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Mepolizumab (eosinophilic granulomatosis with polyangiitis) –

Addendum to Commission A21-151[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ACQ	Asthma Control Questionnaire
ACT	appropriate comparator therapy
AE	adverse event
BVAS	Birmingham Vasculitis Activity Score
EGPA	eosinophilic granulomatosis with polyangiitis
EULAR	European League Against Rheumatism
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimally important difference
OCS	oral corticosteroids
OR	odds ratio
PCS	Physical Component Summary
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SF-36v2	Short Form 36-item Health Survey version 2
SOC	System Organ Class
SNOT	Sinonasal Outcome Test
WPAI	Work Productivity and Activity Impairment

1 Background

On 12 April 2022, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments on Commission A21-152 (Mepolizumab – benefit assessment according to §35a Social Code Book V) [1].

For assessing the benefit of mepolizumab as an add-on treatment for patients aged 6 years and older with relapsing-remitting or refractory eosinophilic granulomatosis with polyangiitis (EGPA), the pharmaceutical company (hereinafter "company") presented the MIRRA study [2]. Said study was disregarded in the benefit assessment because it failed to implement the appropriate comparator therapy (ACT) (also see Section 2).

The G-BA commissioned IQWiG with assessing the data from the MIRRA study presented in the dossier [2], taking into account the information provided in the commenting procedure [3].

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Presentation of the MIRRA study

Below, the MIRRA study is assessed in accordance with the terms of the commission. This study was disregarded in dossier assessment A21-151 [1] because it did not implement the ACT for mepolizumab as an add-on treatment for patients aged 6 years and older with relapsing-remitting or refractory EGPA [4]. For the present therapeutic indication, the G-BA designated as the ACT individualized therapy taking into account the severity of disease (organ- or life-threatening manifestation), symptoms, treatment phase, and course of disease. In its comments on the ACT, the G-BA mentions that, for individualized therapy, glucocorticoids, if applicable in combination with the immunosuppressants cyclophosphamide, rituximab, leflunomide, mycophenolate, mofetil, methotrexate, and azathioprine, are listed in guidelines and deemed suitable comparators in the context of clinical trials, although these immunosuppressants are not approved for the treatment of EGPA. For the implementation of individualized therapy, treatment adjustment is assumed to potentially comprise both dose adjustments and treatment switches/initiations to respond to newly developed symptoms or deterioration of existing symptoms. However, the option to make adjustments in the MIRRA study exists only for oral corticosteroids (OCS), which does not constitute individualized therapy once severity of disease (organ- or life-threatening manifestation), symptoms, treatment phase and disease course are factored in. Implementing the ACT specified by the G-BA would have additionally required an adjustment option for immunosuppressive therapy. MIRRA participants, however, were excluded from further study treatment if they received a dose escalation of existing or initiation of new immunosuppressant therapy.

The commenting procedure revealed no material new aspects which would have led to OCS adjustment as the sole adjustment option in the MIRRA study being deemed a sufficient approximation of the ACT. The commenting procedure underscored, for instance, the importance of or preference for a combination therapy consisting of OCS and immunosuppressants in the therapeutic indication of EGPA. Combination therapy consisting of OCS and immunosuppressants was discussed as likely being less effective in the eosinophilic phenotype of EGPA than in the vasculitic phenotype. But overall, the question remains whether at least some MIRRA participants would have been indicated for a modification or initiation of immunosuppressant therapy [5]. Therefore, the dossier assessment's conclusion that the ACT specified by the G-BA had been inadequately implemented remains unchanged.

Further, dossier assessment A21-151 described, among other things, the subgroup analyses presented in the company's dossier for the characteristic of concomitant immunosuppressant treatment (yes/no), which suggest that immunosuppressant therapy might have prevented relapse or led to remission (see dossier assessment A21-151 [1]). Even after the commenting procedure, these subgroup analyses remain incomplete (failure to submit results from individual subgroups for remission according to European League Against Rheumatism (EULAR) definition [Birmingham Vasculitis Activity Score [BVAS]] = 0 and OCS dose ≤ 7.5 mg/day], where a statistically significant interaction was revealed by the characteristic of

immunosuppressant concomitant therapy [yes/no], [interaction $p < 0.05$, based on odds ratio [OR]]).

2.1 Transferability to children and adolescents

For the derivation of added benefit, the company extrapolated the MIRRA study results obtained in adults to children and adolescents aged 6 years and older, who are also covered by the therapeutic indication of mepolizumab [6,7]. For children and adolescents, neither randomized controlled trials (RCTs) nor other studies with mepolizumab are available in the therapeutic indication of EGPA. The company's approach to extrapolate study results from adults to children is understandable since no comparative data are available for children. However, since the MIRRA study on adults remains irrelevant for the benefit assessment (see Section 2), no data are available to be extrapolated from adults to children and adolescents aged 6 years and older.

