IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Aclidinium bromide/ formoterol – Benefit assessment according to §35a Social Code Book V[1]

Extract

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

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

Medical and scientific advice:

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

IQWiG employees involved in the dossier assessment[2]:

- Daniel Fleer
- Catharina Brockhaus
- Andreas Gerber-Grote
- Tatjana Hermanns
- Florina Kerekes
- Katrin Nink
- Volker Vervölgyi
- Carolin Weigel

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

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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
COPD	chronic obstructive pulmonary disease
E-RS	Exacerbation of Chronic Pulmonary Disease Tool Respiratory Symptoms
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GEE	generalized estimating equation
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HCRU	Health Care Resource Utilization
ICS	inhaled corticosteroid
IPD	individual patient data
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)
SGRQ	St. George’s Respiratory Questionnaire
TDI	Transition Dyspnoea Index
VAS	visual analogue scale

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 aclidinium bromide/formoterol. 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 2 February 2015.

Research question

The aim of the present report is to assess the added benefit of aclidinium bromide/formoterol (hereinafter referred to as "aclidinium/formoterol") as a maintenance bronchodilator treatment for relief of 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 result for the benefit assessment (Table 2).

Table 2: Research questions of the benefit assessment of aclidinium/formoterol

Research question	**Therapeutic indication**	**ACT**[a]
1	Adult patients with COPD from moderate severity (50% ≤ FEV1 < 80% predicted)[b]	LABA (**formoterol**, salmeterol) and/or LAMA (tiotropium)
2	Adult patients with COPD of higher severity (30% ≤ FEV1 < 50% predicted or FEV1 < 30% or respiratory failure) with ≥ 2 exacerbations per year[c]	LABA (**formoterol**, 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 corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist

From the options named by the G-BA, the company chose formoterol for research question 1, and formoterol 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

Three double-blind, multi-centre, randomized controlled approval studies (LAC-MD-32, ACLIFORM and AUGMENT with extension study LAC-MD-36) were included for the direct comparison of aclidinium/formoterol with the ACT. All 3 studies investigated the comparison of one morning and one evening inhalation of the fixed-dose combination of 400 µg aclidinium and 12 µg formoterol versus 12 µg formoterol. The studies lasted 24 weeks (ACLIFORM, AUGMENT) and 52 weeks (LAC-MD-32, AUGMENT with extension study LAC-MD-36). Patients aged 40 years or older with moderate to severe COPD, i.e. of severity grades II and III, were enrolled. Patients also had to have a smoking history of at least 10 pack years at enrolment.

ICS treatment could be continued in all 3 studies as concomitant treatment irrespective of the severity grade and the frequency of exacerbations of the patients. The company conducted analyses of subpopulations for the 2 research questions because, in most study participants, treatment did not concur with the conditions determined by the ACT.

For research question 1, the risk of bias at the study level for the ACLIFORM, AUGMENT and LAC-MD-32 studies was rated as low. For research question 2, in contrast, the risk of bias at the study level for the AUGMENT and LAC-MD-32 studies was rated as high. The results of the extension study LAC-MD-36 generally have a high risk of bias because of the high rate of discontinuation and are therefore only presented as additional information.

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

According to the company's analysis, the assessed subpopulations of the 3 studies included for research question 1 contain all patients with COPD grade II and III without concomitant ICS treatment. No informative data for answering research question 1 were available for patients with COPD grade IV. The subpopulation presented by the company (patients without concomitant ICS treatment) also includes 36 patients with COPD grade III and with 2 or more exacerbations in the previous year; these patients are therefore not relevant for research question 1. Overall, depending on the study, these are only at most 5.3% of the patients. Hence the subpopulation analysed by the company for research question 1 was considered to be evaluable as an approximation for the benefit assessment, and the corresponding analyses were included in the assessment.

The following analyses were available for answering research question 1.

COPD symptoms (TDI responder)

The meta-analysis of the studies included showed a statistically significant difference between the treatment groups in favour of aclidinium/formoterol for the outcome "COPD symptoms (Transition Dyspnoea Index [TDI] responder)" in the relevant subpopulation of research question 1. This was of only marginal effect size. In the subsequent course of the assessment of subgroup characteristics, there was an indication of an effect modification by the characteristic "COPD severity grade". The result of the subgroup analysis in the meta-analysis showed a statistically significant effect only in patients with COPD grade III. This was also of only marginal effect size. Overall, there was no hint of an added benefit of aclidinium/formoterol in comparison with formoterol for patients with COPD grade II or for patients with COPD grade III with fewer than 2 exacerbations per year; an added benefit for the outcome "TDI responder" is therefore not proven.

COPD symptoms (E-RS responder)

The Exacerbation of Chronic Pulmonary Disease Tool Respiratory Symptoms (E-RS) is a questionnaire that measures the severity of respiratory COPD symptoms. The meta-analysis of the studies included showed a statistically significant difference between the treatment groups in favour of aclidinium/formoterol for this outcome in the relevant subpopulation of research question 1. There was an indication of an effect modification regarding COPD severity grade. The result of the subgroup analysis in the meta-analysis showed a statistically significant effect only in patients with COPD grade III. Overall, there was proof of an added benefit in patients with COPD grade III with fewer than 2 exacerbations per year for the outcome "COPD symptoms (E-RS responder)". Despite a non-significant effect, there was an indication of an added benefit for the outcome "COPD symptoms (E-RS responder)" for patients with COPD grade II because there was only an indication of an interaction and the result of the total population was statistically significant.

Severe exacerbations (HCRU)

The meta-analysis of the studies included showed no statistically significant difference between the treatment groups for the outcome "proportion of patients with severe exacerbations (Health Care Resource Utilization [HCRU])" in the relevant subpopulation of research question 1. There was an indication of an effect modification regarding COPD severity grade. The result of the subgroup analysis in the meta-analysis showed a statistically significant effect only in patients with COPD grade III. Overall, there was an indication of an added benefit in patients with COPD grade III with fewer than 2 exacerbations per year for the outcome "severe exacerbations (HCRU)". For patients with COPD grade II, there was no hint of added benefit of aclidinium/formoterol in comparison with formoterol; an added benefit for severe exacerbations is therefore not proven.

Further outcomes

For the further outcomes investigated, the meta-analysis of the studies included showed no statistically significant difference between the treatment groups (mortality, health status

[European Quality of Life-5 Dimensions visual analogue scale – EQ-5D VAS], health-related quality of life [St. George's Respiratory Questionnaire – SGRQ] and adverse events [AEs] [serious AEs – SAEs, discontinuation due to AEs]) or important inexplicable heterogeneity without clear direction of result (moderate exacerbations [HCRU]) in the relevant subpopulation of research question 1. Hence there was no hint of an added benefit or of greater or lesser harm of aclidinium/formoterol in comparison with formoterol for any of these outcomes; an added benefit or greater or lesser harm for these outcomes is therefore not proven.

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

The assessed subpopulations of the 3 studies included for research question 2 contain only patients with COPD grade III with 2 or more exacerbations per year who received concomitant ICS treatment. There were therefore no data of patients with COPD grade IV for answering research question 2.

For adult patients with COPD grade III with 2 or more exacerbations per year, there were no statistically significant differences between the treatment groups for any of the outcomes investigated (mortality, COPD symptoms [TDI responder, E-RS responder], moderate exacerbations, severe exacerbations, health status [EQ-5D VAS], health-related quality of life [SGRQ] and AEs [SAEs, discontinuation due to AEs]). Hence there was no hint of an added benefit or of greater or lesser harm of aclidinium/formoterol + ICS in comparison with formoterol + ICS for any of the outcomes investigated; an added benefit or greater or lesser harm for these outcomes is therefore not proven.

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 aclidinium/formoterol compared with the ACT is assessed as follows.

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

Based on the data presented, there is an indication of minor added benefit of aclidinium/ formoterol in comparison with formoterol for patients with COPD grade II, and proof of considerable added benefit of aclidinium/formoterol in comparison with formoterol for patients with COPD grade III with fewer than 2 exacerbations per year.

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

Since no data were presented for the subpopulation of patients with COPD grade IV with fewer than 2 exacerbations per year, an added benefit of aclidinium/formoterol in comparison with the ACT is not proven for this subpopulation.

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

Neither positive nor negative effects resulted from the data presented for adult patients with COPD grade III with 2 or more exacerbations per year. No data were presented for the subpopulation of patients with COPD grade IV with 2 or more exacerbations per year.

In summary, an added benefit of aclidinium/formoterol + ICS for adult patients with COPD grades III and IV with 2 or more exacerbations per year versus the ACT (formoterol + ICS) is not proven.

Extent and probability of added benefit – summary

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

Table 3: Aclidinium/formoterol – extent and probability of added benefit

Research question	**Therapeutic indication**		**ACT**[a]	**Extent and probability of added benefit**
1	Adult patients with COPD of moderate severity (50% ≤ FEV1 < 80% predicted)[b]		LABA (**formoterol**, salmeterol) and/or LAMA (tiotropium)	Indication of an added benefit (extent: "minor")
	Adult patients with COPD with < 2 exacerbations per year	30% ≤ FEV1 < 50% predicted[c]	LABA (**formoterol**, salmeterol) and/or LAMA (tiotropium)	Proof of added benefit (extent: "considerable")
		FEV1 < 30% predicted or respiratory failure[d]	LABA (**formoterol**, salmeterol) and/or LAMA (tiotropium)	Added benefit not proven
2	Adult patients with COPD of severity above moderate (30% ≤ FEV1 < 50% predicted or FEV1 < 30% or respiratory failure)[e] with ≥ 2 exacerbations per year		LABA (**formoterol**, salmeterol) and/or LAMA (tiotropium) **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 specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: Equivalent to COPD grade II according to spirometric classification of severity.
c: Equivalent to COPD grade III according to spirometric classification of severity.
d: Equivalent to COPD grade IV according to spirometric classification of severity.
e: Equivalent to COPD grade III and IV according to spirometric classification of severity.
ACT: appropriate comparator therapy; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; G-BA: Federal Joint Committee; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist

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

2.2 Research question

The aim of the present report is to assess the added benefit of aclidinium/formoterol as a maintenance bronchodilator treatment for relief of symptoms in adult patients with COPD in comparison with the ACT. The drug aclidinium bromide is referred to as "aclidinium" in the following text to facilitate the presentation and improve readability.

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

Table 4: Research questions of the benefit assessment of aclidinium/formoterol

Research question	Therapeutic indication	ACT[a]
1	Adult patients with COPD from moderate severity (50% ≤ FEV1 < 80% predicted)[b]	LABA (**formoterol**, salmeterol) and/or LAMA (tiotropium)
2	Adult patients with COPD of higher severity (30% ≤ FEV1 < 50% predicted or FEV1 < 30% or respiratory failure) with ≥ 2 exacerbations per year[c]	LABA (**formoterol**, 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 corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist

For easier presentation and better readability, the following terms according to the spirometric COPD severity grades of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations [3] are used for the 2 therapeutic indications 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 formoterol for research question 1, and formoterol 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. This does not concur with the company's approach, which, deviating from the G-BA,

specified patients from COPD grade II without concomitant ICS treatment as relevant subpopulation for research question 1 and therefore did not consider the number of exacerbations.

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 aclidinium-formoterol (studies completed up to 12 December 2014)
- bibliographical literature search on aclidinium-formoterol (last search on 12 December 2014)
- search in trial registries for studies on aclidinium-formoterol (last search on 11 December 2014)

To check the completeness of the study pool:

- search in trial registries for studies on aclidinium-formoterol (last search on 9 February 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: aclidinium/formoterol vs. 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)
ACLIFORM (M/40464/30)	Yes	Yes	No
AUGMENT (LAC-MD-31) with extension study LAC-MD-36	Yes	Yes	No
LAC-MD-32	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, analyses of subpopulations on both research questions were the basis of the assessment.

The assessment of the studies deviated from the company's approach in 2 aspects: The data from the extension study LAC-MD-36 were not considered in the benefit assessment, but only reported as additional information (see Section 2.3.2.1). Where reasonable, the data from the 52-week study LAC-MD-32 were pooled in a meta-analysis together with those of the 2 other 24-week studies (see Section 2.4.3).

