IQWiG Reports – Commission No. A20-69

Indacaterol acetate/ glycopyrronium bromide/ mometasone furoate (asthma) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Indacaterolacetat/Glycopyrroniumbromid/ Mometasonfuroat (Asthma) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 12 November 2020). 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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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACQ	Asthma Control Questionnaire
ACT	appropriate comparator therapy
AE	adverse event
AQLQ-S	standardized Asthma Quality of Life Questionnaire
FEV1	forced expiratory volume in 1 second
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GINA	Global Initiative for Asthma
ICS	inhaled corticosteroid
IND/GLY/MF	indacaterol acetate/glycopyrronium bromide/mometasone furoate
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LABA	long-acting beta-2 agonist
LAMA	long-acting muscarinic antagonist
LTRA	leukotriene receptor antagonist
OCS	oral corticosteroid
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SGRQ	St. George's Respiratory Questionnaire
SOC	System Organ Class
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug combination indacaterol acetate/glycopyrronium bromide/mometasone furoate (IND/GLY/MF). 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 7 August 2020.

Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

Research question

The aim of the present report is the assessment of the added benefit of IND/GLY/MF in comparison with the appropriate comparator therapy (ACT) in adult patients with asthma not adequately controlled with a maintenance combination of a long-acting beta-2 agonist (LABA) and a high dose of an inhaled corticosteroid (ICS) who experienced one or more asthma exacerbations in the previous year.

For the present benefit assessment, the G-BA's specification of the ACT resulted in the research question presented in Table 2.

Table 2: Research question of the benefit assessment of IND/GLY/MF

Research question	Therapeutic indication	ACT[a]
1	Adult patients with asthma not adequately controlled with a maintenance combination of a LABA and a high dose of an ICS who experienced one or more asthma exacerbations in the previous year	High-dose ICS and LABA and LAMA[b, c]

a. Presentation of the respective ACT specified by the G-BA.
b. According to G-BA, the graded scheme of the German National Care Guideline for Asthma (NVL Asthma 2018, 3rd edition, Version 1 [1]) must be taken into account. Based on the drug properties of the combination of mometasone furoate, indacaterol acetate and glycopyrronium bromide, the G-BA determined the ACT for patients who are candidates for a therapy according to step 4 of the NVL Asthma 2018. Accordingly, it is assumed that the patients in the therapeutic indication received at least a dual combination (of high-dose ICS and LABA) as prior therapy without achieving adequate control. In addition, according to the G-BA, it is assumed that the patients are not yet eligible for the administration of antibodies.
c. According to the G-BA, the unchanged continuation of an inadequate asthma treatment does not comply with an ACT in uncontrolled asthma if the option for treatment escalation is still available.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; GLY: glycopyrronium bromide; ICS: inhaled corticosteroid; IND: indacaterol acetate; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; MF: mometasone furoate; NVL: National Care Guideline

The assessment was conducted by means of patient-relevant outcomes on the basis of 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.

Study pool and study characteristics

The ARGON study was used for the assessment of the added benefit of IND/GLY/MF. This is a multicentre, 3-arm RCT comparing IND/GLY/MF at 2 different dosages with salmeterol/ fluticasone (SAL/FLU) + tiotropium (TIO). Patients and study staff were blinded only to the dosages of the 2 intervention arms, i.e. 150/50/80 µg or 150/50/160 µg. Of the 2 intervention arms, the IND/GLY/MF arm in the 150/50/160 µg dosage complies with the approval. The arm with IND/GLY/MF in the dosage of 150/50/80 µg is therefore not considered further in the following.

The study included adult patients with asthma classified as ≥ step 4 according to the Global Initiative for Asthma (GINA), whose asthma was inadequately controlled despite treatment with medium or high-dose ICS and LABA (inadequate control defined as a score of at least 1.5 in the Asthma Control Questionnaire [ACQ]-7 at the time points of screening and randomization). Patients had to have a history of at least one severe asthma exacerbation in the 12 months prior to enrolment, a forced expiratory volume in 1 second (FEV1) of < 85% of the predicted normal value, and an increase in FEV1 of ≥ 12% in the reversibility test.

Randomization to the study arms was stratified by prior therapy and region. 476 patients were randomized to the intervention arm and 476 patients to the comparator arm. Administration of the study medication was in compliance with the Summary of Product Characteristics (SPC). An adjustment of the asthma-related concomitant therapy was possible during the course of the study. The treatment duration was 24 weeks in total.

The primary outcome of the study was health-related quality of life recorded with the standardized Asthma Quality of Life Questionnaire (AQLQ-S). Patient-relevant secondary outcomes were all-cause mortality, severe asthma exacerbations, asthma symptoms, health-related quality of life (St. George's Respiratory Questionnaire [SGRQ]), and adverse events (AEs).

Subpopulation of the ARGON study relevant for the benefit assessment

The ARGON study included patients whose asthma had been pretreated with medium or high-dose ICS and LABA. However, since the administration of IND/GLY/MF is only approved for patients who have previously been treated with a high dose of an ICS and a LABA, the patient population with this pretreatment from the ARGON study is relevant for the present benefit assessment. This applied to a total of 474 patients (242 patients in the intervention arm and 232 patients in the comparator arm).

Risk of bias

The risk of bias across outcomes for the results of the ARGON study was rated as low. The risk of bias was also rated as low for the results on the outcomes "all-cause mortality" and "severe asthma exacerbations". In contrast, the risk of bias was rated as high for the results on the following outcomes: asthma symptoms (recorded using the ACQ-5), health-related quality of life (recorded using the AQLQ-S and the SGRQ), serious adverse events (SAEs), and discontinuation due to AEs.

Results

Mortality

All-cause mortality

There was no statistically significant difference between the treatment groups for the outcome "all-cause mortality". This resulted in no hint of an added benefit of IND/GLY/MF in comparison with the ACT; an added benefit is therefore not proven.

Morbidity

Severe asthma exacerbations

No statistically significant difference between the treatment groups was shown for the outcome "severe asthma exacerbations". This resulted in no hint of an added benefit of IND/GLY/MF in comparison with the ACT; an added benefit is therefore not proven.

Asthma symptoms (recorded by patient diary and ACQ-5)

No usable data were available for the asthma symptoms recorded by patient diary.

No statistically significant difference between the treatment groups was shown for the recording by ACQ-5.

Overall, there was no hint of an added benefit of IND/GLY/MF in comparison with the ACT for the outcome "asthma symptoms"; an added benefit is therefore not proven.

Health-related quality of life (recorded by AQLQ-S and SGRQ)

No statistically significant difference between the treatment groups was shown for the outcome "health-related quality of life", both recorded by AQLQ-S and recorded by SGRQ. In each case, this resulted in no hint of an added benefit of IND/GLY/MF in comparison with the ACT; an added benefit is therefore not proven.

