in favour of indacaterol/glycopyrronium, the difference between the treatment groups of patients with COPD stage II was not statistically significant. As this result was only based on 1 study, this results in an indication of an added benefit for patients with COPD stage III with no more than 2 exacerbations per year, and in a hint of an added benefit for patients with COPD stage II, in each case of indacaterol/glycopyrronium in comparison with the ACT.

COPD Assessment Test

The outcome "COPD Assessment Test (CAT)" is a questionnaire to measure COPD symptoms and the associated impairment in daily life. There was a statistically significant difference – with only marginal effect size, however – between the treatment groups in the relevant subpopulation of the QUANTIFY study for this outcome. Overall, this does not result in an added benefit of indacaterol/glycopyrronium in comparison with the ACT for this outcome.

Moderate and severe exacerbations

There was no statistically significant difference between the treatment groups in the relevant subpopulation of the QUANTIFY study for each of the outcomes "moderate exacerbations"

and "severe exacerbations". In both cases, there was an indication of an interaction with regards to severity. There was a statistically significant difference – with only marginal effect size, however – in favour of indacaterol/glycopyrronium in moderate exacerbations for patients with COPD stage III. The respective difference between the treatment groups of the patients with COPD stage II was not statistically significant, however. The difference between the treatment groups in both severity subgroups was not statistically significant with regards to severe exacerbations. Overall, an added benefit of indacaterol/glycopyrronium in comparison with the ACT is not proven for the 2 outcomes "moderate exacerbations" and "severe exacerbations".

Health-related quality of life

For health-related quality of life, assessed using the St. George's Respiratory Questionnaire for COPD patients (SGRQ-C), there was no statistically significant difference between the treatment groups in the relevant subpopulation. Hence an added benefit of indacaterol/glycopyrronium in comparison with the ACT is not proven for this outcome.

Adverse events

There was no statistically significant difference between the treatment groups in the relevant subpopulation of the QUANTIFY study for each of the outcomes "overall rate of serious adverse events (SAEs)" and "discontinuation due to adverse events (AEs)". No data on the relevant subpopulation were available for specific AEs or SAEs. Overall, lesser/greater harm from indacaterol/glycopyrronium in comparison with the ACT is not proven on the basis of the data on AEs.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[5]

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

For indacaterol/glycopyrronium compared with tiotropium plus formoterol, the data resulted in a hint of an added benefit for patients with COPD stage II, and in an indication of an added benefit for patients with COPD stage III with no more than 2 exacerbations per year with regards to the outcome "TDI". On the basis of the effect size, this results in the following assessment:

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

- There is a hint of a minor added benefit of indacaterol/glycopyrronium compared with the ACT tiotropium plus formoterol for patients with COPD stage II.
- There is an indication of a minor added benefit of indacaterol/glycopyrronium compared with the ACT tiotropium plus formoterol for patients with COPD stage III with no more than 2 exacerbations per year.

Table 2 summarizes the results of the assessment of the added benefit of indacaterol/glycopyrronium versus the ACT.

Table 2: Indacaterol/glycopyrronium: extent and probability of added benefit

Therapeutic indication		**ACT**[a]	**Extent and probability of added benefit**
Adult patients with COPD stage II		LABA (**formoterol**, salmeterol) **and**/or LAMA (**tiotropium bromide**)	Hint of an added benefit (extent: “minor”)
Adult patients with COPD and no more than 2 exacerbations per year	COPD stage III	LABA (**formoterol**, salmeterol) **and**/or LAMA (**tiotropium bromide**)	Indication of an added benefit (extent: “minor”)
	COPD stage IV	LABA (**formoterol**, salmeterol) **and**/or LAMA (**tiotropium bromide**)	Added benefit not proven
Adult patients with COPD stage III or IV and more than 2 exacerbations per year		LABA (**formoterol**, salmeterol) **and**/or LAMA (**tiotropium bromide**) **and additional ICS**	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA’s specifications of the ACT, could choose an ACT from several options, the respective choice of the company is printed in bold. ACT: appropriate comparator therapy; COPD: chronic obstructive pulmonary disease; 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 this report is to assess the added benefit of indacaterol/glycopyrronium in comparison with the ACT in adult patients with COPD for maintenance bronchodilator treatment to relieve symptoms [3].

The G-BA specified the following ACT:

- The treatment of stable COPD of the severity stages "moderate" (stage II), "severe" (stage III) and "very severe" (stage IV) was conducted according to the recommendations of the most recently effective version of the German National Care Guideline COPD[6]. Long-acting beta-2 agonists (formoterol, salmeterol) and/or tiotropium are recommended for long-term drug treatment from stage II.
- In COPD stage III/IV with more than 2 exacerbations per year, ICS should be used in addition.

