Tezepelumab (asthma) –

Benefit assessment according to §35a SGB V[1]

EXTRACT

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
ICS	inhaled corticosteroids
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LABA	long-acting beta-2 agonist
LAMA	long-acting muscarinic antagonist
mITT	modified intention-to-treat
NVL	Nationale VersorgungsLeitlinie (National Care Guideline)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

I 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 tezepelumab. 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 15 November 2022.

Research question

The aim of the present report is to assess the added benefit of tezepelumab as an add-on maintenance treatment in comparison with the appropriate comparator therapy (ACT) in adolescents aged 12 to 17 years and adults with severe asthma who are inadequately controlled despite high-dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment.

The research questions shown in Table 2 result from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of tezepelumab

Research question	Therapeutic indication	ACT[a]
1	Adolescents aged 12 to 17 years with severe asthma who are inadequately controlled despite high-dose ICS plus another medicinal product for maintenance treatment[b]	Individual treatment escalation[c] under consideration of the prior therapy choosing from: ▪ high-dose ICS and LABA and LAMA or ▪ high-dose ICS and LABA and possibly LAMA and omalizumab[d] or ▪ high-dose ICS and LABA and possibly LAMA and mepolizumab[e] or dupilumab[e]
2	Adults with severe asthma who are inadequately controlled despite high-dose ICS plus another medicinal product for maintenance treatment[b]	Individual treatment escalation[c] under consideration of the prior therapy and the pathogenesis of asthma choosing from: ▪ high-dose ICS and LABA and LAMA or ▪ high-dose ICS and LABA and possibly LAMA and omalizumab[d] or ▪ high-dose ICS and LABA and possibly LAMA and mepolizumab[d] or reslizumab[d] or benralizumab[d] or dupilumab[d]

a. Presented is the respective ACT specified by the G-BA.
b. In view of the wording of the therapeutic indication (severe asthma), it is assumed that treatment with tezepelumab is only indicated in addition to high-dose ICS and at least one other drug for maintenance treatment, or, in children and adolescents, also in addition to medium-dose ICS and montelukast and LABA and LAMA.
c. According to the G-BA, the stepwise approach to drug therapy of the 2020 NVL for Asthma, 4th edition, must be taken into account. It is assumed that, in the therapeutic indication of tezepelumab, the patients of research question 1 are represented in steps 5 to 6 of the stepwise approach to drug therapy for children and adolescents, and the patients of research question 2 are represented in steps 4 to 5 of the stepwise approach to drug therapy for adults. Unchanged continuation of inadequate treatment of severe asthma does not comply with an ACT in severe uncontrolled asthma if the option for treatment escalation is still available. If the therapeutic indication also includes patients for whom no further escalation of their existing inadequate treatment is possible, it must be shown for this patient population that no further treatment escalation is possible.
d. If the criteria required for the use are met.
e. If the criteria required for the use of omalizumab are met.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; ICS: inhaled corticosteroids; 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. However, the company did not address the 2 research questions defined by the G-BA separately, but considered adolescent and adult patients together.

In line with the G-BA's specification, the present assessment is conducted separately for the 2 research questions, each in comparison with the ACT specified by the G-BA. Since no suitable data are available for either of the 2 research questions designated by the G-BA, the assessment below is performed in a joint section of the report.

The assessment is 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 are used for the derivation of added benefit.

Results

No relevant study of direct comparison between tezepelumab and the ACT in the present therapeutic indication was identified.

In contrast, the company identified the RCTs NAVIGATOR, PATHWAY and DESTINATION, for each of which it used subpopulations to assess the added benefit of tezepelumab. In addition, the company presented an adjusted indirect comparison using the common comparator placebo versus dupilumab to assess the added benefit of tezepelumab. This included the studies NAVIGATOR and PATHWAY on the intervention side and the QUEST study on the comparator side.

Neither the direct comparison nor the adjusted indirect comparison is suitable for assessing the benefit of tezepelumab in comparison with the ACT. This is explained below.

