IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Aclidiniumbromid – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 12 January 2016). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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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
COPD	chronic obstructive pulmonary disease
EQ-5D	European Quality of Life-5 Dimensions
E-RS	Exacerbation of Chronic Pulmonary Disease Tool Respiratory Symptoms
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICS	inhaled corticosteroids
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
OR	odds ratio
RCT	randomized controlled trial
RR	relative risk
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 (5) Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to reassess the benefit of the drug aclidinium bromide. Because of new scientific findings, the pharmaceutical company (hereinafter referred to as "the company") had applied for this new benefit assessment for the following therapeutic indication: maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD). The assessment was based on a dossier compiled by the company. The dossier was sent to IQWiG on 12 October 2015.

Research question

The aim of the present report was to assess the added benefit of aclidinium bromide (hereinafter referred to as "aclidinium") as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD in comparison with the appropriate comparator therapy (ACT).

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

Table 2: Research questions of the benefit assessment of aclidinium

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% predicted or respiratory failure) with ≥ 2 exacerbations per year[c]	LABA (formoterol, salmeterol) and/or LAMA (tiotropium) and additional ICS[d]

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: For better understandability, the term "adult 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 "adult patients with COPD grades ≥ III with ≥ 2 exacerbations per year" is used in the report.
d: The company did not consider research question 2 in the dossier because, from the company's point of view, there was no sufficient new evidence for research question 2.
ACT: appropriate comparator therapy; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; G-BA: Federal Joint Committee; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist

For research question 1, the assessment was conducted in comparison with formoterol. No data were available for research question 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 analysis.

Results

Study pool and patient population

Two studies of direct comparisons (ACLIFORM and AUGMENT with the extension study LAC-MD-36) were available for the assessment of aclidinium in comparison with the ACT. Both studies were only completed after the first benefit assessment of aclidinium bromide and had therefore not been included in this assessment (commission A12-13). They were double-blind, multicentre RCTs. The study duration was 24 weeks (ACLIFORM, AUGMENT); it was possible for the patients in the AUGMENT study to be enrolled in an optional extension phase (AUGMENT with extension study LAC-MD-36, total duration: 52 weeks). Patients aged 40 years and older with moderate to severe COPD, i.e. with spirometric Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades II and III, were enrolled. Patients also had to have a smoking history of at least 10 pack years at enrolment.

Both were 5-arm studies and already served as the basis of the benefit assessment on aclidinium bromide/formoterol (commission A15-06). Correspondingly, the study contained treatment arms that were not relevant for the present benefit assessment and are not considered further. In the relevant study arms, the comparison of one morning and one evening inhalation of 400 µg aclidinium versus 12 µg formoterol was investigated.

Treatment with inhaled corticosteroids (ICS) could be continued as concomitant treatment in both studies irrespective of the patients' disease severity and frequency of exacerbations. Consequently, the treatment did not comply with the conditions determined by the ACT in a large proportion of the study participants. Hence analyses of subpopulations were the basis of the assessment for research question 1 considered in the dossier. The company presented no data for research question 2.

The data presented on the extension study LAC-MD-36 were not evaluable and were therefore not considered in the assessment.

Risk of bias

For both studies, the risk of bias was rated as low both at study level and at outcome level.

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

The subpopulation of the studies ACLIFORM and AUGMENT relevant for research question 1 included patients with COPD grade II and patients with COPD grade III with fewer than 2 exacerbations per year who received no concomitant ICS treatment. There were no data on patients with COPD grade IV with fewer than 2 exacerbations, who are also relevant for research question 1.

The following analyses were available for answering research question 1.

Exacerbations

The meta-analysis of the included studies showed unexplained heterogeneity without effects in the same direction for the outcome "proportion of patients with exacerbations (moderate or severe)". Hence no common estimate was calculated. Moreover, there was proof of an effect modification by the characteristic "COPD grade". Under consideration of the subgroup data, there was proof of an added benefit of aclidinium in comparison with formoterol for this outcome in patients with COPD grade III and fewer than 2 exacerbations per year. For patients with COPD grade II, however, there was no hint of an added benefit; an added benefit is therefore not proven for these patients.

Further outcomes

The meta-analysis of the included studies showed no statistically significant difference between the treatment groups for each of the further outcomes investigated (severe exacerbations, health status [European Quality of Life-5 Dimensions visual analogue scale (EQ-5D VAS), discontinuation due to adverse events [AEs]) or inexplicable heterogeneity without effects in the same direction (all-cause mortality, COPD symptoms [Transition Dyspnoea Index (TDI) responder, Exacerbation of Chronic Pulmonary Disease Tool Respiratory Symptoms (E-RS) responder], health-related quality of life [St. George's Respiratory Questionnaire (SGRQ) and serious adverse events [SAEs]). There was no hint of an added benefit or of greater or lesser harm of aclidinium 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 company did not consider research question 2 in the dossier. Hence there were no data for the assessment of the added benefit of aclidinium for research question 2. Hence there was no hint of an added benefit of aclidinium in comparison with the ACT for adult patients with COPD grades III and IV with 2 or more exacerbations per year; an added benefit 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 aclidinium versus the ACT is assessed as follows:

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

On the basis of the available results, a positive effect at outcome level in the outcome category "non-serious/non-severe symptoms/late complications (exacerbations)" with the probability "proof" and the extent "considerable" was shown for the group of patients with COPD grade III with fewer than 2 exacerbations. Hence there is proof of considerable added benefit of aclidinium in comparison with formoterol for these patients.

For patients with COPD grade II, the data presented showed neither positive nor negative effects; an added benefit of aclidinium in comparison with formoterol for these patients is therefore not proven.

No data were available for adult patients with COPD grade IV with fewer than 2 exacerbations per year.

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

There were no data for the assessment of the added benefit of aclidinium for research question 2.

