IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A16-03

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Mepolizumab – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 April 2016). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Mepolizumab – Benefit assessment according to §35a Social Code Book V

Commissioning agency:
Federal Joint Committee

Commission awarded on:
29 January 2016

Internal Commission No.:
A16-03

Address of publisher:
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice:

No advisor on medical and scientific questions was available for the present dossier assessment.

IQWiG employees involved in the dossier assessment[2]:

- Ana Liberman
- Anna Catharina Brockhaus
- Wolfram Groß
- Ulrike Lampert
- Miriam Luhnen
- Katrin Nink
- Beate Wieseler
- Min Zhou

Keywords: mepolizumab, asthma, benefit assessment

[2] Due to legal data protection regulations, employees have the right not to be named.

Table of contents

List of tables[3]

Page

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

List of figures

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ACQ	Asthma Control Questionnaire
CSR	clinical study report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GINA	Global Initiative for Asthma
ICS	inhaled corticosteroid
IgE	immunoglobulin E
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LABA	long-acting bronchodilator
OCS	oral corticosteroid
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug mepolizumab. 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 29 January 2016.

Research question

The aim of this report was to assess the added benefit of an add-on treatment with mepolizumab in comparison with the appropriate comparator therapy (ACT) in adult patients with severe refractory eosinophilic asthma.

The G-BA specified the following ACT:

Individually optimized treatment escalation

- of moderate-to-high-dose inhaled corticosteroids (ICS) and of long-acting bronchodilators (LABAs), if applicable with oral corticosteroids (short-term) in their lowest effective dose
- or with tiotropium
- or, if applicable in immunoglobulin E (IgE)-mediated pathogenesis of the asthma, omalizumab in addition to high-dose ICS and LABAs and, if applicable, to oral corticosteroid treatment

The approvals of the drugs and the graded scheme of the Global Initiative for Asthma (GINA) were to be taken into account under the assumption that the therapeutic indication of mepolizumab is represented by the steps 4 to 5 (according to GINA).

The G-BA additionally specified that placebo or unchanged continuation of inadequate treatment of severe asthma, if the option for treatment escalation is still available, does not comply with the ACT.

The company concurred with the G-BA's specification. The present assessment was conducted in comparison with the G-BA's ACT.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier. A minimum study duration of 24 weeks was defined for the derivation of the added benefit.

Results

The data presented by the company were unsuitable to draw conclusions on the added benefit of mepolizumab in comparison with the ACT. This applies both to the studies of direct comparisons and to the indirect comparison presented and the further documents additionally presented.

Direct comparison

The company included 2 RCTs for the assessment of the added benefit of mepolizumab in adult patients with severe refractory eosinophilic asthma: the study MENSA (MEA115588) and the study SIRIUS (MEA115575). Both studies were not relevant for the present assessment.

Both studies were randomized, double-blind placebo-controlled studies with a treatment duration of 32 weeks (MENSA) and 24 weeks (SIRIUS). Patients aged 12 years or older with severe refractory eosinophilic asthma were included in the studies. The patients were randomly assigned to treatment with mepolizumab or placebo, in each case in addition to their ongoing asthma maintenance treatment.

Besides the study medication, the patients in the MENSA study were to continue their ongoing maintenance treatment of ICS and LABA and, if applicable, further treatments until the end of the study. Additional asthma medication was only allowed if these had been taken regularly for at least 3 months before randomization. Maintenance treatment with oral corticosteroids (OCS) was allowed.

In the SIRIUS study, in contrast, all patients were already receiving regular OCS treatment in addition to high-dose ICS and further control medication at enrolment. The aim of the SIRIUS study was to investigate the effect of mepolizumab 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 effective dosage. After randomization and the start of the study treatment, the OCS dose was gradually decreased further. In the SIRIUS study as well, additional asthma medication, apart from rescue medication, was only allowed if this had been regularly taken for at least 3 months before randomization.