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 interventions

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

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ACLIFORM (M/40464/30)	RCT, double-blind, parallel multi-centre	Adults (≥ 40 years) ▪ with moderate to severe COPD (FEV1/FVC < 70% and FEV1 ≥ 30% to < 80% predicted) ▪ current or former cigarette smokers with ≥ 10 pack years	ACL/FOR 400/12 µg (N = 385) ACL/FOR 400/6 µg (N = 381)[b] ACL 400 µg (N = 385)[b] FOR 12 µg (N = 384) PLAC (N = 194)[b] Relevant subpopulation: Research question 1[c, d] ACL/FOR 400/12 µg (n = 182) FOR 12 µg (n = 195) Research question 2[e] ACL/FOR 400/12 µg (n = 20) FOR 12 µg (n = 11)	Run-in: 2–3 weeks Treatment: 24 weeks Follow-up: 2 weeks	193 centres in Europe, South Africa, South Korea 10/2011–1/2013	Primary outcome: FEV1 Secondary outcomes: COPD symptoms, exacerbations, health-related quality of life, AEs

(continued)

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
AUGMENT (LAC-MD-31) with extension study LAC-MD-36	RCT, double-blind, parallel, multicentre	Adults (≥ 40 years) ▪ with moderate to severe COPD (FEV1/FVC < 70% and FEV1 ≥ 30% to < 80% predicted) ▪ current or former cigarette smokers with ≥ 10 pack years	ACL/FOR 400/12 µg (N = 338) ACL/FOR 400/6 µg (N = 338)[b] ACL 400 µg (N = 340)[b] FOR 12 µg (N = 339) PLAC (N = 337)[b] Relevant subpopulation: Research question 1[c, f] ACL/FOR 400/12 µg (n = 214) FOR 12 µg (n = 201) Research question 2[e] ACL/FOR 400/12 µg (n = 6) FOR 12 µg (n = 10)	Run-in: 2–3 weeks Treatment: 24 weeks Follow-up: 2 weeks or inclusion in extension study	205 centres in Australia, Canada, New Zealand, United States 9/2011–2/2013	Primary outcome: FEV1 Secondary outcomes: COPD symptoms, exacerbations, health-related quality of life, AEs
			LAC-MD-36 (extension study): Population included: Research question 1[c, g] ACL/FOR 400/12 µg (n = 129) FOR 12 µg (n = 133) Research question 2[e] ACL/FOR 400/12 µg (n = 2) FOR 12 µg (n = 5)	Treatment: 28 weeks Follow-up: 2 weeks	169 centres in Canada and United States 4/2012–6/2013	

(continued)

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
LAC-MD-32	RCT, double-blind, parallel, multicentre	Adults (≥ 40 years) ▪ with moderate to severe COPD (FEV1/FVC < 70% and FEV1 ≥ 30% to < 80% predicted) ▪ current or former cigarette smokers with ≥ 10 pack years	ACL/FOR 400/12 µg (N = 392) FOR 12 µg (N = 198) Relevant subpopulation: Research question 1[c, h] ACL/FOR 400/12 µg (n = 221) FOR 12 µg (n = 115) Research question 2[e] ACL/FOR 400/12 µg (n = 8) FOR 12 µg (n = 2)	Run-in: 2–3 weeks Treatment: 52 weeks Follow-up: 4 weeks	127 centres in United States 9/2011–3/2013	Primary outcome: none specified Secondary outcomes: exacerbations, AEs

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 no longer shown in the following tables.
c: Research question 1 comprises patients with COPD grade II and patients with COPD grades ≥ III with < 2 exacerbations per year (without use of ICS). As an approximation, patients with severity grade II or III without use of ICS were assessed as relevant subpopulation.
d: Of the 377 patients in the subpopulation for research question 1, 20 (5.3%) had COPD grade III and ≥ 2 exacerbations in the year before the start of the study. The only patient with COPD grade IV (in the formoterol group) was not considered in the assessment.
e: Research question 2 comprises patients with COPD grades ≥ III with ≥ 2 exacerbations per year and use of ICS.
f: Of the 415 patients in the subpopulation for research question 1, 7 (1.7%) had COPD grade III and ≥ 2 exacerbations in the year before the start of the study. The 2 patients with COPD grade IV in each relevant group were not considered in the assessment.
g: Of the 262 patients in the subpopulation for research question 1, 4 (1.5%) had COPD grade III and ≥ 2 exacerbations in the year before the start of the study.
h: Of the 336 patients in the subpopulation for research question 1, 9 (2.7%) had COPD grade III and ≥ 2 exacerbations in the year before the start of the study.
ACL: aclidinium; AE: adverse event; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; FOR: formoterol; FVC: forced vital capacity; ICS: inhaled corticosteroids; N: number of randomized patients; n: relevant subpopulation; PLAC: placebo; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison: aclidinium/formoterol vs. formoterol

Study	Intervention	Comparison
ACLIFORM (M/40464/30)	Aclidinium/formoterol 400 µg/12 µg, inhaled twice daily (morning and evening)	Formoterol 12 µg, inhaled twice daily (morning and evening)
	As-needed medication: ▪ salbutamol **Concomitant medication allowed with restriction:** The following medication was allowed if administered at least 4 weeks before the first study visit and expected to be maintained at a stable dosage during the study: ▪ ICS ▪ oral or parenteral corticosteroids[a] ▪ oral methylxanthines (extended-release formulation) ▪ oxygen treatment (< 15 h/d) **Non-permitted concomitant medication:** ▪ other COPD drugs such as anticholinergics (oral, intranasal or parenteral) and long-acting beta-2 sympathomimetics had to be discontinued before the start of the study ▪ patients pretreated with LABA + ICS combination therapy had to be switched to ICS monotherapy in the wash-out phase	
AUGMENT (LAC-MD-36) with extension study LAC-MD-36	Aclidinium/formoterol 400 µg/12 µg, inhaled twice daily (morning and evening)	formoterol 12 µg, inhaled twice daily (morning and evening)
	As-needed medication: ▪ salbutamol or albuterol **Concomitant medication allowed with restriction:** The following medication was allowed if administered at a stable dosage for at least 4 weeks before the first study visit: ▪ ICS ▪ oral or parenteral corticosteroids[a] ▪ oral methylxanthines (extended-release formulation) ▪ oxygen treatment (< 15 h/d) **Non-permitted concomitant medication:** ▪ other COPD drugs such as anticholinergics (oral, intranasal or parenteral) and long-acting beta-2 sympathomimetics had to be discontinued before the start of the study ▪ patients pretreated with LABA + ICS combination therapy had to be switched to ICS monotherapy in the wash-out phase	

(continued)

Table 7: Characteristics of the interventions – RCT, direct comparison: aclidinium/formoterol vs. formoterol (continued)

Study	Intervention	Comparison
LAC-MD-32	Aclidinium/formoterol 400 µg/12 µg, inhaled twice daily (morning and evening)	Formoterol 12 µg, inhaled twice daily (morning and evening)
	As-needed medication: ▪ albuterol **Concomitant medication allowed with restriction:** The following medication was allowed if administered at a stable dosage for at least 4 weeks before the first study visit: ▪ ICS ▪ oral or parenteral corticosteroids[a] ▪ oral methylxanthines (extended-release formulation) ▪ oxygen treatment (< 15 h/d) **Non-permitted concomitant medication:** ▪ other COPD drugs such as anticholinergics (oral, intranasal or parenteral) and long-acting beta-2 sympathomimetics had to be discontinued before the start of the study ▪ patients pretreated with LABA + ICS combination therapy had to be switched to ICS monotherapy in the wash-out phase	
a: Maximum dose equivalent to prednisone: 10 mg/day or 20 mg every 2 days. COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; RCT: randomized controlled trial; vs.: versus		

The 3 studies included (LAC-MD-32, ACLIFORM and AUGMENT with extension study LAC-MD-36) were double-blind, multicentre, randomized, controlled approval studies. The studies lasted 24 weeks (ACLIFORM, AUGMENT) and 52 weeks (LAC-MD-32, AUGMENT with extension study LAC-MD-36). Patients aged 40 years or older with moderate to severe COPD, i.e. of severity grades II and III, were enrolled. Patients also had to have a smoking history of at least 10 pack years at enrolment.

All 3 studies investigated the comparison of one morning and one evening inhalation of the fixed-dose combination of 400 µg aclidinium and 12 µg formoterol versus 12 µg formoterol; the randomization ratio was 1:1 and 2:1 (LAC-MD-32). The studies ACLIFORM and AUGMENT with the extension study LAC-MD-36 had 5 arms and contained additional treatment arms, which are not relevant for the benefit assessment and are 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 or albuterol as rescue medication. Treatment with oral and parenteral corticosteroids, methylxanthines (extended-release formulation) and oxygen treatment under 15 h/d was allowed to be continued as concomitant medication if this treatment had been ongoing at a stable dosage for at least 4 weeks before the first study visit. This also applied to the use of ICS. Bronchodilators such as

anticholinergics and beta-2 sympathomimetics – apart from rescue medication – had to be discontinued before the start of the study.

Hence ICS treatment could be continued in all 3 studies as concomitant treatment irrespective of the severity grade and the frequency of exacerbations of the patients. 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, analyses of subpopulations for both research questions were therefore the basis of the assessment (see Section 2.3.2.2).

Assessment of the available data on the observation period of 52 weeks

Both results at the end of the study after 24 weeks and results including the extension study LAC-MD-36, i.e. for an observation period of 52 weeks, were available for the AUGMENT study. The 52-week results of the AUGMENT/LAC-MD-36 study had a high risk of bias because of the high rate of discontinuation (see Section 2.3.2.2 and Section 2.7.2.4.2 of the full dossier assessment). In addition, there were no data for some outcomes. The results are therefore presented only as additional information in Appendix A of the full dossier assessment.

Where reasonable, the results of the 52-week study LAC-MD-32 were pooled in meta-analyses together with those of both 24-week studies ACLIFORM and AUGMENT (see Section 2.4.3).

2.3.2.2 Characteristics of the study populations

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, Table 9 and Table 10 show the patient characteristics in the relevant subpopulations of the studies included for research question 1.

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

Study Group	N[a]	Age [years]	Sex [F/M]	Duration of COPD [years]	Smoking status (current smoker/ ex-smoker)	Smoking [pack years]	Treatment discontin-uations
		mean (SD)	%	mean (SD)	%	mean (SD)	n (%)
ACLIFORM							
ACL/FOR	182	63 (9)	32/68	7.8 (6.3)	54/46	40.2 (19.2)	18 (9.9)
FOR	195	63 (8)	32/68	7.8 (6.3)	50/50	42.0 (21.0)	26 (13.3)
AUGMENT/ LAC-MD-36							AUGMENT:
ACL/FOR	214	64 (9)	48/52	8.6 (6.6)	54/46	52.0 (24.9)	46 (21.5)[b]
FOR	201	62 (9)	46/54	8.0 (6.0)	61/39	52.4 (23.3)	36 (17.9)[b]
							AUGMENT/ LAC-MD-36[c]:
ACL/FOR							106 (49.5)[d]
FOR							93 (46.3)[d]
LAC-MD-32							
ACL/FOR	221	62 (10)	44/56	8.0 (6.7)	58/42	49.6 (25.1)	59 (26.7)
FOR	115	63 (10)	41/59	7.4 (5.6)	50/50	54.4 (31.1)	37 (32.2)

a: Number of randomized patients; all percentages, except for patients who discontinued treatment, are based on the ITT population.
b: Patients who discontinued treatment after 24 weeks.
c: Due to the large proportion of patients in the AUGMENT/LAC-MD-36 study who discontinued treatment in the observation period of 52 weeks, the corresponding results are presented only as additional information in Appendix A of the full dossier assessment.
d: Patients who discontinued treatment after 52 weeks including patients who were not included in the extension phase. Of the randomized patients in the AUGMENT study, 168 of 214 patients in the aclidinium/formoterol group, and 165 of 201 patients in the formoterol group completed the first 24 weeks of the study. 39 (18.2%) patients in the aclidinium/formoterol group and 32 (15.9%) patients in the formoterol group did not participate in the extension study after the end of the AUGMENT study. The number of patients who discontinued treatment and percentages were calculated by the Institute.
ACL: aclidinium; COPD: chronic obstructive pulmonary disease; F: female; FOR: formoterol; ITT: intention to treat; M: male; N: number of randomized patients; n: number of patients in the category; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

