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Beclometasone/formoterol/ glycopyrronium (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 *Beclometason/Formoterol/Glycopyrronium (Asthma) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 12 May 2021). 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
BDP	beclometasone
EQ-5D	European Quality of Life-5 Dimensions
FEV1	forced expiratory volume in 1 second
FORM	formoterol
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GLY	glycopyrronium
ICS	inhaled corticosteroid
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
MACE	major adverse cardiovascular event
NVL	Nationale VersorgungsLeitlinie (National Care Guideline)
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
TIO	tiotropium
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug combination beclometasone/formoterol/glycopyrronium (BDP/FORM/GLY). The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 11 February 2021.

Research question

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

For the present benefit assessment, the research questions presented in Table 4 resulted from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of BDP/FORM/GLY

Research question	Subindication	ACT[a]
1	Adult patients whose asthma is not adequately controlled with medium-dose ICS/LABA therapy, and who experienced one or more asthma exacerbations in the previous year	Patient-specific treatment escalation taking into account the prior therapy, the severity of the disease and the symptoms, choosing from[b, c] ▪ medium-dose ICS and LABA and LAMA or ▪ high-dose ICS and LABA
2	Adult patients whose asthma is not adequately controlled with high-dose ICS/LABA therapy, and 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 for adults of the German National Care Guideline for Asthma (NVL Asthma 2018, 3rd edition, Version 1) must be taken into account. The wording of the intended therapeutic indication does not limit the therapeutic indication to a specific step of the NVL Asthma. Based on the drug properties of the combination of beclometasone/formoterol/glycopyrronium, 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 prior therapy of at least a dual combination (of medium-dose ICS and LABA, according to the NVL Asthma) 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; BDP: beclometasone; FORM: formoterol; G-BA: Federal Joint Committee; GLY: glycopyrronium; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; 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.

Research question 1: patients with medium-dose ICS/LABA pretreatment

In its dossier, the company presented no data for the assessment of the added benefit of BDP/FORM/GLY in comparison with the ACT in adult patients with asthma whose disease is not adequately controlled with a combination of a medium-dose ICS and a LABA, and who experienced one or more asthma exacerbations in the previous year. This resulted in no hint of an added benefit of BDP/FORM/GLY in comparison with the ACT; an added benefit is therefore not proven.

Research question 2: patients with high-dose ICS/LABA pretreatment

Study pool and study design

For the present research question, the TRIGGER study was used to assess the added benefit of BDP/FORM/GLY. The TRIGGER study is a 3-arm RCT comparing the triple combination of BDP/FORM/GLY with BDP/FORM and BDP/FORM + tiotropium (TIO). As the administration of TIO was in the form of additional inhalations, the study was blinded only for

the first 2 study arms mentioned. Of the 2 comparator arms, only the triple combination of BDP/FORM + TIO corresponds to the ACT. The comparator arm with the dual combination of BDP/FORM is therefore not considered further in the assessment.

The study included adult patients up to and including 75 years of age whose asthma was not adequately controlled despite pretreatment with high-dose ICS and LABA. Inadequate control was defined by an Asthma Control Questionnaire (ACQ)-7 score of at least 1.5 at screening and the end of run-in. In addition, patients had to have had one or more asthma exacerbations requiring treatment with systemic corticosteroids, an emergency department visit or hospitalization in the year before study start. The patients' forced expiratory volume in 1 second (FEV1) had to be less than 80% of predicted normal value, and had to increase to more than 12% and 200 mL in the reversibility test compared with the pretreatment value.

After a 2-week run-in phase, 573 patients were included in the intervention arm (BDP/FORM/GLY) and 288 in the comparator arm (BDP/FORM + TIO) of the study, with randomization stratified by country. The subsequent treatment duration was 52 weeks. The administration of the study medications was in compliance with the information in the respective Summaries of Product Characteristics (SPCs).

Primary outcomes of the TRIGGER study were the change in FEV1 (pre-bronchodilator) at week 26 and the number of moderate and severe asthma exacerbations over the 52-week treatment period. Other patient-relevant outcomes of the study were all-cause mortality, severe asthma exacerbations, asthma symptoms, health status, and adverse events (AEs). No outcomes on health-related quality of life were recorded in the study.

Risk of bias

The risk of bias across outcomes for the TRIGGER study was rated as low. At outcome level, the risk of bias was rated as low for the results of the following outcomes: all-cause mortality, severe asthma exacerbations and major adverse cardiovascular events (MACE). The risk of bias was rated as high for the results of the following outcomes: asthma symptoms (patient diary), health status (European Quality of Life-5 Dimensions visual analogue scale [EQ-5D VAS]), and discontinuation due to AEs. No usable data are available for the outcome "serious AEs (SAEs)".

