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Benralizumab (asthma) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Benralizumab (Asthma) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 9 May 2018). 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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List of abbreviations

Abbreviation	Meaning
ACQ	Asthma Control Questionnaire
ACT	appropriate comparator therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GINA	Global Initiative for Asthma
ICS	inhaled corticosteroids
IgE	immunoglobulin E
IU	international units
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
OCS	oral corticosteroids
RCT	randomized controlled trial
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book 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 benralizumab. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 15 February 2018.

Research question

The aim of the present report was the assessment of the added benefit of benralizumab in comparison with the appropriate comparator therapy (ACT) as an add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids (ICS) plus long-acting beta-agonists (LABAs).

Table 2 shows the research question of the benefit assessment and the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of benralizumab

Research question	Therapeutic indication	ACT[a]
1	Add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting beta-agonists	Individual treatment escalation[b] ▪ of high-dose inhaled corticosteroids (ICS) and long-acting bronchodilators (LABAs) with tiotropium and possibly oral corticosteroids (OCS)[c], or ▪ in case of IgE-mediated pathogenesis of asthma, possibly omalizumab[d] in addition to high-dose ICS and LABAs and possibly OCS[c], or ▪ possibly of the high-dose ICS and LABAs with OCS[c, e]

a: Presentation of the ACT specified by the G-BA.
b: The Global Initiative for Asthma (GINA) graded scheme is to be taken into account. It is assumed that the therapeutic indication of benralizumab is represented in step 4 to step 5. Placebo or the unchanged continuation of inadequate treatment of severe asthma does not comply with an ACT in severe refractory eosinophilic asthma if the option for treatment escalation is still available. The therapeutic indication also comprises patients for whom there is no further escalation option for their ongoing treatment, however.
c: OCS should only be used on a short-term basis and in their lowest effective dose. It should be ensured in the OCS treatment of asthma that the OCS dosage does not permanently exceed the Cushing threshold if possible. Treatment of exacerbations must be differentiated from this.
d: Omalizumab can be used as an ACT option only in patients who completely fulfil the criteria of the approval and of the note on treatment for omalizumab.
e: In comparison with the other drugs mentioned – if these are suitable – treatment with OCS is not considered the preferred treatment option.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; ICS: inhaled corticosteroids; IgE: immunoglobulin E; LABA: long-acting beta-2 agonist; OCS: oral corticosteroids

The company concurred with the ACT specified by the G-BA.

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.

Results

With its information retrieval, the company identified the 3 RCTs ZONDA, CALIMA and SIROCCO on the comparison of benralizumab with placebo. For the benefit assessment, the company only used the data of those patients from these studies for whom it considered treatment with benralizumab to be an option in the sense of the expected actual health care setting. From the company's point of view, these are patients for whom the relevant treatment options have already been exhausted and only limited treatment adjustments on an individual basis are possible. Consequently, it used the ZONDA study completely, and subpopulations of the studies CALIMA and SIROCCO. The 3 studies were unsuitable for the derivation of the added benefit of benralizumab in comparison with the ACT. The data presented by the company were also unsuitable for the derivation of an added benefit of benralizumab.

The studies CALIMA, SIROCCO and ZONDA

The studies CALIMA, SIROCCO and ZONDA were multicentre, randomized, double-blind, placebo-controlled studies with treatment durations of 56 weeks (CALIMA), 48 weeks (SIROCCO) and 28 weeks (ZONDA), which compared benralizumab (in 2 different dosages) with placebo. In each case, the company considered only the benralizumab arm with approval-compliant dosage. Benralizumab and placebo were each administered in addition to ongoing asthma treatment. In the studies CALIMA and SIROCCO, patients between 12 and 75 years of age with uncontrolled asthma under ongoing treatment with medium- or high-dose ICS plus LABAs with or without further maintenance treatment were included. A further criterion for study inclusion was an Asthma Control Questionnaire (ACQ)-6 score of ≥ 1.5 and at least 2 documented asthma exacerbations within 12 months before randomization. Presence of eosinophilic asthma was not an inclusion criterion in either of both studies. The ZONDA study included adult patients with eosinophilic asthma (eosinophils ≥ 150/µL) and at least 1 documented asthma exacerbation in the 12 months prior to study inclusion. In addition to ongoing treatment with high-dose ICS plus LABAs, all patients were already receiving regular treatment with oral corticosteroids (OCS) at study inclusion. The aim of the ZONDA study was to investigate the effect of benralizumab in comparison with placebo on an intended OCS dose reduction. For this purpose, the patients first underwent an optimization phase before randomization to reduce their OCS treatment to the lowest still effective dosage. After randomization and the start of the study treatment, the OCS dose was gradually decreased further.

During the entire treatment phase, all 3 studies allowed continuation of the asthma maintenance treatment (tiotropium, OCS) started before study inclusion. Unchanged continuation of this treatment was to be conducted in the entire study course (except OCS reduction in the ZONDA

study). Omalizumab was permitted neither within 4 months or 5 half-lives before study start nor as concomitant treatment during the studies.

Implementation of the appropriate comparator therapy

The ACT was not implemented in the studies CALIMA and SIROCCO because treatment escalations (tiotropium, omalizumab, OCS) in the comparator arms were neither performed at the start nor during the studies.

Hence, patients in the studies CALIMA and SIROCCO had inadequately controlled asthma at study start. In this situation, guidelines recommend treatment escalation to achieve symptom control and prevent exacerbations. This was done in the intervention arms (with the administration of benralizumab), but not in the comparator arms. Instead, the maintenance treatment – beyond ICS plus LABAs – that was already ongoing before the start of the studies, was to be maintained at a stable dose until the end of treatment in both treatment arms of the studies.

The ZONDA study reflected a specific therapeutic situation as the study's primary target was the dose reduction of OCS. Individual escalation options of the comparator therapy for these patients particularly consisted in additional administration of tiotropium or omalizumab and dose adjustment of OCS. There was no escalation with long-acting muscarinic antagonists (LAMAs) (including tiotropium) in the course of the study, however. Administration of omalizumab as maintenance treatment was an exclusion criterion and was available neither at the start nor in the course of the study. Information on the treatment adjustment for OCS in the ZONDA study was not interpretable as the primary outcome of the study was an OCS reduction planned per protocol.