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

Study Severity[a] Group	N	COPD exacerbations in the year prior to screening n (%)		
		0	1	≥ 2
ACLIFORM				
Grade II				
ACL/FOR	124	87 (70.2)	27 (21.8)	10 (8.1)
FOR	132	101 (76.5)	23 (17.4)	8 (6.1)
Grade III				
ACL/FOR	58	32 (55.2)	14 (24.1)	12 (20.7)[b]
FOR	63	36 (57.1)	19 (30.2)	8 (12.7)[b]
AUGMENT/ LAC-MD-36				
Grade II				
ACL/FOR	137	114 (83.2)	16 (11.7)	7 (5.1)
FOR	130	105 (80.8)	17 (13.1)	8 (6.2)
Grade III				
ACL/FOR	74	59 (79.7)	12 (16.2)	3 (4.1)[b]
FOR	68	54 (79.4)	10 (14.7)	4 (5.9)[b]
LAC-MD-32				
Grade II				
ACL/FOR	134	113 (84.3)	13 (9.7)	8 (6.0)
FOR	66	50 (75.8)	12 (18.2)	4 (6.1)
Grade III				
ACL/FOR	85	67 (78.8)	13 (15.3)	5 (5.9)[b]
FOR	47	34 (72.3)	9 (19.1)	4 (8.5)[b]

a: Spirometric COPD severity is classified based on the FEV1: 50% ≤ FEV1 < 80% corresponds to grade II, 30% ≤ FEV1 < 50% corresponds to grade III [3].
b: Patients with ≥ 2 exacerbations per year are not relevant for research question 1. However, the company only presented an analysis including these patients (patients with severity grade II or III without use of ICS). Nonetheless, this population was assessed as an approximation to the relevant subpopulation because the proportion of patients with ≥ 2 exacerbations per year is sufficiently small.

ACL: aclidinium; AE: adverse event; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; FOR: formoterol; ICS: inhaled corticosteroids; N: number of patients in the intention-to-treat population; n: number of patients with event; RCT: randomized controlled trial; vs.: versus

Table 10: Characteristics of the study populations (COPD premedication) – RCT, direct comparison: aclidinium/formoterol vs. formoterol (research question 1)

Study Group	N	COPD premedication allowed to be continued during the study n (%)		
		Xanthines	Oxygen treatment	Systemic corticosteroids
ACLIFORM				
ACL/FOR	182	16 (8.8)	0 (0.0)	4 (2.2)
FOR	195	24 (12.3)	1 (0.5)	2 (1.0)
AUGMENT/ LAC-MD-36				
ACL/FOR	211	1 (0.5)	9 (4.3)	1 (0.5)
FOR	198	0 (0.0)	10 (5.1)	1 (0.5)
LAC-MD-32				
ACL/FOR	219	1 (0.5)	3 (1.4)	2 (0.9)
FOR	113	0 (0.0)	1 (0.9)	1 (0.9)

ACL: aclidinium; COPD: chronic obstructive pulmonary disease; FOR: formoterol; N: number of patients in the intention-to-treat population; n: number of patients in the category; RCT: randomized controlled trial; vs.: versus

According to the company's analysis, the assessed subpopulations of the 3 studies included for research question 1 contain all patients with COPD grade II and III without concomitant ICS treatment.

The mean age of patients in this subpopulation was about 63 years, mean duration of COPD was approximately 8 years, and about 60% of the patients were men. Somewhat more than half of the patients were active cigarette smoker at study inclusion. Overall, the mean number of pack years was 40 (ACLIFORM) to over 50.

Patients with COPD grade II constituted approximately 60 to 70% and were therefore the largest group. The proportion of patients with COPD grade III, with 40%, was highest in the LAC-MD-32 study. Due to the inclusion criteria of the studies, there were only 4 participants with COPD grade IV in total, who, according to the company's approach, were not considered for the assessment of research question 1. There were therefore no data of patients with COPD grade IV for answering research question 1. Over 90% of the participants had no or only one exacerbation in the previous year. The difference between research question 1 of this benefit assessment and the corresponding approach by the company becomes apparent in patients with 2 or more exacerbations. The subpopulation presented by the company (patients without concomitant ICS treatment) also includes 36 patients with COPD grade III and with 2 or more exacerbations in the previous year. They are therefore not relevant for research question 1. Overall, depending on the study, these are only 1.7 to at most 5.3% (ACLIFORM) of the patients randomized to the relevant subpopulation. Hence the subpopulation analysed by the company for research question 1 was considered to be evaluable as an approximation for the benefit assessment, and the corresponding analyses were included in the assessment.

The subpopulation presented by the company also includes 45 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 proportion of patients with premedication with influence on the COPD that was also allowed during the study was mostly below 5%. Only in the ACLIFORM study, approximately 10% of the participants were taking xanthine as concomitant medication.

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

The proportion of patients who discontinued treatment reflects the duration of the study and was therefore in the area of 30% (LAC-MD-32) to almost 50% (AUGMENT/LAC-MD-36) across the groups in the 52-week studies, i.e. approximately twice as high as in both 24-week studies ACLIFORM and AUGMENT. Due to the high rate of discontinuation of the AUGMENT/LAC-MD-36 study, its results have a high risk of bias (see Section 2.7.2.4.2 of the full dossier assessment). In addition, there were no data for some outcomes. The results are therefore presented only as additional information in Appendix A of the full dossier assessment.

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

Table 11 and Table 12 show the patient characteristics in the relevant subpopulations of the studies included for research question 2.

Table 11: Characteristics of the study populations – RCT, direct comparison: aclidinium/formoterol + ICS vs. formoterol + ICS (research question 2)

Study Group	N[a]	Age [years] mean (SD)	Sex [F/M] %	Duration of COPD [years] mean (SD)	Smoking status (current smoker/ ex-smoker) %	Smoking [pack years] mean (SD)	Disease severity [COPD grades][b] n (%) III/IV	COPD exacerbations in the year prior to screening n (%) ≥ 2	Treatment discontin-uations n (%)
ACLIFORM									
ACL/FOR + ICS	20	63 (8)	35/65	10.5 (6.8)	30/70	38.2 (16.1)	20 (100)/0 (0)	20 (100)	1 (5)
FOR + ICS	11	62 (9)	45/55	10.1 (5.9)	45/55	41.8 (19.8)	11 (100)/0 (0)	11 (100)	1 (9)
AUGMENT/ LAC-MD-36[c]									AUGMENT:
ACL/FOR + ICS	6	67 (5)	50/50	9.3 (5.6)	50/50	48.1 (18.4)	6 (100)/0 (0)	6 (100)	1 (16.7)[e]
FOR + ICS	10	62 (7)[d]	89/11[d]	9.9 (8.5)	56/44	45.8 (20.1)	9 (100)[d]/0 (0)	9 (100)[d]	4 (40.0)[e]
									AUGMENT/ LAC-MD-36
ACL/FOR + ICS									4 (66.7)[f]
FOR + ICS									5 (50.0)[f]
LAC-MD-32									
ACL/FOR + ICS	8	64 (9)	88/13[g]	8.3 (4.9)	38/63[g]	48.4 (22.2)	8 (100)/0 (0)	8 (100)	4 (50)
FOR + ICS	2	60 (8)	100/0	5.0 (2.8)	0/100	30.0 (14.1)	2 (100)/0 (0)	2 (100)	2 (100)

(continued)

Table 11: Characteristics of the study populations – RCT, direct comparison: aclidinium/formoterol + ICS vs. formoterol + ICS (research question 2) (continued)

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding column if the deviation is relevant.
b: Spirometric COPD severity is classified based on the FEV1: 30% ≤ FEV1 < 50% corresponds to grade III, FEV1 < 30% corresponds to grade IV [3].
c: The patients included in the LAC-MD-36 study are not presented separately in the characteristics table because only the total ITT population of the AUGMENT/LAC-MD-36 study over 52 weeks is relevant for the assessment.
d: Data for the ITT, N = 9.
e: Patients who discontinued treatment after 24 weeks.
f: Patients who discontinued treatment after 52 weeks including patients who were not included in the extension phase. Of the randomized patients in the AUGMENT study, 5 of 6 patients in the aclidinium/formoterol group, and 6 of 10 patients in the formoterol group completed the first 24 weeks of the study. 3 patients in the aclidinium/formoterol group and 1 patient in the formoterol group did not participate in the extension study after the end of the AUGMENT study. No patient discontinued treatment in the extension. The number of patients who discontinued treatment and percentages were calculated by the Institute.
g: > 100% because of rounding.

ACL: aclidinium; COPD: chronic obstructive pulmonary disease; F: female; FEV1: forced expiratory volume in 1 second; FOR: formoterol; ICS: inhaled corticosteroids; ITT: intention to treat; M: male; N: number of randomized patients; n: number of patients in the category; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Table 12: Characteristics of the study populations (COPD premedication) – RCT, direct comparison: aclidinium/formoterol + ICS vs. formoterol + ICS (research question 2)

Study Group	N	COPD premedication allowed to be continued during the study n (%)		
		Xanthines	Oxygen treatment	Systemic corticosteroids
ACLIFORM				
ACL/FOR + ICS	20	6 (30.0)	0 (0)	0 (0)
FOR + ICS	11	4 (36.4)	1 (9.1)	1 (9.1)
AUGMENT/ LAC-MD-36				
ACL/FOR + ICS	6	0 (0)	0 (0)	0 (0)
FOR + ICS	9	1 (11.1)	1 (11.1)	1 (11.1)
LAC-MD-32				
ACL/FOR + ICS	8	0 (0)	0 (0)	0 (0)
FOR + ICS	2	0 (0)	0 (0)	0 (0)

ACL: aclidinium; COPD: chronic obstructive pulmonary disease; FOR: formoterol; ICS: inhaled corticosteroids; N: number of patients in the intention-to-treat population; n: number of patients in the category; RCT: randomized controlled trial; vs.: versus

The relevant subpopulation of the 3 studies included for research question 2 contains only patients with COPD grade III with 2 or more exacerbations in the previous year. All patients received concomitant ICS treatment. This was a small subpopulation with only 57 patients in total.

According to the inclusion criteria of the studies, there was no study participant with COPD grade IV in the relevant subpopulation. There were therefore no data of patients with COPD grade IV for answering research question 2.

Differences in patient characteristics in comparison with research question 1 are difficult to interpret because they might be caused not by the different disease state, but by the small sample size alone. Against this background it can only be determined that the proportion of women was higher in the subpopulation on research question 2 in the AUGMENT/LAC-MD-36 and LAC-MD-32 studies, and that the mean duration of COPD was one year longer in the ACLIFORM and AUGMENT/LAC-MD-36 studies than in the subpopulation on research question 1.

Poor comparability of the study arms within the studies, and of the studies with one another, particularly regarding the distribution of sex, is probably also rather due to the small sample sizes than to inadequate randomization.

In summary it can be noted, however, that the aspects mentioned have to be considered in the interpretation of effects in the subpopulation on research question 2.

The large differences in the proportion of patients who discontinued treatment in the individual studies and study arms were probably also influenced by the small sample sizes. Although no further patient discontinued treatment during the extension study of the AUGMENT study (LAC-MD-36), the overall rate of patients who discontinued treatment was very high because only 9 of 16, i.e. only 56% of the relevant patients participated in the extension. Due to this large proportion of patients who discontinued treatment and the fact that no data were available for some outcomes, these results – in analogy to research question 1 – are presented only as additional information in Appendix A of the full dossier assessment.

2.3.2.3 Risk of bias at study level

Table 13 shows the risk of bias at study level under consideration of the subpopulation relevant for research question 1 and 2 respectively.