Appropriate comparator therapy not implemented in the studies presented

The ACT was not adequately implemented in the 2 studies because the required treatment escalations were not fully exhausted before or during the studies. In both studies, no treatment escalation at the start of the study was envisaged in the control arm besides the additional use of placebo. In the course of the study, administration of as-needed medication was possible in both arms, but initiation or escalation of a control medication was not envisaged. However, different options for treatment escalation would have existed for the patients included. The studies MENSA and SIRIUS were therefore unsuitable for the assessment of the added

benefit of mepolizumab in comparison with the ACT in the form of individually optimized treatment escalation with different options named by the G-BA.

Indirect comparison

The company presented an adjusted indirect comparison for the assessment of the added benefit in comparison with omalizumab. Omalizumab is part of the ACT specified by the G-BA that is an option for patients with additional IgE-mediated pathogenesis of the asthma. The common comparator was placebo in addition to ongoing asthma treatment.

The company's study pool comprised 3 RCTs: the MENSA study on the mepolizumab side, and the studies INNOVATE and Chanez 2010 on the omalizumab side. However, the indirect comparison presented was not relevant for the assessment of the added benefit of mepolizumab in comparison with the ACT omalizumab because the studies on the omalizumab side were unsuitable for answering the present research question.

Study Chanez 2010 had a treatment duration of 16 weeks and therefore did not fulfil the required minimum study duration of 24 weeks.

The INNOVATE study was not relevant for the assessment because the included patients only partly concurred with the present research question. In the indirect comparison of mepolizumab with omalizumab, 2 drugs were compared with each other that are approved for different patient populations. Omalizumab is approved for patients with severe persistent allergic asthma or with the IgE-mediated pathogenesis of asthma. Mepolizumab is approved for the treatment of severe refractory eosinophilic asthma.

On the mepolizumab side, the company analysed a subpopulation suitable for the comparison for its MENSA study: patients who fulfil the prerequisites both of the therapeutic indication of mepolizumab and of the therapeutic indication and of the note on treatment for omalizumab. The company could not conduct such a selection on the omalizumab side of the comparison because only full publications without individual patient data were available to the company for the INNOVATE study and for the other studies on the omalizumab side. Hence the included patients only concurred with the approval of omalizumab, but not with the one of mepolizumab.

Further investigations

Under further investigations, the company presented the studies MEA115661 and DREAM. It did not use them for the assessment of the added benefit, however, but only to investigate the transferability of the study results of the studies MENSA and SIRIUS to a longer period of time. Since the studies MENSA and SIRIUS were not used for the assessment, however, the studies presented in the section of further investigations were not relevant.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

Table 2 presents a summary of the extent and probability of the added benefit of mepolizumab.

Table 2: Mepolizumab – extent and probability of added benefit

Therapeutic indication	Appropriate comparator therapy[a]	Extent and probability of added benefit
Add-on treatment in severe refractory eosinophilic asthma in adult patients	Individually optimized treatment escalation ▪ of moderate-to-high-dose inhaled corticosteroids (ICS) and of long-acting bronchodilators (LABAs), if applicable with oral corticosteroids (short-term) in their lowest effective dose ▪ or with tiotropium ▪ or, if applicable in immunoglobulin E (IgE)-mediated pathogenesis of the asthma, omalizumab in addition to high-dose ICS and LABAs and, if applicable, to oral corticosteroid treatment	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The G-BA decides on the added benefit.

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

2.2 Research question

The aim of this report was to assess the added benefit of an add-on treatment with mepolizumab in comparison with the ACT in adult patients with severe refractory eosinophilic asthma.

The G-BA specified the following ACT:

Individually optimized treatment escalation

- of moderate-to-high-dose ICS and of LABAs, if applicable with oral corticosteroids (short-term) in their lowest effective dose
- or with tiotropium
- or, if applicable in IgE-mediated pathogenesis of the asthma, omalizumab in addition to high-dose ICS and LABAs and, if applicable, to oral corticosteroid treatment

The approvals of the drugs and the graded scheme of GINA were to be taken into account under the assumption that the therapeutic indication of mepolizumab is represented by the steps 4 to 5 (according to GINA) [3].