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 BDP/FORM/GLY in comparison with BDP/FORM + TIO; 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 BDP/FORM/GLY in comparison with BDP/FORM + TIO; an added benefit is therefore not proven.

Asthma symptoms (recorded in a patient diary)

There was no statistically significant difference between the treatment groups for the outcome "asthma symptoms", recorded in a patient diary. This resulted in no hint of an added benefit of BDP/FORM/GLY in comparison with BDP/FORM + TIO for the outcome "asthma symptoms"; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

There was no statistically significant difference between the treatment groups for the outcome "health status measured using the EQ-5D VAS". This resulted in no hint of an added benefit of BDP/FORM/GLY in comparison with BDP/FORM + TIO; an added benefit is therefore not proven.

Health-related quality of life

No patient-relevant outcomes in the category of health-related quality of life were recorded in the TRIGGER study. This resulted in no hint of an added benefit of BDP/FORM/GLY in comparison with BDP/FORM + TIO; an added benefit is therefore not proven.

Side effects

Discontinuation due to AEs and MACE

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

SAEs

There were no usable data for the outcome "SAEs". This resulted in no hint of greater or lesser harm from BDP/FORM/GLY in comparison with BDP/FORM + TIO; greater or lesser harm is therefore not proven.

In summary, there are neither positive nor negative effects for BDP/FORM/GLY compared with high-dose ICS and LABA and long-acting muscarinic antagonists (LAMAs). Thus, there is no hint of an added benefit of BDP/FORM/GLY in comparison with the ACT of high-dose ICS and LABA and LAMA for adult patients with asthma whose disease is not adequately controlled with a combination of a high-dose ICS and LABA, and who experienced one or more asthma exacerbations in the previous year; an added benefit is 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 BDP/FORM/GLY in comparison with the ACT are assessed as follows:

In summary, there is no hint of an added benefit of BDP/FORM/GLY in comparison with the ACT of high-dose ICS and LABA and LAMA for adult patients with asthma whose disease is not adequately controlled with a combination of a medium- or high-dose ICS and LABA, and who experienced one or more asthma exacerbations in the previous year; an added benefit is not proven.

Table 3 shows a summary of probability and extent of the added benefit of BDP/FORM/GLY.

Table 3: BDP/FORM/GLY – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	Adult patients whose asthma is not adequately controlled with medium-dose ICS/LABA therapy, and who experienced one or more asthma exacerbations in the previous year	Patient-specific treatment escalation taking into account the prior therapy, the severity of the disease and the symptoms, choosing from: ▪ medium-dose ICS and LABA and LAMA or ▪ high-dose ICS and LABA	Added benefit not proven
2	Adult patients whose asthma is not adequately controlled with high-dose ICS/LABA therapy, and who experienced one or more asthma exacerbations in the previous year	High-dose ICS and LABA and LAMA	Added benefit not proven
a. Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; BDP: beclometasone; FORM: formoterol; G-BA: Federal Joint Committee; GLY: glycopyrronium; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist			

The approach for the derivation of 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 [1,2].

2.2 Research question

The aim of the present report is the assessment of the added benefit of BDP/FORM/GLY in comparison with the ACT in adult patients with asthma whose disease is not adequately controlled with a combination of a medium- or high-dose ICS and a LABA, and who experienced one or more asthma exacerbations in the previous year.

For the present benefit assessment, the research questions presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of BDP/FORM/GLY

Research question	Subindication	ACT[a]
1	Adult patients whose asthma is not adequately controlled with medium-dose ICS/LABA therapy, and who experienced one or more asthma exacerbations in the previous year	Patient-specific treatment escalation taking into account the prior therapy, the severity of the disease and the symptoms, choosing from[b, c] ▪ medium-dose ICS and LABA and LAMA or ▪ high-dose ICS and LABA
2	Adult patients whose asthma is not adequately controlled with high-dose ICS/LABA therapy, and 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 for adults of the German National Care Guideline for Asthma (NVL Asthma 2018, 3rd edition, Version 1 [3]) must be taken into account. The wording of the intended therapeutic indication does not limit the therapeutic indication to a specific step of the NVL Asthma. Based on the drug properties of the combination of beclometasone/formoterol/glycopyrronium, 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 prior therapy of at least a dual combination (of medium-dose ICS and LABA, according to the NVL Asthma) 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; BDP: beclometasone; FORM: formoterol; G-BA: Federal Joint Committee; GLY: glycopyrronium; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; NVL: National Care Guideline

The company followed the G-BA's specification of the 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 Research question 1: patients with medium-dose ICS/LABA pretreatment

2.3.1 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 BDP/FORM/GLY (status: 14 December 2020)
- bibliographical literature search on BDP/FORM/GLY (last search on 10 December 2020)
- search in trial registries/trial results databases for studies on BDP/FORM/GLY (last search on 11 December 2020)
- search on the G-BA website for BDP/FORM/GLY (last search on 14 December 2020)

To check the completeness of the study pool:

- search in trial registries for studies on BDP/FORM/GLY (last search on 3 March 2021)

Concurring with the company, the check identified no relevant RCTs of direct comparison for the present research question.