The company followed the specification of the G-BA and, from the options mentioned, chose formoterol in combination with tiotropium as the ACT.

In its specification of the criteria for study inclusion, the company considered in principle the requirement that intervention and comparator therapy could also be used in combination with ICS. However, it did not consider the exact conditions for guideline-compliant ICS use (severity and number of exacerbations in the previous year).

Deviating from this, the criteria for ICS treatment specified by the G-BA were used for the present benefit assessment.

In addition, only studies with a minimum duration of 6 months were considered because only such studies are capable of contributing reliable knowledge about the benefit or added benefit of indacaterol/glycopyrronium in the approved maintenance therapy (see Section 2.7.2.1 of the full dossier assessment). This deviates from the company's approach, which specified a minimum duration of 12 weeks. However, no studies were excluded from the assessment because of this deviation.

The assessment was conducted based on patient-relevant outcomes. Only direct comparative RCTs were included in the assessment.

Further information about the research question and the inclusion criteria can be found in Module 3, Section 3.1, and Module 4, Sections 4.2.1 and 4.2.2 of the dossier, and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

[6] The validity of the German National Care Guideline COPD has expired. It is under revision.

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 indacaterol/glycopyrronium (studies completed up to 2 September 2013)
- bibliographical literature search on indacaterol (last search on 2 September 2013) and glycopyrronium (last search on 3 September 2013)
- search in trial registries for studies on indacaterol/glycopyrronium (last search on 5 September 2013)

The Institute's own search to check the completeness of the study pool:

- search in trial registries for studies on indacaterol/glycopyrronium (last search on 18 November 2013)

This check produced no deviation from the study pool presented in the dossier.

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

2.3.1 Studies included

The study included in the benefit assessment is presented in Table 3.

Table 3: Study pool – RCT, direct comparison: indacaterol/glycopyrronium vs. tiotropium + formoterol

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
QUANTIFY (QVA149ADE01)	No	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. RCT: randomized controlled trial; vs.: versus			

The study pool concurred with the study pool of the company. However, only the subpopulation of the patients without concomitant ICS treatment of the QUANTIFY study was relevant for the assessment. More detailed reasons for this are presented in the following Section 2.3.2.

Section 2.6 contains a reference list for the study included.

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

2.3.2 Study characteristics

Characteristics of the studies and of the interventions

Table 4 and Table 5 describe the study used for the benefit assessment.

Table 4: Characteristics of the studies included – RCT, direct comparison: indacaterol/glycopyrronium vs. tiotropium + formoterol

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
QUANTIFY (QVA149A DE01)	RCT, double-blind, parallel, multicentre	Adult patients (≥ 40 years) with moderate to severe stable COPD, with a smoking history of at least 10 pack years; post-bronchodilator $FEV_1 \geq 30\%$ to < 80% of the predicted normal value and $FEV_1/FVC < 0.7$	Indacaterol/glycopyrronium (N = 476) tiotropium + formoterol (N = 458) Relevant subpopulation thereof[b]: indacaterol/glycopyrronium (n = 264) tiotropium + formoterol (n = 271)	Run-in: 2 weeks Treatment: 26 weeks	143 centres in Germany 5/2012–4/2013	Primary outcome: Health-related quality of life (SGRQ-C) Secondary outcomes: COPD symptoms, exacerbations, adverse events

a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: Study participants with COPD stage II or III without ICS treatment.

COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; ICS: inhaled corticosteroids; N: number of randomized patients; n: relevant subpopulation; RCT: randomized controlled trial; SGRQ-C: St. George's Respiratory Questionnaire for COPD patients; vs.: versus

Table 5: Characteristics of the interventions – RCT, direct comparison: indacaterol/glycopyrronium vs. tiotropium + formoterol

Study	Intervention	Comparison	Concomitant medication
QUANTIFY (QVA149ADE01)	Indacaterol/glycopyrronium 110/50 µg once daily placebo for tiotropium and formoterol	Tiotropium 18 µg once daily formoterol 12 µg twice daily placebo for indacaterol/glycopyrronium	Salbutamol 100 µg (rescue medication); ongoing ICS treatment (if ongoing for ≥ 30 days prior to start of the study)
ICS: inhaled corticosteroids; RCT: randomized controlled trial; vs.: versus			

The QUANTIFY study was a double-blind, multicentre RCT with a duration of 6 months. According to the company, the study was conducted especially for the early benefit assessment in Germany. Stable COPD patients aged 40 years or older were enrolled who, apart from a smoking history of at least 10 pack years, had a post-bronchodilator forced expiratory volume in 1 second (FEV_1) value between 30 and 80% of the predicted normal value and a post-bronchodilator ratio of FEV_1 and forced vital capacity (FVC) of < 0.7 at the start of the run-in phase. This corresponds to the COPD severity stages II (moderate, 50% ≤ FEV_1 < 80% predicted) and III (severe, 30% ≤ FEV_1 < 50% predicted) specified in the most recently effective version of the German National Care Guideline COPD.