2.2 Study design

A detailed characterization of the MIRRA study can be found in dossier assessment A21-151 [1] and its Appendix B.

Risk of bias across outcomes (study level)

Table 1 shows the risk of bias across outcomes (risk of bias at study level).

Table 1: Risk of bias across outcomes (study level) – RCT, direct comparison: mepolizumab + OCS ± immunosuppressant versus placebo + OCS ± immunosuppressant

Study	Adequate random sequence generation	Allocation concealment	Blinding		Nonselective reporting	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
MIRRA	Yes	Yes	Yes	Yes	Yes	Yes	Low
OCS: oral corticosteroids ; RCT: randomized controlled trial							

The risk of bias of results across outcomes was rated as low for the MIRRA study.

2.3 Study results

This addendum presents the following patient-relevant outcomes for the MIRRA study:

- Mortality
  - all-cause mortality
- Morbidity

  - remission
  - asthma symptoms (surveyed using the Asthma Control Questionnaire [ACQ]-6)
  - sinonasal symptoms (surveyed using the 22-item Sinonasal Outcome Test [SNOT-22]; total score)
  - activity impairment (surveyed using the Work Productivity and Activity Impairment [WPAI] question 6)
- Health-related quality of life
  - surveyed using the Short Form 36-item Health Survey version 2 (SF-36v2)
- Side effects
  - SAEs
  - discontinuation due to adverse events (AEs)
  - specific AEs, if any

The choice of patient-relevant outcomes deviates from that made by the company, which used additional outcomes in its dossier (Module 4 B) [2].

Table 2 shows the outcomes for which data were available from the MIRRA study.

Table 2: Matrix of outcomes – RCT, direct comparison: mepolizumab + OCS ± immunosuppressant versus placebo + OCS ± immunosuppressant

Study	Outcomes								
	All-cause mortality[a]	Remission[b]	Asthma symptoms (ACQ-6)	Sinonasal symptoms (SNOT-22; total score)	Activity impairment (WPAI question 6)	Health-related quality of life (SF-36v2)	SAEs[c]	Discontinuation due to AEs[d]	Skin and subcutaneous tissue disorders (SOC, AEs)
MIRRA	Yes	Yes	Yes	Yes	Yes	Yes	Yes[e]	Yes[e]	Yes

a. Deaths were recorded as AEs.
b. Operationalized as BVAS = 0 and OCS dose (prednisolone or prednisone) ≤ 7.5 mg/day.
c. Not including fatal events.
d. Discontinuation of treatment or of the study.
e. Includes events which may represent either side effects or symptoms of the disease.

ACQ: Asthma Control Questionnaire; AE: adverse event; BVAS: Birmingham Vasculitis Activity Score; OCS: oral corticosteroids; RCT: randomized controlled trial; SAE: serious adverse event; SF-36v2: Short Form 36-Item Health Survey Version 2; SNOT-22: 22-Item Sinonasal Outcome Test; SOC: system organ class; WPAI: Work Productivity and Activity Impairment

Notes regarding outcomes

Remission

Module 4 B of the company's dossier presents analyses for 2 definitions of remission: (A) BVAS = 0 and OCS dose ≤ 4 mg/day (as per definition of the primary outcome) and (B) BVAS = 0 and OCS dose ≤ 7.5 mg/day (as per EULAR recommendations for the conduct of clinical trials in systemic vasculitis [8] as well as the update on the classification and management of EGPA [9]).

BVAS is an instrument for the clinical assessment of disease activity in systemic vasculitis which is completed by the treating physician. The BVAS is divided into 9 organ-based systems, with each section containing items about signs or symptoms typical for the involvement of the respective organ in systemic vasculitis [10,11]. Several items of this instrument are rated on the basis of laboratory or imaging results, which, individually, are not necessarily patient-relevant. However, the definition of remission requires a BVAS of 0, i.e. no signs of disease activity in any item; the fact that the instrument for surveying disease activity includes laboratory and imaging results is therefore irrelevant in this case.

This addendum uses the definition by EULAR. The threshold for the daily OCS dose defined for remission as per the primary outcome (4 mg) is deemed difficult to achieve and hence too strict for the present therapeutic indication. This view was confirmed by statements made in the commenting procedure [5].

According to EULAR, the probability of relapse is particularly high within the first 6 months of remission [8]. Therefore, this addendum presents an analysis of the percentage of patients who achieved remission as per EULAR within the first 24 weeks and remained in remission until study end (Week 52, i.e. for at least 28 weeks). The other operationalizations of the outcome of remission which were used by the company show consistent effects.