Patient populations of the studies ZONDA, CALIMA and SIROCCO used by the company

The company assessed the added benefit of benralizumab on the basis of the modified intention-to-treat populations (hereinafter referred to as "mITT populations") it had formed from the studies ZONDA, CALIMA and SIROCCO. For this purpose, the company only used those patients from the 3 studies for whom it considered treatment with benralizumab to be an option in the sense of the expected actual health care setting. In the company's assessment, these were patients for whom the following criteria were fulfilled:

Study ZONDA

- approval-compliant administration of benralizumab
- severe eosinophilic asthma (eosinophilia according to the inclusion criterion of eosinophils ≥ 150/µL)
- OCS maintenance treatment according to step 5 of the Global Initiative for Asthma (GINA) scheme in addition to maintenance treatment with high-dose ICS plus LABAs

Studies CALIMA and SIROCCO

- approval-compliant administration of benralizumab
- eosinophils ≥ 300/µL
- high-dose ICS plus LABAs
- at least 1 add-on maintenance treatment according to step 5 of the GINA scheme [OCS, LAMAs (tiotropium) or both] in addition to maintenance treatment with high-dose ICS plus LABAs

As a result of the company's criteria, the company analysed the total population of the ZONDA study, and subpopulations of the other 2 studies, which comprised 9.9% (CALIMA) and 14.3% (SIROCCO) of the total study populations.

Lack of suitability of the data analysed by the company

The company justified the exclusive consideration of these patient populations with the fact that benralizumab is approved for adult patients with severe eosinophilic asthma inadequately controlled despite high-dose ICS plus LABAs. Hence, for the company, in compliance with commonly used national and international guideline recommendations, benralizumab will be used in the actual health care setting particularly in patients with many years of continued inadequate asthma control who have had individual treatment adjustments up to the highest step of the GINA scheme (step 5). According to the company, the relevant treatment options in this specific target population were already exhausted and only limited treatment adjustments on an individual basis were possible in the framework of the ACT.

The company also described that, according to the protocols of the 3 studies ZONDA, CALIMA and SIROCCO, individual adjustments of the maintenance treatment were possible and were performed if these were deemed medically required by the investigator.

The company's argumentation comprised 3 key aspects: a) the target population of the therapeutic indication corresponds to patients for whom the relevant treatment options have already been exhausted, b) the treatment options for patients of the analysed mITT population had already been exhausted in the studies, and c) treatment adjustments on an individual basis were possible in the 3 studies and were performed on an individual basis.

Since further escalation options of their ongoing treatments were possible for the patients of the study analysed by the company, but an escalation was neither mandated nor performed in the study (aspects b and c), the present data were unsuitable for the assessment of the added benefit of benralizumab. The individual aspects cited by the company are commented on below.

The target population according to the therapeutic indication is more comprehensive than described by the company

The company referred to the therapeutic indication of benralizumab (severe eosinophilic asthma inadequately controlled despite high-dose ICS plus LABAs). Together with the

recommendations in guidelines, for the company, this resulted in a target population of those patients for whom relevant treatment options have already been exhausted.

It is correct that the therapeutic indication of benralizumab also comprises patients for whom no further escalation option exists for their ongoing treatment. These constitute only part of the target population according to the therapeutic indication of benralizumab, however. Further treatment options are principally possible for patients with inadequate asthma control despite high-dose ICS plus LABAs. This is also reflected in the guidelines cited by the company, which recommend escalation options with tiotropium or omalizumab for the patient population mentioned. Low-dose OCS is an additional option for treatment escalation. The G-BA also classified the therapeutic indication of benralizumab as steps 4 and 5 of the GINA graded scheme, and specified the escalation options mentioned as ACT.

Despite the limitation to patients for whom the relevant treatment options have already been exhausted, the company derived the added benefit for the population in the entire therapeutic indication.

Treatment options not exhausted in the patients of the studies ZONDA, CALIMA and SIROCCO analysed by the company

The company argued that the treatment options were already exhausted by using the company's criteria for the patients in the mITT populations of the 3 studies ZONDA, CALIMA and SIROCCO analysed by the company. This assessment was not followed. The scope in asthma therapy consists in using combination options of different agents in the individual steps of treatment. Treatment escalations at study start were possible for the populations analysed by the company for the studies ZONDA (maintenance treatment at study start: ICS plus LABAs and additional OCS and possibly LAMAs), and CALIMA and SIROCCO (maintenance treatments at study start: ICS plus LABAs and additional OCS or LAMAs or both). The guidelines provide escalation options particularly for patients with only 1 additional treatment (e.g. tiotropium).

Treatment escalation with tiotropium: Tiotropium is an option for treatment escalation within the G-BA's ACT. In the populations analysed by the company, 25.3% (ZONDA), 48.8% (subpopulation of CALIMA) and 36.4% (subpopulation of SIROCCO) in the placebo arm were receiving tiotropium at study start. The company did not present separate data for tiotropium on the adjustment of the medication in the course of the study, but on the administration of LAMAs overall. In the course of the study, escalation of LAMA treatment in the placebo arm was performed in none of the patients in the ZONDA study and in the analysed subpopulation of the CALIMA study, and in 2 patients of the subpopulation of the SIROCCO study. Since the inclusion criteria of the studies ZONDA, CALIMA and SIROCCO were well covered by the approval of tiotropium, it can be assumed that treatment with tiotropium would have been suitable for a large proportion of the patients requiring additional asthma control medication.

Treatment escalation with omalizumab: Omalizumab can be used in patients with immunoglobulin E (IgE)-mediated pathogenesis of asthma for treatment escalation and was also a treatment option of the ACT. In the studies presented, omalizumab was not allowed in the 4 months or 5 half-lives before the start of the study and during the studies. Hence, this treatment option was not available to the patients in the framework of the studies.