Direct comparison presented by the company

The company used the RCTs NAVIGATOR, PATHWAY und DESTINATION for assessing the added benefit in its jointly considered patient group of adolescents and adults.

NAVIGATOR

The NAVIGATOR study is a randomized, double-blind study on the comparison of tezepelumab (N = 529) with placebo (N = 532). The study included patients aged 12 to 80 years with severe asthma and a history of ≥ 2 asthma exacerbation events within 12 months prior to screening. In addition, all patients must have been treated with medium or high-dose ICS and at least one additional controller medication for at least 3 months prior to screening.

PATHWAY

The PATHWAY study is a randomized, double-blind study comparing different doses of tezepelumab (280 mg every 2 weeks [N = 137], 210 mg every 4 weeks [N = 137], 70 mg every 4 weeks [N = 138]) with placebo (N = 138). The study included patients aged 18 to 75 years with severe asthma and a history of ≥ 2 asthma exacerbation events or one severe exacerbation within 12 months prior to screening. In addition, all patients must have been

treated with medium or high-dose ICS and a long-acting beta-2 agonist (LABA) for ≥ 6 months prior to screening.

DESTINATION

The DESTINATION study is a randomized, double-blind extension study on the comparison of tezepelumab with placebo. The study included patients who had completed the NAVIGATOR study (N = 827) or the SOURCE study (N = 124).

Subpopulations of the studies NAVIGATOR, PATHWAY and DESTINATION considered by the company

For the assessment of the added benefit, the company presented a meta-analysis with the biomarker$_{low}$ population of the studies NAVIGATOR and PATHWAY. These subpopulations included patients who were not eligible for treatment with a biologic of the ACT due to their individual biomarker status, according to the Summary of Product Characteristics (SPC). For the separately presented DESTINATION study, the company also considered the biomarker$_{low}$ population, which it additionally restricted to patients who had completed the NAVIGATOR study.

Appropriate comparator therapy not implemented

The presented data from the NAVIGATOR, PATHWAY and DESTINATION studies are not suitable for assessing the added benefit of tezepelumab in comparison with the ACT, as the various options for individual treatment escalation specified by the G-BA were not implemented.

Patients included in the studies NAVIGATOR, PATHWAY und DESTINATION had inadequately controlled asthma despite their ongoing asthma treatment. The treatment used before the start of the study was therefore inadequate to achieve the treatment goal of asthma control. In this situation, the guidelines recommend treatment escalation. In the respective control arms, no treatment escalation was planned at the start of the study, whereas patients in the intervention arms received tezepelumab as add-on therapy. In the NAVIGATOR study, no treatment escalation was mandated in the framework of the concomitant treatment either. In the PATHWAY study, an adjustment of the controller medication was possible after consultation with the company, but the company did not provide any data on how many patients initiated treatment with long-acting muscarinic antagonists (LAMAs) during the course of the study. For patients in the DESTINATION extension study, which included patients from the NAVIGATOR study, treatment escalation with a third controller medication would also be possible in principle.

The ACT was not implemented in the biomarker$_{low}$ populations of the studies NAVIGATOR, PATHWAY and DESTINATION.

Indirect comparison against dupilumab presented by the company

The company additionally presented an adjusted indirect comparison versus dupilumab using placebo as common comparator. This comparison is also unsuitable for the benefit assessment of tezepelumab in comparison with the ACT.

On the intervention side, the company included the meta-analytically summarized modified intention-to-treat (mITT) population of the studies NAVIGATOR and PATHWAY, which comprised all patients in the ITT population who corresponded to the approved therapeutic indication of tezepelumab. On the comparator side, the company identified the studies QUEST and DRI12544. To derive an added benefit, the company only used the indirect comparison with the QUEST study.

QUEST

The QUEST study is a randomized, double-blind phase 3 study comparing 2 different doses of dupilumab (300 mg every 2 weeks [N = 633], 200 mg every 2 weeks [N = 631]) with placebo (placebo for 300 mg [N = 321] or placebo for 200 mg [N = 317]). Patients 12 years of age and older with uncontrolled moderate to severe asthma who already received ongoing treatment with medium or high-dose ICS and one or 2 additional controller medications (e.g. LABA) with stable dosing were included in the study.