The study investigated the comparison of the combination drug indacaterol/glycopyrronium with the combination treatment of tiotropium and formoterol, each administered separately. Any ICS treatment that was ongoing for at least 30 days was continued in the study.

Characteristics of the study populations

Table 6 and Table 7 show the characteristics of the patients in the study included.

Table 6: Characteristics of the study populations – RCT, direct comparison: indacaterol/glycopyrronium vs. tiotropium + formoterol

Study Group	N	Age [years] mean (SD)	Sex [f/m] %	Duration of COPD [years] mean (SD)	Smoking status (current smoker/ ex-smoker) %	Smoking [pack years] mean (SD)	Treatment discon-tinuation n (%)
QUANTIFY							
Indacaterol/ glycopyrronium	476	63 (8)	33/67	6.5 (5.3)	49.2/50.8	41.1 (19.1)	61 (12.8)
Tiotropium + formoterol	458	63 (8)	35/65	6.8 (5.2)	48.9/51.1	41.8 (19.6)	52 (11.4)
COPD: chronic obstructive pulmonary disease; f: female; m: male; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus							

Table 7: Characteristics of the study populations: number of moderate/severe exacerbations in the previous year according to ICS use and COPD severity – RCT, direct comparison: indacaterol/glycopyrronium vs. tiotropium + formoterol

	Number of moderate/severe exacerbations in the previous year n (%)			
Study **COPD severity stage** **ICS use** **Group**	**0**	**1**	**2**	**> 2**
QUANTIFY				
COPD stage: I (N = 3)				
ICS use: yes				
Ind/gl (N = 0)	0	0	0	0
Tio + for (N = 0)	0	0	0	0
ICS use: no				
Ind/gl (N = 1)	1 (33.3)	0	0	0
Tio + for (N = 2)	2 (66.7)	0	0	0
COPD stage: II (N = 520)				
ICS use: yes				
Ind/gl (N = 100)	76 (14.6)	22 (4.2)	2 (0.4)	0
Tio + for (N = 78)	65 (12.5)	12 (2.3)	1 (0.2)	0
ICS use: no				
Ind/gl (N = 167)	158 (30.4)	9 (1.7)	0	0
Tio + for (N = 175)	160 (30.8)	14 (2.7)	1 (0.2)	0
COPD stage: III (N = 388)				
ICS use: yes				
Ind/gl (N = 97)	75 (19.3)	20 (5.2)	0	2 (0.5)
Tio + for (N = 102)	81 (20.9)	18 (4.6)	2 (0.5)	1 (0.3)
ICS use: no				
Ind/gl (N = 96)	88 (22.7)	7 (1.8)	1 (0.3)	0
Tio + for (N = 93)	83 (21.4)	10 (2.6)	0	0
COPD stage: IV (N = 6)				
ICS use: yes				
Ind/gl (N = 2)	1 (16.7)	1 (16.7)	0	0
Tio + for (N = 3)	1 (16.7)	2 (33.3)	0	0
ICS use: no				
Ind/gl (N = 0)	0	0	0	0
Tio + for (N = 1)	1 (16.7)	0	0	0

(continued)

Table 7: Characteristics of the study populations: number of moderate/severe exacerbations in the previous year according to ICS use and COPD severity – RCT, direct comparison: indacaterol/glycopyrronium vs. tiotropium + formoterol (continued)

	Number of moderate/severe exacerbations in the previous year			
Study	**0**	**1**	**2**	**> 2**
COPD severity stage	**n (%)**	**n (%)**	**n (%)**	**n (%)**
ICS use				
Group				
QUANTIFY				
COPD not categorized[a] (N = 17)				
ICS use: yes				
Ind/gl (N = 2)	2 (11.7)	0	0	0
Tio + for (N = 1)	0	1 (5.9)	0	0
ICS use: no				
Ind/gl (N = 11)	10 (58.8)	1 (5.9)	0	0
Tio + for (N = 3)	3 (17.7)	0	0	0

a: COPD diagnosis plausible according to the company, but not confirmed, therefore no classification in COPD stage possible.
COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroids; ind/gl: indacaterol/glycopyrronium; n: number of patients in the category; N: number of patients in the subgroup; RCT: randomized controlled trial; tio + for: tiotropium + formoterol; vs.: versus

The mean age of the patients in the QUANTIFY study was 63 years in both treatment groups with the proportion of men being approximately twice as high as the proportion of women. Besides 26 participants with COPD stage I, IV or unclear COPD stage, the study population mainly consisted of patients with stage II (56%) and III (42%). 41% of the patients had ongoing ICS treatment at the start of the study, which was continued according to the study protocol. The majority of study participants had experienced no exacerbations in the previous year (86%). No differences in patient characteristics that were relevant for the assessment could be detected between the study arms.