Treatment escalation with OCS: OCS are another option for treatment escalation within the G-BA's ACT. At study start, 65.1% (CALIMA) and 67.3% (SIROCCO) of the patients in the placebo arm of the subpopulation analysed by the company were receiving OCS maintenance treatment. Escalation of OCS treatment in the course of the study (dose increase or initiation) was only performed in 3 (7.0%) patients in the placebo arm of the subpopulation of the CALIMA study, and in only 2 (3.6%) patients in the placebo arm of the subpopulation of the SIROCCO study. It can therefore be assumed that a relevant proportion of the analysed patient populations requiring additional asthma control medication would have been eligible for escalation with OCS in the placebo arm.

Since all patients in the ZONDA study were receiving OCS as maintenance treatment already at study start, OCS as escalation treatment was only available for these patients in the sense of a dose increase. Information on dose increase of the maintenance treatment in the course of the study was not meaningfully interpretable as the study patients' OCS asthma therapy was reduced according to a fixed regimen. OCS increase in the OCS reduction phase was only possible if the criteria for asthma control defined in the study protocol were not met. It was therefore unclear whether patients with dose increase actually received escalation of their maintenance treatment or only returned to a higher dose due to poor asthma control in the OCS reduction phase.

Individual treatment adjustments not possible in the framework of the appropriate comparator therapy and not implemented for the individual patients

The company argued that individual treatment adjustments were possible and were used on an individual basis in the study populations used for the benefit assessment. This cannot be inferred from the study documents. According to the information provided in the protocols of the 3 studies included on concomitant treatments that were disallowed/restricted, maintenance treatments (including ICS plus LABAs, tiotropium and OCS) were only allowed if they had already been taken before study start and were continued without changes during the studies. An exception were OCS in the ZONDA study, where all patients were taking OCS at study start and where OCS reduction was a primary outcome. Omalizumab was not allowed in any of the studies, neither at the start of the studies, nor during the studies. Hence, the study protocols did not provide for individual treatment adjustments in the framework of the ACT.

Summary

In summary, the data presented by the company were unsuitable for the derivation of the added benefit of benralizumab. On the one hand, the company's approach – contrary to its intention – did not ensure the consideration of patients for whom no further escalation options of their

ongoing treatments were available. On the other, the escalation options possible in accordance with the ACT were not implemented in the placebo arms of the 3 studies. The results presented were therefore not interpretable.

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

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

Table 3: Benralizumab – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting beta-agonists	Individual treatment escalation[b] ▪ of high-dose inhaled corticosteroids (ICS) and long-acting bronchodilators (LABAs) with tiotropium and possibly oral corticosteroids (OCS)[c], or ▪ in case of IgE-mediated pathogenesis of asthma, possibly omalizumab[d] in addition to high-dose ICS and LABAs and possibly OCS[c], or ▪ possibly of the high-dose ICS and LABAs with OCS[c, e]	Added benefit not proven

a: Presentation of the ACT specified by the G-BA.
b: The Global Initiative for Asthma (GINA) graded scheme is to be taken into account. It is assumed that the therapeutic indication of benralizumab is represented in step 4 to step 5. Placebo or the unchanged continuation of inadequate treatment of severe asthma does not comply with an ACT in severe refractory eosinophilic asthma if the option for treatment escalation is still available. The therapeutic indication also comprises patients for whom there is no further escalation option for their ongoing treatment, however.
c: OCS should only be used on a short-term basis and in their lowest effective dose. It should be ensured in the OCS treatment of asthma that the OCS dosage does not permanently exceed the Cushing threshold if possible. Treatment of exacerbations must be differentiated from this.
d: Omalizumab can be used as an ACT option only in patients who completely fulfil the criteria of the approval and of the note on treatment for omalizumab.
e: In comparison with the other drugs mentioned – if these are suitable – treatment with OCS is not considered the preferred treatment option.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; ICS: inhaled corticosteroids; IgE: immunoglobulin E; LABA: long-acting beta-2 agonist; OCS: oral corticosteroids

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 was the assessment of the added benefit of benralizumab in comparison with the ACT as an add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose ICS plus LABAs.

Table 4 shows the research question of the benefit assessment and the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of benralizumab

Research question	Therapeutic indication	ACT[a]
1	Add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting beta-agonists	Individual treatment escalation[b] ▪ of high-dose inhaled corticosteroids (ICS) and long-acting bronchodilators (LABAs) with tiotropium and possibly oral corticosteroids (OCS)[c], or ▪ in case of IgE-mediated pathogenesis of asthma, possibly omalizumab[d] in addition to high-dose ICS and LABAs and possibly OCS[c], or ▪ possibly of the high-dose ICS and LABAs with OCS[c, e]

a: Presentation of the ACT specified by the G-BA.
b: The Global Initiative for Asthma (GINA) graded scheme is to be taken into account [3]. It is assumed that the therapeutic indication of benralizumab is represented in step 4 to step 5. Placebo or the unchanged continuation of inadequate treatment of severe asthma does not comply with an ACT in severe refractory eosinophilic asthma if the option for treatment escalation is still available. The therapeutic indication also comprises patients for whom there is no further escalation option for their ongoing treatment, however.
c: OCS should only be used on a short-term basis and in their lowest effective dose. It should be ensured in the OCS treatment of asthma that the OCS dosage does not permanently exceed the Cushing threshold if possible. Treatment of exacerbations must be differentiated from this.
d: Omalizumab can be used as an ACT option only in patients who completely fulfil the criteria of the approval and of the note on treatment for omalizumab [4,5].
e: In comparison with the other drugs mentioned – if these are suitable – treatment with OCS is not considered the preferred treatment option.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; ICS: inhaled corticosteroids; IgE: immunoglobulin E; LABA: long-acting beta-2 agonist; OCS: oral corticosteroids

The company concurred with the ACT specified by the G-BA.

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 concurred with the company's inclusion criteria.

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on benralizumab (status: 16 November 2017)
- bibliographical literature search on benralizumab (last search on 16 November 2017)
- search in trial registries for studies on benralizumab (last search on 16 November 2017)

To check the completeness of the study pool:

- search in trial registries for studies on benralizumab (last search on 21 February 2018)

No relevant study was identified from the check.