2.3.2 Results on added benefit

In its dossier, the company presented no data for the assessment of the added benefit of BDP/FORM/GLY in comparison with the ACT in adult patients with asthma whose disease is not adequately controlled with a combination of a medium-dose ICS and a LABA, and who experienced one or more asthma exacerbations in the previous year. This resulted in no hint of an added benefit of BDP/FORM/GLY in comparison with the ACT; an added benefit is therefore not proven.

2.3.3 Probability and extent of added benefit

As the company did not provide any data for the assessment of the added benefit of BDP/FORM/GLY in comparison with the ACT in adult patients with asthma whose disease is not adequately controlled with a combination of a medium-dose ICS and a LABA, and who experienced one or more asthma exacerbations in the previous year, an added benefit of BDP/FORM/GLY in comparison with the ACT is not proven for these patients.

This concurs with the assessment of the company, which claimed no added benefit in the present therapeutic indication.

2.4 Research question 2: patients with high-dose ICS/LABA pretreatment

2.4.1 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 BDP/FORM/GLY (status: 14 December 2020)
- bibliographical literature search on BDP/FORM/GLY (last search on 10 December 2020)

- search in trial registries/trial results databases for studies on BDP/FORM/GLY (last search on 11 December 2020)
- search on the G-BA website for BDP/FORM/GLY (last search on 14 December 2020)

To check the completeness of the study pool:

- search in trial registries for studies on BDP/FORM/GLY (last search on 3 March 2021)

The check did not identify any additional relevant studies.

2.4.1.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: BDP/FORM/GLY vs. BDP/FORM + 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])
TRIGGER	Yes	Yes	No	No[c]	Yes [4,5]	Yes [6,7]

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. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without access to the CSR in Module 5 of the dossier.

BDP: beclometasone; CSR: clinical study report; FORM: formoterol; G-BA: Federal Joint Committee; GLY: glycopyrronium; RCT: randomized controlled trial; TIO: tiotropium

2.4.1.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: BDP/FORM/GLY vs. BDP/FORM + TIO

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
TRIGGER	RCT, parallel, 3-arm, double-blind with an open-label study arm	Adult patients ≤ 75 years of age with asthma[b] that, despite pretreatment with high-dose ICS[c] and LABA[d], is not adequately controlled[e], and ▪ with ≥ 1 asthma exacerbation[f] in the year before study start ▪ FEV1 < 80% predicted ▪ FEV1 increase of ≥ 12% in the reversibility test	BDP/FORM/GLY (N = 573) BDP/FORM (N = 576)[g] BDP/FORM + TIO (N = 288)[h]	Screening: ≤ 1 week Run-in phase: 2 weeks Treatment: 52 weeks Follow-up observation: none	221 study centres in Argentina, Belarus, Bulgaria, Czech Republic, Germany, Hungary, Italy, Lithuania, Poland, Portugal, Romania, Russia, Slovakia, Spain, Turkey, Ukraine, United Kingdom 4/2016–5/2018	Primary: 1) change in pre-bronchodilator FEV1 at week 26 2) number of moderate/severe asthma exacerbations Secondary: morbidity, 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. Diagnosis before the age of 40.
c. > 1000 µg BDP extrafine or clinically comparable dose of another ICS.
d. ≤ 4 weeks before screening in unchanged daily dose: 24 µg formoterol or 100 µg salmeterol or 25 µg vilanterol or clinically comparable dose of another approved LABA.
e. Defined by an ACQ-7 score of ≥ 1.5 at screening and the end of run-in.
f. Documented by prescription of systemic corticosteroid therapy, an emergency department visit or hospitalization.
g. The study arm does not represent the appropriate therapy. It is therefore not relevant for the assessment and is no longer shown in the following tables.
h. Open-label study arm.