Extent and probability of added benefit – summary

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

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

Table 3: Aclidinium – extent and probability of added benefit

Research question	**Therapeutic indication**	**Subgroup**	**ACT[a]**	**Extent and probability of added benefit**
1	Adult patients with COPD from moderate severity (50% ≤ FEV1 < 80% predicted)	Grade II[b]	LABA (**formoterol**, salmeterol) and/or LAMA (tiotropium)	Added benefit not proven
		Grade III[c] with < 2 exacerbations per year		Proof of considerable added benefit
		Grade IV[d] with < 2 exacerbations per year		Added benefit not proven
2	Adult patients with COPD of moderate severity or greater (30% ≤ FEV1 < 50% predicted or FEV1 < 30% or respiratory failure) with ≥ 2 exacerbations per year	–	LABA (formoterol, salmeterol) and/or LAMA (tiotropium) and additional ICS[e]	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: Corresponds to 50% ≤ FEV1 < 80% predicted.
c: Corresponds to 30% ≤ FEV1 < 50% predicted.
d: Corresponds to FEV1 < 30% predicted or respiratory failure.
e: The company did not consider research question 2 in the dossier because, from the company's point of view, there was no sufficient new evidence for research question 2.
ACT: appropriate comparator therapy; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; G-BA: Federal Joint Committee; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist

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

2.2 Research question

The aim of the present report was to assess the added benefit of aclidinium bromide (hereinafter referred to as "aclidinium") as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD in comparison with the ACT.

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

Table 4: Research questions of the benefit assessment of aclidinium

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% predicted or respiratory failure) with ≥ 2 exacerbations per year[c]	LABA (formoterol, salmeterol) and/or LAMA (tiotropium) and additional ICS[d]

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: For better understandability, the term "adult 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 "adult patients with COPD grades ≥ III with ≥ 2 exacerbations per year" is used in the report.
d: The company did not consider research question 2 in the dossier because, from the company's point of view, there was no sufficient new evidence for research question 2.
ACT: appropriate comparator therapy; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; G-BA: Federal Joint Committee; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist

For easier presentation and better readability, the following terms according to the spirometric classification of COPD severity according to the GOLD recommendations [4] are used for the 2 research questions in the report:

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

The population for research question 1 deviated from that of the company, which did not consider patients with COPD grade IV and fewer than 2 exacerbations per year. For the remaining patients pertaining to research question 1, the company followed the specification of the G-BA for the ACT and chose formoterol as comparator therapy from the options mentioned. The company's choice of the comparator therapy was followed. The exclusion of the patients with COPD grade IV and fewer than 2 exacerbations per year had no consequence

for the present benefit assessment (see Section 2.3.2.2). The company did not consider the entire research question 2 in the dossier.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the analysis. 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 (status: 24 July 2015)
- bibliographical literature search on aclidinium (last search on 20 July 2015)
- search in trial registries for studies on aclidinium (last search on 13 July 2015)

To check the completeness of the study pool:

- search in trial registries for studies on aclidinium (last search on 30 October 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 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)	No	Yes	No
AUGMENT (LAC-MD-31) with extension study LAC-MD-36	No	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. RCT: randomized controlled trial			

For better understandability, the studies ACLIFORM (M/40464/30) and AUGMENT (LAC-MD-31) are referred to as "ACLIFORM" und "AUGMENT" in the report.

Both studies were only completed after the first benefit assessment of aclidinium bromide and had therefore not been included in this assessment (commission A12-13 [1]).

The company only included the 2 studies ACLIFORM and AUGMENT in its assessment. It excluded the extension of the AUGMENT study (study LAC-MD-36) because of the high risk of bias. The AUGMENT study with the extension study LAC-MD-36 is principally relevant for the benefit assessment. The data from the extension study LAC-MD-36 were not evaluable, however, and were not considered in the present assessment (for reasons, see Section 2.7.2.3.2 of the full dossier assessment).

Analogous to the company's approach, analyses of subpopulations on research question 1 were the basis of the assessment. No data were available for research question 2.

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 vs. formoterol

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ACLIFORM	RCT, double-blind, parallel	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 400 µg (N = 385) FOR 12 µg (N = 384) ACL/FOR 400/12 µg (N = 385)[b] ACL/FOR 400/6 µg (N = 381)[b] PLAC (N = 194)[b] subpopulation relevant for research question 1[c]: ACL 400 µg (n = 174) FOR 12 µg (n = 187) Research question 2: no data available[d]	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 status, health-related quality of life, AEs
AUGMENT with extension study LAC-MD-36	RCT, double-blind, parallel	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 400 µg (N = 340) FOR 12 µg (N = 339) ACL/FOR 400/12 µg (N = 338)[b] ACL/FOR 400/6 µg (N = 338)[b] PLAC (N = 337)[b] subpopulation relevant for research question 1[c]: ACL 400 µg (n = 190) FOR 12 µg (n = 197) Research question 2: no data available[d]	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): Included population relevant for research question 1[c]: ACL 400 µg (n = unclear[e]) FOR 12 µg (n = unclear[e]) Research question 2: no data available[d]	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 vs. formoterol (continued)

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: The arm is not relevant for the assessment and is no longer shown in the following tables.
c: Research question 1 comprises patients with COPD grade II (irrespective of the number of previous exacerbations) and patients with COPD grades ≥ III with < 2 exacerbations per year (without use of ICS). The few (< 5%) patients with COPD grade IV included against the inclusion criteria of the study were not considered in the analysis.
d: The company did not consider research question 2.
e: Contradictory information in the dossier: The number of patients in the relevant subpopulation fluctuates, depending on the source, between 112 and 127 (ACL) and 115 and 130 (FOR).