Possibilities of treatment escalation were not exhausted

According to the National Care Guideline (NVL) for Asthma, there is only a therapeutic indication for treatment with monoclonal antibodies if asthma control is not achieved even with 3 months of maximum inhaled combination therapy with a maximum dose of an ICS, a LABA and a LAMA (tiotropium). However, the company did not state to what extent it considered treatment escalation with LAMA to have been implemented, nor did it present any data documenting a non-suitability of LAMA. In the QUEST study, 9% (dupilumab arm) and 10% (comparator arm) continued their ongoing treatment with LAMA as a second or third controller medication. Overall, LAMAs were not available for the escalation of the ongoing treatment within the framework of the study. In the QUEST study, the options for treatment escalation according to the stepwise approach were therefore not exhausted for the majority of patients (before the use of dupilumab). This means that treatment with dupilumab is not the adequate patient-specific treatment escalation (taking into account the prior therapy) for these patients.

Overall, the ACT was not implemented in the indirect comparison of tezepelumab with dupilumab.

Results on added benefit

No suitable data are available for the assessment of the added benefit of tezepelumab as an add-on maintenance treatment in comparison with the ACT in adolescents aged 12 to 17 years and adults with severe asthma who are inadequately controlled despite high-dose ICS plus another medicinal product for maintenance treatment. There is no hint of added benefit of tezepelumab in comparison with the ACT for either research question of the present benefit assessment (adolescents and adults); an added benefit is therefore not proven for either of them.

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

Table 3 summarizes the result of the assessment of added benefit for tezepelumab in comparison with the ACT.

[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].

Table 3: Tezepelumab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adolescents aged 12 to 17 years with severe asthma who are inadequately controlled despite high-dose ICS plus another medicinal product for maintenance treatment[b]	individual treatment escalation[c] under consideration of the prior therapy choosing from: ▪ high-dose ICS and LABA and LAMA or ▪ high-dose ICS and LABA and possibly LAMA and omalizumab[d] or ▪ high-dose ICS and LABA and possibly LAMA and mepolizumab[e] or dupilumab[e]	Added benefit not proven
2	Adults with severe asthma who are inadequately controlled despite high-dose ICS plus another medicinal product for maintenance treatment[b]	Individual treatment escalation[c] under consideration of the prior therapy and the pathogenesis of asthma choosing from: ▪ high-dose ICS and LABA and LAMA or ▪ high-dose ICS and LABA and possibly LAMA and omalizumab[d] or ▪ high-dose ICS and LABA and possibly LAMA and mepolizumab[d] or reslizumab[d] or benralizumab[d] or dupilumab[d]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. In view of the wording of the therapeutic indication (severe asthma), it is assumed that treatment with tezepelumab is only indicated in addition to high-dose ICS and at least one other drug for maintenance treatment, or, in children and adolescents, also in addition to medium-dose ICS and montelukast and LABA and LAMA.
c. According to the G-BA, the stepwise approach to drug therapy of the 2020 NVL for Asthma, 4th edition, must be taken into account. It is assumed that, in the therapeutic indication of tezepelumab, the patients of research question 1 are represented in steps 5 to 6 of the stepwise approach to drug therapy for children and adolescents, and the patients of research question 2 are represented in steps 4 to 5 of the stepwise approach to drug therapy for adults. Unchanged continuation of inadequate treatment of severe asthma does not comply with an ACT in severe uncontrolled asthma if the option for treatment escalation is still available. If the therapeutic indication also includes patients for whom no further escalation of their existing inadequate treatment is possible, it must be shown for this patient population that no further treatment escalation is possible.
d. If the criteria required for the use are met.
e. If the criteria required for the use of omalizumab are met.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; NVL: National Care Guideline

The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report is to assess the added benefit of tezepelumab as an add-on maintenance treatment in comparison with the ACT in adolescents aged 12 to 17 years and adults with severe asthma who are inadequately controlled despite high-dose ICS plus another medicinal product for maintenance treatment.