Table 13: Risk of bias at study level on the basis of the relevant subpopulation for the respective research question – RCT, direct comparison: aclidinium/formoterol (+ ICS) vs. formoterol (+ ICS)

Research question 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: aclidinium/formoterol vs. formoterol							
ACLIFORM[a]	Yes	Yes	Yes	Yes	Yes	Yes	Low
AUGMENT (LAC-MD-31)[a]	Yes	Yes	Yes	Yes	Yes	Yes	Low
AUGMENT with extension study LAC-MD-36[a]	Yes	Yes	Yes	Yes	Yes	No[b]	High[b]
LAC-MD-32[a]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Research question 2: aclidinium/formoterol + ICS vs. formoterol + ICS							
ACLIFORM[c]	Yes	Yes	Yes	Yes	Yes	Yes	Low
AUGMENT (LAC-MD-31)[c]	Yes	Yes	Yes	Yes	Yes	No[b]	High[b]
AUGMENT with extension study LAC-MD-36[c]	Yes	Yes	Yes	Yes	Yes	No[b]	High[b]
LAC-MD-32[c]	Yes	Yes	Yes	Yes	Yes	No[b]	High[b]

a: The assessment of the risk of bias at study level was conducted on the basis of the relevant subpopulation for research question 1.
b: Large proportion of patients who discontinued treatment.
c: The assessment of the risk of bias at study level was conducted on the basis of the relevant subpopulation for research question 2.
ICS: inhaled corticosteroids; RCT: randomized controlled trial; vs.: versus

For research question 1, the risk of bias at study level was rated as low for the ACLIFORM, AUGMENT and LAC-MD-32 studies, and as high for the AUGMENT study with extension study LAC-MD-36. 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.

The assessment of the second subpopulation investigated deviated from the one of research question 1 and therefore from the company's assessment. For research question 2, the risk of bias was rated as high already at study level also for the AUGMENT and LAC-MD-32 studies because of the high proportion of patients who discontinued treatment, which has an influence on all outcomes.

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)
  - COPD symptoms (E-RS)
  - moderate exacerbations (HCRU)
  - severe exacerbations (HCRU)
  - 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 14 shows for which outcomes data were available in the studies included.

Table 14: Matrix of outcomes – RCT, direct comparison: aclidinium/formoterol (+ ICS) vs. formoterol (+ ICS)

Research question / Study	All-cause mortality	COPD symptoms – TDI	COPD symptoms – E-RS	Moderate exacerbations (HCRU)	Severe exacerbations (HCRU)	Health-related quality of life – SGRQ	Health status – EQ-5D VAS	SAEs	Discontinuation due to AEs
Research question 1: aclidinium/formoterol vs. formoterol									
ACLIFORM	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
AUGMENT	Yes	Yes	Yes	Yes	Yes	Yes	No[a]	Yes	Yes
AUGMENT with extension study LAC-MD-36	Yes	No[b]	No[b]	Yes	Yes	No[b]	No[a]	Yes	Yes
LAC-MD-32	Yes	No[a]	No[a]	Yes	Yes	No[a]	No[a]	Yes	Yes
Research question 2: aclidinium/formoterol + ICS vs. formoterol + ICS									
ACLIFORM	Yes	Yes	No[b]	Yes	Yes	Yes	Yes	Yes	Yes
AUGMENT	Yes	No[b]	No[b]	Yes	Yes	No[b]	No[a]	Yes	Yes
AUGMENT with extension study LAC-MD-36	Yes	No[b]	No[b]	No[b]	No[b]	No[b]	No[a]	Yes	Yes
LAC-MD-32	Yes	No[a]	No[a]	Yes	Yes	No[a]	No[a]	Yes	Yes

a: The outcome was not recorded in the study.
b: No evaluable data available.

AE: adverse event; COPD: chronic obstructive pulmonary disease; EQ-5D: European Quality of Life-5 Dimensions; E-RS: Exacerbation of Chronic Pulmonary Disease Tool Respiratory Symptoms; HCRU: Health Care Resource Utilization; ICS: inhaled corticosteroids; 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 15 shows the risk of bias for the relevant outcomes.

Table 15: Risk of bias at study and outcome level – RCT, direct comparison: aclidinium/formoterol (+ ICS) vs. formoterol (+ ICS)

Research question / **Study**	**Study level**	**Outcomes**								
		All-cause mortality	**COPD symptoms – TDI**	**COPD symptoms – E-RS**	**moderate exacerbations (HCRU)**	**Severe exacerbations (HCRU)**	**Health-related quality of life – SGRQ**	**Health status – EQ-5D VAS**	**SAEs**	**Discontinuation due to AEs**
Research question 1: aclidinium/formoterol vs. formoterol										
ACLIFORM[a]	L	L	L	L	H[b]	H[b]	L	L	L	L
AUGMENT (LAC-MD-31)[a]	L	L	L	L	H[b]	H[b]	L	–[c]	L	L
AUGMENT with extension study LAC-MD-36[a]	H[d]	H[d]	–[e]	–[e]	H[d]	H[d]	–[e]	–[c]	H[d]	H[d]
LAC-MD-32[a]	L	L	–[c]	–[c]	L	L	–[c]	–[c]	L	L
Research question 2: aclidinium/formoterol + ICS vs. formoterol + ICS										
ACLIFORM[f]	L	L	H[g]	–[h]	H[b]	H[b]	H[g]	L	L	L
AUGMENT (LAC-MD-31)[f]	H[d]	H[d]	–[i]	–[h]	H[b, d]	H[b, d]	–[i]	–[c]	H[d]	H[d]
AUGMENT with extension study LAC-MD-36[f]	H[d]	H[d]	–[e]	–[h]	–[e]	–[e]	–[e]	–[c]	H[d]	H[d]
LAC-MD-32[f]	H[d]	H[d]	–[c]	–[c]	H[d]	H[d]	–[c]	–[c]	H[d]	H[d]

a: The assessment of the risk of bias at outcome level was conducted on the basis of the relevant subpopulation for research question 1.
b: The analyses presented deviate from the analyses planned a priori; selective reporting cannot be excluded.
c: The outcome was not recorded in the study.
d: Large proportion of patients who discontinued treatment.
e: No evaluable data for the 52-week time period.
f: The assessment of the risk of bias at outcome level was conducted on the basis of the relevant subpopulation for research question 2.
g: Proportion of LOCF-imputed values unclear.
h: No data for the response threshold used in the assessment (score reduction of ≥ 3.35 points).
i: No evaluable data because inadequate implementation of the ITT principle (patients without consideration in the analysis > 30% or difference between the groups in the proportion of patients without consideration in the analysis > 15 percentage points).

AE: adverse event; COPD: chronic obstructive pulmonary disease; EQ-5D: European Quality of Life-5 Dimensions; E-RS: Exacerbation of Chronic Pulmonary Disease Tool Respiratory Symptoms; H: high; HCRU: Health Care Resource Utilization; ICS: inhaled corticosteroids; ITT: intention to treat; L: low; LOCF: last observation carried forward; RCT: randomized controlled trial; SAE: serious adverse event; SGRQ: St. George's Respiratory Questionnaire; TDI: Transition Dyspnoea Index; VAS: visual analogue scale; vs.: versus

This assessment concurs with the company's assessment except for the following aspects: The risk of bias for the outcomes on exacerbations (HCRU) in the ACLIFORM and AUGMENT studies was rated as high for both research questions because the company did not present the planned analysis for the relevant subpopulations.

Moreover, the risk of bias in the ACLIFORM study was rated as low also for research question 2 for the following outcomes: mortality, EQ-5D VAS, SAEs, and discontinuation due to AEs. This does not concur with the general assessment of the company that all outcomes for research question 2 have a high risk of bias due to the low number of patients.

2.4.3 Results

Methods for information synthesis

The results of the 52-week study LAC-MD-32 were pooled in meta-analyses together with those of both 24-week studies ACLIFORM and AUGMENT. In case of important heterogeneity in the meta-analysis, the different study duration was considered as possible explaining factor. However, the study duration was unsuitable in any case to explain the heterogeneity. This deviates from the company's approach, which did not pool the results of the LAC-MD-32 study with those of the ACLIFORM and AUGMENT studies in a meta-analysis for the outcomes included. The company provided no justification for not having conducted a pooled meta-analysis including the LAC-MD-32 study, except for an outcome not included in the assessment. The forest plots of all meta-analyses calculated by the Institute can be found in Appendix B of the full dossier assessment.

Both results at the end of the study after 24 weeks and results including the extension study LAC-MD-36, i.e. for an observation period of 52 weeks, were available for the AUGMENT study. The 52-week results of the AUGMENT/LAC-MD-36 study had a high risk of bias because of the rate of discontinuation of almost 50%. Moreover, data for the 52-week period were not available for all outcomes. The results are therefore presented only as additional information in Appendix A 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 16, Table 17 and Table 18 summarize the results on the comparison of aclidinium/ formoterol versus formoterol in patients with COPD grade II and patients with COPD grade III with fewer than 2 exacerbations per year. No data were available for patients with COPD grade IV with fewer than 2 exacerbations per year. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations.

Analysis of the binary outcomes TDI, E-RS and SGRQ

The company conducted a primarily planned regression model in the analysis of the binary outcomes TDI, E-RS an SGRQ of research question 1, which considers all available information with an additional analysis. This analysis was assessed to be adequate and

included in the assessment because in the present situation it has a lower risk of bias than the calculation of relative risks based on 2x2 tables (see Section 2.7.2.2 of the full dossier assessment). Since the resulting effect estimate is an odds ratio and the determination of the extent of added benefit is based on the relative risk, the relative risks (based on the odds ratios and the estimated baseline risk in the comparator group with all patients who discontinued treatment were categorized as non-responders) were additionally recalculated for all significant effects (see Table 16).

Table 16: Results (morbidity and health-related quality of life – including results from primarily planned regression models) – RCT, direct comparison: aclidinium/formoterol vs. formoterol (research question 1)

Outcome category Outcome	Aclidinium/ formoterol		Formoterol		Aclidinium/formoterol vs. formoterol	
Study	N	Patients with event n (%)	N	Patients with event n (%)	OR [95% CI]; p-value	RR [95% CI][a]
Morbidity						
COPD symptoms (TDI responder)[b]						
ACLIFORM	182	115[c] (63.2)[d]	195	106[c] (54.4)[d]	1.41 [0.80; 2.47][e]; 0.233	
AUGMENT	211	100[c] (47.4)[d]	198	83[c] (41.9)[d]	1.72 [0.97; 3.02][e]; 0.062	
LAC-MD-32	Outcome not recorded					
Total					1.54 [1.04; 2.29][f]; 0.033	1.22 [1.04; 1.44]; 0.017[g]
COPD symptoms (E-RS total score responder[h])						
ACLIFORM	182	67[c] (36.8)[d]	194	57[c] (29.4)[d]	1.60 [0.93; 2.76][e]; 0.088	
AUGMENT	211	80[c] (37.9)[d]	198	51[c] (25.8)[d]	1.89 [1.14; 3.14][e]; 0.014	
LAC-MD-32	Outcome not recorded					
Total					1.75 [1.21; 2.53][f]; 0.003	1.45 [1.16; 1.81]; 0.001[g]
Health-related quality of life						
SGRQ responder[i]						
ACLIFORM	182	93[c] (51.1)[d]	195	97[c] (49.7)[d]	1.05 [0.59; 1.85][e]; 0.869	
AUGMENT	211	100[c] (47.4)[d]	198	75[c] (37.9)[d]	1.70 [0.94; 3.08][e]; 0.078	
LAC-MD-32	Outcome not recorded					
Total					1.34 [0.89; 2.02][f]; 0.164	

(continued)

Table 16: Results (morbidity and health-related quality of life – including results from primarily planned regression models) – RCT, direct comparison: aclidinium/formoterol vs. formoterol (research question 1) (continued)

a: The RRs were calculated by the Institute on the basis of the ORs and the estimated baseline risk in the comparator group to determine the added benefit. All patients who discontinued treatment were classified as non-responders and are only presented in case of significant OR.
b: Patients with TDI total score ≥ 1.
c: Patients with response by the end of the study. These numbers serve as information only and were not used for calculating the OR or the RR.
d: Percentage calculated by the Institute on the basis of the ITT population.
e: OR determined with logistic regression model defined a priori under consideration of missing values using the direct likelihood method [4] on the basis of the ITT population.
f: Calculated from IPD meta-analysis.
g: Institute's calculation of RR based on the effect measure OR provided and on the baseline risk of the control group (imputation of all patients who discontinued treatment with non-response).
h: E-RS total score responder: reduction of ≥ 3.35 points.
i: Patients with a reduction in the SGRQ total score of ≥ 4.