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 vs. formoterol

Study	Intervention	Comparison
ACLIFORM	Aclidinium 400 µg[a], 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[b] ▪ 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 LABA 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 with extension study LAC-MD-36	Aclidinium 400 µg[a], 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[b] ▪ 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 LABA 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: The metered dose of 400 µg aclidinium bromide corresponds to a dose of 322 µg aclidinium delivered through the mouthpiece.
b: Maximum dose equivalent to prednisone: 10 mg/day or 20 mg every 2 days.
COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; RCT: randomized controlled trial; vs.: versus

The 2 studies included (ACLIFORM and AUGMENT with extension study LAC-MD-36) were double-blind, multicentre RCTs. The study duration was 24 weeks (ACLIFORM, AUGMENT); it was possible for the patients in the AUGMENT study to be enrolled in an optional extension phase (AUGMENT with extension study LAC-MD-36, total duration:

52 weeks). Patients aged 40 years and older with moderate to severe COPD, i.e. with spirometric GOLD grades II and III, were enrolled. Patients also had to have a smoking history of at least 10 pack years at enrolment.

The studies followed the same protocols and were conducted at the same time, but in different geographical regions. Whereas the centres of the ACLIFORM study were mainly in Europe, the AUGMENT study was conducted in North America, Australia and New Zealand. Both were 5-arm studies and already served as the basis of the benefit assessment on aclidinium bromide/formoterol (commission A15-06 [5]). Correspondingly, the study contained treatment arms that were not relevant for the present benefit assessment and are not considered further. In the relevant study arms, the comparison of one morning and one evening inhalation of 400 µg aclidinium versus 12 µg formoterol was investigated.

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 corticosteroids, methylxanthines (extended-release formulation) and oxygen treatment under 15 h/d was allowed to be continued as concomitant treatment if this treatment had been ongoing at a stable dosage for at least 4 weeks before the first study visit. Bronchodilators such as anticholinergics and beta-2 sympathomimetics – apart from rescue medication – had to be discontinued before the start of the study.

ICS treatment could therefore be continued as concomitant treatment in both studies irrespective of the patients' disease severity and frequency of exacerbations. Consequently, the treatment did not comply with the conditions determined by the ACT in a large proportion of the study participants. Hence, analogous to the company's approach, analyses of subpopulations were the basis of the assessment for research question 1 considered in the dossier.

No data were available for research question 2.

Available data on the observation period of 52 weeks from the AUGMENT study (with the extension study LAC-MD-36)

As described above, the LAC-MD-36 study was an optional extension study of the AUGMENT study. The company presented results on completion of the study after 24 weeks for the AUGMENT study. Only incomplete results of the extension study (i.e. for an observation period of 52 weeks) were available in Module 5. The AUGMENT study with the extension study LAC-MD-36 is principally relevant for the benefit assessment. The results of this extension study were not evaluable and were therefore not considered in the assessment. The results are also not presented as supplementary presentation (see Section 2.7.2.3.2 of the full dossier assessment).

2.3.2.2 Characteristics of the study populations

Table 8, Table 9 and Table 10 show the characteristics ofthe subpopulation of the studies included relevant for research question 1. No data were available for research question 2.

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

Study Group	N	Age [years]	Sex [F/M]	Duration of COPD [years]	Smoking status [current smoker/ ex-smoker]	Smoking [pack years]	Treatment discontin-uations[a]	Study discontin-uations
		Mean (SD)	%	Mean (SD)	%	Mean (SD)	n (%)	n (%)
ACLIFORM								
ACL	173	62 (8)	33/67	8.1 (6.1)	53/47	37.5 (19.1)	21 (12.1)	ND[b]
FOR	187	63 (8)	32/68	7.8 (6.4)	50/50	41.6 (20.5)	26 (13.9)	ND[b]
AUGMENT								
ACL	188	64 (9)	40/60	7.2 (5.4)	57/43	51.5 (26.9)	39 (20.5)	39 (20.5)[c]
FOR	194	62 (9)	47/53	8.0 (6.1)	60/40	52.2 (23.1)	36 (18.3)	36 (18.3)[c]

a: The information on patients who discontinued treatment were taken from Module 5 because Module 4 A only contained data on the subpopulation including patients with COPD grade III and ≥ 2 exacerbations per year, who are not relevant for research question 1.
b: There were no data on the relevant subpopulation. With regard to the total population, there was no difference in the aclidinium arm between the patients who discontinued treatment and patients who discontinued the study. One patient in the formoterol arm was additionally classified as patient who discontinued the study.
c: There was no explicit information on the relevant subpopulation; however, it can be assumed on the basis of the information provided in the study documents for the total population that the number of patients who discontinued treatment and the number of patients who discontinued the study was identical.
ACL: aclidinium; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; F: female; FOR: formoterol; M: male; N: number of randomized patients with at least one administration of the study medication, one FEV1 value at baseline and at least one value after the start of the study; ND: no data; 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) – RCT, direct comparison: aclidinium vs. formoterol (research question 1)

Study Severity[a] Group	N	COPD exacerbations in the year prior to screening n (%)		
		0	1	≥ 2
ACLIFORM				
GOLD II				
ACL	124	91 (73.4)	23 (18.5)	10 (8.1)
FOR	132	101 (76.5)	23 (17.4)	8 (6.1)
GOLD III				
ACL	49	36 (73.5)	13 (26.5)	-
FOR	55	36 (65.5)	19 (34.5)	-
AUGMENT				
GOLD II				
ACL	117	100 (85.5)	11 (9.4)	6 (5.1)
FOR	130	105 (80.8)	17 (13.1)	8 (6.1)
GOLD III				
ACL	71	62 (87.3)	9 (12.7)	-
FOR	64	54 (84.4)	10 (15.6)	-

a: Spirometric COPD severity is classified based on the FEV1: 50% ≤ FEV1 < 80% corresponds to grade II, 30% ≤ FEV1 < 50% corresponds to grade III.