Usability of the data of the QUANTIFY study

COPD stages II and III

According to the specification of the ACT, ICS were only to be used in patients with COPD stage III or IV with more than 2 exacerbations per year. According to the company's information on the ACT, the company concurred with this specification, but did not consider it in the present QUANTIFY study. Patients with ongoing ICS treatment were enrolled and their treatment was continued, regardless of whether or not this treatment concurred with the specifications of the ACT. As can be seen in Table 7, overall, approximately 1 third of the patients with COPD stage II and approximately half of the patients with COPD stage III received ICS.

79% of the study participants with COPD stage II under ICS treatment had not experienced any exacerbations in the previous year. However, the ACT did not envisage ICS treatment of these patients because of their severity stage or because of the frequency of exacerbations. Hence they were rated as irrelevant for the benefit assessment.

78% of the study participants with COPD stage III under ICS treatment had also not experienced any exacerbations in the previous year. So their ICS treatment also did not concur with the specifications of the ACT because the frequency of exacerbations was too low. Hence these study participants were also rated as irrelevant for the assessment.

See Section 2.7.2.3.2 of the full dossier assessment for more information on the exclusion of the subpopulation treated with ICS.

Except for the study characteristics presented in Table 6, the company additionally presented the results of all relevant outcomes in such a way that it was possible to conduct the benefit assessment solely on the basis of the data of the relevant subpopulation of the QUANTIFY study: patients with COPD stage II or III without ICS treatment.

COPD stages I and IV

Only 3 patients with COPD stage I were enrolled in the QUANTIFY study. This did not influence the benefit assessment because this patient group was rated as irrelevant (see Section 2.7.1 of the full dossier assessment).

Because the participants of the QUANTIFY study only comprised 6 patients with COPD stage IV, no sufficient data were available for the assessment of this relevant patient group.

Risk of bias at study level

Table 8 shows the risk of bias at study level.

Table 8: Risk of bias at study level – RCT, direct comparison: indacaterol/glycopyrronium vs. tiotropium + formoterol

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			
QUANTIFY	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

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

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

2.4 Results on added benefit

2.4.1 Relevant outcomes

The following patient-relevant outcomes were considered in this assessment:

- mortality
  - all-cause mortality
- morbidity
  - COPD symptoms
    - TDI
    - CAT
  - moderate and severe exacerbations
- health-related quality of life
  - SGRQ-C
- adverse events
  - overall rate of SAEs
  - treatment discontinuations due to AEs

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

2.4.2 Data availability and risk of bias

Table 9 shows for which outcomes data were available in the study included. Data were available for all outcomes included in the benefit assessment.

Table 9: Matrix of outcomes – RCT, direct comparison: indacaterol/glycopyrronium vs. tiotropium + formoterol

Study	Outcomes							
	All-cause mortality	COPD symptoms – TDI	COPD symptoms – CAT	Moderate exacerbations	Severe exacerbations	Health-related quality of life – (SGRQ-C)	Serious adverse events	Discontinuation due to adverse events
QUANTIFY	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; RCT: randomized controlled trial; SGRQ-C: St. George's Respiratory Questionnaire for COPD patients; TDI: Transition Dyspnoea Index; vs.: versus

Table 10 shows the risk of bias for these outcomes.

Table 10: Risk of bias at study and outcome level for the relevant subpopulation – RCT, direct comparison: indacaterol/glycopyrronium vs. tiotropium + formoterol

Study		Outcomes							
	Study level	All-cause mortality	COPD symptoms – TDI	COPD symptoms – CAT	Moderate exacerbations	Severe exacerbations	Health-related quality of life – (SGRQ-C)	Serious adverse events	Discontinuation due to adverse events
QUANTIFY[a]	L	L	L	L	L	L	L	L	L

a: The assessment of the risk of bias at outcome level was conducted based on the relevant subpopulation, i.e. patients with COPD stage II or III without ICS treatment.

CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroids; L: low; RCT: randomized controlled trial; SGRQ-C: St. George's Respiratory Questionnaire for COPD patients; TDI: Transition Dyspnoea Index; vs.: versus

The risk of bias for the relevant subpopulation (patients with COPD stages II or III without ICS treatment) was rated as low for all outcomes. This assessment concurs with the company's rating on the basis of all participants of the QUANTIFY study.

Further information about the choice of outcomes and risk of bias at outcome level can be found in Module 4, Sections 4.3.1.2.2 and 4.3.1.3 of the dossier and in Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.

2.4.3 Results

The results of the direct comparison of indacaterol/glycopyrronium with tiotropium plus formoterol in the relevant subpopulation (patients with COPD stage II or III without ICS treatment) are summarized in Table 11. All numbers on the total relevant subpopulation were calculated by the Institute from the data on the 2 subgroups according to severity/ICS treatment. The individual results of the 2 subgroups according to COPD stage of the relevant subpopulation were investigated for interactions using Cochran's Q test. The corresponding individual results are presented in the table only if this test provided indication or proof of interaction.

Table 11: Results (dichotomous outcomes), relevant subpopulation, RCT, direct comparison: indacaterol/glycopyrronium vs. tiotropium + formoterol

Study Outcome category Outcome Subgroup category Subgroup	Indacaterol/ glycopyrronium		Tiotropium + formoterol		Indacaterol/ glycopyrronium vs. tiotropium + formoterol	
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI]	p-value
QUANTIFY[a]						
Mortality						
All-cause mortality	264	0 (0)	271	2 (0.7)	0.14 [0.01; 2.22]	0.171[b]
Morbidity						
TDI responder[c]	258	142 (55.0)	267	124 (46.4)	1.19 [1.00[d]; 1.40]	0.049[e]
Subgroups according to severity stage						
COPD stage II	163	88 (54.0)	175	89 (50.9)	1.06 [0.87; 1.30]	0.564[f]
COPD stage III	95	54 (56.8)	92	35 (38.0)	1.49 [1.09; 2.03]	0.013[f]
					Interaction:	0.073[g]
CAT responder[h]	263	117 (44.5)	271	92 (33.9)	1.31 [1.06; 1.62]	0.013[e]
Moderate exacerbations	264	22 (8.3)	271	30 (11.1)	0.75 [0.45; 1.27]	0.294[e]
Subgroups according to severity stage						
COPD stage II	168	14 (8.3)	177	13 (7.3)	1.14 [0.56; 2.30]	0.776[f]
COPD stage III	96	8 (8.3)	94	17 (18.1)	0.46 [0.22; 1.03]	0.0499[i]
					Interaction:	0.100[g]
Severe exacerbations	264	4 (1.5)	271	2 (0.7)	2.01 [0.40; 10.05]	0.442[b]
Subgroups according to severity stage						
COPD stage II	168	1 (0.6)	177	2 (1.1)	0.53 [0.06; 5.22]	0.670[b]
COPD stage III	96	3 (3.1)	94	0 (0)	7.39 [0.76; 71.93]	0.095[b]
					Interaction:	0.110[g]
Health-related quality of life						
SGRQ-C responder[j]	247	124 (50.2)	262	111 (42.4)	1.18 [0.98; 1.43]	0.079[e]
Adverse events						
Overall rate of AEs (as additional information)[k]	264	110 (41.7)	271	104 (38.4)		
Overall rate of SAEs[k]	264	13 (4.9)	271	12 (4.4)	1.11 [0.52; 2.39]	0.819[e]
Discontinuation due to AEs[k]	264	12 (4.5)	271	8 (3.0)	1.54 [0.64; 3.71]	0.394[e]

(continued)

Table 11: Results (dichotomous outcomes), relevant subpopulation, RCT, direct comparison: indacaterol/glycopyrronium vs. tiotropium + formoterol (continued)

a: All numbers on the total relevant subpopulation were calculated by the Institute from the data on the 2 relevant subgroups of the patients with COPD stage II or III (without ICS treatment).
b: Institute's calculation: asymptotic estimate and CI, Peto OR due to event rates of ≤ 1% in at least 1 cell; unconditional exact test (CSZ method according to [4]) for p-value.
c: Patients with a focal score (sum score) ≥ 1.
d: More exact value: 1.0003.
e: Institute's calculation: asymptotic estimate and CI, unconditional exact test (CSZ method according to [4]) for p-value.
f: Institute's calculation, unconditional exact test (CSZ method according to [4]).
g: Institute's calculation: Cochran's Q test.
h: Patients with a reduction in score ≥ 2.
i: Institute's calculation, unconditional exact test (CSZ method according to [4]). Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods. The p-value is decisive for the assessment.
j: Patients with a reduction in total score ≥ 4.
k: Events excluding exacerbations.
AE: adverse event; CI: confidence interval; CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; CSZ: convexity, symmetry, z score; ICS: inhaled corticosteroids; N: number of analysed patients; n: number of patients with event; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SGRQ-C: St. George's Respiratory Questionnaire for COPD patients; TDI: Transition Dyspnoea Index; vs.: versus

Mortality

There was no statistically significant difference between the treatment groups in the relevant subpopulation of the QUANTIFY study for the outcome "all-cause mortality". Hence an added benefit of indacaterol/glycopyrronium in comparison with the ACT tiotropium plus formoterol is not proven for this outcome. This concurs with the company's assessment.