BVAS = 0 (no disease activity) within the first 24 weeks until study end (Week 52) is presented as supplementary information.

Relapse

The MIRRA study defines the outcome of relapse as worsening or persistence of active disease since the last visit. Worsening or persistence of active disease is characterized by vasculitis (BVAS > 0) or asthma signs or with corresponding worsening in ACQ-6 score (compared with the last visit) or nasal/sinus disease with corresponding worsening in at least 1 symptom in the questionnaire on sinonasal symptoms (compared with the last visit).
In addition, 1 or more of the following measures had to have been taken: dose increase in corticosteroids (including systemic corticosteroids) to > 4 mg/day, dose increase or addition of immunosuppressive therapy, or hospitalization related to EGPA worsening. Severe relapse is defined as any organ- or life-threatening EGPA-induced event, BVAS ≥ 6 (with at least 2 affected organ systems), asthma exacerbation requiring hospitalization, or sinonasal relapse requiring hospitalization.

At baseline, the study population had a median BVAS of 1, with 46% of patients in the intervention arm and 29% in the control arm exhibiting BVAS = 0 (no disease activity). A total of only 6 patients (2 in the control arm) were in remission at baseline as per EULAR definition (BVAS = 0 and OCS dose ≤ 7.5 mg/day). In this situation, the achievement of remission can be safely assumed to represent the analysis of primary relevance. In addition, the threshold for daily OCS dose used in the MIRRA study's definition of relapse (4 mg) is not found in any guidelines, and, like the relapse definition for the primary outcome (see above), it is deemed inadequately substantiated. Additionally, since the present assessment analyses remission in accordance with EULAR recommendations (see above), patients might be double counted in the analysis of a survey point, i.e. individual patients might be simultaneously classified as both being in remission and relapsed. Therefore, the outcome of relapse in the form of an annualized rate is presented only as supplementary information.

Asthma symptoms (ACQ-6)

ACQ-6 is an instrument for surveying patients' asthma control [12,13]. The questionnaire surveys the frequency and/or severity of 5 symptoms (waking at night due to symptoms,

symptoms when waking up in the morning, limitation of activities, shortness of breath, and wheezing) within the past week. Each question is answered on a scale of 0 (no impairment/limitation) to 6 (maximum impairment/limitation). In addition, the questionnaire records the number of puffs of inhalations of a short-acting bronchodilator which were necessary each day within the past week. A total score is calculated, ranging from 0 to 6. Lower values indicate less pronounced symptoms.

In the MIRRA study, the EGPA diagnosis of all patients was based, among other things, on their medical history or the presence of asthma. Since asthma is one of the main symptoms particularly of the eosinophilic component of EGPA and the inclusion criteria required asthma symptoms in patients' medical history or at baseline, this addendum presents this outcome in the form of the percentage of patients with an improvement in ACQ-6 score by ≥ 0.9 points (15% improvement). The company indicates that this improvement is measured at Weeks 49–52. However, it is unclear at what point a patient was rated as a responder, i.e. whether long-term improvement had been seen in Weeks 49–52.

Sinonasal symptoms (SNOT-22)

SNOT-22 is a disease-specific, patient-reported questionnaire containing 22 individual questions to survey the severity and frequency of symptoms and social/emotional consequences of rhinosinusitis. Each question is answered on a scale of 0 (no problem) to 5 (problem as bad as it can be). From the individual score for each question, a total score (0 to 110) is calculated, with lower values indicating less impairment.

In addition to the SNOT-22, individual sinonasal symptoms (blockage/congestion of nose, facial pain/pressure, sense of taste/smell, postnasal discharge [dripping perception at the back of your nose]) were surveyed. For each symptom, patients were to indicate whether, over the past week, it was very severe, severe, moderate, mild, or not present.

Sinonasal symptoms are among the typical symptoms of EGPA [14]. Since in the MIRRA study, 128 of 136 patients (94%) had a medical history of sinonasal abnormalities, this addendum presents SNOT-22 as the percentage of patients with an improvement by ≥ 16.5 points (15% improvement by Week 52).

2.3.1 Risk of bias

Table 3 shows the risk of bias for the results of the relevant outcomes.