CI: confidence interval; COPD: chronic obstructive pulmonary disease; E-RS: Exacerbation of Chronic Pulmonary Disease Tool Respiratory Symptoms; IPD: individual patient data; ITT: intention to treat; N: number of analysed patients; n: number of patients with event; NC: not calculable; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk; SGRQ: St. George's Respiratory Questionnaire; TDI: Transition Dyspnoea Index; vs.: versus

Table 17: Results (mortality, morbidity and AEs) – RCT, direct comparison: aclidinium/formoterol vs. formoterol (research question 1)

Outcome category Outcome Study	Aclidinium/ formoterol		Formoterol		Aclidinium/formoterol vs. formoterol
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Mortality					
All-cause mortality					
ACLIFORM	182	0 (0)	195	1 (0.5)	ND
AUGMENT	211	1 (0.5)	198	0 (0)	ND
LAC-MD-32	220	2 (0.9)	115	0 (0)	ND
Total					1.41 [0.23; 8.65]; 0.708[a]
Morbidity					
Moderate exacerbations (HCRU)					
ACLIFORM	182	9 (4.9)	195	22 (11.3)	0.44 [0.21; 0.93]; 0.031[b]
AUGMENT	211	23 (10.9)	198	18 (9.1)	1.20 [0.67; 2.15]; 0.543[b]
LAC-MD-32	220	44 (20.0)	115	25 (21.7)	0.92 [0.59; 1.42]; 0.708[b]
Total	heterogeneity[a]: Q = 4.46; df = 2; p = 0.108; I^2 = 55.1%				
Severe exacerbations (HCRU)					
ACLIFORM	182	2 (1.1)	195	1 (0.5)	2.14 [0.20; 23.43]; 0.532[b]
AUGMENT	211	1 (0.5)	198	4 (2.0)	0.23 [0.03; 2.08]; 0.193[b]
LAC-MD-32	220	7 (3.2)	115	8 (7.0)[c]	0.46 [0.17; 1.23]; 0.121[b, c]
Total					0.50 [0.22; 1.17]; 0.109[a]
Adverse events					
AEs					
ACLIFORM	182	88 (48.4)	195	106 (54.4)	
AUGMENT	211	132 (62.6)	198	106 (53.5)	
LAC-MD-32	220	149 (67.7)	115	76 (66.1)	
SAEs					
ACLIFORM	182	9 (4.9)	195	10 (5.1)	0.96 [0.40; 2.32]; 0.935
AUGMENT	211	12 (5.7)	198	4 (2.0)	2.82 [0.92; 8.58]; 0.069
LAC-MD-32	220	23 (10.5)	115	13 (11.3)	0.92 [0.49; 1.76]; 0.811
Total					1.21 [0.65; 2.22]; 0.548[a]
Discontinuation due to AEs					
ACLIFORM	182	4 (2.2)	195	5 (2.6)	0.86 [0.23; 3.14]; 0.816
AUGMENT	211	13 (6.2)	198	6 (3.0)	2.03 [0.79; 5.25]; 0.142
LAC-MD-32	220	14 (6.4)	115	6 (5.2)	1.22 [0.48; 3.09]; 0.675
Total					1.38 [0.77; 2.50]; 0.282[a]

(continued)

Table 17: Results (mortality, morbidity and AEs) – RCT, direct comparison: aclidinium/formoterol vs. formoterol (research question 1) (continued)

a: Institute's calculation from meta-analysis.
b: Effect from logistic regression model.
c: Discrepancies between information in Module 4 A and Module 5 of the dossier. The values presented are from additional analyses by the company in Module 5.
AE: adverse event; CI: confidence interval; HCRU: Health Care Resource Utilization; N: number of analysed patients; n: number of patients with (at least one) event; ND: no data; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Table 18: Results (morbidity: health status) – RCT, direct comparison: aclidinium/formoterol vs. formoterol (research question 1)

Outcome category **Outcome** **Study**	**Aclidinium/formoterol**			**Formoterol**			**Aclidinium/ formoterol vs. formoterol**
	N[a]	**Baseline values mean (SD)**	**Change at end of study mean[b] (SE)**	**N[a]**	**Baseline values mean (SD)**	**Change at end of study mean[b] (SE)**	**Mean difference [95% CI][b]; p-value**
Morbidity							
Health status (EQ-5D VAS)							
ACLIFORM	182	65.59 (16.85)	4.92 (1.05)	195	65.60 (15.76)	4.32 (1.01)	0.60 [−2.23; 3.43]; 0.677
AUGMENT	Outcome not recorded						
LAC-MD-32	Outcome not recorded						

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: Results from MMRM.
CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale; vs.: versus

Mortality

The meta-analysis of the studies included showed no statistically significant difference between the treatment groups for the outcome "all-cause mortality" in the relevant subpopulation of research question 1. This results in no hint of an added benefit of aclidinium/formoterol in comparison with formoterol; an added benefit for overall survival is therefore not proven.

This concurs with the company's assessment.

Morbidity

COPD symptoms (TDI responder)

The meta-analysis of the studies included showed a statistically significant difference between the treatment groups in favour of aclidinium/formoterol for the outcome "COPD symptoms (TDI responder)" in the relevant subpopulation of research question 1. This was of only marginal effect size (see Section 2.5.1.1.1). In the subsequent course of the assessment of subgroup characteristics, there was an indication of an effect modification by the characteristic "COPD severity grade". As a result, possible conclusions on added benefit regarding this outcome were based on the subgroups. 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 of aclidinium/formoterol in comparison with formoterol for patients with COPD grade II or for patients with COPD grade III with fewer than 2 exacerbations per year; an added benefit for the outcome "TDI responder" is therefore not proven.

This deviates from the company's assessment, which claimed proof of an added benefit both for patients with COPD grade II and for patients with COPD grade III with fewer than 2 exacerbations per year.

COPD symptoms (E-RS responder)

The meta-analysis of the studies included showed a statistically significant difference between the treatment groups in favour of aclidinium/formoterol for the outcome "COPD symptoms (E-RS responder – response threshold based on distribution: total score reduction of ≥ 3.35 points)" in the relevant subpopulation of research question 1. In the subsequent course of the assessment of subgroup characteristics, there was an indication of an effect modification by the characteristic "COPD severity grade". As a result, possible conclusions on added benefit regarding this outcome were based on the subgroups. 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 in patients with COPD grade II and proof of an added benefit in patients with COPD grade III with fewer than 2 exacerbations per year for the proportion of E-RS responders.

The company came to similar results based on a different response threshold (total score reduction of ≥ 2 points), but claimed proof of an added benefit both for patients with COPD grade II and for patients with COPD grade III with fewer than 2 exacerbations per year.

Moderate exacerbations (HCRU)

The meta-analysis of the studies included showed important inexplicable heterogeneity without clear direction of result for the outcome "proportion of patients with moderate exacerbations (HCRU)" in the relevant subpopulation of research question 1. Overall, this

results in no hint of an added benefit of aclidinium/formoterol in comparison with formoterol; an added benefit for moderate exacerbations is therefore not proven.

This concurs with the company's assessment. The results on the outcome "rate of moderate exacerbations" presented as additional information can be found in Appendix A, Table 35, of the full dossier assessment.

Severe exacerbations (HCRU)

The meta-analysis of the studies included showed no statistically significant difference between the treatment groups for the outcome "proportion of patients with severe exacerbations (HCRU)" in the relevant subpopulation of research question 1. In the subsequent course of the assessment of subgroup characteristics, there was an indication of an effect modification by the characteristic "COPD severity grade", however. As a result, possible conclusions on added benefit regarding this outcome were based on the subgroups. 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 in patients with COPD grade III with fewer than 2 exacerbations per year for the proportion of patients with severe exacerbation (HCRU).

This deviates from the company's assessment, which derived no added benefit from this outcome for research question 1.

The results on the outcome "rate of severe exacerbations" presented as additional information can be found in Appendix A, Table 35, of the full dossier assessment.

Health status (EQ-5D VAS)

There was no statistically significant difference between the treatment groups in the relevant subpopulation of research question 1 in the ACLIFORM study for the outcome "health status (EQ-5D)". This outcome was not recorded in the 2 other studies. This results in no hint of an added benefit of aclidinium/formoterol in comparison with formoterol; an added benefit for health status is therefore not proven.

This concurs with the company's assessment.

Health-related quality of life

SGRQ responder

The meta-analysis of the studies included showed no statistically significant difference between the treatment groups for the outcome "SGRQ responder" in the relevant subpopulation of research question 1. This results in no hint of an added benefit of aclidinium/formoterol in comparison with formoterol; an added benefit for the proportion of SGRQ responders is therefore not proven.

This concurs with the company's assessment.

Adverse events

SAEs and discontinuation due to AEs

The meta-analysis of the studies included showed no statistically significant difference between the treatment groups for the outcomes "SAEs" and "discontinuation due to AEs" in the relevant subpopulation of research question 1. This results in no hint of greater or lesser harm of aclidinium/formoterol in comparison with formoterol; greater or lesser harm for SAEs and discontinuation due to AEs is therefore not proven.

This concurs with the company's assessment.

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

Table 19, Table 20 and Table 21 summarize the results on the comparison of aclidinium/ formoterol versus formoterol in patients with COPD grade III with 2 or more exacerbations per year. No data were available for patients with COPD grade IV with 2 or more exacerbations per year. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations.

Analysis of the binary outcomes "TDI", "E-RS" and "SGRQ"

A logistic regression model for correlated data on the basis of a generalized estimating equation (GEE) was used in the analysis of the binary outcomes "TDI", "E-RS" and "SGRQ" of research question 2. The effect estimate of this analysis was an odds ratio so that in principle an additional calculation of the relative risk would have been required for determining the extent of added benefit. Since no significant effect resulted for any of the binary outcomes, however, no such calculation was conducted (see Table 19).

Table 19: Results (morbidity and health-related quality of life – results from logistic regression for correlated data [GEE model]) – RCT, direct comparison: aclidinium/formoterol + ICS vs. formoterol + ICS (research question 2)

Outcome category Outcome Study	Aclidinium/ formoterol + ICS		Formoterol + ICS		Aclidinium/formoterol + ICS vs. formoterol + ICS
	N	Patients with event n (%)	N	Patients with event n (%)	OR [95% CI]; p-value
Morbidity					
COPD symptoms (TDI responder[a])					
ACLIFORM	20	12 (60.0)[b]	10	5 (50.0)[b]	1.38 [0.26; 7.26][c]; 0.705
AUGMENT	6	ND[d]	6	ND[d]	ND[d]
LAC-MD-32	Outcome not recorded				
COPD symptoms (E-RS total score responder[e])					
ACLIFORM	20	ND	10	ND	ND
AUGMENT	6	ND	9	ND	ND
LAC-MD-32	Outcome not recorded				
Health-related quality of life					
SGRQ responder[f]					
ACLIFORM	19	9 (47.4)[g]	10	5 (50.0)[g]	0.73 [0.12; 4.24][c]; 0.722
AUGMENT	4	ND[h]	4	ND[h]	ND[h]
LAC-MD-32	Outcome not recorded				

a: Patients with TDI total score ≥ 1.
b: Number of responders from LOCF analysis for patients with at least one TDI value.
c: OR determined with logistic regression for correlated data based on GEE.
d: The results are not presented because there was a difference of > 15% in the proportion of patients not considered in the analysis between the arms.
e: E-RS total score responder: reduction of ≥ 3.35 points.
f: Patients with a reduction in the SGRQ total score of ≥ 4.
g: Number of responders from LOCF analysis for patients with at least one SGRQ value.
h: The results are not presented because < 70% of the patients were analysed.