With its information retrieval, the company identified the 3 RCTs ZONDA [6,7], CALIMA [8,9] and SIROCCO [10,11] on the comparison of benralizumab with placebo. For the benefit assessment, the company only used the data of those patients from these studies for whom it considered treatment with benralizumab to be an option in the sense of the expected actual health care setting. Consequently, it used the ZONDA study completely, and subpopulations of the studies CALIMA and SIROCCO.

The 3 studies were unsuitable for the derivation of the added benefit of benralizumab in comparison with the ACT. The data presented by the company were also unsuitable for the derivation of an added benefit of benralizumab. This deviates from the approach of the company, which included the subpopulations of the studies CALIMA and SIROCCO and the total population of the ZONDA study in its assessment, and derived the added benefit on the basis of these data.

Hereinafter, the studies included by the company are described in more detail, providing reasons why the studies were unsuitable for the assessment of the added benefit of benralizumab in comparison with the ACT. A detailed explanation on the subpopulations formed by the company as well as the assessment of the relevance of these data can be found in Section 2.3.2 of the present benefit assessment.

2.3.1 The studies CALIMA, SIROCCO and ZONDA presented by the company

Studies CALIMA and SIROCCO

The studies CALIMA and SIROCCO were multicentre, randomized, double-blind, placebo-controlled studies with treatment durations of 56 weeks (CALIMA) and 48 weeks (SIROCCO), which compared benralizumab (in 2 different dosages) with placebo. They included patients between 12 and 75 years of age with uncontrolled asthma under ongoing treatment with medium- or high-dose ICS plus LABAs with or without further maintenance treatment. A further criterion for study inclusion was an ACQ-6 score of ≥ 1.5 and at least 2 documented asthma exacerbations within 12 months before randomization. In addition, at least 1 of the following events had to have occurred in the patients within 7 days before randomization: > 2 days with a daytime or nighttime symptoms score ≥1; rescue short-acting beta agonist use on > 2 days; ≥ 1 nocturnal awakening due to asthma. Presence of eosinophilic asthma was not

an inclusion criterion in either of both studies. Eosinophil count (≥ 300 cells/µL and < 300 cells/µL) was a stratification characteristic, however. According to the sample size planning, the number of patients with an eosinophil count of ≥ 300 cells/µL was to be twice as high as the number of patients with an eosinophil count of < 300 cells/µL.

A total of 1306 (CALIMA) and 1205 (SIROCCO) patients were allocated in a ratio of 1:1:1 to subcutaneous administration of benralizumab 30 mg every 4 weeks, to benralizumab 30 mg every 4 weeks initially and every 8 weeks after the first 3 administrations, and to placebo. The exact number of patients in the different treatment groups is shown in Table 10 (see Appendix A of the full dossier assessment). The first dosage mentioned (30 mg benralizumab every 4 weeks) is not approved in Germany [12]. Correspondingly, the company did not give further consideration to these arms of both studies in Module 4 A of the dossier.

During the entire treatment phase, continuation of the asthma maintenance treatment (e.g. tiotropium or OCS) started before study inclusion was allowed. These were to be continued without changes during the entire studies. Omalizumab was permitted neither within 4 months or 5 half-lives before the start of the study nor as concomitant treatment during the studies. Further information on the characteristics of the studies, the interventions and the patient characteristics of the studies CALIMA and SIROCCO can be found in Table 10 to Table 12 in Appendix A of the full dossier assessment.

Overall, it should be noted that the studies CALIMA and SIROCCO also included patients who did not concur with the target population of the present benefit assessment. Besides patients with high-dose ICS, the studies also investigated patients with medium-dose ICS (CALIMA study) as well as patients under 18 years of age and with non-eosinophilic asthma (studies CALIMA and SIROCCO). The exact proportion of the patients who did not concur with the target population could not be inferred from the available study documents. In addition, a large proportion of the study populations in both studies received drugs that are not approved in Germany for the treatment of severe eosinophilic asthma, such as montelukast.

Implementation of the appropriate comparator therapy

The ACT was not implemented in the studies CALIMA and SIROCCO because treatment escalations (tiotropium, omalizumab, OCS) in the comparator arms were neither performed at the start nor during the studies.

For instance, asthma control was inadequate in the patients in the studies CALIMA and SIROCCO who had a mean ACQ-6 score of just under 3 and a mean number of exacerbations in the previous year of just under 3 (see Table 12 in Appendix A of the full dossier assessment). The treatment used before the start of the study was therefore inadequate to ensure the treatment goal of asthma control. In this situation, guidelines recommend treatment escalation to achieve symptom control and prevent exacerbations [3]. This was done in the intervention arms (with the administration of benralizumab), but not in the comparator arms. Instead, the maintenance treatment – beyond ICS plus LABAs – that was already ongoing before the start of the studies,

was to be maintained at a stable dose until the end of treatment in both treatment arms of the studies.

No comprehensive data on the escalation or adjustment of maintenance treatments were available for the total population. However, the available data for the 2 studies CALIMA and SIROCCO showed that fewer than 10% of the patients received additional maintenance treatment with LAMAs at study start. Fewer than 10% (CALIMA) and 20% (SIROCCO) of the patients also received OCS maintenance treatment at study start (see Table 13 of Appendix A of the full dossier assessment). Optimization with tiotropium was only performed in rare cases, if any, as escalation in the placebo arm. No data on treatment adjustment for the total population of the 2 studies CALIMA and SIROCCO were available on OCS. Under the condition stipulated in the study protocol to continue the concomitant treatment without changes, it can be assumed that only minor or no optimizations were performed also for OCS. Omalizumab as maintenance treatment was an exclusion criterion and was available neither at the start nor during the studies.

Study ZONDA

The ZONDA study was a multicentre, randomized, double-blind, placebo-controlled study with a treatment duration of 28 weeks, which compared benralizumab (in 2 different dosages) with placebo. It included adult patients with eosinophilic asthma (eosinophil count ≥ 150 cells/µL) and at least 1 documented asthma exacerbation in the 12 months prior to study inclusion. At study inclusion, all patients had been receiving regular OCS treatment in addition to ongoing treatment with high-dose ICS plus LABAs for at least 6 months, and therefore concurred with step 5 of the GINA recommendations [3]. Hence, the study population of the ZONDA study largely represented part of the therapeutic indication of benralizumab. See Section 2.3.3 for deviations from the therapeutic indication (*Further limitations of the presented studies*).