Table 3: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: mepolizumab + OCS ± immunosuppressant versus placebo + OCS ± immunosuppressant

Study	Study level	Outcomes								
		All-cause mortality[a]	Remission[b]	Asthma symptoms (ACQ-6)	Sinonasal symptoms (SNOT-22; total score)	Activity impairment (WPAI question 6)	Health-related quality of life (SF-36v2)	SAEs[c]	Discontinuation[d] due to AEs	Skin and subcutaneous tissue disorders (SOC, AEs)
MIRRA	L	H[e]	H[e]	H[f]	H[g]	L	L	H[e]	L	H[e]

a. Deaths were recorded as AEs.
b. Operationalized as BVAS = 0 and OCS dose (prednisolone or prednisone) ≤ 7.5 mg/day.
c. Not including fatal events.
d. Discontinuation of treatment or of the study.
e. Treatment arms differ (by > 5 percentage points) in the proportion of patients with study and treatment discontinuation.
f. High percentage (> 10%) of missing values replaced as nonresponders.
g. Treatment groups exhibit a relevant difference (> 5 percentage points) in missing values which are replaced as nonresponders.

ACQ: Asthma Control Questionnaire; AE: adverse event; BVAS: Birmingham Vasculitis Activity Score; OCS: oral corticosteroids; RCT: randomized controlled trial; SAE: serious adverse event; SF-36v2: Short Form 36-Item Health Survey Version 2; SNOT-22: 22-item Sinonasal Outcome Test; SOC: system organ class

The risk of bias for the results of each of the outcomes of activity impairment (WPAI question 6), health-related quality of life (SF-36v2), and discontinuation due to AEs is rated as low.

The risk of bias of results for each of the outcomes of all-cause mortality, remission, serious adverse events (SAEs), and skin and subcutaneous tissue disorders (System Organ Class [SOC], AEs) is rated as high. For each of them, this is due to the difference between treatment arms regarding the percentage of patients with study and treatment discontinuation (> 5 percentage points). For the results on the outcome of asthma symptoms (ACQ-6), the risk of bias is rated as high due to the high percentage (> 10%) of missing values. The risk of bias for the results on sinonasal symptoms (SNOT-22) is rated as high due to the relevant between-group difference in missing values, which are rated as nonresponders (> 5 percentage points).

2.3.2 Results

Table 4, Table 5, and Table 6 summarize the results of the comparison of mepolizumab with placebo, each in combination with OCS and if applicable immunosuppressants, in adult patients with relapsing-remitting or refractory EGPA. Where necessary, IQWiG calculations are provided in addition to the data from the company's dossier.

Results on common AEs, SAEs, and discontinuation due to AEs are presented in Appendix A.

Table 4: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: mepolizumab + OCS ± immunosuppressant versus placebo + OCS ± immunosuppressant (multipage table)

Study **Outcome category** **Outcome** **Time point**	**Mepolizumab + OCS ± immunosuppressant**		**Placebo + OCS ± immunosuppressant**		**Mepolizumab + OCS ± immunosuppressant vs. placebo + OCS ± immunosuppressant**
	N	**Patients with event n (%[a])**	**N**	**Patients with event n (%[a])**	**RR [95% CI][b]; p-value[c]**
MIRRA					
Mortality					
All-cause mortality[d] within 52 weeks	68	1 (1.5)	68	0 (0)	–
Morbidity					
Remission[e] Within the first 24 weeks until study end	68	16 (23.5)	68	2 (2.9)	0.13 [0.01; 0.48][f]; < 0.001
BVAS = 0 within the first 24 weeks until study end (presented as supplementary information)	*68*	*20 (29.4)*	*68*	*10 (14.7)*	*0.50 [0.23; 0.99][f]; 0.042*
Asthma symptoms (ACQ-6[g], improvement by ≥ 0.9 points[h])[i]	68	9 (13.2)	68	5 (7.4)	0.56 [0.15; 1.63][f]; 0.282
Sinonasal symptoms (SNOT-22 total score, improvement by ≥ 16.5 points[j])[i]	68	17 (25.0)	68	7 (10.3)	0.41 [0.14; 0.95][f]; 0.026
Sinonsasal symptoms (SNOT-22 total score, improvement by ≥ 8.9 points[j], presented as supplementary information)[i]	*68*	*26 (38.2)*	*68*	*14 (20.6)*	*0.54 (0.29; 0.96)[f]; 0.038*
Hospitalization (presented as supplementary information)	*56*	*9 (16.1)*	*54*	*10 (18.5)*	*0.87 [0.35; 2.02]; 0.806*

Table 4: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: mepolizumab + OCS ± immunosuppressant versus placebo + OCS ± immunosuppressant (multipage table)