Side effects

SAEs, discontinuation due to AEs

There was no statistically significant difference between the treatment groups for each of the outcomes "SAEs" and "discontinuation due to AEs". In each case, this resulted in no hint of greater or lesser harm from IND/GLY/MF in comparison with the ACT; greater or lesser harm is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, probability and extent of the added benefit of the drug combination of IND/GLY/MF in comparison with the ACT is assessed as follows:

In summary, there is no hint of an added benefit of IND/GLY/MF in comparison with the ACT of high-dose ICS and LABA and long-acting muscarinic antagonist (LAMA) for patients with asthma not adequately controlled with a maintenance combination of a LABA and a high dose of an ICS who experienced one or more asthma exacerbations in the previous year.

Table 3 shows a summary of probability and extent of the added benefit of IND/GLY/MF.

Table 3: IND/GLY/MF – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adult patients with asthma not adequately controlled with a maintenance combination of a LABA and a high dose of an ICS who experienced one or more asthma exacerbations in the previous year	High-dose ICS and LABA and LAMA[b, c]	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
b. According to G-BA, the graded scheme of the German National Care Guideline for Asthma (NVL Asthma 2018, 3rd edition, Version 1 [1]) must be taken into account. Based on the drug properties of the combination of mometasone furoate, indacaterol acetate and glycopyrronium bromide, the G-BA determined the ACT for patients who are candidates for a therapy according to step 4 of the NVL Asthma 2018. Accordingly, it is assumed that the patients in the therapeutic indication received at least a dual combination (of high-dose ICS and LABA) as prior therapy without achieving adequate control. In addition, according to the G-BA, it is assumed that the patients are not yet eligible for the administration of antibodies.
c. According to the G-BA, the unchanged continuation of an inadequate asthma treatment does not comply with an ACT in uncontrolled asthma if the option for treatment escalation is still available.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; GLY: glycopyrronium bromide; ICS: inhaled corticosteroid; IND: indacaterol acetate; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; MF: mometasone furoate; NVL: National Care Guideline

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

[3] 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, added benefit not proven, or less benefit). For further details see [2,3].

2.2 Research question

The aim of the present report is the assessment of the added benefit of IND/GLY/MF in comparison with the ACT in adult patients with asthma not adequately controlled with a maintenance combination of a LABA and a high dose of an ICS who experienced one or more asthma exacerbations in the previous year.

For the present benefit assessment, the G-BA's specification of the ACT resulted in the research question presented in Table 4.

Table 4: Research question of the benefit assessment of IND/GLY/MF

Research question	Therapeutic indication	ACT[a]
1	Adult patients with asthma not adequately controlled with a maintenance combination of a LABA and a high dose of an ICS who experienced one or more asthma exacerbations in the previous year	High-dose ICS and LABA and LAMA[b, c]

a. Presentation of the respective ACT specified by the G-BA.
b. According to G-BA, the graded scheme of the German National Care Guideline for Asthma (NVL Asthma 2018, 3rd edition, Version 1 [1]) must be taken into account. Based on the drug properties of the combination of mometasone furoate, indacaterol acetate and glycopyrronium bromide, the G-BA determined the ACT for patients who are candidates for a therapy according to step 4 of the NVL Asthma 2018. Accordingly, it is assumed that the patients in the therapeutic indication received at least a dual combination (of high-dose ICS and LABA) as prior therapy without achieving adequate control. In addition, according to the G-BA, it is assumed that the patients are not yet eligible for the administration of antibodies.
c. According to the G-BA, the unchanged continuation of an inadequate asthma treatment does not comply with an ACT in uncontrolled asthma if the option for treatment escalation is still available.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; GLY: glycopyrronium bromide; ICS: inhaled corticosteroid; IND: indacaterol acetate; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; MF: mometasone furoate; NVL: National Care Guideline

The company deviated from the G-BA's specification insofar as it considered some of the patients in the therapeutic indication, in principle, to be candidates also for antibody therapy. The company's deviation had no consequence for the present assessment, as only few patients received such a therapy in the study presented by the company (see Section 2.3.2). The present benefit assessment of IND/GLY/MF was conducted in comparison with the G-BA's ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of 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 inclusion criteria.

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:

- List of studies on IND/GLY/MF (status: 16 June 2020)
- bibliographical literature search on IND/GLY/MF (last search on 16 June 2020)
- search in trial registries/trial results databases for studies on IND/GLY/MF (last search on 16 June 2020)
- search on the G-BA website for IND/GLY/MF (last search on 16 June 2020)

To check the completeness of the study pool:

- search in trial registries for studies on IND/GLY/MF (last search on 14 August 2020)

The check did not identify any additional relevant studies.

2.3.1 Studies included

The study listed in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: IND/GLY/MF vs. SAL/FLU + TIO

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
CQVM149B2306 (ARGON[c])	No	Yes	No	No[d]	Yes [4-8]	Yes [9]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. In the following tables, the study is referred to with this abbreviated form.
d. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

CSR: clinical study report; FLU: fluticasone; GLY: glycopyrronium bromide; IND: indacaterol acetate; MF: mometasone furoate; RCT: randomized controlled trial; SAL: salmeterol; TIO: tiotropium; vs.: versus

2.3.2 Study characteristics

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

Table 6: Characteristics of the included study – RCT, direct comparison: IND/GLY/MF vs. SAL/FLU + TIO

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ARGON	RCT, parallel, multicentre, partially blinded[b]	Adult patients with asthma ▪ who are not adequately controlled despite pretreatment with medium or high-dose ICS and LABA[c] ▪ with an asthma classification of ≥ step 4[d] ▪ with ≥ 1 severe asthma exacerbation[e] within 12 months before baseline ▪ FEV1 < 85% predicted ▪ increase in FEV1 of ≥ 12% in the reversibility test	IND/GLY/MF 150/50[f]/80 µg (N = 474)[g] IND/GLY/MF 150/50[f]/160 µg (N = 476) SAL/FLU + TIO (N = 476) Relevant subpopulation thereof[h]: IND/GLY/MF 150/50[f]/160 µg (n = 242) SAL/FLU + TIO (n = 232)	Screening: 1 week Run-in phase: 2 weeks Treatment: 24 weeks Follow-up observation: up to 7 days or 30 days for mortality and SAEs	166 study centres[i] in Argentina, Chile, Colombia, Czech Republic, Germany, Greece, Hungary, India, Israel, Mexico, Peru, Poland, Russia, Serbia, Slovakia, South Africa, Spain, Taiwan, Turkey, Vietnam 2/2018 until 7/2019	Primary: health-related quality of life (AQLQ-S) Secondary: mortality, morbidity, health-related quality of life (SGRQ), AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Patients and study staff were blinded only to the dosages of the intervention arms, i.e. 150/50/80 or 150/50/160 µg.
c. Defined by an ACQ-7 score of ≥ 1.5 at the time points of screening and randomization.
d. According to GINA 2017 [10].
e. Which required medical care from a physician, emergency room visit (or equivalent structure) or hospitalization and OCS treatment for at least 3 days.
f. The dosage of 50 µg refers to glycopyrronium (equivalent to 63 µg glycopyrronium bromide).
g. The study arm is not relevant for the assessment (as the dosage is not in compliance with the approval) and will not be presented in the following tables.
h. Patients who were pretreated with high-dose ICS and LABA.
i. According to Gessner 2020 [9], patients were recruited from 180 study centres.