The aim of the ZONDA study was to investigate the effect of benralizumab in comparison with placebo on an intended OCS dose reduction.

A total of 220 patients were allocated in a ratio of 1:1:1 to subcutaneous administration of benralizumab 30 mg every 4 weeks, to benralizumab 30 mg every 4 weeks initially and every 8 weeks after the first 3 administrations, and to placebo (N = 72 versus N = 73 versus N = 75 patients). The first dosage mentioned (30 mg benralizumab every 4 weeks) is not approved in Germany [12]. Correspondingly, the company did not give further consideration to this arm in Module 4 A of the dossier. Benralizumab and placebo were each administered in addition to ongoing asthma treatment.

The patients underwent an optimization phase of at most 8 weeks before randomization. In this phase, there was a biweekly stepwise reduction of OCS treatment to the lowest dosage that was still effective while maintaining asthma control. Optimization of the OCS dosage was made based on a titration schedule planned in the protocol. If the criteria of asthma control specified in the study protocol were not fulfilled, further reduction of the OCS dose was stopped, and

treatment was returned to an OCS dose that was at least one step higher while still achieving asthma control. After the optimization phase, only those patients were randomized to the treatment arms who were able to remain on the same OCS dose for at least 2 weeks prior to randomization. Patients who achieved asthma control with an OCS dose of ≤ 5.0 mg during the OCS optimization phase were excluded. After randomization, the patients received benralizumab or placebo. A 4-week maintenance phase with stable OCS dose was followed by another phase with 4-week stepwise reduction until week 24 after randomization. This also followed a specified titration schedule. Subsequently, the patients were to remain on their last OCS dosage for a maintenance phase of 4 week.

During the entire treatment phase, additional asthma maintenance medication (e.g. tiotropium) was only allowed as continuation of the stable dose taken during the 2 weeks prior to randomization. Omalizumab was permitted neither within 4 months or 5 half-lives before study start nor as concomitant treatment during the study. Further information on the characteristics of the study, the interventions and the patient characteristics of the ZONDA study can be found in Table 10 to Table 12 in Appendix A of the full dossier assessment.

Implementation of the appropriate comparator therapy

The ZONDA study reflected a specific therapeutic situation as its primary target was the dose reduction of OCS. Individual escalation options of the comparator therapy for the patients included particularly consisted in additional administration of tiotropium or omalizumab and dose adjustment of OCS.

As can be seen in Table 13, Appendix A of the full dossier assessment, LAMAs were neither increased nor initiated in the course of the study. Hence, there was no escalation with tiotropium in the course of the study. Administration of omalizumab as maintenance treatment was an exclusion criterion and was available neither at the start nor in the course of the study. Information on the treatment adjustment for OCS in the ZONDA study was not interpretable as the primary outcome of the study was an OCS reduction planned per protocol.

2.3.2 Patient populations of the studies ZONDA, CALIMA and SIROCCO used by the company

The company assessed the added benefit of benralizumab on the basis of the mITT populations it had formed from the studies ZONDA, CALIMA and SIROCCO. For this purpose, the company only used those patients from the 3 studies for whom it considered treatment with benralizumab to be an option in the sense of the expected actual health care setting. In the company's assessment, these were patients for whom the following criteria were fulfilled:

Study ZONDA

- approval-compliant administration of benralizumab (intervention and patient characteristics); exclusion of the treatment arm with 4-week administration of benralizumab
- severe eosinophilic asthma (eosinophilia according to the inclusion criterion of eosinophils ≥ 150/µL)
- OCS maintenance treatment according to step 5 of the GINA scheme in addition to maintenance treatment with high-dose ICS plus LABAs (high-dose ICS defined according to the GINA recommendations and in compliance with local regulations [3], with the company citing the 2017 GINA recommendation [13])

Studies CALIMA and SIROCCO

- approval-compliant administration of benralizumab (intervention and patient characteristics); exclusion of the treatment arm with 4-week administration of benralizumab
- eosinophils ≥ 300/µL
- high-dose ICS plus LABAs (high-dose ICS defined according to the GINA recommendations and in compliance with local regulations [3], with the company citing the 2017 GINA recommendation [13])
- at least 1 add-on maintenance treatment according to step 5 of the GINA scheme (OCS, LAMAs [tiotropium] or both) in addition to maintenance treatment with high-dose ICS plus LABAs

As a result of the company's criteria, the company analysed the total population of the ZONDA study, and subpopulations of the other 2 studies, which comprised 9.9% (CALIMA) and 14.3% (SIROCCO) of the total study populations.

Lack of suitability of the data analysed by the company

The company justified the exclusive consideration of these patient populations with the fact that benralizumab is approved for adult patients with severe eosinophilic asthma inadequately controlled despite high-dose ICS plus LABAs. Hence, for the company, in compliance with commonly used national and international guideline recommendations, benralizumab will be used in the actual health care setting particularly in patients with many years of continued inadequate asthma control who have had individual treatment adjustments up to the highest step of the GINA scheme (step 5). According to the company, the relevant treatment options in this specific target population were already exhausted and only limited treatment adjustments on an individual basis were possible in the framework of the ACT. The company claimed that, according to the current S2k guideline [14], add-on maintenance treatment with LAMAs (tiotropium) is no compulsory prerequisite for the use of monoclonal antibodies in severe asthma, but that such a treatment attempt should be aimed at in advance. For the company,

benralizumab will therefore probably be used particularly in patients who receive possibly LAMAs (tiotropium), and/or OCS as add-on maintenance treatment, possibly in combination with further maintenance treatments, in addition to their treatment with high-dose ICS plus LABAs.

The company also described that, according to the protocols of the 3 studies ZONDA, CALIMA and SIROCCO, individual adjustments of the maintenance treatment were possible and were performed if these were deemed medically required by the investigator.