The G-BA additionally specified that placebo or unchanged continuation of inadequate treatment of severe asthma, if the option for treatment escalation is still available, does not comply with the ACT.

The company concurred with the G-BA's specification.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier. A minimum study duration of 24 weeks was defined for the derivation of the added benefit. This deviates from the company's approach, which used studies with a minimum duration of 12 weeks. In addition, deviating from the company's specification on the indirect comparison, single-blind or open-label studies were also relevant for the assessment (see Section 2.7.2.1 of the full dossier assessment).

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 lists on mepolizumab (status: 2 November 2015)
- bibliographical literature search on mepolizumab (last search on 6 November 2015)
- search in trial registries for studies on mepolizumab (last search on 24 November 2015)
- bibliographical literature search on the ACT (last search on 6 November 2015)

- search in trial registries for studies on the ACT (last search on 24 November 2015)

To check the completeness of the study pool:

- search in trial registries for studies on mepolizumab (last search on 11 February 2016)
- search in trial registries for studies on the comparator therapy omalizumab for the indirect comparison (last search on 18 February 2016)

No additional relevant study was identified from the check.

The data identified by the company from the steps of information retrieval mentioned were unsuitable for the derivation of conclusions on the added benefit of mepolizumab versus the ACT. This applies both to the studies of direct comparisons and to the indirect comparison presented and the further documents additionally presented. The study pool of the company is described below, and the reasons why the respective data were unsuitable for the derivation of the added benefit are explained.

Direct comparison

The company identified 2 RCTs for the assessment of the added benefit of mepolizumab in adult patients with severe refractory eosinophilic asthma: the study MENSA (MEA115588) [4] and the study SIRIUS (MEA115575) [5], hereinafter referred to as "MENSA" and "SIRIUS".

Study MENSA

The MENSA study was a multicentre, randomized, double-blind, placebo-controlled study with a 32-week treatment duration. Patients aged 12 years or older with severe refractory eosinophilic asthma who additionally had required regular treatment with high-dose ICS and further control medication for at least 12 months, and who additionally had had at least 2 exacerbations requiring OCS treatment in the year before the study were enrolled. These were step 4 and step 5 patients according to the GINA recommendations [3]. The aim of the study was to compare the efficacy of mepolizumab in dosages of 75 mg IV and 100 mg SC with placebo every 4 weeks.

The patients were to continue their ongoing maintenance treatment besides the study medication until the end of the study. Additional asthma medication was only allowed if these had been taken regularly for at least 3 months before randomization. OCS maintenance treatment was allowed. Further information on the MENSA study can be found in Table 8 and Table 9 in Appendix A of the full dossier assessment.

Study SIRIUS

The SIRIUS study was a multicentre, randomized, double-blind, placebo-controlled study with a 24-week treatment duration. Patients aged 12 years or older with severe refractory eosinophilic asthma were included in the study. All patients were already receiving regular

OCS treatment in addition to high-dose ICS and a further control medication at enrolment, thus concurring with step 5 of the GINA recommendations [3]. The aim of the SIRIUS study was to investigate the effect of mepolizumab in a dosage of 100 mg SC in comparison with placebo on an intended OCS dose reduction. Mepolizumab and placebo were each administered in addition to ongoing asthma treatment.

The patients underwent an optimization phase of 3 to 8 weeks before randomization. In this phase, there was a weekly stepwise reduction of OCS treatment to the lowest dosage that was still effective. If symptoms worsened after a dose reduction (increase in the Asthma Control Questionnaire [ACQ]-5 score by ≥ 0.5) or exacerbation occurred, the OCS dose was returned to the prior dose level. Titration of the OCS dosage was made based on a schedule planned in the protocol.

After the optimization phase, only those patients were randomized to the treatment arms who were able to remain on the same OCS dosage for at least 2 weeks prior to randomisation and who fulfilled further randomization criteria regarding asthma symptoms.