ACL: aclidinium; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; FOR: formoterol; GOLD: Global Initiative for Chronic Obstructive Lung Disease; N: number of randomized patients with at least one administration of the study medication, one FEV1 value at baseline and at least one value after the start of the study; RCT: randomized controlled trial; vs.: versus

Table 10: Characteristics of the study populations (COPD premedication) – RCT, direct comparison: aclidinium 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	173	13 (7.5)	0 (0)	1 (0.6)
FOR	187	23 (12.3)	1 (0.5)	2 (1.1)
AUGMENT				
ACL	188	0 (0)	2 (1.1)	2 (1.1)
FOR	194	0 (0)	9 (4.6)	1 (0.5)

ACL: aclidinium; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; FOR: formoterol; N: number of randomized patients with at least one administration of the study medication, one FEV1 value at baseline and at least one value after the start of the study; RCT: randomized controlled trial; vs.: versus

The subpopulations of the relevant studies presented by the company for research question 1 included patients with COPD grade II (irrespective of the number of exacerbations) without concomitant ICS treatment and patients with COPD grade III and fewer than 2 exacerbations in the previous year also without concomitant ICS treatment.

The mean age of patients in the relevant 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) and 50 (AUGMENT).

Patients with COPD grade II constituted approximately 60 to 70% and were therefore the largest group. Due to the inclusion criteria of the studies, there were only few participants with COPD grade IV (< 0.5%), who, according to the company's approach, were not considered for the assessment of research question 1. There were therefore no evaluable data of patients with COPD grade IV for answering research question 1. 73% (ACLIFORM) and 84% (AUGMENT) of the participants had no exacerbation in the previous year.

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, about 10% of the participants were taking xanthines as concomitant medication.

The proportion of patients who discontinued treatment was higher in the AUGMENT study (19%) than in the ACLIFORM study (13%).

In summary, no differences relevant for the assessment were shown between the studies or between the treatment arms within the studies for any of the patient characteristics for the subpopulation of research question 1.

2.3.2.3 Risk of bias at study level

Table 11 shows the risk of bias at study level for research question 1 under consideration of the relevant subpopulations. No data were available for research question 2.

Table 11: Risk of bias at study level – RCT, direct comparison: aclidinium vs. formoterol (research question 1)

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
ACLIFORM	Yes	Yes	Yes	Yes	Yes	Yes	Low
AUGMENT	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at the study level for the studies ACLIFORM and AUGMENT was rated as low for research question 1. This concurs with the company's assessment.

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)
  - exacerbations
  - severe exacerbations
  - health status (EQ-5D VAS)
- Health-related quality of life
  - health-related quality of life (SGRQ)
- Adverse events
  - SAEs
  - discontinuation due to AEs
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviates from that of the company (see also Section 2.7.2.4.3 of the full dossier assessment). Instead of the outcome "exacerbations" (consisting of moderate and severe exacerbations), the company included the outcome "moderate exacerbations". The company did not use the outcome "health status" for the assessment of the added benefit.

Table 12 shows for which outcomes data for the assessment of research question 1 were available in the studies included. No data were available for research question 2.

Table 12: Matrix of outcomes – RCT, direct comparison: aclidinium vs. formoterol (research question 1)

Study	Outcomes								
	All-cause mortality	COPD symptoms – TDI	COPD symptoms – E-RS	Exacerbations[a]	Severe exacerbations	Health-related quality of life – SGRQ	Health status – EQ-5D VAS	SAEs	Discontinuation due to AEs
ACLIFORM	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
AUGMENT	Yes	Yes	Yes	Yes	Yes	Yes	No[b]	Yes	Yes

a: Includes moderate and severe exacerbations.
b: The outcome was not recorded in the study.

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; RCT: randomized controlled trial; SAE: serious adverse event; SGRQ: St. George's Respiratory Questionnaire; TDI: Transition Dyspnoea Index; VAS: visual analogue scale; vs.: versus

2.4.2 Risk of bias

Table 13 shows the risk of bias for the relevant outcomes for the assessment of research question 1. No data were available for research question 2.

Table 13: Risk of bias at study and outcome level – RCT, direct comparison: aclidinium vs. formoterol (research question 1)

Study		Outcomes								
	Study level	All-cause mortality	COPD symptoms – TDI	COPD symptoms – E-RS	Exacerbations[a]	Severe exacerbations	Health-related quality of life – SGRQ	Health status – EQ-5D VAS	SAEs	Discontinuation due to AEs
ACLIFORM[b]	L	L	L	L	L	L	L	L	L	L
AUGMENT[b]	L	L	L	L	L	L	L	–[c]	L	L

a: Includes moderate and severe exacerbations.
b: The assessment of the risk of bias at study level was conducted on the basis of the relevant subpopulation for research question 1.
c: The outcome was not recorded in the study.
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; L: low; RCT: randomized controlled trial; SAE: serious adverse event; SGRQ: St. George's Respiratory Questionnaire; TDI: Transition Dyspnoea Index; VAS: visual analogue scale; vs.: versus

The risk of bias for all outcomes was rated as low. This concurs with the company's assessment (see Section 2.7.2.4.2 of the full dossier assessment).

2.4.3 Results

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

Table 14, Table 15, Table 16 and Table 17 summarize the results on research question 1, i.e. on the comparison of aclidinium versus formoterol in patients with COPD grade II and patients with COPD grade III with fewer than 2 exacerbations per year. There were no data on patients with COPD grade IV with fewer than 2 exacerbations, who are also relevant for research question 1.

Where necessary, the data from the company's dossier were supplemented by the Institute's calculations.