Morbidity

Transition Dyspnoea Index

The outcome "TDI" is a questionnaire for the direct measurement of the change of dyspnoea, one of the main symptoms of COPD, in comparison with the baseline status. The assessment was conducted on the basis of responder analyses of the sum score, i.e. the proportion of patients with a so-called focal score of at least 1. There was a statistically significant difference between the treatment groups in favour of indacaterol/glycopyrronium in the relevant subpopulation of the QUANTIFY study for this outcome. There was an indication of an interaction with regards to severity ($p < 0.2$). Whereas in patients with COPD stage III (without ICS), there was a statistically significant difference in favour of indacaterol/glycopyrronium, the difference between the treatment groups of patients with COPD stage II (without ICS) was not statistically significant. Because this result was only based on 1 study, for the COPD symptom dyspnoea – measured using the TDI – this results in

- an indication of an added benefit for patients with COPD stage III with no more than 2 exacerbations per year and

- a hint of an added benefit for patients with COPD stage II

in each case of indacaterol/glycopyrronium compared with the ACT. This deviates from the company's assessment, which derived an indication of an added benefit for all patients with COPD stage II or III (with and without ICS) from the TDI result because it considered the entire study population, in which there was also a statistically significant advantage in favour of indacaterol/glycopyrronium.

COPD Assessment Test

The outcome "CAT" is a questionnaire to measure COPD symptoms and the associated impairment in daily life. The assessment was conducted on the basis of responder analyses of the sum score, i.e. the proportion of patients with a reduction in score of at least 2. There was a statistically significant difference – with only marginal effect size, however – between the treatment groups in the relevant subpopulation of the QUANTIFY study for this outcome (see Section 2.5.1). Overall, this does not result in an added benefit of indacaterol/ glycopyrronium in comparison with the ACT tiotropium plus formoterol for this outcome. This concurs with the company's assessment, which only sees a "trend in favour" of the indacaterol/glycopyrronium treatment because there was only a numerical difference, but no statistically significant difference, between the treatment groups in the total study population considered by the company.

Moderate exacerbations

There was no statistically significant difference between the treatment groups in the relevant subpopulation of the QUANTIFY study for the outcome "proportion of patients with moderate exacerbation". There was an indication of an interaction with regards to severity ($p < 0.2$). Whereas in patients with COPD stage III (without ICS), there was a statistically significant difference in favour of indacaterol/glycopyrronium, the difference between the treatment groups of patients with COPD stage II (without ICS) was not statistically significant. However, the effect was no more than marginal in patients with COPD stage III (for the assessment of the effect size, see [1]). Overall, an added benefit of indacaterol/ glycopyrronium in comparison with the ACT tiotropium plus formoterol is not proven for the outcome "moderate exacerbations". This concurs with the company's assessment.

Severe exacerbations

There was no statistically significant difference between the treatment groups in the relevant subpopulation of the QUANTIFY study for the outcome "proportion of patients with severe exacerbation". There was an indication of an interaction with regards to severity ($p < 0.2$). In both subgroups, the difference between the treatment groups was not statistically significant, however. Hence an added benefit of indacaterol/glycopyrronium in comparison with the ACT tiotropium plus formoterol is not proven for this outcome. This concurs with the company's assessment.

Health-related quality of life (using the SGRQ-C)

For health-related quality of life, recorded in the QUANTIFY study as primary outcome using the SGRQ-C, there was no statistically significant difference between the treatment groups in the relevant subpopulation. Hence an added benefit of indacaterol/glycopyrronium in comparison with the ACT tiotropium plus formoterol is not proven for this outcome. This concurs with the company's assessment.

Adverse events

There was no statistically significant difference between the treatment groups in the relevant subpopulation of the QUANTIFY study for each of the outcomes "overall rate of SAEs" and "discontinuation due to AEs". No data on the relevant subpopulation were available for specific AEs or SAEs. Overall, lesser/greater harm from indacaterol/glycopyrronium in comparison with the ACT tiotropium plus formoterol is not proven on the basis of the data on AEs. This concurs with the company's assessment.