AE: adverse event; ACQ: Asthma Control Questionnaire; AQLQ-S: standardized Asthma Quality of Life Questionnaire; FEV1: forced expiratory volume in 1 second; FLU: fluticasone; GINA: Global Initiative for Asthma; GLY: glycopyrronium bromide; ICS: inhaled corticosteroid; IND: indacaterol acetate; LABA: long-acting beta-2 agonist; MF: mometasone furoate; n: number of patients in the relevant subpopulation; N: number of randomized patients; OCS: oral corticosteroids; RCT: randomized controlled trial; SAE: serious adverse event; SAL: salmeterol; SGRQ: St. George's Respiratory Questionnaire; TIO: tiotropium; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: IND/GLY/MF vs. SAL/FLU + TIO (multipage table)

Study	Intervention	Comparison
ARGON	IND/GLY/MF 150/50[a]/160 µg once daily, in the evening	SAL/FLU 50/500 µg twice daily, in the morning and evening, + TIO 5 µg once daily, in the evening
	▪ ICS/LABA dose adjustment/interruption was not permitted, except restricted for AEs, at the investigator's discretion. ▪ Treatment with tiotropium could be discontinued if the asthma was well controlled.	
	Pretreatment ▪ stable treatment with medium or high-dose ICS[b]/LABA for ≥ 3 months before screening **Treatment during run-in phase** ▪ SAL/FLU 50/250 µg twice daily or 50/500 µg twice daily depending on pretreatment **Permitted concomitant treatment** ▪ Continuation if at stable dose for 1 or 3 months (depending on the drug) prior to screening: ▫ monoclonal antibodies ▫ immune maintenance therapies for allergies ▫ LTRA or leukotriene synthesis inhibitors ▫ long- or short-acting theophylline (methylxantine) ▫ OCS ▫ mucolytic drugs (not containing bronchodilators) ▫ intranasal or topical corticosteroids ▪ As an add-on in the course of the study: ▫ LTRA or leukotriene synthesis inhibitors ▫ long- or short-acting theophylline (methylxantine) ▫ OCS ▫ monoclonal antibodies ▪ salbutamol/albuterol (rescue medication) **Prohibited asthma-related prior and concomitant treatment** ▪ LAMA 3 months before screening ▪ SABA (other than study-supplied rescue medication) ▪ parenteral, intravenous or intramuscular corticosteroids: 4 weeks before run-in ▪ intramuscular depot corticosteroids: 3 months before run-in ▪ Not allowed shortly before examinations before run-in phase: ▫ SAMA ▫ fixed combination of beta-2 sympathomimetic and ICS ▫ SABA/SAMA fixed combination	

a. The dosage of 50 µg refers to glycopyrronium (equivalent to 63 µg glycopyrronium bromide).
b. Dosage category (low, medium, high dose) according to GINA 2017 [10].

AE: adverse event; FLU: fluticasone; GINA: Global Initiative for Asthma; GLY: glycopyrronium bromide; ICS: inhaled corticosteroid; IND: indacaterol acetate; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonists; MF: mometasone furoate; OCS: oral corticosteroid; RCT: randomized controlled trial; SABA: short-acting beta-2 agonist; SAL: salmeterol; SAMA: short-acting muscarinic antagonist; TIO: tiotropium; vs.: versus

Description of the ARGON study

The ARGON study is a multicentre, 3-arm RCT comparing IND/GLY/MF at 2 different dosages with SAL/FLU + TIO. Patients and study staff were blinded only to the dosages of the intervention arms, i.e. 150/50/80 or 150/50/160 µg. Of the 2 intervention arms, the IND/GLY/MF arm in the 150/50/160 µg dosage complies with the approval. The arm with IND/GLY/MF in the dosage of 150/50/80 µg is therefore not considered further in the following.

The study included adult patients with asthma classified as ≥ step 4 according to GINA [10], whose asthma was inadequately controlled despite treatment with medium or high-dose ICS and LABA. Inadequate control was defined as a score of at least 1.5 in the ACQ-7 at the time points of screening and randomization. Patients also had to have a history of at least one severe asthma exacerbation in the 12 months prior to enrolment. Only patients with an FEV1 of < 85% of the predicted normal value, and an increase in FEV1 of ≥ 12% in the reversibility test were enrolled.

The ARGON study started with a 2-week run-in phase after screening. During these 2 weeks, the patients' previous ICS and LABA drugs were switched to the 2 ICS and LABA drugs used in the comparator arm of the study, i.e. fluticasone and salmeterol, twice daily. The dosage of the SAL/FLU combination was based on the respective pretreatment of the patients and was 50/250 µg or 50/500 µg. It could not be inferred from the information provided in Module 4 A which algorithm was used to decide to switch to the lower or higher dosage or which drugs the patients had previously received.

After the run-in phase, the patients were randomized to the study arms, stratified by prior therapy and region. 476 patients were randomized to the intervention arm (IND/GLY/MF 150/50/160) and 476 to the comparator arm (SAL/FLU + TIO). Administration of the study medications was in compliance with the SPC [11].

The treatment duration was 24 weeks in total.

The primary outcome of the study was health-related quality of life recorded with the AQLQ-S. Patient-relevant secondary outcomes were all-cause mortality, severe asthma exacerbations, asthma symptoms, health-related quality of life (SGRQ), and AEs.

Note on ICS dosage (fluticasone) in the comparator arm of the ARGON study

The dosage of fluticasone – administered as propionate in the ARGON study – was administered at a dose of 500 µg twice daily, i.e. the patients received a daily dose of 1000 µg. According to the NVL [1,12], a daily dose of ≥ 1000 µg is no longer a high dose but the lower limit of the maximum dose. However, the ACT comprises a high dose of ICS (> 500 to 999 µg according to the NVL), and thus does not comprise a daily dose of 1000 µg. However, due to the small deviation, this dosage is not expected to have important effects on the results of the study. Hence, this had no consequences for the present assessment.