The research questions shown in Table 4 result from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of tezepelumab

Research question	Therapeutic indication	ACT[a]
1	Adolescents aged 12 to 17 years with severe asthma who are inadequately controlled despite high-dose ICS plus another medicinal product for maintenance treatment[b]	Individual treatment escalation[c] under consideration of the prior therapy choosing from: ▪ high-dose ICS and LABA and LAMA or ▪ high-dose ICS and LABA and possibly LAMA and omalizumab[d] or ▪ high-dose ICS and LABA and possibly LAMA and mepolizumab[e] or dupilumab[e]
2	Adults with severe asthma who are inadequately controlled despite high-dose ICS plus another medicinal product for maintenance treatment[b]	Individual treatment escalation[c] under consideration of the prior therapy and the pathogenesis of asthma choosing from: ▪ high-dose ICS and LABA and LAMA or ▪ high-dose ICS and LABA and possibly LAMA and omalizumab[d] or ▪ high-dose ICS and LABA and possibly LAMA and mepolizumab[d] or reslizumab[d] or benralizumab[d] or dupilumab[d]

a. Presented is the respective ACT specified by the G-BA.
b. In view of the wording of the therapeutic indication (severe asthma), it is assumed that treatment with tezepelumab is only indicated in addition to high-dose ICS and at least one other drug for maintenance treatment, or, in children and adolescents, also in addition to medium-dose ICS and montelukast and LABA and LAMA.
c. According to the G-BA, the stepwise approach to drug therapy of the 2020 NVL for Asthma, 4th edition, must be taken into account. It is assumed that, in the therapeutic indication of tezepelumab, the patients of research question 1 are represented in steps 5 to 6 of the stepwise approach to drug therapy for children and adolescents, and the patients of research question 2 are represented in steps 4 to 5 of the stepwise approach to drug therapy for adults. Unchanged continuation of inadequate treatment of severe asthma does not comply with an ACT in severe uncontrolled asthma if the option for treatment escalation is still available. If the therapeutic indication also includes patients for whom no further escalation of their existing inadequate treatment is possible, it must be shown for this patient population that no further treatment escalation is possible.
d. If the criteria required for the use are met.
e. If the criteria required for the use of omalizumab are met.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; ICS: inhaled corticosteroids; 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. However, the company did not address the 2 research questions defined by the G-BA separately, but considered adolescent and adult patients together.

In line with the G-BA's specification, the present assessment is conducted separately for the 2 research questions, each in comparison with the ACT specified by the G-BA. Since no suitable data are available for either of the 2 research questions designated by the G-BA, the assessment below is performed in a joint section of the report.

The assessment is 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 are used for the derivation of added benefit. This concurs with the company's inclusion criteria.

I 3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on tezepelumab (status: 2 September 2022)
- bibliographical literature search on tezepelumab (last search on 2 September 2022)
- search in trial registries/trial results databases for studies on tezepelumab (last search on 2 September 2022)
- search on the G-BA website for tezepelumab (last search on 2 September 2022)
- bibliographical literature search on the ACT (last search on 2 September 2022)
- search in trial registries/trial results databases for studies on the ACT (last search on 2 September 2022)
- search on the G-BA website for the ACT (last search on 5 September 2022)

To check the completeness of the study pool:

- search in trial registries for studies on tezepelumab (last search on 24 November 2022); for search strategies, see I Appendix A of the full dossier assessment

No relevant study of direct comparison between tezepelumab and the ACT in the present therapeutic indication was identified from the check.