2.4.4 Subgroup analyses

There were no subgroup analyses for the relevant subpopulation consisting of patients with COPD stage II or III without ICS treatment. Results on subgroup analyses according to COPD stage for the relevant subpopulation were already presented in Section 2.4.3.

Further information on the choice of outcomes, on risk of bias at outcome level, and on outcome results can be found in Module 4, Sections 4.3.1.2.2 and 4.3.1.3 of the dossier and in Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.

2.5 Extent and probability of added benefit

The derivation of extent and probability of the added benefit of indacaterol/glycopyrronium at outcome level is shown below, taking into account the various outcome categories and effect sizes (see [1] for information on the methods used).

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

2.5.1 Assessment of added benefit at outcome level

For the main COPD symptom dyspnoea, measured with the instrument TDI, the data presented in Section 2.4 resulted in the following assessments for indacaterol/glycopyrronium compared with the ACT (tiotropium plus formoterol):

- a hint of an added benefit regarding TDI responders for patients with COPD stage II
- an indication of an added benefit regarding TDI responders for patients with COPD stage III with no more than 2 exacerbations per year

Moreover, there was a statistically significant difference for the entire relevant subpopulation in favour of indacaterol/glycopyrronium compared with tiotropium plus formoterol for the outcome “CAT responders”.

Determination of the outcome category for the outcomes “TDI responders” and “CAT responders”

An assessment of whether the TDI is an outcome of the category “serious/severe symptoms/late complications” depends on the patients’ initial situation, particularly on the severity of their symptoms or dyspnoea. Apart from the average baseline values of the entire subpopulation, this would also require the responders’ baseline data to exclude that, in an extreme example, the responders only include patients with mild symptoms. However, the company did not present a stratified analysis of TDI responders according to baseline value. Hence only the baseline data of the entire subpopulation could be used for the assessment. The respective patients had a Baseline Dyspnoea Index (BDI) value of 7.0 (COPD stage II) and 6.2 (COPD stage III). 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. A considerable limitation of the patients can already be derived from a comparison with the BDI questions. Hence the TDI results were allocated to the outcome category “serious/severe symptoms/late complications)”.

Resulting from the consideration of the baseline CAT values in connection with the dimensions collected, CAT, in contrast, was 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 the available results (see Table 12).

Table 12: Extent of added benefit at outcome level: indacaterol/glycopyrronium vs. tiotropium + formoterol (patients with COPD stage II or stage III with no more than 2 exacerbations per year)

Outcome category **Outcome**	**Indacaterol/glycopyrronium vs. tiotropium + formoterol** **proportion of events** **effect estimates [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0.7% Peto OR: 0.14 [0.01; 2.22] p = 0.171	Lesser benefit/added benefit not proven
Morbidity		
TDI responders	55.0% vs. 46.6% RR: 1.19 [1.00[c]; 1.40] p = 0.049	
COPD stage II	54.0% vs. 50.9% RR: 1.06 [0.87; 1.30] p = 0.564 probability: "hint"	Outcome category: serious/severe symptoms/late complications added benefit, extent: "minor"
COPD stage III	56.8% vs. 38.0% RR: 1.49 [1.09; 2.03] RR: 0.67 [0.49; 0.92][d] p = 0.013 probability: "indication"	Outcome category: serious/severe symptoms/late complications $1 > CI_u > 0.90$ added benefit, extent: "minor"
CAT responders	44.5% vs. 33.9% RR: 1.31 [1.06; 1.62] RR: 0.76 [0.62; 0.95][d] p = 0.013	Outcome category: non-serious/non-severe symptoms/late complications $1 > CI_u > 0.90$ Lesser benefit/added benefit not proven
Moderate exacerbations	8.3% vs. 11.1% RR: 0.75 [0.45; 1.27] p = 0.294	Lesser benefit/added benefit not proven
Severe exacerbations	1.5% vs. 0.7% Peto OR: 2.01 [0.40; 10.05] p = 0.442	Lesser benefit/added benefit not proven
Health-related quality of life		
SGRQ-C responders	50.2% vs. 42.4% RR: 1.18 [0.98; 1.43] p = 0.079	Lesser benefit/added benefit not proven

(continued)

Table 12: Extent of added benefit at outcome level: indacaterol/glycopyrronium vs. tiotropium + formoterol (patients with COPD stage II or stage III with no more than 2 exacerbations per year) (continued)