After randomization, the patients received a first dose of their blinded study treatment – mepolizumab or placebo – before further monthly gradual OCS dose reductions were continued. These were also based on a specified titration plan. Subsequently, the study patients were to remain on their last OCS dosage in addition to maintenance treatment and study medication for 4 weeks.

During the entire study, additional asthma medication, apart from rescue medication, was only allowed if this had been regularly taken for at least 3 months before randomization. Further information on the SIRIUS study can be found in Table 8 and Table 9 in Appendix A of the full dossier assessment.

Additional analyses for the benefit assessment

For both studies, the company analysed a subpopulation comprising 94% (MENSA) and 97% (SIRIUS) of the study population. The company excluded few patients who did not concur with the inclusion criteria of the present research question, such as non-adult patients or patients who were not yet receiving a combination therapy of ICS and LABA. This approach of the company was adequate.

Appropriate comparator therapy not implemented in the studies presented

The studies MENSA and SIRIUS were unsuitable for the assessment of the added benefit of mepolizumab in comparison with the ACT in the form of individually optimized treatment escalation with different options named by the G-BA. The ACT was not adequately implemented in the 2 studies because the required treatment escalations were not fully exhausted before or during the studies. In both studies, no treatment escalation at the start of the study was envisaged in the control arm besides the additional use of placebo. In the course of the study, administration of as-needed medication was possible in both arms, but initiation

or escalation of a control medication was not envisaged. Hence the ACT of individually optimized treatment escalation was not implemented.

This deviates from the company's assessment that all options for treatment escalation according to the ACT had already been exhausted before and also during the study in the patients in both studies, and that therefore the patients were not continuing an inadequate treatment in the studies, but that they were receiving the maximum possible treatment. This assessment was not followed and the situation for the different treatment options of the ACT is explained below. The treatments specified by the G-BA are cited in the GINA treatment regimen for treatment steps 4 and 5 [3].

Options for treatment escalation in the MENSA study

Treatment escalation using dose increase of ICS and LABA

One option of treatment escalation according to the G-BA's ACT would be a dose increase of the ICS and LABA. The company claimed that fulfilling the inclusion criteria – ICS dose at enrolment ≥ 880 µg/day fluticasone propionate or equivalent, or highest approved maintenance dose in the respective country for the ICS/LABA fixed combination – the option of dose escalation was already exhausted for all patients.

The company's assessment was shared regarding the dose escalation of long-term ICS maintenance treatment. According to the approval, however, short-term ICS dose escalation, e.g. of up to 2000 µg/day for fluticasone, is possible in deterioration of symptoms [6]. This type of treatment escalation was not envisaged in the MENSA study and it was not clear in how far it was an option for the study patients after individual consideration. It was therefore assumed that this option of temporary treatment escalation was not used in the MENSA study.

Treatment escalation using additional administration of OCS

A further option of treatment escalation according to the G-BA's ACT would be the initiation of a (temporary) systemic maintenance treatment with OCS. OCS were generally allowed as concomitant treatment in the MENSA study. According to the study description, concomitant medication (such as theophylline and antileukotrienes) was only allowed if it had been taken regularly for the 3 months before randomization. In addition, OCS maintenance treatment was allowed, according to the study documents. It remained unclear whether only continuation of ongoing maintenance treatments with OCS was allowed or whether the new initiation of OCS treatment in the sense of a maintenance treatment was also possible.

About 25% of the patients in the MENSA study were receiving OCS maintenance treatment at enrolment. The proportion of patients with OCS use increased in the course of the treatment phase. However, there was no information whether the OCS was used as maintenance treatment or as exacerbation treatment in these cases. The company itself attributed this increase to the treatment of exacerbations and explicitly described that the administration of OCS for the treatment of exacerbations was allowed. On the other hand, it described in the

inclusion criteria for studies for the indirect comparison (in Section 4.3.2.1.1.2) that in the MENSA study, there was stable OCS dosage during the study.

Under consideration of all available information it therefore remained unclear whether treatment escalation with initiation of an OCS maintenance treatment was possible in the study. The only comprehensible aspect was that OCS was available for short-term treatment of exacerbations.