ACQ: Asthma Control Questionnaire; AE: adverse event; BDP: beclometasone; FEV1: forced expiratory volume in 1 second; FORM: formoterol; GLY: glycopyrronium; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; N: number of randomized patients; RCT: randomized controlled trial; TIO: tiotropium

Table 7: Characteristics of the intervention – RCT, direct comparison: BDP/FORM/GLY vs. BDP/FORM + TIO

Study	Intervention	Comparison
TRIGGER	BDP/FORM/GLY, 200/6/12.5[a] µg, 2 puffs twice daily	BDP/FORM, 200/6 µg, 2 puffs twice daily + TIO, 2.5 µg, 2 puffs once daily
	Pretreatment ▪ High-dose ICS[b]/LABA[c] combination in stable dose for ≥ 4 weeks before screening **Treatment during run-in phase** ▪ BDP/FORM, 200/6 µg, 2 puffs twice daily **Permitted concomitant treatment** ▪ inhaled salbutamol as rescue medication ▪ short-term[d] in severe asthma exacerbations: ▫ systemic corticosteroids ▫ beta-2 agonist inhalation ▫ corticosteroid inhalation ▫ antibiotics ▪ Continuation at stable dosage ≥ 1 month before study start: ▫ antihistamines or nasal corticosteroids ▫ desensitization therapies ▪ continuation of sublingual immunotherapies **Prohibited asthma-related prior and concomitant treatment** ▪ ≤ 4 weeks before screening: systemic corticosteroids, or ≤ 12 weeks before screening: slow-release corticosteroids ▪ During the study: ▫ other ICS, inhaled LABAs or combinations of ICS/LABA and/or LAMA ▫ SAMAs ▫ LAMAs ▫ theophyllines and other asthma medications (e.g. cromoglicic acid, nedocromil, leukotriene receptor antagonists) ▫ systemic anticholinergics	

a. The dosage information of 12.5 µg refers to glycopyrronium bromide and is equivalent to 10 µg glycopyrronium.
b. > 1000 µg BDP non-extrafine or clinically comparable dose of another ICS.
c. 24 µg formoterol or 100 µg salmeterol or 25 µg vilanterol or clinically comparable dose of another approved LABA.
d. Treatment: ≤ 14 days.

BDP: beclometasone; FORM: formoterol; GLY: glycopyrronium; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; RCT: randomized controlled trial; SAMA: short-acting muscarinic antagonist; TIO: tiotropium

Description of the TRIGGER study

The TRIGGER study is a 3-arm RCT comparing the triple combination of BDP/FORM/GLY with BDP/FORM and BDP/FORM + TIO. As the administration of TIO was in the form of additional inhalations, the study was blinded only for the first 2 study arms mentioned.

Of the 2 comparator arms, only the study arm with the triple combination of BDP/FORM+ TIO implemented the ACT of the present benefit assessment. The comparator arm with the dual combination of BDP/FORM is therefore not considered further.

The study included adult patients up to and including 75 years of age whose asthma was not adequately controlled despite pretreatment with high-dose ICS and LABA. Inadequate control was defined by an ACQ-7 score of at least 1.5 at screening and the end of run-in. In addition, patients had to have had one or more asthma exacerbations requiring treatment with systemic corticosteroids, an emergency department visit or hospitalization in the year before study start. The patients' FEV1 had to be less than 80% of predicted normal value, and had to increase to more than 12% and 200 mL in the reversibility test compared with the pretreatment value.

In the beginning of the TRIGGER study, the treatment of all participants was switched to the dual combination of BDP/FORM in a 2-week run-in phase. The patients were then randomly allocated to the study arms in a ratio of 2:1 and stratified by country. The intervention arm (BDP/FORM/GLY) included 573 patients and the comparator arm (BDP/FORM + TIO) included 288 patients. The subsequent treatment duration was 52 weeks. The administration of the study medications was in compliance with the information in the respective SPCs [8-10].

Primary outcomes of the TRIGGER study were the change in FEV1 (pre-bronchodilator) at week 26 and the number of moderate and severe asthma exacerbations over the 52-week treatment period. Other patient-relevant outcomes of the study were all-cause mortality, severe asthma exacerbations, asthma symptoms, health status, and AEs. No outcomes on health-related quality of life were recorded in the study.

Note on the study design

According to the recommendations of NVL, asthma control should be reviewed at regular intervals and therapy reduced if necessary to avoid overtreatment [3]. The period of stable asthma control should be at least 3 months. This recommendation is also reflected in the SPC of BDP/FORM/GLY [9]. In the TRIGGER study, no adjustments to the dose of the study medication were planned after randomization, with the exception of short-term treatment of severe exacerbations. Thus, the treatment in the study does not fully comply with the guideline recommendations. It is not assumed that this deviation from the guideline recommendations had relevant effects on the study results. One reason is that the deviation affected both arms equally. Also, a dose reduction was probably not indicated for more than half of the patients in the study, as they had at least one severe or moderate exacerbation during the course of the study, according to the information provided in Module 4 A. Asthma symptoms also persisted to a relevant extent during the study. In addition, dose reduction is mainly aimed at avoiding side effects, and the most common SAE reported was the disease itself (asthma).