The company's argumentation comprised 3 key aspects: a) the target population of the therapeutic indication corresponds to patients for whom the relevant treatment options have already been exhausted, b) the treatment options for patients of the analysed mITT population had already been exhausted in the studies, and c) treatment adjustments on an individual basis were possible in the 3 studies and were performed on an individual basis.

Since further escalation options of their ongoing treatments were possible for the patients of the study analysed by the company, but an escalation was neither mandated nor performed in the study (aspects b and c), the present data were unsuitable for the assessment of the added benefit of benralizumab. The individual aspects cited by the company are commented on below.

The target population according to the therapeutic indication is more comprehensive than described by the company

The company referred to the therapeutic indication of benralizumab (severe eosinophilic asthma inadequately controlled despite high-dose ICS plus LABAs). Together with the recommendations in guidelines [13,14], for the company, this resulted in a target population of those patients for whom relevant treatment options have already been exhausted.

It is correct that the therapeutic indication of benralizumab also comprises patients for whom no further escalation option exists for their ongoing treatment. These constitute only part of the target population according to the therapeutic indication of benralizumab, however. Further treatment options are principally possible for patients with inadequate asthma control despite high-dose ICS plus LABAs. This is also reflected in the guidelines cited by the company [13,14], which recommend escalation options with tiotropium or omalizumab for the patient population mentioned. Low-dose OCS is an additional option for treatment escalation. The G-BA also classified the therapeutic indication of benralizumab as steps 4 and 5 of the GINA graded scheme [3], and specified the escalation options mentioned as ACT.

Despite the limitation to patients for whom the relevant treatment options have already been exhausted, the company derived the added benefit for the population in the entire therapeutic indication.

Treatment options not exhausted in the patients of the studies ZONDA, CALIMA and SIROCCO analysed by the company

The company argued that the treatment options were already exhausted by using the company's criteria for the patients in the mITT populations of the 3 studies ZONDA, CALIMA and SIROCCO analysed by the company.

This assessment was not followed. The scope in asthma therapy consists in using combination options of different agents in the individual steps of treatment. Treatment escalations at study start were possible for the populations analysed by the company for the studies ZONDA (maintenance treatment at study start: ICS plus LABAs and additional OCS and possibly LAMAs), and CALIMA and SIROCCO (maintenance treatments at study start: ICS plus LABAs and additional OCS or LAMAs or both). These were the following:

- escalation with tiotropium in patients who were not receiving tiotropium at study start and were eligible for this treatment
- escalation with omalizumab in patients who were eligible for this treatment
- escalation with OCS in patients who were not receiving OCS at study start (only CALIMA and SIROCCO)
- possibly further dose increase of the ongoing OCS medication (as last treatment option)

The guidelines [3,14] provide escalation options particularly for patients with only 1 additional treatment (e.g. tiotropium). Treatment escalation was possibly exhausted in those patients who were already receiving tiotropium and OCS besides high-dose ICS plus LABAs. However, the proportion of these patients was low in the mITT populations analysed by the company. In the placebo arm, only 28.0% (ZONDA), 20.9% (subpopulation of CALIMA) and 7.3% (subpopulation of SIROCCO) patients were receiving a combination of OCS and LAMAs at study start.

Below, the options of treatment escalation and the treatment escalations implemented in the studies are presented for the ZONDA, CALIMA and SIROCCO populations analysed by the company.

Table 5 shows the information provided in Module 4 A and the study documents on the maintenance treatments mentioned in the ACT for the populations analysed by the company. If available, information on patient history, study start and adjustments during the studies are presented.

Table 5: Maintenance treatments in the framework of the ACT in the mITT populations analysed by the company

Asthma maintenance treatment[a]	**ZONDA**		**CALIMA**		**SIROCCO**	
	Benralizumab	Placebo	Benralizumab	Placebo	Benralizumab	Placebo
	N = 73	N = 75	N_{SP} = 44	N_{SP} = 43	N_{SP} = 60	N_{SP} = 55
LAMAs[b] **or tiotropium**[c]**, n (%)**						
At study start						
LAMAs	21 (28.8)	21 (28.0)	27 (61.4)	24 (55.8)	25 (41.7)	22 (40.0)
tiotropium	18 (24.7[d])	19 (25.3[d])	24 (54.5[d])	21 (48.8[d])	24 (40.0[d])	20 (36.4[d])
In the course of the study[e]						
LAMAs						
dose increased	0 (0)	0 (0)	1 (2.3)	0 (0)	0 (0)	1 (1.8)
dose reduced	0 (0)	2 (2.7)	4 (9.1)	3 (7.0)	2 (3.3)	0 (0)
dose unchanged	21 (28.8)	19 (25.3)	22 (50.0)	21 (48.8)	23 (38.3)	21 (38.2)
initiated	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.8)
tiotropium bromide	18 (24.7)	19 (25.3)	ND	ND	ND	ND
tiotropium	0 (0)	2 (2.7)	ND	ND	ND	ND
In the patient history[f]						
tiotropium bromide	2 (2.7)	1 (1.3)	ND	ND	ND	ND
tiotropium	0 (0)	0 (0)	ND	ND	ND	ND
Omalizumab[g]**, n (%)**						
At study start	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
in the course of the study	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
in the patient history[h]	9 (12.3)	8 (10.7)	2 (4.5)	6 (14.0)	12 (20.0)	13 (23.6)
OCS, n (%)						
At study start	73 (100)	75 (100)	24 (54.5)	28 (65.1)	50 (83.3)	37 (67.3)
In the course of the study[e]						
dose increased	5 (6.8)	14 (18.7)	2 (4.5)	2 (4.7)	2 (3.3)	0 (0)
dose reduced	58 (79.5)	40 (53.3)	3 (6.8)	5 (11.6)	14 (23.3)	5 (9.1)
dose unchanged	10 (13.7)	21 (28.0)	19 (43.2)	21 (48.8)	34 (56.7)	32 (58.2)
initiated	0 (0)	0 (0)	0 (0)	1 (2.3)	0 (0)	2 (3.6)

(continued)