Adjustment of the accompanying therapy was possible

In the ARGON study, patients were allowed to continue a stable asthma-related therapy started before baseline, for example with antibodies, leukotriene receptor antagonists (LTRAs) or oral corticosteroids (OCS), after randomization. During the course of the study, therapy adjustments were allowed in cases of inadequate asthma control. However, it was not allowed in either treatment arm to adjust or discontinue the administration of ICS and LABA. The investigators could escalate the patients' concomitant medication and/or initiate new maintenance therapies (e.g. OCS, antibodies, theophylline, LTRA) if patients remained uncontrolled or experienced severe asthma exacerbations. On the other hand, de-escalation of therapy was possible if the asthma symptoms were well controlled (stable lung function for ≥ 3 months and no risk of exacerbations). Priority was to be given to reducing OCS therapy. Under the same conditions, the additional therapy with the LAMA, i.e. with tiotropium, could also be discontinued in the comparator arm.

According to Gessner 2020 [9], there were overall neither escalations nor de-escalations in the ARGON study. The authors attributed this, among other things, to the duration of the study. With the exception of OCS therapy, Module 4 A contained no information on therapy adjustments of the concomitant medication actually performed during the course of the study. Thus, 19.0% of the patients in the intervention arm and 12.1% in the comparator arm started OCS therapy in the study, with a median treatment duration of 5.5 to 10 days. In a small proportion of patients (0.4% vs. 0.9% of the patients in the intervention arm and in the comparator arm), the OCS therapy already taken at the start of the study was escalated in the course of the study. The median treatment duration in these cases was about 18 days. Due to the short median treatment durations, the company assumed that the vast majority were acute exacerbation therapies.

Subpopulation of the ARGON study relevant for the benefit assessment

The ARGON study included patients whose asthma had been pretreated with medium or high-dose ICS and LABA. However, according to the SPC [11], the administration of IND/GLY/MF is only approved for patients who have previously been treated with high-dose ICS and LABA.

About half of the 476 patients included in each the intervention arm and the comparator arm of the ARGON study had been pretreated with high-dose ICS. Accordingly, 242 versus 232 patients of the ARGON study represent the relevant subpopulation for the present benefit assessment.

Patient characteristics of the ARGON study

Table 8 shows the characteristics of the patients of the relevant subpopulation in the study included.

Table 8: Characteristics of the relevant subpopulation – RCT, direct comparison: IND/GLY/MF vs. SAL/FLU + TIO (multipage table)

Study **Characteristic** **Category**	**IND/GLY/MF** **N = 242**	**SAL/FLU + TIO** **N = 232**
Study ARGON		
Age [years], mean (SD)	53 (13)	54 (13)
Sex [F/M], %	64/36	65/35
Ethnicity[a], n (%)		
Latin America	103 (42.6)	88 (37.9)
East Asia	1 (0.4)	0 (0)
South-East Asia	9 (3.7)	10 (4.3)
South Asia	1 (0.4)	0 (0)
West Asia	6 (2.5)	5 (2.2)
Russia	33 (13.6)	32 (13.8)
Germany	35 (14.5)[b]	36 (15.5)[b]
Mixed ethnicity	2 (0.8)	0 (0)
No data	7 (2.9)	6 (2.6)
Unknown	2 (0.8)	2 (0.9)
Other	43 (17.8)[b]	53 (22.8)[b]
Duration of asthma [years], mean (SD)	24.0 (16.9)	21.3 (15.5)
Number of asthma exacerbations in the 12 months prior to baseline		
1	176 (72.7)	184 (79.3)
2	50 (20.7)	39 (16.8)
3	14 (5.8)	9 (3.9)
≥ 4	2 (0.8)	0 (0)
Smoking history, n (%)		
Never smoker	178 (73.6)	174 (75.0)
Ex-smoker	62 (25.6)	54 (23.3)
Current smoker	2 (0.8)	4 (1.7)
ACQ-7 total score, mean (SD)	2.7 (0.53)	2.6 (0.52)
Eosinophils at baseline (cells/µL), n (%)		
< 300	141 (58.3)	140 (60.3)
≥ 300	98 (40.5)	90 (38.8)
No data	3 (1.2)	2 (0.9)
FEV1 in % predicted, mean (SD)	60.4 (14.90)	62.9 (13.30)
IgE concentration (IU/mL), n (%)		
≤ 75	74 (30.6)	69 (29.7)
< 75–≤ 1500	145 (59.9)	143 (61.6)
> 1500	15 (6.2)	14 (6.0)
No data	8 (3.3)	6 (2.6)

Table 8: Characteristics of the relevant subpopulation – RCT, direct comparison: IND/GLY/MF vs. SAL/FLU + TIO (multipage table)

Study Characteristic Category	IND/GLY/MF N = 242	SAL/FLU + TIO N = 232
Concomitant asthma medication at baseline, n (%)		
OCS	4 (1.7)	5 (2.2)
LTRA	31 (12.8)	29 (12.5)
Mepolizumab	1 (0.4)	3 (1.3)
Omalizumab	7 (2.9)	7 (3.0)
Reslizumab	0 (0)	0 (0)
Other	12 (5.0)	14 (6.0)
Treatment discontinuation, n (%)	11 (4.5)	14 (6.0)
Study discontinuation, n (%)	9 (3.7)	10 (4.3)

a. The company uses the term "ethnicity". However, it is unclear whether this actually refers to the ethnicity or the region of the patients.
b. Institute's calculation.

ACQ: Asthma Control Questionnaire; F: female; FEV1: forced expiratory volume in 1 second; FLU: fluticasone; GLY: glycopyrronium bromide; IgE: immunoglobulin E; IND: indacaterol acetate; LTRA: leukotriene antagonist; M: male; MF: mometasone furoate; n: number of patients in the category; N: number of randomized patients in the relevant subpopulation; OCS: oral corticosteroid; RCT: randomized controlled trial; SAL: salmeterol; SD: standard deviation; TIO: tiotropium; vs.: versus

The demographic and asthma-specific characteristics of the patients were comparable between the treatment arms.

The mean age of the patient population of the study was 54 years, and about 64% were female. The patients had had the diagnosis of asthma for about 23 years, had a score of 2.7 in the ACQ-7, and 76% of them had had one single asthma exacerbation in the previous year. The majority of the patients (74%) had never smoked. Overall, few of the patients in the relevant subpopulation were receiving an antibody at baseline, namely mepolizumab (0.8%) or omalizumab (3.0%).

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: IND/GLY/MF vs. SAL/FLU + TIO

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
ARGON	Yes	Yes	No	No	Yes	Yes	Low

FLU: fluticasone; GLY: glycopyrronium bromide; IND: indacaterol acetate; MF: mometasone furoate; RCT: randomized controlled trial; SAL: salmeterol; TIO: tiotropium; vs.: versus

The risk of bias across outcomes was rated as low for the study. This concurs with the company's assessment.

Limitations resulting from the unblinded comparison are described in Section 2.4 with the outcome-specific risk of bias.

Transferability of the study results to the German health care context

The company described in Module 4 A that 14.9% of the relevant population of the ARGON study were treated at German study centres. Furthermore, a total of 34.6% of the patients were in the subgroup "Europe".