Patient characteristics of the TRIGGER study

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

Table 8: Characteristics of the study population – RCT, direct comparison: BDP/FORM/GLY vs. BDP/FORM + TIO

Study Characteristic Category	**BDP/FORM/GLY N[a] = 571**	**BDP/FORM + TIO N[a] = 287**
Study TRIGGER		
Age [years], mean (SD)	53 (12)	52 (12)
Sex [F/M], %	63/37	64/36
Family origin, n (%)		
Asian	2 (0.4)	0 (0)
Black/African American	0 (0)	0 (0)
White	569 (99.6)	286 (99.7)
Other	0 (0)	1 (0.3)
Duration of asthma disease, n (%)		
< 5 years	26 (4.6)	13 (4.5)
5–20 years	180 (31.5)	96 (33.4)
≥ 20 years	365 (63.9)	178 (62.0)
Asthma exacerbations in the previous year, n (%)		
1	439 (76.9)	229 (79.8)
> 1	132 (23.1)	58 (20.2)
Smoking status at screening, n (%)		
Ex-smoker	83 (14.5)	42 (14.6)
Never smoker	488 (85.5)	245 (85.4)
FEV1 (in% predicted), mean (SD)	57.2 (12.6)	56.7 (12.5)
ACQ-7 score, mean (SD)	2.5 (0.5)	2.4 (0.5)
Treatment discontinuation, n (%)	37 (6.5[b])	25 (8.7[b])
Study discontinuation, n (%)	ND	ND

a. Number of patients in the safety population, which includes all randomized patients who received at least one dose of the respective treatment. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Institute's calculation.

ACQ: Asthma Control Questionnaire; BDP: beclometasone; F: female, FEV1: forced expiratory volume in 1 second; FORM: formoterol; GLY: glycopyrronium; M: male; n: number of patients in the category; N: number of patients included; ND: no data; RCT: randomized controlled trial; SD: standard deviation; TIO: tiotropium

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

The respective mean age of the patients was 53 and 52 years, and 63 and 64% were female. Most of them had had asthma for more than 20 years. The mean ACQ-7 score was 2.5 and 2.4, respectively, and FEV1 was around 57%. The majority of patients (77% and 80% respectively) had had a single asthma exacerbation in the year before the study started.

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: BDP/FORM/GLY vs. BDP/FORM + 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			
TRIGGER	Yes	Yes	No	No	Yes	Yes	Low

BDP: beclometasone; FORM: Formoterol; GLY: glycopyrronium; RCT: randomized controlled trial; TIO: tiotropium

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

Limitations resulting from the lack of blinding are described in Section 2.4.2.2 under 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 56% of the patients in the 2 arms of the TRIGGER study that are relevant to the assessment belonged to the subgroup "Europe" and thus came from countries that are comparable to the German health care context. Furthermore, it stated that the demographic parameters in the TRIGGER study corresponded to the sex-specific distribution in the therapeutic indication known from the literature as well as to the observed age distribution in Germany.

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

2.4.2 Results on added benefit

2.4.2.1 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 in a patient diary
- health status measured with the EQ-5D VAS

- Health-related quality of life
- Side effects
  - SAEs
  - discontinuation due to AEs
  - MACE
  - 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: BDP/FORM/GLY vs. BDP/FORM + TIO

Study	Outcomes								
	All-cause mortality	Severe asthma exacerbations[a]	Asthma symptoms (patient diary)	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Discontinuation due to AEs	MACE[b]	Further specific AEs
TRIGGER	Yes	Yes	Yes	Yes	No[c]	No[d]	Yes	Yes	No[e]

a. Defined as a worsening of asthma symptoms requiring treatment with systemic corticosteroids for at least 3 days.
b. The following AEs were considered: acute myocardial infarction (acute coronary syndrome, nonfatal myocardial infarction), stroke (nonfatal stroke), death due to a cardiovascular event (cardiac arrest, sudden death), arrhythmia (sustained supraventricular and sustained ventricular), cardiac failure.
c. No outcomes of the category "health-related quality of life" were recorded. The ACQ-5 used by the company to describe health-related quality of life does not represent health-related quality of life, but the symptoms of the disease.
d. No usable data, as the recordings also included a relevant proportion of events related to the PT "asthma".
e. No specific AEs were identified.