CI: confidence interval; GEE: generalized estimating equation; ICS: inhaled corticosteroids; LOCF: last observation carried forward; N: number of analysed patients; n: number of patients with event; ND: no data; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk; SGRQ: St. George's Respiratory Questionnaire; TDI: Transition Dyspnoea Index; vs.: versus

Table 20: Results (mortality, morbidity and AEs) – RCT, direct comparison: aclidinium/formoterol + ICS vs. formoterol + ICS (research question 2)

Outcome category Outcome Study	Aclidinium/formoterol + ICS		Formoterol + ICS		Aclidinium/formoterol + ICS vs. formoterol + ICS
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Mortality					
All-cause mortality					
ACLIFORM	20	0 (0)	11	0 (0)	NC
AUGMENT	6	0 (0)	9	0 (0)	NC
LAC-MD-32	8	0 (0)	2	0 (0)	NC
Total					NC
Morbidity					
Moderate exacerbations (HCRU)					
ACLIFORM	20	4 (20.0)	11	4 (36.4)	0.55 [0.17; 1.78]; 0.318
AUGMENT	6	2 (33.3)	9	3 (33.3)	1.00 [0.23; 4.31]; > 0.999
LAC-MD-32	8	7 (87.5)	2	1 (50.0)	1.75 [0.43; 7.17]; 0.437
Total					0.91 [0.42; 1.97]; 0.819[a]
Severe exacerbations (HCRU)					
ACLIFORM	20	0 (0)	11	0 (0)	NC
AUGMENT	6	0 (0)	9	0 (0)	NC
LAC-MD-32	8	0 (0)	2	0 (0)	NC
Total					NC
Adverse events					
AEs					
ACLIFORM	20	10 (50.0)	11	5 (45.5)	
AUGMENT	6	5 (83.3)	9	4 (44.4)	
LAC-MD-32	8	7 (87.5)	2	0 (0)	
SAEs					
ACLIFORM	20	1 (5.0)	11	0 (0)	1.71 [0.08; 38.86]; 0.572[b]
AUGMENT	6	0 (0)	9	0 (0)	NC
LAC-MD-32	8	0 (0)	2	0 (0)	NC
Total					NC
Discontinuation due to AEs					
ACLIFORM	20	0 (0)	11	1 (9.1)	0.19 [0.01; 4.32]; 0.172[b]
AUGMENT	6	0 (0)	9	0 (0)	NC
LAC-MD-32	8	0 (0)	2	0 (0)	NC
Total					NC

a: Institute's calculation from meta-analysis.
b: Institute's calculation with continuity correction.
AE: adverse event; CI: confidence interval; HCRU: Health Care Resource Utilization; ICS: inhaled corticosteroids; N: number of analysed patients; n: number of patients with (at least one) event; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Table 21: Results (morbidity: health status) – RCT, direct comparison: aclidinium/formoterol + ICS vs. formoterol + ICS (research question 2)

Outcome category Outcome Study	Aclidinium/formoterol + ICS			Formoterol + ICS			Aclidinium/formoterol + ICS vs. formoterol + ICS
	N[a]	Baseline values mean (SD)	Change at end of study mean[b] (SE)	N[a]	Baseline values mean (SD)	Change at end of study mean[b] (SE)	Mean difference [95% CI][b]; p-value
Morbidity							
Health status (EQ-5D VAS)							
ACLIFORM	16	53.00 (8.99)	5.51 (3.99)	10	58.00 (16.69)	6.08 (4.92)	−0.57 [−13.15; 12.01]; 0.928
AUGMENT	Outcome not recorded						
LAC-MD-32	Outcome not recorded						

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: Results from MMRM.
CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; ICS: inhaled corticosteroids; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale; vs.: versus

Mortality

No deaths occurred in any of the studies in the relevant subpopulation of research question 2. This results in no hint of an added benefit of aclidinium/formoterol + ICS in comparison with formoterol + ICS; an added benefit for overall survival is therefore not proven.

This concurs with the company's assessment.

Morbidity

COPD symptoms (TDI responder)

There was no statistically significant difference between the treatment groups in the relevant subpopulation of research question 2 in the ACLIFORM study for the outcome "COPD symptoms (TDI responder)". This outcome was not recorded in the 2 other studies or no evaluable data were available. This results in no hint of an added benefit of aclidinium/formoterol + ICS in comparison with formoterol + ICS; an added benefit for the proportion of TDI responders is therefore not proven.

This concurs with the company's assessment.

COPD symptoms (E-RS responder)

No evaluable data were available for research question 2 for the response threshold based on distribution (total score reduction of ≥ 3.35 points) for the outcome "COPD symptoms (E-RS

responder)". This results in no hint of an added benefit of aclidinium/formoterol + ICS in comparison with formoterol + ICS; an added benefit for the proportion of E-RS responders is therefore not proven.

The company did not present the outcome on the basis of the response threshold based on distribution in Module 4 A of the dossier. However, it came to the same assessment on the basis of a different response threshold (total score reduction of ≥ 2 points).

Moderate exacerbations (HCRU)

The meta-analysis of the studies included showed no statistically significant difference between the treatment groups for the outcome "proportion of patients with moderate exacerbations (HCRU)" in the relevant subpopulation of research question 2. This results in no hint of an added benefit of aclidinium/formoterol + ICS in comparison with formoterol + ICS; an added benefit for moderate exacerbations is therefore not proven.

This concurs with the company's assessment. The results on the outcome "rate of moderate exacerbations" presented as additional information can be found in Appendix A, Table 36, of the full dossier assessment.

Severe exacerbations (HCRU)

No severe exacerbations occurred in any of the studies in the relevant subpopulation of research question 2. This results in no hint of an added benefit of aclidinium/formoterol + ICS in comparison with formoterol + ICS; an added benefit for severe exacerbations is therefore not proven.

This concurs with the company's assessment. The results on the outcome "rate of severe exacerbations" presented as additional information can be found in Appendix A, Table 36, of the full dossier assessment.

Health status (EQ-5D VAS)

There was no statistically significant difference between the treatment groups in the relevant subpopulation of research question 2 in the ACLIFORM study for the outcome "health status (EQ-5D)". This outcome was not recorded in the 2 other studies. This results in no hint of an added benefit of aclidinium/formoterol + ICS in comparison with formoterol + ICS; an added benefit for health status is therefore not proven.

This concurs with the company's assessment.

Health-related quality of life

SGRQ responder

There was no statistically significant difference between the treatment groups in the relevant subpopulation of research question 2 in the ACLIFORM study for the outcome "health-related quality of life (SGRQ responder)". This outcome was not recorded in the 2 other

studies or no evaluable data were available. This results in no hint of an added benefit of aclidinium/formoterol + ICS in comparison with formoterol + ICS; an added benefit for the proportion of SGRQ responders is therefore not proven.

This concurs with the company's assessment.

Adverse events

SAEs and discontinuation due to AEs

In total, there was only one patient with SAE and one patient with discontinuation due to AEs in the relevant subpopulation of research question 2 of all studies included. This results in no hint of greater or lesser harm of aclidinium/formoterol + ICS in comparison with formoterol + ICS; greater or lesser harm for SAEs and discontinuation due to AEs is therefore not proven.

This concurs with the company's assessment.

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 years and ≥ 65 years)
- COPD severity (grade II and grade III)

The company additionally presented investigations on the characteristic "region", which are not considered because the classification in country groups is not comprehensible.

The subgroup results of the 52-week study LAC-MD-32 were pooled in meta-analyses together with those of both 24-week studies ACLIFORM and AUGMENT. In case of important heterogeneity in the meta-analysis, the different study duration was considered as possible explaining factor. However, the study duration was unsuitable in any case to explain the heterogeneity. This deviates from the company's approach, which did not pool the subgroup results of the LAC-MD-32 study with those of the ACLIFORM and AUGMENT studies.

The 52-week results of the AUGMENT/LAC-MD-36 study had a high risk of bias because of the rate of discontinuation of almost 50%. Hence deviating from the company, the results of subgroup analyses of this observation period were not considered in the benefit assessment.

Only the results on subgroups and outcomes with at least indications of an interaction between treatment effect and subgroup characteristic and with statistically significant results in at least one subgroup are presented. The prerequisite for proof of different subgroup effects

is a statistically significant interaction ($p < 0.05$). A p-value ≥ 0.05 and < 0.2 provides an indication of an effect modification. The forest plots of meta-analyses calculated by the Institute can be found in Appendix B of the full dossier assessment.

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

Table 22 and Table 23 present the relevant results on subgroups in patients with COPD grade II and patients with COPD grade III with fewer than 2 exacerbations per year. No data were available for patients with COPD grade IV with fewer than 2 exacerbations per year.

Table 22: Subgroups (morbidity – including results from primarily planned regression models) – RCT, direct comparison: aclidinium/formoterol vs. formoterol (research question 1)

Outcome Characteristic Study Subgroup	Aclidinium/ formoterol		Formoterol		Aclidinium/formoterol vs. formoterol	
	N	Patients with event n (%)	N	Patients with event n (%)	OR [95% CI]; p-value	RR [95% CI][a]
COPD symptoms (TDI responder[b])						
COPD severity grade						
ACLIFORM						
Grade II	124	74[c] (59.7)[d]	132	72[c] (54.5)[d]	1.25 [0.64; 2.45][e]; 0.522	
Grade III	58	41[c] (70.7)[d]	63	34[c] (54.0)[d]	1.91 [0.67; 5.45][e]; 0.225	
AUGMENT						
Grade II	137	63[c] (46.0)[d]	130	58[c] (44.6)[d]	1.32 [0.65; 2.66][e]; 0.440	
Grade III	74	37[c] (50.0)[d]	68	25[c] (36.8)[d]	2.87 [1.08; 7.66][e]; 0.035	
LAC-MD-32	Outcome not recorded					
Total					Interaction: 0.169[f]	
Grade II					1.27 [0.78; 2.06]; 0.332[f]	1.12 [0.91; 1.39]; 0.292[g]
Grade III					2.31 [1.14; 4.68]; 0.020[f]	1.46 [1.106; 1.92]; 0.008[g]
COPD symptoms (E-RS responder[h])						
COPD severity grade						
ACLIFORM						
Grade II	124	45[c] (36.3)[d]	131	40[c] (30.5)[d]	1.43 [0.74; 2.80][e]; 0.290	
Grade III	58	22[c] (37.9)[d]	63	17[c] (27.0)[d]	2.02 [0.77; 5.25][e]; 0.151	
AUGMENT						
Grade II	137	44[c] (32.1)[d]	130	32[c] (24.6)[d]	1.46 [0.77; 2.79][e]; 0.249	
Grade III	74	36[c] (48.6)[d]	68	19[c] (27.9)[d]	2.97 [1.29; 6.84][e]; 0.010	
LAC-MD-32	Outcome not recorded					
Total					Interaction: 0.185[f]	
Grade II					1.46 [0.92; 2.30]; 0.106[f]	1.29 [0.96; 1.73]; 0.095[g]
Grade III					2.45 [1.32; 4.56]; 0.005[f]	1.80 [1.31; 2.47]; < 0.001[g]

(continued)

Table 22: Subgroups (morbidity – including results from primarily planned regression models) – RCT, direct comparison: aclidinium/formoterol vs. formoterol (research question 1) (continued)

a: The RRs were calculated by the Institute on the basis of the ORs and the estimated baseline risk in the comparator group to determine the added benefit. All patients who discontinued treatment were classified as non-responders and are only presented in case of significant OR.
b: Patients with TDI total score ≥ 1.
c: Patients with response by the end of the study. These numbers serve as information only and were not used for calculating the OR or the RR.
d: Percentage calculated by the Institute on the basis of the ITT population.
e: OR determined with logistic regression model defined a priori under consideration of missing values using the direct likelihood method [4] on the basis of the ITT population.
f: Calculated from IPD meta-analysis.
g: Institute's calculation of RR based on the effect measure OR provided and on the baseline risk of the control group (imputation of all patients who discontinued treatment with non-response).
h: E-RS total score responder: reduction of ≥ 3.35 points.