In contrast, the company identified the RCTs NAVIGATOR [3], PATHWAY [4] and DESTINATION [5], for each of which it used subpopulations to assess the added benefit of tezepelumab. The company additionally identified the RCTs SOURCE [6] and CASCADE [7], but presented the results of these studies only as supplementary information. As justification, the company stated that oral corticosteroids, which are classified as a secondary treatment option in the guidelines, were used in the SOURCE study. Regarding the CASCADE study, the company stated that it was very small, with a total of 12 patients in the relevant subpopulation, and that it had a different study objective. The company's reasoning is not appropriate. In agreement with the company, the SOURCE and CASCADE studies are nevertheless not used for the benefit assessment because (as in the NAVIGATOR, PATHWAY and DESTINATION studies) the ACT was not implemented in either study.

As the company did not identify any active-controlled studies in its search, the company conducted an additional information retrieval for studies for an adjusted indirect comparison using placebo as common comparator. For this purpose, it identified the studies NAVIGATOR

and PATHWAY on the intervention side, and the studies QUEST [8] and DRI12544 [9] on the comparator side.

Neither the direct comparison based on the subpopulations of the studies NAVIGATOR, PATHWAY and DESTINATION nor the adjusted indirect comparison are suitable for the benefit assessment of tezepelumab in comparison with the ACT. This is explained below.

Direct comparison presented by the company

The company used the RCTs NAVIGATOR, PATHWAY und DESTINATION for assessing the added benefit in its jointly considered patient group of adolescents and adults. From all 3 studies, the company formed subpopulations of patients who were not eligible for treatment with a biologic of the ACT due to their individual biomarker status ($biomarker_{low}$ population, see below). Based on these subpopulations, the company conducted a meta-analysis with the NAVIGATOR and PATHWAY studies; the results of the DESTINATION extension study were presented separately by the company.

NAVIGATOR

The NAVIGATOR study is a randomized, double-blind study on the comparison of tezepelumab with placebo. The study included patients aged 12 to 80 years with severe asthma and a history of ≥ 2 exacerbation events of their disease within 12 months prior to screening, defined by treatment with systemic corticosteroids or hospitalization or an emergency room visit. In addition, all patients must have been treated with medium or high-dose ICS and at least one additional controller medication for at least 3 months prior to screening.

A total of 1061 patients were randomly allocated to treatment with tezepelumab (N = 529) or placebo (N = 532). Stratification factors were age (adults versus adolescents) and region.

Treatment with tezepelumab was in compliance with the recommendations of the SPC [10]. All patients had to continue their initial asthma medication unchanged throughout the study. Adjustment of medication was not allowed. Similarly, biologics were not allowed to be used for treatment.

The NAVIGATOR study included a screening period of 5 to 6 weeks followed by a 52-week treatment phase. After the treatment phase, patients were followed up for 12 weeks or could be included in the DESTINATION extension study.

The primary outcome of the NAVIGATOR study was the annualized exacerbation rate.

PATHWAY

The PATHWAY study is a randomized, double-blind study on the comparison of different doses of tezepelumab with placebo. The study included patients aged 18 to 75 years with severe

asthma and a history of ≥ 2 asthma exacerbation events or one severe exacerbation within 12 months prior to screening. Deterioration was defined as treatment with systemic corticosteroids for ≥ 3 days or an emergency room visit or hospitalization. Severe deterioration was defined as hospitalization for ≥ 24 hours within 12 months prior to screening. In addition, all patients must have been treated with medium or high-dose ICS and a LABA for ≥ 6 months prior to screening.

A total of 584 patients were randomly allocated in a 1:1:1:1 ratio to treatment with tezepelumab with dosages of 280 mg every 2 weeks (N = 137), 210 mg every 4 weeks (N = 137), 70 mg every 4 weeks (N = 138), or placebo (N = 138); 34 patients from a study centre that was not in compliance with good clinical practice were excluded from the analyses. Stratification factors were region (Japan versus rest of the world), blood eosinophil count (≥ 250 versus < 250 cells/µL) and ICS dosage (medium versus high).

Treatment with tezepelumab with a dosage of 210 mg every 4 weeks is in compliance with the recommendations of the SPC [10]. It was recommended that all patients continue their initial asthma medication unchanged throughout the study. However, changes in asthma medication were possible at the physician's discretion and after consultation with the sponsor. The use of biologics was not allowed during the study.