Study **Outcome category** **Outcome** **Time point**	**Mepolizumab + OCS ± immunosuppressant**		**Placebo + OCS ± immunosuppressant**		**Mepolizumab + OCS ± immunosuppressant vs. placebo + OCS ± immunosuppressant**
	N	**Patients with event n (%[a])**	**N**	**Patients with event n (%[a])**	**RR [95% CI][b]; p-value[c]**
Health-related quality of life					
SF-36v2[i, k]					
PCS (improvement by ≥ 9.4 points[l])	67	8 (11.9)	68	9 (13.2)	1.11 [0.43; 3.19][f]; 0.876
PCS (improvement by ≥ 5 points[l], presented as supplementary information)	*67*	*18 (26.9)*	*68*	*17 (25.0)*	*0.93 [0.49; 1.67][f]; 0.860*
MCS (improvement by ≥ 9.6 points[m])	67	10 (14.9)	68	3 (4.4)	0.30 [0.07; 0.98][f]; 0.040
MCS (improvement by ≥ 5 points[m], presented as supplementary information)	*67*	*11 (16.4)*	*68*	*15 (22.1)*	*1.34 [0.65; 3.19][f]; 0.530*
Side effects					
AEs (supplementary information)[n]	68	66 (97.1)	68	64 (94.1)	–
SAEs[n, o]	68	11 (16.2)	68	18 (26.5)	0.61 [0.29; 1.19]; 0.150
Discontinuation[p] due to AEs	68	2 (2.9)	68	1 (1.5)	2.00 [0.18; 54.34]; 0.682
Skin and subcutaneous tissue disorders (SOC, AEs)	68	30 (44.1)	68	13 (19.1)	2.31 [1.32; 4.03]; 0.002

Table 4: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: mepolizumab + OCS ± immunosuppressant versus placebo + OCS ± immunosuppressant (multipage table)

Study Outcome category Outcome Time point	Mepolizumab + OCS ± immunosuppressant		Placebo + OCS ± immunosuppressant		Mepolizumab + OCS ± immunosuppressant vs. placebo + OCS ± immunosuppressant
	N	Patients with event n (%[a])	N	Patients with event n (%[a])	RR [95% CI][b]; p-value[c]

a. IQWiG calculation.
b. Exact unconditional CI, calculated by inversion of 2 separate one-sided tests on the basis of the score statistics.
c. IQWiG calculation, unconditional exact test (CSZ method according to [15]).
d. Deaths were recorded as AEs.
e. Operationalized as BVAS = 0 and OCS dose (prednisolone or prednisone) ≤ 7.5 mg/day.
f. Information based on the comparison of placebo + OCS ± immunosuppressant vs. mepolizumab + OCS ± immunosuppressant.
g. The ACQ-6 total score includes 5 questions on symptoms and 1 question on medication as needed.
h. Percentage of patients with an ACQ-6 score decrease by ≥ 0.9 points from baseline to Weeks 49–52, at a scale range of 0 to 6. Lower (decreasing) values indicate an improvement in symptoms.
i. The company replaced missing values as nonresponders.
j. Percentage of patients with a SNOT-22 total score decrease by ≥ 16.5 points (or ≥ 8.9 points, presented as supplementary information) from baseline to Week 52, at a scale range of 0 to 110. Lower (decreasing) values indicate an improvement in symptoms.
k. Information on subscales was not available.
l. Percentage of patients with a PCS score increase by ≥ 9.4 points (or ≥ 5 points, presented as supplementary information) from baseline to Week 52, using a normalized scale with a minimum of about 7 to a maximum of about 70. Higher (increasing) values indicate an improvement in health-related quality of life.
m. Percentage of patients with an increase in MCS score by ≥ 9.6 points (or ≥ 5 points presented as supplementary information) from baseline to Week 52 using a normalized scale with a minimum of approx. 6 and a maximum of approx. 70. Higher (increasing) values indicate an improvement in health-related quality of life.
n. Includes events which can be both side effects and symptoms of the disease.
o. Not including fatal events.
p. Discontinuation of treatment or study.

ACQ: Asthma Control Questionnaire; AE: adverse event; BVAS: Birmingham Vasculitis Activity Score; CI: confidence interval; CSZ: convexity, symmetry, z-score; MCS: Mental Component Summary; n: number of patients with (at least 1) event; N: number of analysed patients; OCS: oral corticosteroids; PCS: Physical Component Summary; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SF-36v2: Short Form 36-item Health Survey version 2; SNOT-22: 22-item Sinonasal Outcome Test; SOC: System Organ Class

Table 5: Results (morbidity, continuous) – RCT, direct comparison: mepolizumab + OCS ± immunosuppressant versus placebo + OCS ± immunosuppressant