Analyses of the binary outcomes TDI, E-RS, SGRQ and exacerbations

The company presented a number of operationalizations/analyses for the investigated outcomes in the dossier. The following analyses were considered in the present benefit assessment (see Section 2.7.2.4.3 of the full dossier assessment for reasons for the choice of outcomes):

A predefined analysis by the company using a logistic regression model with direct likelihood analysis was used for the binary outcomes TDI, E-RS and SGRQ responder [6]. Since the effect estimate of this analysis is an odds ratio (OR) and the determination of the extent of added benefit is based on the relative risk (RR), the relative risks (based on the ORs and the estimated baseline risk in the comparator group with all patients who discontinued treatment being categorized as non-responders) were to be additionally recalculated for all significant effects (analogous to the benefit assessment of aclidinium bromide/formoterol [5]). However, no statistically significant effect was shown in any of the corresponding outcomes.

As planned a priori, the company analysed the exacerbation outcomes using a logistic regression model, the result of which represented an estimation of the OR. In case of a significant effect, RRs using a random-effects meta-analysis based on the 2x2 tables were used to determine the extent of the added benefit. This concurs with the company's approach.

Table 14: Results (dichotomous outcomes, regression model with direct likelihood method) – RCT, direct comparison: aclidinium vs. formoterol

Outcome category Outcome Study	Aclidinium N	Aclidinium Patients with event n (%)[a]	Formoterol N	Formoterol Patients with event n (%)[a]	Aclidinium vs. formoterol OR [95% CI][b]; p-value
Morbidity					
COPD symptoms (TDI responder)[c]					
ACLIFORM	173	82 (53.9)	187	100 (63.3)	0.64 [0.37; 1.11]; 0.113
AUGMENT	188	82 (54.7)	194	80 (51.9)	1.13 [0.64; 1.99]; 0.681
Total				Heterogeneity[d]: p = 0.144	
COPD symptoms (E-RS total score responder)[e]					
ACLIFORM	173	50 (29.2)	186	54 (29.3)	0.91 [0.52; 1.60]; 0.742
AUGMENT	187	64 (34.8)	194	49 (25.7)	1.63 [0.96; 2.74]; 0.068
Total				Heterogeneity[d]: p = 0.138	
COPD symptoms (E-RS breathlessness subscale responder)[f]					
ACLIFORM	173	44 (25.7)	186	48 (26.1)	0.92 [0.52; 1.63]; 0.774
AUGMENT	187	54 (29.3)	194	45 (23.6)	1.48 [0.85; 2.57]; 0.161
Total					1.17 [0.79; 1.74][d]; 0.432
COPD symptoms (E-RS cough and sputum responder)[g]					
ACLIFORM	173	44 (25.7)	186	47 (25.5)	1.08 [0.63; 1.86]; 0.779
AUGMENT	187	45 (24.5)	194	37 (19.4)	1.44 [0.82; 2.53]; 0.206
Total					1.24 [0.84; 1.83][d]; 0.277
COPD symptoms (E-RS chest symptoms subscale responder)[h]					
ACLIFORM	173	48 (28.1)	186	55 (29.9)	0.69 [0.40; 1.18]; 0.175
AUGMENT	187	55 (29.9)	194	46 (24.1)	1.45 [0.83; 2.54]; 0.193
Total				Heterogeneity[d]: p = 0.055	
Health-related quality of life					
SGRQ responder[i]					
ACLIFORM	173	78 (51.7)	187	91 (57.2)	0.76 [0.42; 1.36]; 0.348
AUGMENT	188	77 (53.1)	194	72 (47.7)	1.40 [0.77; 2.55]; 0.270
Total				Heterogeneity[d]: p = 0.140	

a: Descriptive percentages based on the N provided excluding patients categorized as "missing" (without classification as "response"/"non-response").
b: OR determined with predefined logistic regression model under consideration of patients with partly missing values using the direct likelihood method [6].
c: Patients with TDI total score ≥ 1.
d: Calculated with IPD meta-analysis.
e: E-RS total score responder: reduction of ≥ 3.35 points.
f: Symptom complex breathlessness responder: reduction of ≥ 1.85 points.
g: Symptom complex cough and sputum responder: reduction of ≥ 1.15 points.
h: Symptom complex chest symptoms: reduction of ≥ 1.05 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; N: number of analysed patients; n: number of patients with response at the end of the study; OR: odds ratio; RCT: randomized controlled trial; SGRQ: St. George's Respiratory Questionnaire; TDI: Transition Dyspnoea Index; vs.: versus

Table 15: Results (dichotomous outcomes, logistic regression model) – RCT, direct comparison: aclidinium vs. formoterol

Outcome category Outcome Study	Aclidinium N	Aclidinium Patients with event n (%)	Formoterol N	Formoterol Patients with event n (%)	Aclidinium vs. formoterol Effect estimates [95% CI][a]; p-value
Morbidity					
Exacerbations[b]					
ACLIFORM	174	6 (3.4)	187	22 (11.8)	OR 0.29 [0.12; 0.71]; 0.006
AUGMENT	188	20 (10.6)	194	22 (11.3)	OR 0.91 [0.52; 1.61]; 0.750
Total				Heterogeneity[c]: p = 0.026	
Severe exacerbations					
ACLIFORM	174	1 (0.6)	187	1 (0.5)	POR 1.07 [0.07; 17.28][d]; > 0.999[e]
AUGMENT	188	3 (1.6)	194	4 (2.1)	OR 0.70 [0.16; 3.08]; 0.639
Total					OR 0.90 [0.19; 4.31]; 0.893[c]

a: Calculation using the predefined regression model, exceptions provided.
b: Includes moderate and severe exacerbations.
c: Calculated with IPD meta-analysis.
d: Institute's calculation. OR not calculable using logistic regression model (lack of convergence).
e: p-value from CSZ test [7], Institute's calculation.