The PATHWAY study included a screening of 5 weeks, followed by a 52-week treatment phase and a follow-up observation of 12 weeks.

The primary outcome of the study was the annualized exacerbation rate.

DESTINATION

The DESTINATION study is a randomized, double-blind extension study on the comparison of tezepelumab with placebo. The study included patients who had completed the NAVIGATOR study or the SOURCE study.

A total of 827 patients from the NAVIGATOR study and 124 patients from the SOURCE study were included in the DESTINATION study. Patients who had previously received tezepelumab were included in the tezepelumab arm while blinding was maintained. Patients who had previously received placebo were randomized in a 1:1 ratio to treatment with tezepelumab or placebo.

Treatment with tezepelumab was in compliance with the recommendations of the SPC [10]. The ongoing controller medication could be reduced during the study at the physician’s discretion if the symptoms were stable. Any exacerbations that occurred during the study had to be treated adequately. The use of biologics was not allowed.

The DESTINATION study included a 52-week treatment phase for patients from the NAVIGATOR study. These were followed up for 12 weeks after the treatment phase.

The primary outcome of the study was the incidence of adverse events and serious adverse events.

Subpopulations of the studies NAVIGATOR, PATHWAY and DESTINATION considered by the company

For the assessment of the added benefit, the company presented a meta-analysis with the biomarker$_{low}$ population of the studies NAVIGATOR and PATHWAY. These subpopulations included patients who were not eligible for treatment with a biologic (omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab) of the ACT due to their individual biomarker status (total immunoglobulin E, eosinophil count and fractional nitric oxide), according to the SPCs. The subpopulations considered by the company include 95 patients in the NAVIGATOR study (tezepelumab: n = 55; placebo: n = 40) and 21 patients in the PATHWAY study (tezepelumab: n = 12; placebo: n = 9).

For the DESTINATION study, the company also used the results of the biomarker$_{low}$ population. In addition, the company restricted the population to patients who were previously treated in the NAVIGATOR study. This subpopulation comprises 64 patients (tezepelumab: n = 45; placebo: n = 19).

Appropriate comparator therapy not implemented

The presented data from the NAVIGATOR, PATHWAY and DESTINATION studies are not suitable for assessing the added benefit of tezepelumab in comparison with the ACT, as the various options for individual treatment escalation specified by the G-BA were not implemented. Regarding the biomarker$_{low}$ population, the company explained that continued previous treatment with high-dose ICS + LABA and possibly LAMA was representative of an exhausted inhaled maintenance therapy. According to the company, further treatment escalation was therefore not an option for patients in these subpopulations and the continuation of the ongoing treatment corresponded to the G-BA's ACT. This reasoning of the company is not appropriate.

Treatment escalation with LAMA

Additional administration of a LAMA such as tiotropium represents a possible treatment escalation within the ACT specified by the G-BA for patients receiving maintenance treatment with 2 controller medications (e.g. ICS and LABA) who are not candidates for a biologic agent.

73% (intervention arm) and 60% (placebo arm) in the biomarker$_{low}$ population of the NAVIGATOR study, and 100% (intervention arm) and 89% (placebo arm) in the corresponding population of the PATHWAY study did not receive a LAMA at baseline. Taking into account the

current NVL for Asthma [11], treatment escalation with a third controller medication with a LAMA (e.g. tiotropium) is basically an option for these patients in both studies. However, initiation of a controller medication with a LAMA during the treatment phase was not allowed in the NAVIGATOR study. In the PATHWAY study, an adjustment of the controller medication was possible after consultation with the company, but the company did not provide any data on how many patients initiated treatment with LAMAs during the course of the study. For patients in the DESTINATION extension study, which included patients from the NAVIGATOR study, treatment escalation with a third controller medication would also be possible in principle. However, it is also not clear from the study documents how many patients treatment with a LAMA was initiated in the course of the study. The information in the clinical study report only shows that fewer than a quarter of the patients received tiotropium. It is unclear for how many of these this was a continuation of their previously existing treatment.