Study Outcome category Outcome	Mepolizumab + OCS ± immunosuppressant			Placebo + OCS ± immunosuppressant			Mepolizumab + OCS ± immunosuppressant vs. placebo + OCS ± immunosuppressant
	N[a]	Values at baseline mean (SD)	Change by Week 52 mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change by Week 52 mean[b] (SE)	MD [95% CI]; p-value[b]
MIRRA							
Morbidity							
Activity impairment [%][c]	ND	36.8 (29.14)	-1.54 (2.44)	ND	39.6 (28.68)	-7.28 (2.61)	5.74 [-1.34; 12.81]; 0.111

a. Number of patients taken into account in the analysis for calculating the effect estimation; baseline values may be based on different patient numbers.
b. MMRM with treatment, baseline WPAI, baseline OCS dose, region, and visit as well as interaction terms for visit and baseline WPAI as well as visit and treatment group.
c. Lower percentages indicate less daily activity impairment; negative effects (intervention minus control) indicate an advantage for the intervention (scale range of 0 to 100).

CI: confidence interval; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; ND: no data; OCS: oral corticosteroid; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; WPAI: Work Productivity and Activity Impairment

Table 6: Results (morbidity, dichotomous) – RCT, direct comparison: mepolizumab + OCS ± immunosuppressant versus placebo + OCS ± immunosuppressant

Study Outcome category Outcome	Mepolizumab + OCS ± immunosuppressant		Placebo + OCS ± immunosuppressant		Mepolizumab + OCS ± immunosuppressant vs. placebo + OCS ± immunosuppressant
	N	Number of events (annualized rate [95% CI])	N	Number of events (annualized rate [95% CI])	Rate ratio [95% CI]; p-value[a]
MIRRA					
Morbidity					
Relapse[b, c] (presented as supplementary information)	*68*	*ND 1.14 [ND]*	*68*	*ND 2.27 [ND]*	*0.50 [0.36; 0.70]; < 0.001*
Severe relapse[d, e] (presented as supplementary information)	*68*	*ND 0.12 [ND]*	*68*	*ND 0.21 [ND]*	*0.56 [0.28; 1.14]; 0.109*

a. Negative binomial generalized linear model with treatment group, baseline OCS dose, baseline BVAS, region, and logarithmic treatment duration (offset variable).
b. Defined as worsening or persistence of active disease since the last visit. Worsening or persistence of active disease is characterized by vasculitis (BVAS > 0) or asthma signs or with corresponding worsening in ACQ-6 score (compared with the last visit) or nasal/sinus disease with corresponding worsening in at least 1 symptom in the questionnaire on sinonasal symptoms (compared with the last visit). In addition, 1 or more of the following measures had to have been taken: dose increase in corticosteroids (including systemic corticosteroids) to > 4 mg/day, dose increase or addition of immunosuppressive therapy, or hospitalization related to EGPA worsening.
c. Patients with at least 1 relapse: 38 (intervention) versus 56 (control).
d. Defined as any organ- or life-threatening EGPA-induced event, BVAS ≥ 6 (with at least 2 affected organ systems), asthma exacerbation requiring hospitalization or sinonasal relapse requiring hospitalization.
e. Patients with at least 1 severe relapse: 15 (intervention) versus 24 (control).

ACQ: Asthma Control Questionnaire; BVAS: Birmingham Vasculitis Activity Score; CI: confidence interval; EGPA: eosinophilic granulomatosis with polyangiitis; N: number of analysed patients; ND: no data; OCS: oral corticosteroids; RCT: randomized controlled trial

Overall, due to the high risk of bias at outcome level, the certainty of conclusions is reduced for each of the outcomes of all-cause mortality, remission, asthma symptoms (ACQ-6), sinonasal symptoms (SNOT-22) as well as the side effects outcomes of SAEs and skin and subcutaneous tissue disorders (AEs).

Mortality

All-cause mortality

For the outcome of all-cause mortality, 1 death occurred in the intervention arm and 0 deaths in the control arm.

Morbidity

Remission and SNOT-22 (symptoms and social/emotional consequences of rhinosinusitis)

For each of the outcomes of remission and sinonasal symptoms (percentage of patients with improvement in SNOT-22 total score by ≥ 16.5 points at Week 52), a statistically significant difference was found in favour of mepolizumab in comparison with placebo, each in combination with OCS and if applicable immunosuppressants.

Asthma symptoms (ACQ-6) and activity impairment (WPAI question 6)

For each of the outcomes of asthma symptoms (ACQ-6; percentage of patients with improvement by ≥ 0.9 points at Weeks 49–52) and activity impairment (WPAI question 6; mean change by Week 52), there is a statistically significant difference between treatment groups.