CI: confidence interval; COPD: chronic obstructive pulmonary disease; CSZ: convexity, symmetry, z score; IPD: individual patient data; N: number of analysed patients; n: number of patients with event; OR: odds ratio; POR: Peto odds ratio; RCT: randomized controlled trial; vs.: versus

Table 16: Results (continuous outcomes, MMRM) – RCT, direct comparison: aclidinium vs. formoterol

Outcome category Outcome Study	Aclidinium N[a]	Aclidinium Baseline values mean (SD)	Aclidinium Change at end of study mean[b] (SE)	Formoterol N[a]	Formoterol Baseline values mean (SD)	Formoterol Change at end of study mean[b] (SE)	Aclidinium vs. formoterol MD [95% CI][b]; p-value
Morbidity							
Health status (EQ-5D VAS)							
ACLIFORM	182	64.62 (15.74)	3.65 (1.04)	195	65.60 (15.76)	4.32 (1.01)	-0.66 [-3.49; 2.17]; 0.646
AUGMENT	Outcome not recorded						

a: In contrast to all other outcomes, the number of patients considered in the analysis for the calculation of the effect estimate in total included 16 patients more than can be expected on the basis of the randomized patients. Due to the low proportion of these patients in the analysis (4%), the subpopulation analysed by the company were considered to be usable for the assessment as an approximation.
b: Results from MMRM calculation.

CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; MD: mean difference; 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

Table 17: Results (dichotomous outcomes, naive proportions) – RCT, direct comparison: aclidinium vs. formoterol

Outcome category Outcome Study	Aclidinium N	Aclidinium Patients with event n (%)	Formoterol N	Formoterol Patients with event n (%)	Aclidinium vs. formoterol RR[a] [95% CI]; p-value[b]
Mortality					
All-cause mortality					
ACLIFORM	174	0 (0)	187	1 (0.5)	0.36 [0.01; 8.73][c]; 0.515
AUGMENT	188	2 (1.1)	194	0 (0)	5.16 [0.25; 106.75][c]; 0.159
Total				Heterogeneity: p = 0.086	
Adverse events					
AEs					
ACLIFORM	174	81 (46.6)	187	102 (54.5)	-
AUGMENT	188	110 (58.5)	194	104 (53.6)	-
SAEs					
ACLIFORM	174	5 (2.9)	187	10 (5.3)	0.54 [0.19; 1.54]; 0.256
AUGMENT	188	10 (5.3)	194	4 (2.1)	2.58 [0.82; 8.08]; 0.097
Total				Heterogeneity: p = 0.042	
Discontinuation due to AEs					
ACLIFORM	174	3 (1.7)	187	5 (2.7)	0.64 [0.16; 2.66]; 0.599
AUGMENT	188	7 (3.7)	194	6 (3.1)	1.20 [0.41; 3.52]; 0.775
Total					0.96 [0.41; 2.25]; 0.924[d]

a: Calculation from 2x2 table.
b: p-value from CSZ test [7], Institute's calculation.
c: Institute's calculation with continuity correction.
d: Institute's calculation, meta-analysis based on separate 2x2 tables.
AE: adverse event; CI: confidence interval; CSZ: convexity symmetry, z score; 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

Mortality

The meta-analysis of the included studies showed heterogeneous results without effects in the same direction for the outcome "all-cause mortality" with only 3 deaths in total. Based on the data, there was no hint of an added benefit of aclidinium in comparison with formoterol; an added benefit for all-cause mortality is therefore not proven.

The company derived no conclusions on the added benefit from the results on mortality because of the low number of events.

Morbidity

COPD symptoms (TDI responder)

The meta-analysis of the included studies showed unexplained heterogeneity without effects in the same direction for the outcome "COPD symptoms (TDI responder)". Hence no common estimate was calculated. Based on the data, there was no hint of an added benefit of aclidinium in comparison with formoterol; an added benefit for the outcome "TDI responder" is therefore not proven.

This concurs with the company's assessment.

COPD symptoms (E-RS responder)

The meta-analysis of the included studies showed unexplained heterogeneity without effects in the same direction for the outcome "COPD symptoms (E-RS responder total score)". Hence no common estimate was calculated. Based on the data, there was no hint of an added benefit of aclidinium in comparison with formoterol; an added benefit for the outcome "E-RS responder" is therefore not proven.

This concurs with the company's assessment.

Exacerbations

The meta-analysis of the included studies showed unexplained heterogeneity without effects in the same direction for the outcome "proportion of patients with exacerbations (moderate or severe)". Hence no common estimate was calculated. Moreover, there was proof of an effect modification by the characteristic "COPD grade" (see Section 2.4.4). Under consideration of the subgroup data, there was proof of an added benefit of aclidinium in comparison with formoterol for this outcome in patients with COPD grade III and fewer than 2 exacerbations per year. For patients with COPD grade II, however, there was no hint of an added benefit; an added benefit is therefore not proven for these patients.

The company included results for the outcome "moderate exacerbations" in the assessment, but also derived proof of an added benefit for patients with COPD grade III and fewer than 2 exacerbations per year from them.

Severe exacerbations

The meta-analysis of the included studies showed no statistically significant difference between the treatment groups for the outcome "proportion of patients with severe exacerbations". This resulted in no hint of an added benefit of aclidinium in comparison with formoterol; an added benefit for the outcome "severe exacerbations" is therefore not proven.

This concurs with the company's assessment.

Health status (EQ-5D VAS)

No statistically significant difference between the treatment groups was shown in the ACLIFORM study for the outcome "health status (EQ-5D VAS)". This outcome was not recorded in the AUGMENT study. This resulted in no hint of an added benefit of aclidinium in comparison with formoterol; an added benefit for the outcome "health status (EQ-5D VAS)" is therefore not proven.

The company did not include this outcome in the assessment and derived no conclusions on the added benefit on its basis.

Health-related quality of life

SGRQ responder

The meta-analysis of the included studies showed unexplained heterogeneity without effects in the same direction for the outcome "SGRQ responder". Hence no common estimate was calculated. Based on the data, there was no hint of an added benefit of aclidinium 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

Serious adverse events

The meta-analysis of the included studies showed unexplained heterogeneity without effects in the same direction for the outcome "SAEs". Hence no common estimate was calculated. Based on the data, there was no hint of greater or lesser harm of aclidinium in comparison with formoterol; greater or lesser harm for SAEs is therefore not proven.