The company did not explain to what extent it considered a treatment escalation with a LAMA to have been implemented. The ACT was not implemented in the biomarker$_{low}$ populations of the studies NAVIGATOR, PATHWAY and DESTINATION.

Indirect comparison against dupilumab presented by the company

The company additionally presented an adjusted indirect comparison versus dupilumab using placebo as common comparator. This comparison is also unsuitable for the benefit assessment of tezepelumab in comparison with the ACT.

Studies included

On the intervention side, the company included the meta-analytically pooled mITT population of the NAVIGATOR and PATHWAY studies. According to the company, the mITT population comprises all patients in the ITT population who correspond to the approved therapeutic indication of tezepelumab (tezepelumab: n = 446; placebo: n = 436). Adolescents are not included in this subpopulation. A description of the studies can be found above.

On the comparator side, the company identified the studies QUEST and DRI12544. To derive an added benefit, the company only used the indirect comparison with the QUEST study. Due to different study durations, it presented the indirect comparison with the DRI12544 study as supplementary information.

Studies on the comparator therapy side

The QUEST study is a randomized, double-blind, phase 3 study on the comparison of 2 different dupilumab dosages with placebo. Patients 12 years of age and older with uncontrolled moderate to severe asthma who already received ongoing treatment with medium or high-dose ICS and one or 2 additional controller medications (e.g. LABA) with stable dosing were included in the study. A total of 1902 patients were randomly (2:2:1:1)

assigned to the study arms of dupilumab 300 mg every 2 weeks (N = 633), dupilumab 200 mg every 2 weeks (N = 631), placebo for 300 mg dupilumab (N = 321) or placebo for 200 mg dupilumab (N = 317). The treatment duration was 52 weeks.

The DRI12544 study is a randomized, double-blind phase IIb study on the comparison of 4 different dosages of dupilumab with placebo. The study included adult patients with uncontrolled moderate to severe asthma who already received treatment with medium or high-dose ICS and LABA at a stable dosage. A total of 776 patients were randomly (1:1:1:1:1) assigned to treatment with dupilumab 300 mg every 2 weeks (N = 157), dupilumab 200 mg every 2 weeks (N = 150), dupilumab 300 mg every 4 weeks (N = 157), dupilumab 200 mg every 4 weeks (N = 154) or placebo (N = 158). The treatment duration was 24 weeks.

Further information on the study design of the QUEST and DRI12544 studies can be found in benefit assessment A19-74 [12].

Appropriate comparator therapy not implemented in the studies on the comparator therapy

The G-BA specified patient-specific treatment escalation for both research questions of the benefit assessment, taking into account different combination therapies. The company presented an adjusted indirect comparison of tezepelumab with dupilumab, but did not show that dupilumab was the most suitable escalation treatment for the individual patients included in the QUEST and DRI12544 studies.

Possibilities of treatment escalation were not exhausted

According to the NVL for Asthma [11], there is only a therapeutic indication for treatment with monoclonal antibodies if asthma control is not achieved even with 3 months of maximum inhaled combination therapy with a maximum dose of an ICS, a LABA and a LAMA (tiotropium). As described in benefit assessment A19-74, treatment escalation with a third controller medication with a LAMA was in principle possible for the patients in the QUEST and DRI12544 studies. However, the company did not state to what extent it considered treatment escalation with LAMA to have been implemented, nor did it present any data documenting a non-suitability of LAMA. In the QUEST study, only 9% (dupilumab arm) and 10% (comparator arm) continued their ongoing treatment with a LAMA as a second or third controller medication. In the DRI12544 study, only 2.6% of the patients received tiotropium (LAMA) as concomitant treatment. Overall, LAMAs were not available for the escalation of the ongoing treatment within the framework of the 2 studies. In the studies QUEST and DRI12544, the options for treatment escalation according to the stepwise approach were therefore not exhausted for the majority of patients (before the use of dupilumab). This means that treatment with dupilumab is not the adequate patient-specific treatment escalation (taking into account the prior therapy) for these patients.