Treatment escalation using additional administration of tiotropium

Tiotropium has been approved since September 2014 as long-term treatment of severe asthma in addition to high-dose ICS and LABA [7], and therefore is an option for treatment escalation within the ACT. The company itself pointed out that tiotropium was approved for the therapeutic indication of asthma only after completion of the MENSA study. It stated that continuation of an ongoing asthma maintenance treatment was allowed in both studies (MENSA and SIRIUS) and inferred from this that there were no limitations regarding specific medications such as tiotropium. Instead, regarding tiotropium, the treating investigators had all the options for optimum treatment of the patients. This statement of the company could not be followed.

In the MENSA study, 16% of the placebo patients and 17% of the mepolizumab patients were receiving tiotropium as concomitant medication at enrolment and were able to continue this treatment until the end of the study. Treatment escalation with tiotropium in the framework of the study was not possible according to the planning of the study, however. Only few patients – at most 6 patients in the placebo arm and 1 patient in the mepolizumab arm – started tiotropium treatment during the study. Since the approval of tiotropium covered the inclusion criteria of the MENSA study well, however, it was assumed that treatment with tiotropium would have been suitable for a large proportion of the study patients requiring additional asthma control medication.

Treatment escalation using additional administration of omalizumab

In the MENSA study, administration of omalizumab was not allowed during the study. Patients who had taken omalizumab less than 130 days before the start of the study were also not included in the study. Hence this treatment option was not available to the patients at all. The company justified this by claiming that not enough information on possible interactions was available for the concomitant administration of different monoclonal antibodies. Irrespective of this argument, however, the exclusion of omalizumab means that patients in the comparator group did not have this option of treatment escalation according to the ACT.

It could be assumed, however, that patients for whom omalizumab would have been an adequate treatment escalation were included in the MENSA study. Even though already 13% of the MENSA study patients had received omalizumab in the past, and 75% of them had discontinued this treatment due to ineffectiveness, it remained unclear for how many further study patients omalizumab could have represented an adequate treatment escalation.

According to information provided by the company itself (in Module 4 A, Section 4.3.2.1.2), about one quarter of the patients included would be eligible for omalizumab treatment.

Study SIRIUS

The reasons for inadequate implementation of the individual options of the ACT in the MENSA study stated above largely also apply to the SIRIUS study. Deviating from the MENSA study however, all patients in the SIRIUS study, besides high-dose ICS and LABA, had already received stable OCS treatment for at least 6 months at enrolment. Individually optimized escalation options of the comparator therapy for these patients would have particularly consisted of additional administration of omalizumab or tiotropium and dose adjustment of OCS.

As already described for the MENSA study, omalizumab and tiotropium were not available as options for treatment escalation in the SIRIUS study. The company described that 33% of the study patients had a history of omalizumab treatment and that a large proportion of them (82%) had discontinued treatment due to lack of effectiveness. It could be assumed, however, that patients suitable for omalizumab (e.g. omalizumab-naive patients) and particularly patients for whom tiotropium would be an option, were included in the SIRIUS study.

In addition, the SIRIUS study reflected a very specific treatment situation of patients with severe asthma because it primarily aimed at the dose reduction of OCS. The patients in the study first underwent an optimization phase, in which they were titrated in weekly steps to the lowest still effective OCS dose. Subsequently, they were randomized to treatment with mepolizumab or placebo, followed by a further phase of OCS reduction at an interval of 4 weeks. Reduction of the OCS dose was envisaged in both adjustment phases. Returning to a higher dose was possible if asthma symptoms deteriorated. Hence the patients in the SIRIUS study received no escalation in the control arm, but a reduction of their asthma treatment instead.

In contrast, the company stated that individually optimized treatment escalation was possible in the SIRIUS study at any time and also took place if required. Regarding the administration of OCS it added that all SIRIUS patients received OCS and that all patients had the option of OCS dose escalation for the treatment of exacerbations in the course of the study. This assessment, particularly regarding the escalation options of the maintenance treatment, was not comprehensible for the reasons described above and was reflected neither in the design nor in the documentation of the concomitant medication. The information provided in the clinical study report (CSR) also showed that patients principally still had options for treatment escalation. According to the CSR, patients who did not participate in the extension phase after the end of the study were to receive a suitable treatment alternative at the investigator's discretion, if required.