According to the company, the demographic and clinical patient characteristics of the patients treated at German study centres are highly comparable with those of the relevant subpopulation. For clarification, the company presented the patient characteristics of these patients in Module 4 A.

In addition, the company described that it was possible in all treatment arms to continue ongoing concomitant treatment with antiasthmatic drugs for long-term therapy to reflect the best clinical practice or to adapt it in accordance with the guidelines.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be considered in the assessment:

- Mortality
  - all-cause mortality

- Morbidity
  - severe asthma exacerbations
  - asthma symptoms recorded by patient diary and ACQ-5
- Health-related quality of life
  - health-related quality of life recorded by AQLQ-S and SGRQ
- Side effects
  - SAEs
  - discontinuation due to AEs
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4 A).

Table 10 shows for which outcomes data were available in the study included.

Table 10: Matrix of outcomes – RCT, direct comparison: IND/GLY/MF vs. SAL/FLU + TIO

Study	Outcomes							
	All-cause mortality	Severe asthma exacerbations[a]	Asthma symptoms (patient diary)	Asthma symptoms (ACQ-5)	Health-related quality of life (recorded by AQLQ-S and SGRQ)	SAEs[c]	Discontinuation due to AEs	Further specific AEs
ARGON	Yes	Yes	No[b]	Yes	Yes	Yes	Yes	No[d]

a. Defined as an aggravation of asthma symptoms (like shortness of breath, cough, wheezing, or chest tightness) that required the following interventions: administration or increase of OCS for ≥ 3 consecutive days and/or a need for an emergency room visit (or local equivalent structure), and/or hospitalization due to asthma and/or death due to asthma.
b. No usable data available (see Section 2.4.3).
c. Without the PT "asthma".
d. No specific AEs selected.

ACQ: Asthma Control Questionnaire; AE: adverse event; AQLQ-S: standardized Asthma Quality of Life Questionnaire; FLU: fluticasone; GLY: glycopyrronium bromide; IND: indacaterol acetate; MF: mometasone furoate; OCS: oral corticosteroids; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SAL: salmeterol; SGRQ: St. George's Respiratory Questionnaire; TIO: tiotropium; vs.: versus

Note on responder analyses on the outcome "health-related quality of life"

For the outcome "health-related quality of life" recorded using the instruments AQLQ-S and SGRQ, the company presented responder analyses for the proportion of patients with an improvement by at least 0.5 (AQLQ-S) or 4 points (SGRQ) in its dossier.

These were not used for the dossier assessment. As explained in the General Methods of the Institute [2], for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to at least 15% of the scale range of an instrument (in post-hoc analyses exactly 15% of the scale range).

The responder analyses presented by the company are presented in Appendix B of the full dossier assessment.

Application of the elevation rule

The company applied the elevation rule for the benefit assessment of IND/GLY/MF in the present therapeutic indication. It justified this by stating that, due to the approved therapeutic indication of IND/GLY/MF, consideration is given only to the results for the subpopulation of patients in the ARGON study whose asthma was inadequately controlled under high-dose ICS/LABA therapy. From the point of view of the company, this is accompanied by a considerable loss of power, which could be compensated by applying the elevation rule.

The company described that for the applicability of the elevation rule, under certain conditions, a test for an effect at the increased significance level of 15% instead of the usual 5% could be performed in the relevant subpopulation of a study and used to assess the added benefit. The company explained that it performed the elevation rule for the prespecified primary analysis for all outcomes.

It is correct that, according to the elevation rule, the treatment effect in the relevant subpopulation can be tested at the increased significance level of 15% under certain conditions [13]. The necessary conditions for applying the elevation rule were not fulfilled for the outcomes and operationalizations used in the present dossier assessment, however. The two reasons for this are that either there was no statistically significant difference (at the level of 5%) between the treatment arms in the total population of the ARGON study (a basic prerequisite for the application of the elevation rule), or that there was no statistically significant effect in the relevant subpopulation for the outcome used at the increased level of 15%.

In addition, the company referred to the fact that, for the application of the elevation rule, the relevant subpopulation and the total study population must be medically comparable patient populations. However, it is rather assumed instead that the results of the non-relevant subpopulation of the study ("non-target population") are sufficiently transferable to the relevant subpopulation ("target population"). The company did not address this issue.

Overall, the company's approach is not commented on further, as the necessary prerequisites for the application of the elevation rule were not fulfilled for the patient-relevant outcomes and operationalizations used in the present benefit assessment.

2.4.2 Risk of bias

Table 11 describes the risk of bias for the results of the relevant outcomes.

Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: IND/GLY/MF vs. SAL/FLU + TIO

Study	Study level	Outcomes							
		All-cause mortality	Severe asthma exacerbations[a]	Asthma symptoms (patient diary)	Asthma symptoms (ACQ-5)	Health-related quality of life (recorded by AQLQ-S and SGRQ)	SAEs	Discontinuation due to AEs	Further specific AEs
ARGON	L	L	L	–[b]	H[c]	H[c]	H[d]	H[c]	–[e]

a. See Table 10 for definition.
b. No usable data available; see Section 2.4.3 for reasons.
c. Lack of blinding in subjective recording of outcomes.
d. The analyses on SAEs do not include the PT "asthma", but it is unclear whether other events are included that can potentially be attributed to the underlying disease. The company did not address this issue in Module 4 A.
e. No specific AEs selected.

ACQ: Asthma Control Questionnaire; AE: adverse event; AQLQ-S: standardized Asthma Quality of Life Questionnaire; FLU: fluticasone; GLY: glycopyrronium bromide; H: high; IND: indacaterol acetate; L: low; MF: mometasone furoate; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SAL: salmeterol; SGRQ: St. George's Respiratory Questionnaire; TIO: tiotropium; vs.: versus

The risk of bias of the results for the outcomes "all-cause mortality" and "severe asthma exacerbations" was rated as low. This concurs with the company's assessment.

The risk of bias of the results for the patient-reported outcomes "asthma symptoms" (ACQ-5), "health-related quality of life" (AQLQ-S, SGRQ) and of the outcome "discontinuation due to AEs" was rated as high due to the lack of blinding in subjective recording of outcomes. This concurs with the company's assessment.

Deviating from the company, the risk of bias of the results for the outcome "SAEs" was rated as high. The PT "asthma" was not considered in the analysis, but it is unclear whether other

events are included that can potentially be attributed to the underlying disease. The company did not address this issue in Module 4 A.

2.4.3 Results

Table 12, Table 13 and Table 14 summarize the results of the comparison of IND/GLY/MF with SAL/FLU + TIO in patients with asthma not adequately controlled with a maintenance combination of a LABA and a high dose of an ICS who experienced one or more asthma exacerbations in the previous year. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Results at System Organ Class (SOC) and Preferred Term (PT) level on common AEs and AEs that led to treatment discontinuation are presented as supplementary information in Appendix A of the full dossier assessment. The common SAEs are not listed, as there were no events at SOC and PT level that met the criteria for presentation.