Table 5: Maintenance treatments in the framework of the ACT in the mITT populations analysed by the company (continued)

a: According to Module 4 A, medications were rated as maintenance treatment if the reason for the treatment was recorded as "investigated disease" in the CRF. This differentiates maintenance treatment from the treatment for "protocol-defined exacerbation of the investigated disease" also recorded in the CRF.
b: Information on LAMAs are presented as additional information because the information provided on tiotropium was incomplete.
c: The CSR differentiates between tiotropium bromide and tiotropium. Patients may have been recorded in both categories (multiple answers).
d: Institute's calculation.
e: Initiated before or at randomization and continued after randomization, or initiated after randomization.
f: Completed before or at randomization.
g: In the studies ZONDA, SIROCCO and CALIMA, omalizumab was neither allowed within 4 months or 5 half-lives before the informed consent was signed, nor as concomitant treatment.
h: For omalizumab, the CSR provided 2 pieces of information with different sample sizes: "discontinued before or at randomization" and "patient history". The table shows the information provided on "patient history" as larger sample sizes are shown here.
ACT: appropriate comparator therapy; CFR: case report form; CSR: clinical study report: LAMA: long-acting muscarinic antagonist; mITT: modified intention-to-treat; n: number of patients with the respective medication; N: number of randomized patients; N_{SP}: number of patients in the subpopulation analysed by the company; ND: no data; OCS: oral corticosteroid; RCT: randomized controlled trial

Treatment escalation with tiotropium

Tiotropium was an option for treatment escalation within the G-BA's ACT. In the studies presented, tiotropium was only allowed as continuation of the ongoing pretreatment without change in the course of the study during the treatment phase.

In the populations analysed by the company, 25.3% (ZONDA), 48.8% (subpopulation of CALIMA) and 36.4% (subpopulation of SIROCCO) in the placebo arm were receiving tiotropium at study start. The company's documents showed for the total populations that the proportion of patients who discontinued tiotropium treatment before or at randomization was below 2% (Table 13, Appendix A of the full dossier assessment). There was no corresponding information on the analysed subpopulations of the studies CALIMA and SIROCCO (Table 5).

The company did not present separate data for tiotropium on the adjustment of the medication in the course of the study, but on the administration of LAMAs overall. However, it could be inferred from the study documents that tiotropium constituted a large proportion of the LAMAs used in the subpopulation, i.e. 88.1% (ZONDA), 88.2% (subpopulation of CALIMA) and 93,6% (subpopulation of SIROCCO). The drugs aclidinium and glycopyrronium, which are not approved for asthma, were used as further LAMAs. In the course of the study, escalation of LAMA treatment (dose increase or initiation) in the placebo arm was performed in none of the patients in the ZONDA study and in the analysed subpopulation of the CALIMA study, and in 2 patients of the subpopulation of the SIROCCO study (see Table 5).

The number of analysed patients for whom tiotropium was an option as treatment escalation was unclear. The company did not address this issue. However, since the inclusion criteria of

the studies ZONDA, CALIMA and SIROCCO were well covered by the approval of tiotropium [15], it can be assumed that treatment with tiotropium would have been suitable for a large proportion of the patients requiring additional asthma control medication.

Treatment escalation with omalizumab

Omalizumab can be used in patients with IgE-mediated pathogenesis of asthma for treatment escalation and was also a treatment option of the ACT. According to the G-BA, the criteria of the approval and of the note on treatment for omalizumab have to be completely fulfilled [4,5]. In the studies presented, omalizumab was not allowed in the 4 months or 5 half-lives before the start of the study and during the studies. Hence, this treatment option was not available to the patients in the framework of the studies.

The number of analysed patients for whom omalizumab would have been an option as treatment escalation could not be inferred from the study documents. In the placebo arms, 10.7% (ZONDA), 14.0% (subpopulation of CALIMA) and 23.6% (subpopulation of SIROCCO) of the patients had already received previous treatment with omalizumab (Table 5). The Summary of Product Characteristics (SPC) and the note on treatment for omalizumab list a number of cumulative criteria that have to be fulfilled for a prescription [4,5]. These include IgE-mediated asthma, at least 2 severe asthma exacerbations treated with systemic corticosteroids despite high-dose ICS plus LABAs, reduced lung function, as well as frequent documented symptoms during the day or nocturnal awakening. The SPC of omalizumab lists dosage information from a baseline IgE of > 30 international units [IU]/mL [4]; according to the note on treatment, omalizumab should be prescribed in IgE levels between 76 and 1500 IU/mL [5]. According to the company's additional analyses, the proportion with IgE ≥ 30 IU/mL in the placebo arms was 87.0% (SIROCCO, 1 patient without information) and 90.7% (CALIMA) in the subpopulations analysed by the company. Information on IgE levels for the ZONDA study could not be inferred from the study documents. Based on the information provided on patient histories, the inclusion criteria and information on IgE titres in the studies, it can be assumed that a relevant proportion of the analysed patient population in the placebo arms would have been eligible for omalizumab.

Treatment escalation with OCS

OCS are another option for treatment escalation within the G-BA's ACT. In the studies CALIMA and SIROCCO, OCS were only allowed as continuation of the ongoing pretreatment without change in the course of the study during the treatment phase.

At study start, 65.1% (CALIMA) and 67.3% (SIROCCO) of the patients in the placebo arm of the subpopulation analysed by the company were receiving OCS maintenance treatment. Escalation of OCS treatment in the course of the study (dose increase or initiation) was only performed in 3 (7.0%) patients in the placebo arm of the subpopulation of the CALIMA study, and in only 2 (3.6%) patients in the placebo arm of the subpopulation of the SIROCCO study (Table 5). It can therefore be assumed that a relevant proportion of the analysed patient

populations requiring additional asthma control medication would have been eligible for escalation with OCS in the placebo arm.

Since all patients in the ZONDA study were receiving OCS as maintenance treatment already at study start, OCS as escalation treatment was only available for these patients in the sense of a dose increase. According to the information provided by the company in Module 4 A, dosing was increased in 14 (18.7%) of the patients in the placebo arm (see Table 5). This information is not meaningfully interpretable as escalation of the maintenance treatment, however, because the study patients' OCS asthma therapy was reduced according to a fixed regimen. OCS increase in the OCS reduction phase was only possible if the criteria for asthma control defined in the study protocol were not met. It was therefore unclear whether the patients with dose increase actually received escalation of their maintenance treatment or only returned to a higher dose due to poor asthma control in the OCS reduction phase.