Outcome category **Outcome**	**Indacaterol/glycopyrronium vs. tiotropium + formoterol** **proportion of events** **effect estimates [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Adverse events		
Overall rate SAEs[e]	4.9% vs. 4.4% RR: 1.11 [0.52; 2.39] p = 0.819	Greater/lesser harm not proven
Discontinuation due to AEs[e]	4.5% vs. 3.0% RR: 1.54 [0.64; 3.71] p = 0.394	Greater/lesser harm not proven
a: Probability provided if statistically significant differences were present. b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u. c: More exact value: 1.0003. d: Institute's calculation: reversed direction of effect to enable direct use of limits to derive added benefit. e: Events excluding exacerbations. AE: adverse event; CAT: COPD Assessment Test; CI: confidence interval; CI_u: upper limit of CI; COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroids; OR: odds ratio; RR: relative risk; SAE: serious adverse event; SGRQ-C: St. George's Respiratory Questionnaire for COPD patients; TDI: Transition Dyspnoea Index; vs.: versus		

2.5.2 Overall conclusion on added benefit

Table 13 and Table 14 summarize the results that were considered in the overall conclusion on the extent of added benefit, separated according to the relevant subgroups.

Table 13: Patients with COPD stage II: positive and negative effects from the assessment of indacaterol/glycopyrronium compared with tiotropium + formoterol

Positive effects	**Negative effects**
Hint of an added benefit – extent "minor" (serious/severe symptoms/late complications): TDI	
COPD: chronic obstructive pulmonary disease; TDI: Transition Dyspnoea Index	

Overall, on the basis of the available results, only a positive effect remains at outcome level for the group of patients with COPD stage II. This consists of a hint of a minor added benefit in the outcome category "serious/severe symptoms/late complications" (COPD symptom dyspnoea, recorded as TDI responders).

In summary, there is a hint of a minor added benefit of indacaterol/glycopyrronium compared with tiotropium plus formoterol for patients with COPD stage II.

Table 14: Patients with COPD stage III with no more than 2 exacerbations per year: positive and negative effects from the assessment of indacaterol/glycopyrronium compared with tiotropium + formoterol

Positive effects	**Negative effects**
Indication of an added benefit – extent "minor" (serious/severe symptoms/late complications): TDI	
COPD: chronic obstructive pulmonary disease; TDI: Transition Dyspnoea Index	

Overall, on the basis of the available results, only a positive effect remains at outcome level for the group of patients with COPD stage III with no more than 2 exacerbations per year. This consists of an indication of a minor added benefit in the outcome category "serious/severe symptoms/late complications" (TDI responders).

In summary, there is an indication of a minor added benefit of indacaterol/glycopyrronium compared with tiotropium plus formoterol for patients with COPD stage III with no more than 2 exacerbations per year.

2.5.3 Extent and probability of added benefit – summary

An overview of the extent and probability of the added benefit for the benefit assessment of indacaterol/glycopyrronium compared with the ACT for the relevant subpopulation is given below:

Table 15: Indacaterol/glycopyrronium: extent and probability of added benefit

Therapeutic indication		**ACT**[a]	**Extent and probability of added benefit**
Adult patients with COPD stage II		LABA (**formoterol**, salmeterol) **and**/or LAMA (**tiotropium bromide**)	Hint of an added benefit (extent: "minor")
Adult patients with COPD and no more than 2 exacerbations per year	COPD stage III	LABA (**formoterol**, salmeterol) **and**/or LAMA (**tiotropium bromide**)	Indication of an added benefit (extent: "minor")
	COPD stage IV	LABA (**formoterol**, salmeterol) **and**/or LAMA (**tiotropium bromide**)	Added benefit not proven
Adult patients with COPD stage III or IV and more than 2 exacerbations per year		LABA (**formoterol**, salmeterol) **and**/or LAMA (**tiotropium bromide**) **and additional ICS**	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specifications of the ACT, could choose an ACT from several options, the respective choice of the company is printed in bold. ACT: appropriate comparator therapy; COPD: chronic obstructive pulmonary disease; 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, which claimed an indication of a considerable added benefit for all patients with COPD stage II or III. Furthermore, the company assumed a non-quantifiable benefit for stage IV patients.

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

2.6 List of included studies

QUANTIFY (QVA149ADE01)

Novartis. A 26-week treatment, multicenter, randomized, parallel group, blinded study to assess the efficacy and safety of QVA149 (110/50µg q.d.) in patients with moderate to severe chronic obstructive pulmonary disease (COPD), using tiotropium plus formoterol as an active control: study CQVA149ADE01; clinical study report [unpublished]. 2013.

References for English extract

Please see full dossier assessment for full reference list.

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The full report (German version) is published under https://www.iqwig.de/download/A13-40_Indacaterol-Glycopyrronium_Nutzenbewertung-35a-SGB-V.pdf.