This concurs with the company's assessment.

Discontinuation due to adverse events

The meta-analysis of the included studies showed no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". This resulted in no hint of greater or lesser harm of aclidinium in comparison with formoterol; greater or lesser harm for 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

The company did not consider research question 2 in the dossier. Correspondingly, there were no data for the assessment of the added benefit of aclidinium for research question 2. Hence there was no hint of an added benefit of aclidinium in comparison with the ACT for adult

patients with COPD grades III and IV with 2 or more exacerbations per year; an added benefit is therefore not proven.

2.4.4 Subgroups and other effect modifiers

For selected characteristics, the respective subgroups were investigated for the presence of heterogeneous treatment effects in order to identify possible effect modifiers.

Subgroup analyses for the following characteristics were considered:

- sex
- age group (< 65 years and ≥ 65 years)
- COPD grade (II and III)

Only the results on subgroups and outcomes with at least an indication of an interaction between treatment effect and subgroup characteristic and with statistically significant results or effects in the same direction in at least one subgroup are presented in this assessment. The prerequisite for proof of different subgroup effects is a statistically significant interaction test ($p < 0.05$). A p-value of ≥ 0.05 and < 0.2 provides an indication of an effect modification.

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

Table 18 presents the relevant results on subgroups in patients with COPD grade II and patients with COPD grade III with fewer than 2 exacerbations per year. There were no data on patients with COPD grade IV with fewer than 2 exacerbations, who are also relevant for research question 1.

Table 18: Subgroups (morbidity: exacerbations) – RCT, direct comparison: aclidinium vs. formoterol

Outcome Characteristic Study Subgroup	Aclidinium N	Aclidinium Patients with event n (%)	Formoterol N	Formoterol Patients with event n (%)	Aclidinium vs. formoterol OR [95% CI][a]; p-value	Aclidinium vs. formoterol RR [95% CI][b]
Exacerbations[c]						
COPD severity						
ACLIFORM						
GOLD II	125	5 (4.0)	132	14 (10.6)	0.35 [0.13; 0.95]; 0.039	
GOLD III	49	1 (2.0)	55	8 (14.5)	0.15 [0.02; 1.17]; 0.070	
AUGMENT						
GOLD II	117	16 (13.7)	130	12 (9.2)	1.45 [0.72; 2.93]; 0.296	
GOLD III	71	4 (5.6)	64	10 (15.6)	0.35 [0.12; 1.06]; 0.064	
Total					Interaction: 0.028[d]	
GOLD II					Heterogeneity[e]: Q = 5.23; df = 1; p = 0.022; I^2 = 80.9%	
GOLD III					0.27 [0.11; 0.71]; 0.008[f]	0.29 [0.11; 0.77]

a: Odds ratio determined with logistic regression model.
b: Institute's calculation of the RR based on 2x2 tables.
c: Includes moderate and severe exacerbations.
d: Calculated with Breslow-Day-Tarone test.
e: Institute's calculation based on OR estimates.
f: Calculated with IPD meta-analysis.
CI: confidence interval; COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease; IPD: individual patient data; N: number of analysed patients; n: number of patients with event; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Morbidity

Exacerbations

The subgroup analysis on the outcome "exacerbations (moderate or severe)" provided proof of an effect modification regarding the characteristic "severity". The meta-analysis still showed unexplained heterogeneity without effects in the same direction for patients with COPD grade II (as in the total subpopulation) in the result of the subgroup analysis. Hence no common estimate was calculated. The meta-analysis showed a statistically significant effect in favour of aclidinium in patients with COPD grade III and fewer than 2 exacerbations per year.

Overall, there was proof of an added benefit of aclidinium in comparison with formoterol for the outcome "exacerbations" in patients with COPD grade III and fewer than 2 exacerbations

per year. For patients with COPD grade II, there was no hint of added benefit of aclidinium in comparison with formoterol; an added benefit for these patients is therefore not proven.

The company also derived proof of an added benefit for patients with COPD grade III and fewer than 2 exacerbations per year. It based this assessment on the outcome "moderate exacerbations", however.

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

The company did not consider research question 2 in the dossier. Hence no data from subgroup analyses for the investigation of effect modifiers of treatment with aclidinium according to research question 2 were available.

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit of aclidinium 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].

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

2.5.1.1 Evaluation of added benefit at outcome level

The data presented in Section 2.4.3.1 resulted in proof of an added benefit in patients with COPD grade III and fewer than 2 exacerbations per year for the outcome "exacerbations".

Determination of the outcome category for the outcome "exacerbations"

The assessment of the outcome category of exacerbations depends on the severity of the events categorized as exacerbations. The outcome was comprised of moderate and severe exacerbations. Both types of events were defined in the study as an increase of COPD symptoms on at least 2 consecutive days and differed by the corresponding changes in treatment. Moderate exacerbations are characterized by treatment with antibiotics and/or systemic corticosteroids or an increased dosage of systemic corticosteroids. Severe exacerbation was only determined if this led to hospitalization. Moderate exacerbations as outpatient events treatable with drugs were allocated to the outcome category "non-serious/non-severe symptoms/late complications". A total of 23 patients with COPD grade III and fewer than 2 exacerbations per year had at least one exacerbation in the course of the study. Severe exacerbations occurred in only 2 of these patients. Hence the composite outcome of moderate and severe exacerbations was also 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. The corresponding Table 19 contains the assessment of the data presented by the company for

research question 1 for adult patients with COPD grade II and adult patients with COPD grade III with fewer than 2 exacerbations per year. There were no data on patients with COPD grade IV with fewer than 2 exacerbations, who are also relevant for research question 1.