AE: adverse event; BDP: beclometasone; EQ-5D: European Quality of Life-5 Dimensions; FORM: formoterol; GLY: glycopyrronium; MACE: major adverse cardiovascular event; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; TIO: tiotropium; VAS: visual analogue scale

2.4.2.2 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: BDP/FORM/GLY vs. BDP/FORM + TIO

Study	Study level	Outcomes								
		All-cause mortality	Severe asthma exacerbations[a]	Asthma symptoms (patient diary)	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Discontinuation due to AEs	MACE	Further specific AEs
TRIGGER	L	L	L	H[b]	H[b]	–[c]	–[d]	H[b]	L	–

a. Defined as a worsening of asthma symptoms requiring treatment with systemic corticosteroids for at least 3 days.
b. Lack of blinding in subjective recording of outcomes.
c. Outcome not recorded.
d. No usable data, as the recordings also included a relevant proportion of events related to the PT "asthma".

AE: adverse event; BDP: beclometasone; EQ-5D: European Quality of Life-5 Dimensions; FORM: formoterol; GLY: glycopyrronium; H: high; L: low; MACE: major adverse cardiovascular event; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; TIO: tiotropium; VAS: visual analogue scale

The outcome-specific risk of bias was rated as low for the results of the outcomes "all-cause mortality", "severe asthma exacerbations" and "MACE", and, due to the lack of blinding in subjective recording of outcomes, as high for the results of the outcomes "asthma symptoms" (patient diary) and "health status" (EQ-5D VAS). This concurs with the company's assessment.

The risk of bias of the results for the outcome "discontinuation due to AEs" was also rated as high due to the lack of blinding in subjective recording of outcomes. This deviates from the assessment of the company, which assessed the risk of bias of the results for all side effect outcomes as low.

No usable data are available for the outcome "SAEs", as the recordings included a relevant proportion of the Preferred Term (PT) "asthma", which is to be allocated to the underlying disease. This deviates from the company's assessment, which used this outcome and rated the risk of bias as low.

2.4.2.3 Results

Table 12, Table 13 and Table 14 summarize the results of the comparison of BDP/FORM/GLY with BDP/FORM + TIO in patients with asthma whose disease is not adequately controlled with a combination of a high-dose ICS and a LABA, and 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. Tables on common AEs are presented in Appendix A of the full dossier assessment.

Table 12: Results (mortality, morbidity, side effects, dichotomous) – RCT, direct comparison: BDP/FORM/GLY vs. BDP/FORM + TIO

Study Outcome category Outcome	BDP/FORM/GLY		BDP/FORM + TIO		BDP/FORM/GLY vs. BDP/FORM + TIO
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
TRIGGER					
Mortality					
All-cause mortality	571	1 (0.2)	287	0 (0)	1.51 [0.06; 36.96]; 0.573
Morbidity					
Severe asthma exacerbations[b] (supplementary information)	571	119 (20.8)	287	47 (16.4)	1.27 [0.94; 1.73]; 0.128
Health-related quality of life	No outcomes recorded in this category				
Side effects					
AEs (supplementary information)	571	410 (71.8)	287	210 (73.2)	–
SAEs	No usable data[c]				
Discontinuation due to AEs	571	4 (0.7)	287	2 (0.7)	1.01 [0.19; 5.46]; > 0.999
MACE[d]	571	3 (0.5)	287	0 (0)	3.52 [0.18; 68.00]; 0.268

a. Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [11]). In case of 0 events in one study arm, the correction factor 0.5 was used for the calculation of effect and CI in both study arms.
b. Defined as a worsening of asthma symptoms requiring treatment with systemic corticosteroids for at least 3 days.
c. No usable data, as the recordings include a relevant proportion of events related to the PT "asthma".
d. The following AEs were considered: acute myocardial infarction (acute coronary syndrome, nonfatal myocardial infarction), stroke (nonfatal stroke), death due to cardiovascular events (cardiac arrest, sudden death), arrhythmia (sustained supraventricular and sustained ventricular), cardiac failure.

AE: adverse event; BDP: beclometasone, CI: confidence interval; CSZ: convexity, symmetry, z-score; MACE: major adverse cardiovascular event; 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; TIO: tiotropium

Table 13: Results (morbidity, dichotomous) – RCT, direct comparison: BDP/FORM/GLY vs. BDP/FORM + TIO

Study Outcome category Outcome	BDP/FORM/GLY		BDP/FORM + TIO		BDP/FORM/GLY vs. BDP/FORM + TIO
	N	Adjusted annual rate [95% CI][a]	N	Adjusted annual rate [95% CI][a]	Rate ratio [95% CI]; p-value[a]
TRIGGER					
Morbidity					
Severe asthma exacerbations[b]	571	0.27 [0.22; 0.32]	287	0.22 [0.16; 0.29]	1.24 [0.88; 1.75]; 0.214

a. Adjusted annual rates with CI (per treatment group) and rate ratio with CI and p-value (group comparison): presumably negative-binomial regression with the variables treatment, region and number of asthma exacerbations in the previous year as well as the logarithm of the time the patient was in the study as offset.
b. Defined as a worsening of asthma symptoms requiring treatment with systemic corticosteroids for at least 3 days.