Summary

The ACT was not implemented in studies MENSA and SIRIUS because no treatment escalation was conducted in the control arm at the start of the treatment. No corresponding

options for an escalation in the control arm were available in the further course of the study, either. However, different options for escalation would have existed for the patients included. Hence the 2 studies MENSA and SIRIUS were not relevant for the present assessment.

Study pool: indirect comparison

The company presented an adjusted indirect comparison for the assessment of the added benefit of mepolizumab in comparison with omalizumab. Omalizumab is part of the ACT specified by the G-BA that is an option for patients with additional IgE-mediated pathogenesis of the asthma. The company presented this indirect comparison because omalizumab was not allowed in its studies of direct comparisons. The common comparator was placebo in addition to ongoing asthma treatment (see Section 2.7.2.3.2 of the full dossier assessment).

The company's study pool comprised 3 RCTs: On the mepolizumab side, it included one of its pivotal approval studies, the MENSA study. On the omalizumab side, it included the studies INNOVATE [8] and Chanez 2010 [9] (see Figure 1). In addition, it used the study EXTRA [10] for sensitivity analyses. The study characteristics are further described in Table 10 and Table 11 in Appendix B of the full dossier assessment.

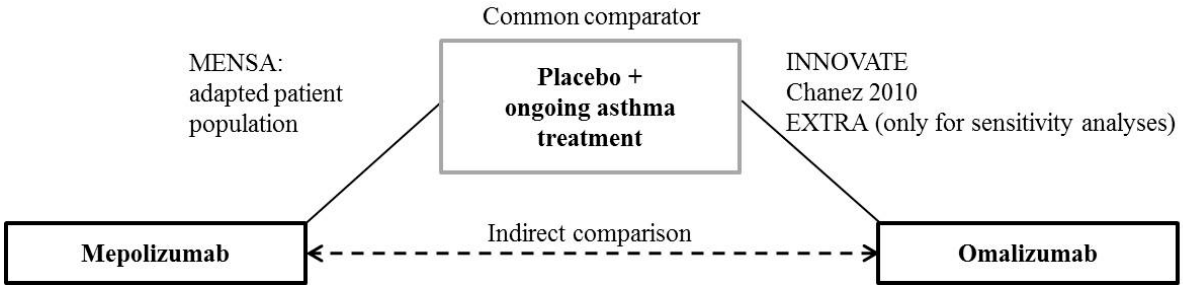

Figure 1: Study pool of the company for the indirect comparison between mepolizumab and omalizumab

The company analysed a subpopulation suitable for the comparison for its MENSA study: patients who fulfil the prerequisites both of the therapeutic indication of mepolizumab and of the therapeutic indication and of the note on treatment for omalizumab.

The company's assessment regarding the relevance of the studies presented was not shared. The studies Chanez 2010 and INNOVATE (as well as the EXTRA study for sensitivity analyses) identified by the company were unsuitable for conducting an indirect comparison between mepolizumab and omalizumab.

Study Chanez 2010 had a treatment duration of 16 weeks and therefore did not fulfil the required minimum study duration of 24 weeks and was therefore not used for the assessment (for explanations regarding the minimum study duration, see Section 2.7.2.1 of the full dossier assessment).

The INNOVATE study was not relevant for the assessment because the included patients only partly concurred with the present research question. In the indirect comparison of mepolizumab with omalizumab, 2 drugs were compared with each other that are approved for different patient populations. Omalizumab is approved for patients with severe persistent allergic asthma or with the IgE-mediated pathogenesis of asthma [11]. Mepolizumab is approved for the treatment of severe refractory eosinophilic asthma [12].