Table 19: Extent of added benefit at outcome level: aclidinium 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** **Effect modifier**	**Aclidinium 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	Heterogeneous results without effects in the same direction[d]	Lesser benefit/added benefit not proven
Morbidity		
COPD symptoms (TDI responder)	Heterogeneous results without effects in the same direction[d]	Lesser benefit/added benefit not proven
COPD symptoms (E-RS total score responder)	Heterogeneous results without effects in the same direction[d]	Lesser benefit/added benefit not proven
Exacerbations		
COPD grade II	Heterogeneous results without effects in the same direction[d]	Lesser benefit/added benefit not proven
COPD grade III	ACL: 2% to 6% FOR: 15% to 16% RR: 0.29 [0.11; 0.77] p = 0.008[e] probability: "proof"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.8$ added benefit, extent: "considerable"
Severe exacerbations	ACL: 1% to 2% FOR: 1% to 2% OR 0.90 [0.19; 4.31] p = 0.893	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	ACL: 3.7[f] FOR: 4.3[f] MD: -0.66 [-3.49; 2.17] p = 0.646	Lesser benefit/added benefit not proven
Health-related quality of life		
SGRQ responder	Heterogeneous results without effects in the same direction[d]	Lesser benefit/added benefit not proven
Adverse events		
SAEs	Heterogeneous results without effects in the same direction[d]	Greater/lesser harm not proven
Discontinuation due to AEs	ACL: 2% to 4% FOR: 3% RR: 0.96 [0.41; 2.25] p = 0.924	Greater/lesser harm not proven

(continued)

Table 19: Extent of added benefit at outcome level: aclidinium 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 included studies.
b: Probability given if statistically significant differences are present.
c: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
d: No common effect estimate provided due to heterogeneous data.
e: p-value on OR from logistic regression.
f: 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; 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 Overall conclusion on added benefit

Table 20 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 20: Positive and negative effects from the assessment of aclidinium compared with formoterol (research question 1)

Positive effects	**Negative effects**
Adult patients with COPD grade II	
–	–
Adult patients with COPD grade III with < 2 exacerbations	
Proof of added benefit – extent "considerable" (non-serious /non-severe symptoms/late complications: exacerbations)	–
COPD: chronic obstructive pulmonary disease	

Overall, on the basis of the available results, a positive effect in the outcome category "non-serious/non-severe symptoms/late complications (exacerbations)" was shown for the group of patients with COPD grade III with fewer than 2 exacerbations per year. Based on the available results, neither positive nor negative effects were shown in the group of patients with COPD grade II.

In summary, there is proof of considerable added benefit of aclidinium in comparison with the ACT formoterol for adult patients with COPD grade III with fewer than 2 exacerbations per year. An added benefit of aclidinium in comparison with formoterol is not proven for adult patients with COPD grade II.

No data were available for adult patients with COPD grade IV with fewer than 2 exacerbations per year. Hence an added benefit of aclidinium in comparison with formoterol is not proven for these patients.

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

The company did not consider research question 2 in the dossier. Hence there were no data for the assessment of the added benefit of aclidinium for research question 2. An added benefit of aclidinium in comparison with the ACT for adult patients with COPD grades III and IV with 2 or more exacerbations per year is therefore not proven.

2.5.3 Extent and probability of added benefit – summary

The result of the assessment of the added benefit of aclidinium in comparison with the ACT is summarized in Table 21.

Table 21: Aclidinium – extent and probability of added benefit

Research question	**Therapeutic indication**	**Subgroup**	**ACT**[a]	**Extent and probability of added benefit**
1	Adult patients with COPD from moderate severity (50% ≤ FEV1 < 80% predicted)	Grade II[b]	LABA (**formoterol**, salmeterol) and/or LAMA (tiotropium)	Added benefit not proven
		Grade III[c] with < 2 exacerbations per year		Proof of considerable added benefit
		Grade IV[d] with < 2 exacerbations per year		Added benefit not proven
2	Adult patients with COPD of moderate severity or greater (30% ≤ FEV1 < 50% predicted or FEV1 < 30% or respiratory failure) with ≥ 2 exacerbations per year	–	LABA (formoterol, salmeterol) and/or LAMA (tiotropium) and additional ICS[e]	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: Corresponds to 50% ≤ FEV1 < 80% predicted.
c: Corresponds to 30% ≤ FEV1 < 50% predicted.
d: Corresponds to FEV1 < 30% predicted or respiratory failure.
e: The company did not consider research question 2 in the dossier because, from the company's point of view, there was no sufficient new evidence for research question 2.

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

This concurs with the company's assessment.

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

2.6 List of included studies

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 November 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. 29 May 2015 [accessed: 9 November 2015]. URL: https://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/40464/30R; clinical study report [unpublished]. 2013.

AstraZeneca. Additional analyses for study: 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/40464/30R [unpublished]. 2015.

Singh D, Jones PW, Bateman ED, Korn S, Serra C, Molins E et al. Efficacy and safety of aclidinium bromide/formoterol fumarate fixed-dose combinations compared with individual components and placebo in patients with COPD (ACLIFORM-COPD): a multicentre, randomised study. BMC Pulm Med 2014; 14: 178.

AUGMENT (LAC-MD-31)

AstraZeneca. Additional analyses for study: 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 [unpublished]. 2015.

D'Urzo AD, Rennard SI, Kerwin EM, Mergel V, Leselbaum AR, Caracta CF. Efficacy and safety of fixed-dose combinations of aclidinium bromide/formoterol fumarate: the 24-week, randomized, placebo-controlled AUGMENT COPD study. Respir Res 2015; 15: 123.

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) (LAC): full text view [online]. In: ClinicalTrials.gov. 5 April 2013 [accessed: 11 September 2015]. URL: https://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-36

AstraZeneca. Additional analyses for study: 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 [unpublished]. 2015.

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. 27 February 2015 [accessed: 9 November 2015]. URL: https://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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