Individual treatment adjustments not possible in the framework of the appropriate comparator therapy and not implemented for the individual patients

The company argued that individual treatment adjustments were possible and were used on an individual basis in the study populations used for the benefit assessment. This cannot be inferred from the study documents. According to the information provided in the protocols of the 3 studies included on concomitant treatments that were disallowed/restricted, maintenance treatments (including ICS plus LABAs, tiotropium and OCS) were only allowed if they had already been taken before study start and were continued without changes during the studies. An exception were OCS in the ZONDA study, where all patients were taking OCS at study start and where OCS reduction was a primary outcome. Omalizumab was not allowed in any of the studies, neither at the start of the studies, nor during the studies. The study documents contained the information that a change was possible if this was deemed medically reasonable by the investigator only for ICS plus LABAs, but not for the other maintenance treatments in the framework of the ACTs. Hence, the study protocols did not provide for individual treatment adjustments in the framework of the ACT.

Summary

In summary, the data presented by the company were unsuitable for the derivation of the added benefit of benralizumab. On the one hand, the company's approach – contrary to its intention – did not ensure the consideration of patients for whom no further escalation options of their ongoing treatments were available. On the other, the escalation options possible in accordance with the ACT were not implemented in the placebo arms of the 3 studies. The results presented were therefore not interpretable.

2.3.3 Further limitations of the presented studies

The studies presented by the company had the following additional limitations. These had no consequences for the assessment, however, as the studies used and the data presented by the company were not relevant for the assessment for the reasons described above.

- Benralizumab is approved for patients with severe eosinophilic asthma inadequately controlled despite high-dose ICS plus LABAs. All 3 RCTs used by the company defined the high dose of ICS according to the GINA recommendation and local regulations. According to the GINA recommendation, the high dose of ICS as fluticasone propionate is > 500 µg/day [3]. The company did not present information on the local regulations in the respective countries of the studies. However, it could be inferred from the study documents that an unclear number of patients with treatment below the threshold of 500 µg/day fluticasone propionate equivalent were included. The inclusion of these patients was inadequate. The mean ICS dose of the patients included by the company was > 1000 µg/day fluticasone propionate equivalent, however, and thus far above the 500 µg/day threshold for a high dose.
- The studies used by the company did not have a uniform definition for the criterion of eosinophilia for the severe eosinophilic asthma according to the therapeutic indication. In accordance with the inclusion criteria for the ZONDA study, the company defined eosinophilic asthma with a threshold value of eosinophils ≥ 150/µL for this study, whereas it used a threshold value of eosinophils ≥ 300/µL for the subpopulations of the studies SIROCCO and CALIMA used by the company. The company did not justify its use of different criteria. The threshold value of eosinophil concentration in the blood for eosinophilia is not clearly defined in the German S2k guideline [14]. The German National Care Guideline for asthma in its 2018 consultation version considers that detection of more than 300 eosinophils/µL blood at least twice in the last 12 months outside exacerbations and without medication with systemic corticosteroids is necessary for the diagnosis of severe eosinophilic asthma in patients with severe asthma. It must be taken into account that treatment with systemic corticosteroids may reduce the number of eosinophilic granulocytes in the blood [16]. The SPC of benralizumab does not cite a threshold value for eosinophils for the definition of eosinophilic asthma.
- Overall, 35.8% (ZONDA), 41.4% (CALIMA) and 47.8% (SIROCCO) of the patients in the mITT populations analysed by the company were being treated with montelukast at study inclusion and continued this treatment during the studies. In Germany, montelukast is not approved for severe asthma so that the use of this drug in the study patients was not in compliance with the approval [17]. Hence, the inclusion of these patients was inadequate. However, the company conducted post-hoc subgroup analyses by concomitant medication with montelukast at study start to be able to analyse a possible effect modification.

2.4 Results on added benefit

The company provided no suitable data for the assessment of the added benefit of benralizumab in comparison with the ACT as an add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose ICS plus LABAs. This resulted in no hint of an added benefit of benralizumab in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

The result of the assessment of the added benefit of benralizumab in comparison with the ACT is shown in Table 6.

Table 6: Benralizumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting beta-agonists	Individual treatment escalation[b] ▪ of high-dose inhaled corticosteroids (ICS) and long-acting bronchodilators (LABAs) with tiotropium and possibly oral corticosteroids (OCS)[c], or ▪ in case of IgE-mediated pathogenesis of asthma, possibly omalizumab[d] in addition to high-dose ICS and LABAs and possibly OCS[c], or ▪ possibly of the high-dose ICS and LABAs with OCS[c, e]	Added benefit not proven

a: Presentation of the ACT specified by the G-BA.
b: The Global Initiative for Asthma (GINA) graded scheme is to be taken into account. It is assumed that the therapeutic indication of benralizumab is represented in step 4 to step 5. Placebo or the unchanged continuation of inadequate treatment of severe asthma does not comply with an ACT in severe refractory eosinophilic asthma if the option for treatment escalation is still available. The therapeutic indication also comprises patients for whom there is no further escalation option for their ongoing treatment, however.
c: OCS should only be used on a short-term basis and in their lowest effective dose. It should be ensured in the OCS treatment of asthma that the OCS dosage does not permanently exceed the Cushing threshold if possible. Treatment of exacerbations must be differentiated from this.
d: Omalizumab can be used as an ACT option only in patients who completely fulfil the criteria of the approval and of the note on treatment for omalizumab.
e: In comparison with the other drugs mentioned – if these are suitable – treatment with OCS is not considered the preferred treatment option.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; ICS: inhaled corticosteroids; IgE: immunoglobulin E; LABA: long-acting beta-2 agonist; OCS: oral corticosteroids

This assessment deviates from that of the company, which derived an indication of a considerable added benefit on the basis of the data of the studies ZONDA, CALIMA and SIROCCO it presented in Module 4 A.

2.6 List of included studies

Not applicable as the company presented no relevant data for the benefit assessment.

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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