CI: confidence interval; COPD: chronic obstructive pulmonary disease; E-RS: Exacerbation of Chronic Pulmonary Disease Tool Respiratory Symptoms; IPD: individual patient data; ITT: intention to treat; N: number of analysed patients; n: number of patients with event; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk; TDI: Transition Dyspnoea Index; vs.: versus

Table 23: Subgroups (morbidity) – RCT, direct comparison: aclidinium/formoterol vs. formoterol (research question 1)

Outcome / Characteristic / Study / Subgroup	Aclidinium/formoterol N	Aclidinium/formoterol Patients with events n (%)	Formoterol N	Formoterol Patients with events n (%)	Aclidinium/formoterol vs. formoterol RR [95% CI]	p-value
Severe exacerbations (HCRU)						
COPD severity grade						
ACLIFORM						
Grade II	124	2 (1.6)	132	1 (0.8)	2.13 [0.20; 23.19]	0.535
Grade III	58	0 (0.0)	63	0 (0.0)	NC	NC
AUGMENT						
Grade II	137	1 (0.7)	130	2 (1.5)	0.47 [0.04; 5.17]	0.541
Grade III	74	0 (0.0)	68	2 (2.9)	0.18 [0.01; 3.77][b]	0.151[c]
LAC-MD-32						
Grade II	134	3 (2.2)	68	0 (0.0)	3.58 [0.19; 68.29][b]	0.233[c]
Grade III	86	4 (4.7)	47	8 (17.0)[d]	0.27 [0.09; 0.86][d]	0.027[d]
Total					Interaction:	0.072[a]
Grade II					1.38 [0.32; 5.95][a]	0.670[a]
Grade III					0.26 [0.09; 0.76][a]	0.014[a]

a: Institute's calculation from meta-analysis.
b: Institute's calculation with continuity correction.
c: p-value from CSZ test [5], Institute's calculation.
d: Discrepancies between information in Module 4 A and Module 5 of the dossier. The values presented are from additional analyses by the company in Module 5.

CI: confidence interval; CSZ: convexity, symmetry, z score; HCRU: Health Care Resource Utilization; N: number of analysed patients; n: number of patients with event; NC: not calculable; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Mortality

For the outcome "overall survival", no effect modification by sex, age or severity grade was identified for research question 1.

This concurs with the company's assessment.

Morbidity

COPD symptoms (TDI responder)

There was a statistically significant difference between the treatment groups in favour of aclidinium/formoterol for the outcome "COPD symptoms (TDI responder)" in the total subpopulation of research question 1. This was of only marginal effect size (see Table 16). There was an indication of interaction regarding the characteristic "severity grade". The result of the subgroup analysis in the meta-analysis showed a statistically significant effect only in patients with COPD grade III. This was of only marginal effect size (see Section 2.5.1.1.1).

Overall, there was no hint of an added benefit of aclidinium/formoterol in comparison with formoterol for patients with COPD grade II or for patients with COPD grade III with fewer than 2 exacerbations per year; an added benefit for the outcome "TDI responder" is therefore not proven.

This deviates from the company's assessment, which interpreted the results in such a way that the effect was "particularly strongly pronounced" in the subgroup of patients with COPD grade III. It claimed proof of an added benefit both for patients with COPD grade II and for patients with COPD grade III with fewer than 2 exacerbations per year.

For the outcome "COPD symptoms (TDI responder)", no effect modification by sex or age was identified for research question 1.

This concurs with the company's assessment.

COPD symptoms (E-RS responder)

There was a statistically significant difference between the treatment groups in favour of aclidinium/formoterol for the outcome "COPD symptoms (E-RS responder – response threshold based on distribution: total score reduction of ≥ 3.35 points)" in the total subpopulation of research question 1 (see Table 16). There was an indication of interaction regarding the characteristic "severity grade". The result of the subgroup analysis in the meta-analysis showed a statistically significant effect only in patients with COPD grade III.

Overall, there was proof of an added benefit in patients with COPD grade III with fewer than 2 exacerbations per year for the outcome "COPD symptoms (E-RS responder)". Despite a non-significant effect, there was an indication of an added benefit for the outcome "COPD symptoms (E-RS responder)" for patients with COPD grade II because there was only an indication of an interaction and the result of the total population was statistically significant.

The company did not present the outcome on the basis of the response threshold based on distribution in Module 4 A of the dossier. However, it came to similar results on the basis of a different response threshold (total score reduction of ≥ 2 points). It determined a statistically significant difference between the treatment groups in favour of aclidinium/formoterol in the total subpopulation of research question 1, and found proof of interaction regarding the characteristic "severity grade". The company claimed that it considered the results of the subgroup analysis of the meta-analysis on the basis of the individual patient data (IPD) to be the decisive basis of the assessment of added benefit, but interpreted this in such a way that the subgroup of patients of COPD grade III "has greater benefit". Overall, it claimed proof of an added benefit both for patients with COPD grade II and for patients with COPD grade III with fewer than 2 exacerbations per year.

For the outcome "COPD symptoms (E-RS responder – response threshold based on distribution)", no effect modification by sex or age was identified for research question 1.

This deviates from the company's assessment, which found proof of an effect modification by age on the basis of the anchor-based response threshold. According to the company's interpretation, patients aged over 65 years with COPD grade II and III "have particular benefit". Overall, it claimed proof of an added benefit both for patients with COPD grade II and for patients with COPD grade III with fewer than 2 exacerbations per year, irrespective of the age group.

Moderate exacerbations (HCRU)

For the outcome "proportion of patients with moderate exacerbations (HCRU)", no effect modification by sex, age or severity grade was identified for research question 1.

This concurs with the company's assessment.

Severe exacerbations (HCRU)

There was no statistically significant difference between the treatment groups for the outcome "proportion of patients with severe exacerbations (HCRU)" in the total subpopulation of research question 1 (see Table 17). There was an indication of interaction regarding the characteristic "severity grade". The result of the subgroup analysis in the meta-analysis showed a statistically significant effect only in patients with COPD grade III.

Overall, there was an indication of an added benefit in patients with COPD grade III with fewer than 2 exacerbations per year for the outcome "severe exacerbations (HCRU)" because the result of the total population was not statistically significant. For patients with COPD grade II, there was no hint of added benefit of aclidinium/formoterol in comparison with formoterol; an added benefit for severe exacerbations is therefore not proven.

This deviates from the company's approach, which conducted no meta-analysis including the LAC-MD-32 study for this outcome and which made no overall conclusion of the study results of the different studies. It determined that the smaller sample size has to be taken into account in the interpretation of the results. Overall, it derived no added benefit for research question 1 from this outcome.

For the outcome "severe exacerbations (HCRU)", no effect modification by sex or age was identified for research question 1.

This concurs with the company's assessment.

Health status (EQ-5D VAS)

For the outcome "health status (EQ-5D VAS)", no effect modification by sex, age or severity grade was identified for research question 1.

This concurs with the company's assessment.

Health-related quality of life

SGRQ responder

For the outcome "SGRQ responder", no effect modification by sex, age or severity grade was identified for research question 1.

This concurs with the company's assessment.

Adverse events

SAEs and discontinuation due to AEs

For the outcomes "SAEs" and "discontinuation due to AEs", no effect modification by sex, age or severity grade was identified for research question 1.

This concurs with the company's assessment.

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

It was not possible to investigate the results of patients with COPD grades ≥ III with 2 or more exacerbations per year regarding effect modification by severity grade because no data on patients with COPD grade IV with 2 or more exacerbations per year were available.

No effect modification by age or sex was identified for any of the outcomes included.

The company did not present subgroup analyses on research question 2 and made its corresponding investigations available only as additional analyses in Module 5.

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit of aclidinium/formoterol 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 Assessment of added benefit at outcome level

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

2.5.1.1.1 Assessment of added benefit at outcome level

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

- an indication of an added benefit regarding COPD symptoms (E-RS total score responder) for patients with COPD grade II
- proof of an added benefit regarding COPD symptoms (E-RS total score responder) for patients with COPD grade III with fewer than 2 exacerbations per year
- an indication of an added benefit regarding severe exacerbations for patients with COPD grade III with fewer than 2 exacerbations per year

Furthermore, there was an indication of interaction regarding the characteristic "severity grade" in the total relevant subpopulation of research question 1 in the outcome "TDI responder". The result of the subgroup analysis in the meta-analysis showed a statistically significant difference only in patients with COPD grade III, which was in favour of aclidinium/formoterol in comparison with formoterol. The effect size in conjunction with the classification in the outcome categories "non-serious/non-severe symptoms/late complications" (see next section) was assessed as "marginal".

Determination of the outcome category for the outcomes "TDI responder" and "E-RS 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. Apart from the average baseline values of the entire subpopulations relevant for research question 1, this would also require the responders' data to check whether, in an extreme scenario, the responders only include patients with 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 relevant studies (ACLIFORM, AUGMENT) had a mean Baseline Dyspnoea Index (BDI) with a minimum value of 5.7 and a maximum value of 6.9, depending on the study, COPD severity grade, and 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. The corresponding questions of the BDI and the magnitude of the patients' respiratory symptoms according to the breathlessness subscale of the E-RS questionnaire were considered to assess the outcome category. Overall, a rather moderate limitation of the patients could be derived. Hence the TDI results were allocated to the outcome category "non-serious/non-severe symptoms/late complications)".

Depending on the study and the study arm, the mean baseline E-RS scores of the subpopulation relevant for research question 1 were between 9.8 and 12.3 (COPD grade II) and between 12.4 and 14.6 (COPD grade III), which is to be rated rather as mild respiratory symptoms, according to the questionnaire. Resulting from this consideration in conjunction with the dimensions recorded, the E-RS 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 these results (see Table 24). In the overall assessment, it was investigated whether different conclusions on the extent of added benefit arise for the individual patient groups.

Table 24: Extent of added benefit at outcome level: aclidinium/formoterol vs. formoterol (research question 1: adult patients with COPD grade II and adult patients with COPD grade III with < 2 exacerbations per year)

Outcome category **Outcome**	**Aclidinium/formoterol vs. formoterol** **Proportion of events[a]/mean if applicable** **effect estimate [95% CI]** **p-value** **probability[b]**	**Derivation of extent[c]**
Mortality		
All-cause mortality	ACL/FOR: 0% to 1% FOR: 0% to 1% RR: 1.41 [0.23; 8.65][d] p = 0.708	Added benefit not proven
Morbidity		
COPD symptoms (TDI responder)	ACL/FOR: 47% to 63% FOR: 42% to 54% RR: 1.22 [1.04; 1.44][e] RR: 0.82 [0.69; 0.96][f] p = 0.017	
COPD grade II	ACL/FOR: 46% to 60% FOR: 45% to 55% RR: 1.12 [0.91; 1.39][e] p = 0.292	Added benefit not proven
COPD grade III with < 2 exacerbations per year	ACL/FOR: 50% to 71% FOR: 37% to 54% RR: 1.46 [1.106; 1.92][e] RR: 0.68 [0.52; 0.904][f] p = 0.008	Outcome category: non-serious/non-severe symptoms/late complications $1 > CI_u > 0.90$ Added benefit not proven[g]
COPD symptoms (E-RS total score responder)	ACL/FOR: 37% to 38% FOR: 26% to 29% RR: 1.45 [1.16; 1.81][e] RR: 0.69 [0.55; 0.86][f] p = 0.001	
COPD grade II	ACL/FOR: 32% to 36% FOR: 25% to 31% RR: 1.29 [0.96; 1.73][e] p = 0.095 probability: "indication"	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "minor"[h]
COPD grade III with < 2 exacerbations per year	ACL/FOR: 38% to 49% FOR: 27% to 28% RR: 1.80 [1.31; 2.47][e] RR: 0.56 [0.40; 0.76][f] p < 0.001 probability: "proof"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 > CI_u$ added benefit, extent: "considerable"

(continued)

Table 24: Extent of added benefit at outcome level: aclidinium/formoterol vs. formoterol (research question 1: adult patients with COPD grade II and adult patients with COPD grade III with < 2 exacerbations per year) (continued)

Outcome category **Outcome**	**Aclidinium/formoterol vs. formoterol** **Proportion of events[a]/mean if applicable** **effect estimate [95% CI]** **p-value** **probability[b]**	**Derivation of extent[c]**
Moderate exacerbations	Heterogeneity without clear direction of result	Added benefit not proven
Severe exacerbations	ACL/FOR: 1% to 3% FOR: 1% to 7% RR: 0.50 [0.22; 1.17][d] p = 0.109	
COPD grade II	ACL/FOR: 1% to 2% FOR: 0% to 2% RR: 1.38 [0.32; 5.95][d] p = 0.670	Added benefit not proven
COPD grade III	ACL/FOR: 0% to 5% FOR: 0% to 17% RR: 0.26 [0.09; 0.76][d] p = 0.014 probability: “indication”	Outcome category: Serious/severe symptoms/late complications $0.9 > CI_u > 0.75$ added benefit, extent: “non-quantifiable” (at most “considerable”)
Health status (EQ-5D VAS)	ACL/FOR: 4.9[i] FOR: 4.3[i] MD: 0.60 [−2.23; 3.43] p = 0.677	Added benefit not proven
Health-related quality of life		
SGRQ responder	ACL/FOR: 47% to 51% FOR: 38% to 50% OR: 1.34 [0.89; 2.02][d] p = 0.164	Added benefit not proven
Adverse events		
SAEs	ACL/FOR: 5% to 11% FOR: 2% to 11% RR: 1.21 [0.65; 2.22][d] p = 0.548	Greater/lesser harm not proven
Discontinuation due to AEs	ACL/FOR: 2% to 6% FOR: 3% to 5% RR: 1.38 [0.77; 2.50][d] p = 0.282	Greater/lesser harm not proven

(continued)

Table 24: Extent of added benefit at outcome level: aclidinium/formoterol vs. formoterol (research question 1: adult patients with COPD grade II and adult patients with COPD grade III with < 2 exacerbations per year) (continued)

a: Minimum and maximum proportions of events in each treatment arm in the studies included.
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 from meta-analysis.
e: Institute's calculation of RR based on the effect measure OR provided and on the baseline risk of the control group (imputation of all patients who discontinued treatment with non-response).
f: Institute's calculation: reversed direction of effect to enable direct use of limits to derive added benefit.
g: The added benefit is not proven because the effect size was only marginal.
h: The extent of added benefit was derived from the effect of the total population because there was only an indication of interaction. The CI_u for the total population was between 0.9 and 0.80.
i: Mean change from baseline.