The company addressed this problem by identifying those patients in its MENSA study for whom treatment with both drugs was an option. The company could not conduct such a selection on the omalizumab side of the comparison because only full publications without individual patient data were available to the company. Hence the INNOVATE study did not cover the research question of the present assessment because the included patients only concurred with the approval of omalizumab, but not with the one of mepolizumab. This also applied to the remaining studies on the omalizumab side (Chanez 2010 and EXTRA) as well as to the unblinded study Bousquet 2011 [13] initially also identified, which otherwise would have fulfilled all inclusion criteria, but was also not relevant for the present assessment (see Section 2.7.2.3.1 of the full dossier assessment).

The proportion of patients in the studies on the omalizumab side for whom treatment with mepolizumab was an option was unknown. Nonetheless, the company used the studies on the omalizumab side for the indirect comparison. The company itself described in the dossier that it was unable to select the relevant population but provided no further arguments why these populations might still be suitable for the present research question.

However, the company itself investigated a cohort of patients with severe asthma in its IDEAL study for their eligibility for treatment options. In Module 3 A of its dossier, it also derived information from this study for the estimation of the target populations for the treatment [14,15]. It could be inferred from the study that only part of the patients with IgE-mediated pathogenesis of asthma (approval of omalizumab) had eosinophilic inflammation (approval of mepolizumab) and vice versa:

- 38.6% of the patients for whom treatment with mepolizumab was an option were eligible for treatment with omalizumab.
- 33.9% of the patients for whom treatment with omalizumab was an option were eligible for treatment with mepolizumab.

Assuming that the distribution of patient characteristics in the INNOVATE study was similar to the one in the IDEAL study, only about one third of the patients included in the INNOVATE study would have been equally eligible for treatment with both drugs. This proportion was insufficient, however, to use the total population of the study for the present research question, and, in addition, no sufficient similarity of the patient populations on both sides of the comparison could be assumed.

Moreover, the difference between the study populations was notable in the different frequency of exacerbations in the year prior to screening, which indicates that the severity of the disease possibly differed between the patients (see Table 3).

Table 3: Number of exacerbations in the previous year in the studies MENSA and INNOVATE

Study **Population** **Treatment arm**	**N**	**Number of exacerbations 12 months[a] before screening** **Mean (SD)**
MENSA		
Relevant subpopulation[b]		
Mepolizumab 100 mg SC	47	4.3 (3.3)
Placebo	46	4.0 (3.3)
INNOVATE		
Total study population		
Omalizumab	209	2.6 (1.6)
Placebo	210	2.4 (1.1)

a: In the INNOVATE study, the number of exacerbations in the last 14 months before screening was recorded.
b: The subpopulation includes patients who are eligible both for treatment with mepolizumab and for treatment with omalizumab.
N: number of patients treated or relevant subpopulation; SD: standard deviation

Study pool: further investigations

Besides the direct and indirect comparison used by the company for the derivation of the added benefit, the company presented additional evidence in the Section "Further investigations".

The company did not use the presented studies MEA115661 [16] and DREAM [17] for the assessment of the added benefit, but only used them to investigate the transferability of the study results of the studies MENSA and SIRIUS to a longer period of time. Since the studies MENSA and SIRIUS were not used for the assessment, however, the studies presented in the section of further investigations were not relevant (see Section 2.7.2.3.2 of the full dossier assessment).

2.4 Results on added benefit

No suitable data were available for assessing the added benefit of mepolizumab, neither in a direct comparison nor in an indirect comparison. Hence the added benefit of mepolizumab versus the ACT is not proven.

This deviates from the assessment of the company, which derived an added benefit from the studies it included.

2.5 Extent and probability of added benefit

The result of the assessment of the added benefit of mepolizumab in comparison with the ACT is shown in Table 4.