Table 12: Results (mortality, morbidity, side effects, dichotomous) – RCT, direct comparison: IND/GLY/MF vs. SAL/FLU + TIO

Study (time point) Outcome category Outcome	IND/GLY/MF		SAL/FLU + TIO		IND/GLY/MF vs. SAL/FLU + TIO
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
ARGON					
Mortality					
All-cause mortality	242	0 (0)	232	1 (0.4)	0.32 [0.01; 7.81]; 0.484
Morbidity					
Severe asthma exacerbations[a] (supplementary information)	242	43 (17.8)	232	28 (12.1)	1.47 [0.95; 2.29]; 0.084[b]
Side effects					
AEs[e] (supplementary information)	242	126 (52.1)	232	107 (46.1)	-
SAEs[c]	242	9 (3.7)	232	10 (4.3)	0.86 [0.36; 2.09]; 0.743
Discontinuation due to AEs	242	1 (0.4)	232	3 (1.3)	0.32 [0.03; 3.05]; 0.322

a. See Table 10 for definition.
b. Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [14]).
c. Without the PT "asthma".

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; FLU: fluticasone; GLY: glycopyrronium bromide; IND: indacaterol acetate; MF: mometasone furoate; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SAL: salmeterol; TIO: tiotropium; vs.: versus

Table 13: Results (mortality, morbidity, side effects, dichotomous) – RCT, direct comparison: IND/GLY/MF vs. SAL/FLU + TIO

Study (time point) Outcome category Outcome	IND/GLY/MF		SAL/FLU + TIO		IND/GLY/MF vs. SAL/FLU + TIO
	N	Mean annual rate [95% CI][b]	N	Mean annual rate [95% CI][b]	Rate ratio [95% CI]; p-value[b]
ARGON					
Morbidity					
Severe asthma exacerbations[a]	242	0.49 [0.36; 0.68]	232	0.34 [0.23; 0.49]	1.46 [0.91; 2.35]; 0.121

a. See Table 10 for definition.
b. Mean rates with CI (per treatment group) and rate ratio with CI and p-value (group comparison): negative binomial regression with the variables treatment, region and history of exacerbations, and the offset variable log(exposure).

CI: confidence interval; FLU: fluticasone; GLY: glycopyrronium bromide; IND: indacaterol acetate; MF: mometasone furoate; N: number of analysed patients; RCT: randomized controlled trial; SAL: salmeterol; TIO: tiotropium; vs.: versus

Table 14: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: IND/GLY/MF vs. SAL/FLU + TIO (multipage table)

Study (time point) Outcome category Outcome	IND/GLY/MF			SAL/FLU + TIO			IND/GLY/MF vs. SAL/FLU + TIO
	N[a]	Values at baseline mean (SD)	Change at week 24 mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change at week 24 mean[b] (SE)	Mean difference [95% CI]; p-value[b]
ARGON							
Morbidity							
Asthma symptoms (patient diary)	No usable data[c]						
Asthma symptoms (ACQ-5)[d]	232	2.59 (0.60)	−1.25 (0.08)	219	2.52 (0.57)	−1.24 (0.09)	−0.01 [−0.17; 0.16]; 0.926
Health-related quality of life							
Health-related quality of life (AQLQ-S)							
Total score[e]	231	4.69 (0.86)	0.74 (0.08)	215	4.71 (0.88)	0.74 (0.08)	0.00 [−0.15; 0.16]; 0.957
Domains[e] (supplementary information)							
Symptom score	231	4.70 (0.86)	0.76 (0.08)	215	4.79 (0.84)	0.80 (0.09)	−0.05 [−0.21; 0.12]
Activity limitation score	231	4.60 (0.90)	0.75 (0.08)	215	4.61 (0.92)	0.78 (0.08)	−0.04 [−0.20; 0.12]
Emotional function score	231	5.02 (1.17)	0.74 (0.10)	215	4.92 (1.31)	0.61 (0.11)	0.12 [−0.08; 0.33]
Environmental exposure score	231	4.46 (1.28)	0.66 (0.11)	215	4.52 (1.36)	0.57 (0.12)	0.09 [−0.13; 0.32]
Health-related quality of life (SGRQ)							
Total score[f]	228	39.86 (16.08)	−11.85 (1.64)	211	38.51 (17.27)	−10.19 (1.68)	−1.66 [−4.64; 1.31]; 0.273
Domains[f] (supplementary information)							
Symptom score	228	51.50 (18.61)	−16.78 (2.17)	211	51.44 (20.76)	−17.25 (2.22)	0.48 [−3.46; 4.41]
Activity score	228	54.09 (20.44)	−11.54 (2.13)	211	50.81 (21.29)	−9.60 (2.19)	−1.94 [−5.82; 1.95]
Impact score	228	28.24 (17.75)	−10.49 (1.67)	211	27.55 (19.31)	−8.37 (1.71)	−2.12 [−5.16; 0.91]

a. Number of patients considered in the analysis for the calculation of the effect estimation; the values at baseline may be based on other patient numbers.
b. Mean and SE (change at week 24 per treatment group) and MD and p-value (group comparison); for the instruments ACQ-5 and AQLQ-S: MMRM with the variables treatment, region, visit and baseline value as well as the interactions baseline value x visit and treatment x visit; for the instrument SGRQ: ANCOVA with the variables treatment, region and baseline value.
c. See Section 2.4.3.
d. Symptoms on the ACQ-5 are rated on a scale from 0 to 6. Lower (decreasing) values indicate better symptoms; negative statistically significant effects (intervention minus control) indicate an advantage for IND/GLY/MF.
e. Higher (increasing) values indicate better health-related quality of life; positive statistically significant effects (intervention minus control) indicate an advantage for IND/GLY/MF.
f. Lower (decreasing) values indicate better health-related quality of life; negative statistically significant effects (intervention minus control) indicate an advantage for IND/GLY/MF.

Table 14: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: IND/GLY/MF vs. SAL/FLU + TIO (multipage table)

Study (time point) Outcome category Outcome	IND/GLY/MF			SAL/FLU + TIO			IND/GLY/MF vs. SAL/FLU + TIO
	N[a]	Values at baseline mean (SD)	Change at week 24 mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change at week 24 mean[b] (SE)	Mean difference [95% CI]; p-value[b]
ACQ: Asthma Control Questionnaire; ANCOVA: analysis of covariance; AQLQ-S: standardized Asthma Quality of Life Questionnaire; CI: confidence interval; FLU: fluticasone; GLY: glycopyrronium bromide; IND: indacaterol acetate; MD: mean difference; MF: mometasone furoate; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SAL: salmeterol; SD: standard deviation; SE: standard error; SGRQ: St. George's Respiratory Questionnaire; TIO: tiotropium; vs.: versus							

Based on the available data, at most indications, e.g. of an added benefit, can be determined for the outcomes "all-cause mortality" and "severe asthma exacerbations"; and, due to the high risk of bias of the results, at most hints for the following outcomes: asthma symptoms, health-related quality of life, SAEs, and discontinuation due to AEs.