ACL: aclidinium; 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; E-RS: Exacerbation of Chronic Pulmonary Disease Tool Respiratory Symptoms; FOR: formoterol; MD: mean difference; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SGRQ: St. George's Respiratory Questionnaire; TDI: Transition Dyspnoea Index; VAS: visual analogue scale; vs.: versus

2.5.1.1.2 Overall conclusion on added benefit

Table 25 and Table 26 summarize the results that were considered in the overall conclusion on the extent of added benefit, separated according to the relevant subgroups.

Table 25: Patients with COPD grade II: positive and negative effects from the assessment of aclidinium/formoterol in comparison with formoterol (research question 1)

Positive effects	**Negative effects**
Indication of added benefit – extent "minor" (non-serious /non-severe symptoms/late complications: E-RS)	–

COPD: chronic obstructive pulmonary disease; E-RS: Exacerbation of Chronic Pulmonary Disease Tool Respiratory Symptoms

Overall, on the basis of the available results, a positive effect at outcome level in the outcome category "non-serious/non-severe symptoms/late complications (E-RS)" was shown for the group of patients with COPD grade II.

In summary, there is an indication of a minor added benefit of aclidinium/formoterol in comparison with formoterol for patients with COPD grade II.

Table 26: Patients with COPD grade III with < 2 exacerbations: positive and negative effects from the assessment of aclidinium/formoterol in comparison with formoterol (research question 1)

Positive effects	**Negative effects**
Proof of added benefit – extent "considerable" (non-serious /non-severe symptoms/late complications: E-RS)	–
Indication of added benefit, extent: "non-quantifiable", at most "considerable" (serious/severe symptoms/late complications: severe exacerbations)	–
COPD: chronic obstructive pulmonary disease; E-RS: Exacerbation of Chronic Pulmonary Disease Tool Respiratory Symptoms	

Overall, on the basis of the available results, 2 positive effects at outcome level in the outcome categories "serious/severe symptoms/late complications (severe exacerbations)" and "non-serious/non-severe symptoms/late complications (E-RS)" were shown for the group of patients with COPD grade III with fewer than 2 exacerbations per year.

In summary, there is proof of considerable added benefit of aclidinium/formoterol in comparison with formoterol for patients with COPD grade III with fewer than 2 exacerbations per year.

Since no data were presented for the subpopulation of patients with COPD grade IV with fewer than 2 exacerbations per year, an added benefit of aclidinium/formoterol in comparison with the ACT is not proven for this subpopulation.

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

2.5.1.2.1 Assessment of added benefit at outcome level

The data presented in Section 2.4 for research question 2 resulted in no added benefit of aclidinium/formoterol + ICS versus formoterol + ICS for any outcome. The corresponding extent of added benefit is described in Table 27.

Table 27: Extent of added benefit at outcome level: aclidinium/formoterol + ICS vs. formoterol + ICS (research question 2, adult patients with COPD grade III with ≥ 2 exacerbations per year)

Outcome category **Outcome**	**Aclidinium/formoterol + ICS vs. formoterol + ICS** **Proportion of events[a]/mean if applicable** **effect estimate [95% CI]** **p-value** **probability[b]**	**Derivation of extent[c]**
Mortality		
All-cause mortality	0% vs. 0%	Added benefit not proven
Morbidity		
COPD symptoms (TDI responder)	60% vs. 50% OR: 1.38 [0.26; 7.26] p = 0.705	Added benefit not proven
COPD symptoms (E-RS total score responder)	No evaluable data available	Added benefit not proven
Moderate exacerbations	ACL/FOR: 20% to 88% FOR: 33% to 50% RR: 0.91 [0.42; 1.97] p = 0.819	Added benefit not proven
Severe exacerbations	0% vs. 0%	Added benefit not proven
Health status (EQ-5D VAS)	5.5[d] vs. 6.1[d] MD: −0.57 [−13.15; 12.01] p = 0.928	Added benefit not proven
Health-related quality of life		
SGRQ responder	47% vs. 50% OR: 0.73 [0.12; 4.24] p = 0.722	Added benefit not proven
Adverse events		
SAEs	ACL/FOR: 5% to 0% FOR: 0% 1.71 [0.08; 38.86] p = 0.572	Greater/lesser harm not proven
Discontinuation due to AEs	ACL/FOR: 0% FOR: 0% to 9% 0.19 [0.01; 4.32] p = 0.172	Greater/lesser harm not proven

(continued)

Table 27: Extent of added benefit at outcome level: aclidinium/formoterol + ICS vs. formoterol + ICS (research question 2, adult patients with COPD grade III with ≥ 2 exacerbations per year) (continued)

a: Minimum and maximum proportions of events in each treatment arm in the studies included.
b: Probability provided if statistically significant differences were present.
c: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
d: Mean change from baseline.
ACL: aclidinium; 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; E-RS: Exacerbation of Chronic Pulmonary Disease Tool Respiratory Symptoms; FOR: formoterol; MD: mean difference; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SGRQ: St. George's Respiratory Questionnaire; TDI: Transition Dyspnoea Index; VAS: visual analogue scale; vs.: versus

2.5.1.2.2 Overall conclusion on added benefit

Table 28 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 28: Patients with COPD grade III with ≥ 2 exacerbations: positive and negative effects from the assessment of aclidinium/formoterol + ICS in comparison with formoterol + ICS (research question 2)

Positive effects	**Negative effects**
–	–
COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroids	

There are neither positive nor negative effects for adult patients with COPD grade III with 2 or more exacerbations per year. No data were presented for the subpopulation of patients with COPD grade IV with 2 or more exacerbations per year.

In summary, an added benefit of aclidinium/formoterol + ICS for adult patients with COPD grades III and IV with 2 or more exacerbations per year versus the ACT (formoterol + ICS) is not proven.

2.5.2 Extent and probability of added benefit – summary

The result of the assessment of the added benefit of aclidinium/formoterol in comparison with the ACT is summarized in Table 29.

Table 29: Aclidinium/formoterol – extent and probability of added benefit

Research question	Therapeutic indication		ACT[a]	Extent and probability of added benefit
1	Adult patients with COPD of moderate severity (50% ≤ FEV1 < 80% predicted)[b]		LABA (**formoterol**, salmeterol) and/or LAMA (tiotropium)	Indication of an added benefit (extent: "minor")
	Adult patients with COPD with < 2 exacerbations per year	30% ≤ FEV1 < 50% predicted[c]	LABA (**formoterol**, salmeterol) and/or LAMA (tiotropium)	Proof of added benefit (extent: "considerable")
		FEV1 < 30% predicted or respiratory failure[d]	LABA (**formoterol**, salmeterol) and/or LAMA (tiotropium)	Added benefit not proven
2	Adult patients with COPD of severity above moderate (30% ≤ FEV1 < 50% predicted or FEV1 < 30% or respiratory failure)[e] with ≥ 2 exacerbations per year		LABA (**formoterol**, salmeterol) and/or LAMA (tiotropium) **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 specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: Equivalent to COPD grade II according to spirometric classification of severity [3].
c: Equivalent to COPD grade III according to spirometric classification of severity [3].
d: Equivalent to COPD grade IV according to spirometric classification of severity [3].
e: Equivalent to COPD grade III and IV according to spirometric classification of severity [3].
ACT: appropriate comparator therapy; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; G-BA: Federal Joint Committee; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist

The overall assessment deviates from that of the company, which claimed proof of considerable added benefit not only for patients with COPD grade III with fewer than 2 exacerbations per year, but also for patients with COPD grade II.

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

ACLIFORM (M/40464/30)

Almirall. Efficacy and safety of aclidinium bromide/formoterol fumarate fixed-dose combinations compared with individual components and placebo when administered to patients with stable chronic obstructive pulmonary disease [online]. In: EU Clinical Trials Register. [Accessed: 9 February 2015]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2011-001524-38.

Almirall. Long-term efficacy and safety of aclidinium/formoterol fixed-dose combination: full text view [online]. In: ClinicalTrials.gov. 8 February 2013 [accessed: 9 February 2015]. URL: http://ClinicalTrials.gov/show/NCT01462942.

Almirall. Efficacy and safety of aclidinium bromide/formoterol fumarate fixed-dose combinations compared with individual components and placebo when administered to patients with stable chronic obstructive pulmonary disease: study M/40464/30; clinical study report [unpublished]. 2013.

AUGMENT (LAC-MD-31)

Forest Laboratories. Efficacy, safety and tolerability of aclidinium bromide/formoterol fumarate compared with formoterol fumarate in patients with moderate to severe chronic obstructive pulmonary disease (COPD): full text view [online]. In: ClinicalTrials.gov. 5 April 2013 [accessed: 9 February 2015]. URL: http://ClinicalTrials.gov/show/NCT01437397.

Forest Research Institute. A phase III, randomized, double-blind, placebo-controlled study evaluating the efficacy, safety, and tolerability of two fixed-dose combinations of aclidinium bromide/formoterol fumarate compared with aclidinium bromide, formoterol fumarate and placebo for 24-weeks treatment in patients with moderate to severe, stable chronic obstructive pulmonary disease (COPD): study LAC-MD-31; clinical study report [unpublished]. 2013.

LAC-MD-32

Forest Laboratories. Safety and tolerability of aclidinium bromide/formoterol fumarate compared with formoterol fumarate in patients with moderate to severe chronic obstructive pulmonary disease (LAC): full text view [online]. In: ClinicalTrials.gov. 5 April 2013 [accessed: 9 February 2015]. URL: http://ClinicalTrials.gov/show/NCT01437540.

Forest Research Institute. A long-term, randomized study of the safety and tolerability of a fixed-dose combination of aclidinium bromide/formoterol fumarate compared with formoterol fumarate in patients with moderate to severe, stable chronic obstructive pulmonary disease (COPD): study LAC-MD-32; clinical study report [unpublished]. 2013.

LAC-MD-36

Forest Laboratories. Efficacy, safety and tolerability of two fixed dose combinations of aclidinium bromide/formoterol fumarate, aclidinium bromide, formoterol fumarate and placebo for 28-weeks treatment in patients with moderate to severe, stable chronic obstructive pulmonary disease (COPD): full text view [online]. In: ClinicalTrials.gov. 30 June 2013 [accessed: 9 February 2015]. URL: http://ClinicalTrials.gov/show/NCT01572792.

Forest Research Institute. A phase III, long-term, randomized, double-blind, extension study of the efficacy, safety and tolerability of two fixed-dose combinations of aclidinium bromide/formoterol fumarate, aclidinium bromide, formoterol fumarate, and placebo for 28-weeks treatment in patients with moderate to severe, stable chronic obstructive pulmonary disease (COPD): study LAC-MD-36; clinical study report [unpublished]. 2013.

References for English extract

Please see full dossier assessment for full reference list.

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