AE: adverse event; BDP: beclometasone; CI: confidence interval; FORM: formoterol; GLY: glycopyrronium; N: number of analysed patients; RCT: randomized controlled trial; SAE: serious adverse event; TIO: tiotropium

Table 14: Results (morbidity, continuous) – RCT, direct comparison: BDP/FORM/GLY vs. BDP/FORM + TIO

Study Outcome category Outcome	BDP/FORM/GLY			BDP/FORM + TIO			BDP/FORM/GLY vs. BDP/FORM + TIO
	N[a]	Values at baseline mean (SD)	Change mean [95% CI]	N[a]	Values at baseline mean (SD)	Change mean [95% CI]	MD [95% CI]; p-value
TRIGGER							
Morbidity							
Proportion of asthma symptom-free days[b] (%)	571	10.16 (23.09)	16.57 [14.30; 18.84][c]	287	10.78 (26.58)	12.73 [9.51; 15.94][c]	3.84 [−0.09; 7.78]; 0.055[c]
Health status (EQ-5D VAS[b])	535	67.20 (13.51)	9.49 [8.47; 10.51][d]	263	68.37 (14.31)	8.83 [7.38; 10.27][d]	0.66 [−1.11; 2.43]; 0.464[d]

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 Higher (increasing) values indicate a larger proportion of symptom-free days or better health status; positive effects (intervention minus control) indicate an advantage for the intervention.
c. Mean with CI (mean change over the course of the study per treatment group) and MD with CI and p-value: MMRM with the variables treatment, time period between visits, region and value of the run-in phase as well as the interactions treatment x time period between visits and value of the run-in phase x time period between visits; effect refers to the changes averaged over the course of the study between the respective time period between visits and the run-in phase.
d. Mean with CI (change at end of study per treatment group) and MD with CI and p-value: MMRM with the variables treatment, visits, region and value at baseline as well as the interactions treatment x visit and value at baseline x visit; effect refers to the difference between end of study and baseline.

BDP: beclometasone; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; FORM: formoterol; GLY: glycopyrronium; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; TIO: tiotropium; VAS: visual analogue scale

Based on the available data, at most indications, e.g. of an added benefit, can be determined for the outcomes “all-cause mortality”, “severe asthma exacerbations” and “MACE”, and, due to the high risk of bias, at most hints for the outcomes “asthma symptoms” (patient diary)” , “health status” (EQ-5D VAS) 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 BDP/FORM/GLY in comparison with BDP/FORM + TIO; 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 BDP/FORM/GLY in comparison with BDP/FORM + TIO; an added benefit is therefore not proven.

This concurs with the company's assessment.

Asthma symptoms (recorded in a patient diary)

Operationalization

For the recording of asthma symptoms, analyses of both an electronic patient diary and of the ACQ-5 are available for the TRIGGER study. In the patient diary, which had to be filled out by the patients in the morning and in the evening, it was asked whether or with what severity symptoms had occurred at night or during the day. The symptoms of coughing, wheezing, chest tightness and dyspnoea/shortness of breath were also specifically recorded. The ACQ-5 was completed after 4, 12, 26, 40 and 52 weeks of treatment. The questions also cover the symptoms and refer to the last 7 days [12].

Both instruments are suitable for recording asthma symptoms. The results of the patient diary were used for the present benefit assessment, as this was filled out daily and thus provides a more reliable representation of the symptoms, whereas the questions of the ACQ-5 only refer to the last 7 days.

Of the 3 analyses on the patient diary presented in Module 4 A, the change in the percentage of asthma symptom-free days (asthma symptom score = 0 for day and night) from the run-in phase over the 52-week study period was used.

Results

There was no statistically significant difference between the treatment groups for the outcome "asthma symptoms", recorded in the patient diary. This is consistent with the results for the ACQ-5, which were also not statistically significant; however, the ACQ-5 was not used for this benefit assessment (see section on operationalization above). This resulted in no hint of an added benefit of BDP/FORM/GLY in comparison with BDP/FORM + TIO for the outcome "asthma symptoms"; an added benefit is therefore not proven.

This concurs with the assessment of the company, which also derived no added benefit for this outcome.

Health status (EQ-5D VAS)

There was no statistically significant difference between the treatment groups for the outcome "health status" measured using the EQ-5D VAS. This resulted in no hint of an added benefit of

BDP/FORM/GLY in comparison with BDP/FORM + TIO; an added benefit is therefore not proven.