Mortality

All-cause mortality

There was no statistically significant difference between the treatment groups for the outcome "all-cause mortality". This resulted in no hint of an added benefit of IND/GLY/MF in comparison with the ACT; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

Severe asthma exacerbations

No statistically significant difference between the treatment groups was shown for the outcome "severe asthma exacerbations". This resulted in no hint of an added benefit of IND/GLY/MF in comparison with the ACT; an added benefit is therefore not proven.

This concurs with the company's assessment.

Asthma symptoms (recorded by patient diary and ACQ-5)

Operationalization

In the ARGON study, asthma symptoms were recorded both by an electronic patient diary and by ACQ-5. The patient diary contains 7 questions on symptoms, of which patients had to answer 2 questions in the morning and 5 questions in the evening each day. The questions relate to nocturnal awakening, asthma symptoms upon awakening in the morning, activity restrictions, dyspnoea/shortness of breath, coughing, chest tightness and panting/wheezing. The ACQ-5 [15] includes a total of 5 questions on asthma symptoms, each relating to the last 7 days. The

questions of the ACQ-5 address the same aspects as the patient diary except for coughing and chest tightness. According to the company, the ACQ-7 was used in the ARGON study to assess asthma symptoms. For the dossier, however, the company analysed the ACQ-5, which does not contain 2 questions on the following aspects: use of rescue medication and restriction of lung function (FEV1).

Both instruments are suitable for recording asthma symptoms, but the recording by patient diary is more comprehensive than by ACQ-5 because it additionally records the symptoms of coughing and chest tightness and also because the symptoms are documented daily by the patients.

For the present benefit assessment, however, only the presented analyses of the ACQ-5 are usable.

For the patient diary, the company presented several analyses, which are not usable for the present benefit assessment, however:

- The company considered the daily response, i.e. whether the patient had "no limitation" because of asthma symptoms. The company considered 4 operationalizations of the response using different combinations of the above mentioned questions. Either all 7 questions were considered simultaneously ("days without asthma symptoms") or 3 subsets of the questions ("morning without symptoms upon awakening", "days without symptoms during the day", "days without nocturnal awakening"). For example, there was one "day without asthma symptoms" if the patient answered all 7 questions with "no limitation". For the other 3 operationalizations of response, only a defined subset of the questions had to be answered with "no limitation" in each case. The company considered the change from baseline in the proportion of days or mornings with the respective response. It is unclear which of the 4 operationalizations of response described had been planned, if any. It is also unclear whether the type of analysis regarding the proportion of days or mornings had been prespecified. Furthermore, it is unclear for all 4 analyses how these were actually carried out (e.g. which period of time for the proportion of days or mornings without asthma symptoms was used as the baseline value at the start of the study).
- The company additionally presented analyses of the change from baseline in the 7 individual questions and in 3 "scores" not described in more detail, including a score referred to by the company as "Mean Total Daily Symptom Score". However, it is not clear how these scores were determined and whether they had been prespecified.

Results

No usable data were available for the asthma symptoms recorded by patient diary. For the outcome "asthma symptoms", recorded by ACQ-5, no statistically significant difference between the treatment groups was shown based on the results.

Overall, there was no hint of an added benefit of IND/GLY/MF in comparison with the ACT for the outcome "asthma symptoms"; an added benefit is therefore not proven.

This deviates from the assessment of the company in that the company used the analyses of the change from baseline in the proportion of days or mornings without limitation because of asthma symptoms regarding the patient diary, and derived a minor added benefit on the basis of the analysis "proportion of days without asthma symptoms" and by applying the elevation rule.

For the ACQ-5, the approach deviated only in that the company additionally used the responder analyses, but also derived no hint of an added benefit on this basis.

Health-related quality of life (recorded by AQLQ-S and SGRQ)

Operationalization

The analysis of the mean change from baseline was used for the benefit assessment.

Results

No statistically significant difference between the treatment groups was shown for the outcome "health-related quality of life", both recorded by AQLQ-S and recorded by SGRQ. In each case, this resulted in no hint of an added benefit of IND/GLY/MF in comparison with the ACT; an added benefit is therefore not proven.

This deviates from the assessment of the company, which used the responder analyses in addition to the mean change from baseline. On the basis of these responder analyses and applying the elevation rule, the company derived a minor added benefit.

Side effects

SAEs and discontinuation due to AEs

Operationalization

Analyses excluding the PT "asthma" were available for the outcome "SAEs".

Results

There was no statistically significant difference between the treatment groups for the outcome "SAEs" or for the outcome "discontinuation due to AEs". In each case, this resulted in no hint of greater or lesser harm from IND/GLY/MF in comparison with the ACT; greater or lesser harm is therefore not proven.

In each case, this concurs with the company's assessment.

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics were considered in the present benefit assessment:

- age (18–39, 40–64, ≥ 65)
- sex (female, male)

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there must be 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

In accordance with the methods described, no relevant effect modification by age or sex was identified for the outcomes for which usable analyses were available.

2.5 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [2].

The approach for deriving an overall conclusion on the 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 the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 15).

Table 15: Extent of added benefit at outcome level: IND/GLY/MF vs. SAL/FLU + TIO

Outcome category **Outcome**	**IND/GLY/MF vs. SAL/FLU + TIO** **Proportion of events (%) or mean annual rate or mean change** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	Proportions of events: 0% vs. 0.4% RR: 0.32 [0.01; 7.81]; p = 0.484	Lesser benefit/added benefit not proven
Morbidity		
Severe asthma exacerbations	Mean annual rate: 0.49 vs. 0.34 Rate ratio: 1.46 [0.91; 2.35]; p = 0.121	Lesser benefit/added benefit not proven
Asthma symptoms		
Recorded by patient diary	No usable data	Lesser benefit/added benefit not proven
Recorded by ACQ-5	Mean change: −1.25 vs. −1.24 −0.01 [−0.17; 0.16]; p = 0.926	
Health-related quality of life		
Health-related quality of life		
Recorded by AQLQ-S	Mean change: 0.74 vs. 0.74 0.00 [−0.15; 0.16]; p = 0.957	Lesser benefit/added benefit not proven
Recorded by SGRQ	Mean change: −11.85 vs. −10.19 −1.66 [−4.64; 1.31]; p = 0.273	Lesser benefit/added benefit not proven
Side effects		
SAEs	Proportions of events: 3.7% vs. 4.3% RR: 0.86 [0.36; 2.09]; p = 0.743	Greater/lesser harm not proven
Discontinuation due to AEs	Proportions of events: 0.4% vs. 1.3% RR: 0.32 [0.03; 3.05]; p = 0.322	Greater/lesser harm not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).