Health-related quality of life

SF-36v2

For the outcome of health-related quality of life (SF-36v2), responder analyses are presented using improvement by ≥ 9.4 points for the Physical Component Summary (PCS) and improvement by ≥ 9.6 points for the Mental Component Summary (MCS), each at Week 52. As supplementary information, responder analyses of improvement by ≥ 5 points at Week 52 are presented.

No statistically significant difference between treatment groups was found for the SF-36v2 PCS.

For the SF-36v2 MCS, there is a statistically significant difference in favour of mepolizumab versus placebo, each in combination with OCS and if applicable immunosuppressants.

Side effects

SAEs and discontinuation due to AEs

No statistically significant difference was found between treatment groups for either of the outcomes of SAEs or discontinuation due to AEs.

Skin and subcutaneous tissue disorders (System Organ Class [SOC], AEs)

For the outcome of skin and subcutaneous tissue disorders (SOC, AEs), a statistically significant difference was found to the disadvantage of mepolizumab in comparison with placebo, each in combination with OCS and if applicable immunosuppressants.

2.3.3 Subgroups and other effect modifiers

The following potential effect modifiers were taken into account for the present addendum:

- sex (female versus male)
- age (< 50 years versus ≥ 50 years)

The subgroup characteristics were prespecified for the primary outcomes.

The subgroup analyses submitted by the company are unusable. The reasons are as follows:

The subgroup analyses for the morbidity outcomes, asthma symptoms (ACQ-6), and sinonasal symptoms (SNOT-22) as well as for health-related quality of life (SF-36v2) are based on responder analyses conducted with response criteria not used in the present benefit assessment. For the ACQ-6, the company chooses improvement by a minimally important difference (MID) ≥ 0.5 points as the basis for the analysis. For the benefit assessment, however, subgroup analyses based on the response criterion of 15% (≥ 0.9 points) would be relevant. Further, the company chose improvement by a MID ≥ 8.9 points as the basis for analysing SNOT-22. For the benefit assessment, however, subgroup analyses based on the response criterion of 15% (≥ 16.5 points) would be relevant. For both the SF-36v2 PCS and MCS component summaries, the company chose improvement by a MID ≥ 5 points. An analysis based on the response criterion of 15% (≥ 9.4 points for PCS or ≥ 9.6 points for MCS) would again be relevant.

Furthermore, neither for binary nor for continuous analyses does the company identify the methods used to calculate subgroup results and perform interaction testing. For the subgroup analyses of the outcomes of remission, asthma symptoms (ACQ-6), sinonasal symptoms (SNOT-22), health-related quality of life (SF-36v2), and side effects, the company likewise failed to report the effect measure on which the interaction tests are based. Presumably, OR was used for interaction testing. What would be required, in contrast, is a test for subgroup effects regarding the effect measure of relative risk (RR). The 2 effect measures can lead to different results in the evaluation of an effect modification.

2.4 Summary

Overall, the MIRRA study's results for mepolizumab versus placebo, each in combination with OCS and if applicable immunosuppressants, show the following:

- Advantage of mepolizumab in combination with OCS and if applicable immunosuppressants:
  - remission
  - sinonasal symptoms (SNOT-22)
  - SF-36v2 MCS
- No advantage or disadvantage of mepolizumab in combination with OCS and if applicable immunosuppressants:
  - all-cause mortality
  - asthma symptoms (ACQ-6)
  - SF-36v2 PCS
  - SAEs

- discontinuation due to AEs

- Disadvantage of mepolizumab in combination with OCS and, if applicable, immunosuppressants:
  - skin and subcutaneous tissue disorders (SOC, AEs)

The G-BA decides on the added benefit.

3 References

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Appendix A Results on side effects

For total rates of AEs and SAEs, the tables below present events for SOCs and Preferred Terms (PTs) as per Medical Dictionary for Regulatory Activities (MedDRA), each on the basis of the following criteria:

- total rate of AEs (irrespective of severity grade): events which occurred in at least 10% of the patients in 1 study arm
- SAEs: events which occurred in at least 5% of patients in 1 study arm
- In addition for all events irrespective of the severity grade: events that occurred in at least 10 patients and in at least 1% of the patients in 1 study arm.

For the outcome of discontinuation due to AEs, a complete presentation of all events (SOCs/PTs) which resulted in discontinuation is provided.