This concurs with the company's assessment.

Health-related quality of life

No patient-relevant outcomes in the category of health-related quality of life were recorded in the TRIGGER study. This resulted in no hint of an added benefit of BDP/FORM/GLY in comparison with BDP/FORM + TIO; an added benefit is therefore not proven.

The company used the results of the ACQ-5 to record health-related quality of life, but derived no added benefit from this.

Side effects

Discontinuation due to AEs and MACE

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

This corresponds to the assessment of the company, which, however, used the rate ratio for the outcome "discontinuation due to AEs" to assess the added benefit.

SAEs

Events of the PT "asthma" were included in the recording of SAEs. However, SAEs without events attributable to the underlying disease are relevant for the benefit assessment. For this reason, the results for the outcome "SAEs" from the TRIGGER study are not usable (see Table 23 in Appendix A of the full dossier assessment). This resulted in no hint of greater or lesser harm from BDP/FORM/GLY in comparison with BDP/FORM + TIO; greater or lesser harm is therefore not proven.

This deviates from the assessment of the company insofar as the company did use this outcome for the assessment. From the data, it did not derive greater or lesser harm of the intervention, however.

2.4.2.4 Subgroups and other effect modifiers

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

- age (< 65, ≥ 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 had to 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.

2.4.3 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are derived 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 [1].

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.

2.4.3.1 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 2.4.2.3 (see Table 15).

Table 15: Extent of added benefit at outcome level: BDP/FORM/GLY vs. BDP/FORM + TIO

Outcome category **Outcome**	**BDP/FORM/GLY vs. BDP/FORM + TIO** **Proportion of events (%) or adjusted annual rate or mean change** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	Proportions of events: 0.2% vs. 0% RR: 1.51 [0.06; 36.96]; p = 0.573	Lesser benefit/added benefit not proven
Morbidity		
Severe asthma exacerbations	Adjusted annual rate: 0.27 vs. 0.22 rate ratio: 1.24 [0.88; 1.75]; p = 0.214	Lesser benefit/added benefit not proven
Proportion of asthma symptom-free days (%)	Mean change: 16.57 vs. 12.73 MD: 3.84 [-0.09; 7.78]; p = 0.055	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	Mean change: 9.49 vs. 8.83 MD: 0.66 [−1.11; 2.43]; p = 0.464	Lesser benefit/added benefit not proven
Health-related quality of life		
Outcomes from this category were not recorded		
Side effects		
SAEs	No usable data	Greater/lesser harm not proven
Discontinuation due to AEs	Proportions of events: 0.7% vs. 0.7% RR: 1.01 [0.19; 5.46]; p > 0.999	Greater/lesser harm not proven
MACE	Proportions of events: 0.5% vs. 0% RR: 3.52 [0.18; 68.00]; p = 0.268	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).

AE: adverse event; BDP: beclometasone; CI: confidence interval; CI_u: upper limit of the confidence interval; EQ-5D: European Quality of Life-5 Dimensions; FORM: formoterol; GLY: glycopyrronium; MACE: major adverse cardiovascular event; MD: mean difference; RR: relative risk; SAE: serious adverse event; TIO: tiotropium; VAS: visual analogue scale

2.4.3.2 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 BDP/FORM/GLY in comparison with high-dose ICS and LABA and LAMA

Positive effects	Negative effects
–	–
BDP: beclometasone; FORM: formoterol; GLY: glycopyrronium; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist	

There are neither positive nor negative effects for BDP/FORM/GLY compared with high-dose ICS and LABA and LAMAs. There are no or no usable data available on health-related quality of life and SAEs.

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

This concurs with the assessment of the company, which claimed no added benefit in the present therapeutic indication.

2.5 Probability and extent of added benefit – summary

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

Table 17: BDP/FORM/GLY – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	Adult patients whose asthma is not adequately controlled with medium-dose ICS/LABA therapy, and who experienced one or more asthma exacerbations in the previous year	Patient-specific treatment escalation taking into account the prior therapy, the severity of the disease and the symptoms, choosing from: ▪ medium-dose ICS and LABA and LAMA or ▪ high-dose ICS and LABA	Added benefit not proven
2	Adult patients whose asthma is not adequately controlled with high-dose ICS/LABA therapy, and who experienced one or more asthma exacerbations in the previous year	High-dose ICS and LABA and LAMA	Added benefit not proven
a. Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; BDP: beclometasone; FORM: formoterol; G-BA: Federal Joint Committee; GLY: glycopyrronium; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist			

The approach for the derivation of 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.

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