ACQ: Asthma Control Questionnaire; AE: adverse event; AQLQ-S: standardized Asthma Quality of Life Questionnaire; CI: confidence interval; CI_u: upper limit of confidence interval; FLU: fluticasone; GLY: glycopyrronium bromide; IND: indacaterol acetate; MF: mometasone furoate; RR: relative risk; SAE: serious adverse event; SAL: salmeterol; SGRQ: St. George's Respiratory Questionnaire; TIO: tiotropium; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 16 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 16: Positive and negative effects from the assessment of IND/GLY/MF in comparison with high-dose ICS + LABA + LAMA

Positive effects	Negative effects
–	–
GLY: glycopyrronium bromide; ICS: inhaled corticosteroid; IND: indacaterol acetate; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; MF: mometasone furoate	

In summary, there is no hint of an added benefit of IND/GLY/MF in comparison with the ACT of high-dose ICS and LABA and LAMA for patients with asthma not adequately controlled with a maintenance combination of a LABA and a high dose of an ICS who experienced one or more asthma exacerbations in the previous year.

Table 17 summarizes the result of the assessment of the added benefit of IND/GLY/MF in comparison with the ACT.

Table 17: IND/GLY/MF – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adult patients with asthma not adequately controlled with a maintenance combination of a LABA and a high dose of an ICS who experienced one or more asthma exacerbations in the previous year	High-dose ICS and LABA and LAMA[b, c]	Added benefit not proven
a. Presentation of the respective ACT specified by the G-BA. b. According to G-BA, the graded scheme of the German National Care Guideline for Asthma (NVL Asthma 2018, 3rd edition, Version 1 [1]) must be taken into account. Based on the drug properties of the combination of mometasone furoate, indacaterol acetate and glycopyrronium bromide, the G-BA determined the ACT for patients who are candidates for a therapy according to step 4 of the NVL Asthma 2018. Accordingly, it is assumed that the patients in the therapeutic indication received at least a dual combination (of high-dose ICS and LABA) as prior therapy without achieving adequate control. In addition, according to the G-BA, it is assumed that the patients are not yet eligible for the administration of antibodies. c. According to the G-BA, the unchanged continuation of an inadequate asthma treatment does not comply with an ACT in uncontrolled asthma if the option for treatment escalation is still available. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; GLY: glycopyrronium bromide; ICS: inhaled corticosteroid; IND: indacaterol acetate; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; MF: mometasone furoate; NVL: National Care Guideline		

The assessment described above deviates from that of the company, which overall derived an indication of a minor added benefit.

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

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Bundesärztekammer, Kassenärztliche Bundesvereinigung, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften. Nationale VersorgungsLeitlinie Asthma; Langfassung; 3. Auflage [online]. 2018 [Accessed: 13.10.2020]. URL: https://www.leitlinien.de/mdb/downloads/nvl/asthma/archiv/asthma-3aufl-vers1-lang.pdf.

2. Institute for Quality and Efficiency in Health Care. General methods 6.0 (German version) [online]. 2020 [Accessed: 06.11.2020]. URL: https://www.iqwig.de/download/Allgemeine-Methoden_Version-6-0.pdf.

3. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

4. Novartis Bioscienses Peru. A multicenter, partially-blinded, randomized, 24-week, parallel-group, non-inferiority, open-label active controlled study to compare the efficacy and safety of qvm149 with a free triple combination of salmeterol/fluticasone + tiotropium in patients with uncontrolled asthma [online]. 2018 [Accessed: 20.08.2020]. URL: https://www.ins.gob.pe/ensayosclinicos/rpec/recuperarECPBNuevoEN.asp?numec=013-18.

5. Novartis Healthcare. A 24-week clinical study to check the efficacy and safety of QVM149 with a free triple combination of salmeterol/fluticasone plus tiotropium in patients with uncontrolled asthma [online]. 2020 [Accessed: 20.08.2020]. URL: http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=26659.

6. Novartis Pharma. A multicenter, partially-blinded, randomized, 24-week, parallel-group, non-inferiority, open-label active controlled study to compare the efficacy and safety of QVM149 with a free triple combination of salmeterol/fluticasone + tiotropium in patients with uncontrolled asthma [online]. [Accessed: 20.08.2020]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2017-000136-34.

7. Novartis Pharmaceuticals. Study to compare QVM149 and free triple combination of salmeterol/fluticasone + tiotropium: study details [online]. 2020 [Accessed: 20.08.2020]. URL: https://ClinicalTrials.gov/show/NCT03158311.

8. Novartis Pharma. A multicenter, partially-blinded, randomized, 24-week, parallel-group, non-inferiority, open-label active controlled study to compare the efficacy and safety of QVM149 with a free triple combination of salmeterol/fluticasone + tiotropium in patients with uncontrolled asthma: clinical trial results [online]. 2020 [Accessed: 20.08.2020]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-000136-34/results.

9. Gessner C, Kornmann O, Maspero J et al. Fixed-dose combination of indacaterol/glycopyrronium/mometasone furoate once-daily versus salmeterol/fluticasone twice-daily plus tiotropium once-daily in patients with uncontrolled asthma: A randomised, Phase IIIb, non-inferiority study (ARGON). Respir Med 2020; 170: 106021. https://dx.doi.org/10.1016/j.rmed.2020.106021.

10. Global Initiative for Asthma. Global strategy for asthma management and prevention [online]. 2017 [Accessed: 06.08.2019]. URL: https://ginasthma.org/gina-reports/.

11. Novartis Pharma. Enerzair Breezhaler; Fachinformation [online]. 2020 [Accessed: 23.07.2020]. URL: https://www.fachinfo.de/.

12. Bundesärztekammer, Kassenärztliche Bundesvereinigung, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften. Nationale VersorgungsLeitlinie Asthma; Langfassung; 4. Auflage [online]. 2020 [Accessed: 13.10.2020]. URL: https://www.leitlinien.de/mdb/downloads/nvl/asthma/asthma-4aufl-vers1-lang.pdf.

13. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. IQWiG-Berichte – Nr. 638, Untersuchung der statistischen Eigenschaften von Verfahren zur Übertragbarkeit von Studienergebnissen auf Teilpopulationen [online]. 2018 [Accessed: 31.01.2020]. URL: https://www.iqwig.de/download/GA18-01_Uebertragbarkeit-von-Studienergebnissen-auf-Teilpopulationen_Arbeitspapier_V1-0.pdf.

14. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574. https://dx.doi.org/10.1016/0167-9473(94)90148-1.

15. Juniper EF, Svensson K, Mörk AC et al. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. Respir Med 2005; 99(5): 553-558. https://dx.doi.org/10.1016/j.rmed.2004.10.008.

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