Table 4: Mepolizumab – extent and probability of added benefit

Therapeutic indication	**Appropriate comparator therapy**[a]	**Extent and probability of added benefit**
Add-on treatment in severe refractory eosinophilic asthma in adult patients	Individually optimized treatment escalation ▪ of moderate-to-high-dose inhaled corticosteroids (ICS) and of long-acting bronchodilators (LABAs), if applicable with oral corticosteroids (short-term) in their lowest effective dose ▪ or with tiotropium ▪ or, if applicable in IgE-mediated pathogenesis of the asthma, omalizumab in addition to high-dose ICS and LABAs and, if applicable, to oral corticosteroid treatment	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

This assessment deviates from the company's approach, which derived the following added benefit.

The company derived proof of considerable added benefit of mepolizumab in comparison with the ACT for the total population (all adult patients with severe refractory eosinophilic asthma, including IgE population).

It derived a hint of a minor added benefit for mepolizumab in comparison with omalizumab for the IgE population (all adult patients with severe refractory eosinophilic asthma and with IgE-mediated pathogenesis of asthma who completely fulfil the criteria of the approval and the note on treatment for omalizumab).

The G-BA decides on the added benefit.

2.6 List of included studies

Not applicable as no studies were included in the benefit assessment.

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General Methods: version 4.2 [online]. 22.04.2015 [accessed: 01.03.2016]. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-2.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58

3. Global Initiative for Asthma. Global strategy for asthma management and prevention [online]. 2015 [accessed: 17.06.2015]. URL: http://www.ginasthma.org/local/uploads/files/GINA_Report_2015_Aug11.pdf.

4. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med 2014; 371(13): 1198-1207.

5. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med 2014; 371(13): 1189-1197.

6. GlaxoSmithKline. Flutide Diskus: Fachinformation [online]. 10.2014 [accessed: 19.06.2015]. URL: http://www.fachinfo.de.

7. Boehringer Ingelheim. Spiriva Respimat: Fachinformation [online]. 11.2014 [accessed: 04.08.2015]. URL: http://www.fachinfo.de.

8. Humbert M, Beasley R, Ayres J, Slavin R, Hebert J, Bousquet J et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. Allergy 2005; 60(3): 309-316.

9. Chanez P, Contin-Bordes C, Garcia G, Verkindre C, Didier A, De Blay F et al. Omalizumab-induced decrease of FceRI expression in patients with severe allergic asthma. Respir Med 2010; 104(11): 1608-1617.

10. Hanania NA, Alpan O, Hamilos DL, Condemi JJ, Reyes-Rivera I, Zhu J et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. Ann Intern Med 2011; 154(9): 573-582.

11. Novartis Pharma. Xolair 75 mg Injektionslösung: Fachinformation [online]. 06.2015 [accessed: 23.02.2016]. URL: http://www.fachinfo.de.

12. GlaxoSmithKline. Nucala 100 mg Pulver zur Herstellung einer Injektionslösung: Fachinformation [online]. 12.2015 [accessed: 31.03.2016]. URL: http://www.fachinfo.de.

13. Bousquet J, Siergiejko Z, Swiebocka E, Humbert M, Rabe KF, Smith N et al. Persistency of response to omalizumab therapy in severe allergic (IgE-mediated) asthma. Allergy 2011; 66(5): 671-678.

14. GlaxoSmithKline. Identification and description of severe asthma patients in a cross-sectional study: the IDEAL study; study 201722; protocol amendment number 02 [unpublished]. 2015.

15. GlaxoSmithKline. Identification and description of severe asthma patients in a cross-sectional study: the IDEAL study; study 201722; clinical study report [unpublished]. 2015.

16. GlaxoSmithKline. A study to determine long-term safety of mepolizumab in asthmatic subjects: full text view [online]. In: ClinicalTrials.gov. 20.08.2015 [accessed: 02.11.2015]. URL: https://clinicaltrials.gov/show/NCT01842607.

17. ClinicalsTrials.gov. A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group, Dose Ranging Study to Determine the Effect of Mepolizumab on Exacerbation Rates in Subjects With Severe Uncontrolled Refractory Asthma (NCT01000506). 2014. URL: https://clinicaltrials.gov/show/NCT01000506.

The full report (German version) is published under https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/a16-03-mepolizumab-nutzenbewertung-gemaess-35a-sgb-v.7199.html.