Table 7: Common AEs[a] – RCT, direct comparison: mepolizumab + OCS ± immunosuppressant versus placebo + OCS ± immunosuppressant (multipage table)

Study	**Patients with event n (%[b])**	
SOC[c] **PT[c]**	**Mepolizumab + OCS ± immunosuppressant N = 68**	**Placebo + OCS ± immunosuppressant N = 68**
MIRRA		
Overall AE rate[d]	66 (97.1)	64 (94.1)
Infections and infestations	57 (83.8)	53 (77.9)
Nasopharyngitis	12 (17.6)	16 (23.5)
Sinusitis	14 (20.6)	11 (16.2)
Upper respiratory tract infection	14 (20.6)	11 (16.2)
Bronchitis	7 (10.3)	9 (13.2)
Influenza	7 (10.3)	8 (11.8)
Respiratory tract infection	6 (8.8)	8 (11.8)
Nervous system disorders	38 (55.9)	32 (47.1)
Headache	22 (32.4)	12 (17.6)
General disorders and administration site conditions	40 (58.8)	28 (41.2)
Fatigue	10 (14.7)	10 (14.7)
Injection site reactions	9 (13.2)	7 (10.3)
Pyrexia	7 (10.3)	8 (11.8)
Musculoskeletal and connective tissue disorders	38 (55.9)	30 (44.1)
Arthralgia	15 (22.1)	12 (17.6)
Back pain	9 (13.2)	6 (8.8)
Myalgia	6 (8.8)	9 (13.2)
Neck pain	8 (11.8)	2 (2.9)
Gastrointestinal disorders	34 (50.0)	31 (45.6)
Nausea	11 (16.2)	13 (19.1)
Diarrhoea	12 (17.6)	8 (11.8)
Vomiting	11 (16.2)	4 (5.9)
Respiratory, thoracic, and mediastinal disorders	35 (51.5)	28 (41.2)
Asthma	11 (16.2)	11 (16.2)
Cough	5 (7.4)	8 (11.8)
Oropharyngeal pain	8 (11.8)	5 (7.4)
Productive cough	6 (8.8)	7 (10.3)
Skin and subcutaneous tissue disorders	30 (44.1)	13 (19.1)
Rash	9 (13.2)	6 (8.8)
Injury, poisoning and procedural complications	22 (32.4)	10 (14.7)
Investigations	15 (22.1)	11 (16.2)

Table 7: Common AEs[a] – RCT, direct comparison: mepolizumab + OCS ± immunosuppressant versus placebo + OCS ± immunosuppressant (multipage table)

Study	**Patients with event n (%[b])**	
SOC[c] PT[c]	**Mepolizumab + OCS ± immunosuppressant N = 68**	**Placebo + OCS ± immunosuppressant N = 68**
Eye disorders	16 (23.5)	9 (13.2)
Ear and labyrinth disorders	13 (19.1)	10 (14.7)
Vascular disorders	9 (13.2)	2 (2.9)

a. Events that occurred in ≥ 10% of the patients in at least one study arm.
b. IQWiG calculation.
c. MedDRA version: ND; SOC and PT terminology adopted unmodified from Module 4 B.
d. Includes events which can be both side effects and symptoms of the disease.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; ND: no data; OCS: oral corticosteroids; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 8: Common SAEs[a] – RCT, direct comparison: mepolizumab + OCS ± immunosuppressant versus placebo + OCS ± immunosuppressant

Study	**Patients with event n (%[b])**	
SOC[c] PT[c]	**Mepolizumab + OCS ± immunosuppressant N = 68**	**Placebo + OCS ± immunosuppressant N = 68**
MIRRA		
Total SAE rate[d]	11 (16.2)	18 (26.5)
Infections and infestations	4 (5.9)	10 (14.7)
Respiratory, thoracic, and mediastinal disorders	2 (2.9)	7 (10.3)
Asthma	2 (2.9)	4 (5.9)

a. Events that occurred in ≥ 5% of the patients in at least 1 study arm.
b. IQWiG calculation.
c. MedDRA version: ND; SOC and PT terminology adopted unmodified from Module 4 B.
d. Without fatal events; includes events which might be deemed either side effects or symptoms of the disease.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; ND: no data; OCS: oral corticosteroids; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 9: Discontinuation[a] due to AEs – RCT, direct comparison: mepolizumab + OCS ± immunosuppressant versus placebo + OCS ± immunosuppressant

Study	**Patients with event n (%[b])**	
PT[c]	**Mepolizumab + OCS ± immunosuppressant N = 68**	**Placebo + OCS ± immunosuppressant N = 68**
MIRRA		
Overall rate of discontinuations[a] due to AEs	2 (2.9)	1 (1.5)
Cardiac arrest	1 (0.1)	0 (0)
Hypersensitivity/intolerance	1 (0.1)	0 (0)
Pneumonia	0 (0)	1 (0.1)

a. Discontinuation of treatment or study.
b. IQWiG calculation.
c. MedDRA version: ND; PT terminology adopted unmodified from Module 4 B.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; ND: no data; OCS: oral corticosteroids; PT: Preferred Term; RCT: randomized controlled trial