Overall, the ACT was therefore generally not implemented in the indirect comparison of tezepelumab with dupilumab presented by the company. No further check of the similarity of the studies on the comparator and intervention side was therefore performed.

Conclusion

The comparisons of tezepelumab with placebo presented by the company for the biomarker$_{low}$ populations of the NAVIGATOR, PATHWAY and DESTINATION studies are not suitable for the benefit assessment, as the options for treatment escalation were not exhausted for these populations and a continuation of an existing controller medication in the placebo arms of the studies is not an adequate implementation of the ACT. The presented indirect comparison of tezepelumab with dupilumab for the mITT population of the studies NAVIGATOR and PATHWAY and the comparator study QUEST (as well as the comparison with the DRI12544 study presented as supplementary information) also does not correspond to an adequate implementation of the ACT because in the QUEST study (and the DRI12544 study), the ACT of patient-specific treatment escalation was not adequately implemented in accordance with the specifications of the stepwise approach in the NVL for Asthma. In summary, no suitable data are available for the assessment of the added benefit of tezepelumab in comparison with the ACT.

I 4 Results on added benefit

No suitable data are available for the assessment of the added benefit of tezepelumab as an add-on maintenance treatment in comparison with the ACT in adolescents aged 12 to 17 years and adults with severe asthma who are inadequately controlled despite high-dose ICS plus another medicinal product for maintenance treatment. There is no hint of added benefit of tezepelumab in comparison with the ACT for either research question of the present benefit assessment (adolescents and adults); an added benefit is therefore not proven for either of them.

I 5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of added benefit for tezepelumab in comparison with the ACT.

Table 5: Tezepelumab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adolescents aged 12 to 17 years with severe asthma who are inadequately controlled despite high-dose ICS plus another medicinal product for maintenance treatment[b]	Individual treatment escalation[c] under consideration of the prior therapy choosing from: ▪ high-dose ICS and LABA and LAMA or ▪ high-dose ICS and LABA and possibly LAMA and omalizumab[d] or ▪ high-dose ICS and LABA and possibly LAMA and mepolizumab[e] or dupilumab[e]	Added benefit not proven
2	Adults with severe asthma who are inadequately controlled despite high-dose ICS plus another medicinal product for maintenance treatment[b]	Individual treatment escalation[c] under consideration of the prior therapy and the pathogenesis of asthma choosing from: ▪ high-dose ICS and LABA and LAMA or ▪ high-dose ICS and LABA and possibly LAMA and omalizumab[d] or ▪ high-dose ICS and LABA and possibly LAMA and mepolizumab[d] or reslizumab[d] or benralizumab[d] or dupilumab[d]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. In view of the wording of the therapeutic indication (severe asthma), it is assumed that treatment with tezepelumab is only indicated in addition to high-dose ICS and at least one other drug for maintenance treatment, or, in children and adolescents, also in addition to medium-dose ICS and montelukast and LABA and LAMA.
c. According to the G-BA, the stepwise approach to drug therapy of the 2020 NVL for Asthma, 4th edition, must be taken into account. It is assumed that, in the therapeutic indication of tezepelumab, the patients of research question 1 are represented in steps 5 to 6 of the stepwise approach to drug therapy for children and adolescents, and the patients of research question 2 are represented in steps 4 to 5 of the stepwise approach to drug therapy for adults. Unchanged continuation of inadequate treatment of severe asthma does not comply with an ACT in severe uncontrolled asthma if the option for treatment escalation is still available. If the therapeutic indication also includes patients for whom no further escalation of their existing inadequate treatment is possible, it must be shown for this patient population that no further treatment escalation is possible.
d. If the criteria required for the use are met.
e. If the criteria required for the use of omalizumab are met.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; NVL: National Care Guideline

The assessment described above differs from that of the company, which derived a hint of an at least considerable added benefit for both research questions together on the basis of the results of the studies of direct comparison against placebo and the adjusted indirect comparison against dupilumab.

The G-BA decides on the added benefit.

I 6 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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