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Mepolizumab (hypereosinophilic syndrome) –

Addendum to Commission A21-152[1]

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BFI	Brief Fatigue Inventory
CI	confidence interval
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
DS	Daily Symptoms
HES	hypereosinophilic syndrome
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MCS	Mental Component Summary
MD	mean difference
MID	minimal important difference
MMRM	mixed model repeated measurement
MSAS-SF	Memorial Symptom Assessment Scale-Short Form
OCS	oral corticosteroids
OR	odds ratio
PCS	Physical Component Summary
PROMIS	Patient Reported Outcome Measurement Information System
PT	Preferred Term
RTS	Response to Therapy Score
SAE	serious adverse event
SF-36v2	Short Form-36 Health Survey version 2
SMD	standardized mean difference
SOC	System Organ Class
SSR	Subject-Rated Symptom Severity
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].

The G-BA commissioned IQWiG with assessing the data from the 200622 study presented in the dossier [2], taking into account the information provided in the commenting procedure [3]. If possible, patients' prior treatment was to be taken into account in the process. In addition, hypereosinophilic syndrome (HES) flares were to be analysed exclusively using the operationalization of clinical manifestation.

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

2 Assessment of the 200622 study

The research question of the benefit assessment was to assess the added benefit of mepolizumab as add-on therapy in comparison with treatment according to physician's choice as the appropriate comparator therapy (ACT) for adult patients with inadequately controlled HES without an identifiable non-haematological secondary cause.

Addressing this research question in its dossier, the pharmaceutical company (hereinafter referred to as "company") has submitted the 200622 study [4-8] for comparing mepolizumab with placebo, each in addition to standard HES treatment. The 200622 study was disregarded in the benefit assessment since the study's comparator arm was deemed an inadequate implementation of treatment according to physician's choice (ACT). The written comments [3] and the discussion in the oral hearing [9] resulted in the 200622 study's comparator therapy being deemed to represent a sufficient approximation of the ACT and the study therefore being suitable for the benefit assessment. However, on the basis of the available information, it remains unclear whether the therapy used in the study's comparator arm represents a complete implementation of the ACT.

The 200622 study administered mepolizumab and placebo, each in addition to standard HES therapy. According to the 200622 study's inclusion criteria, enrolled patients had to have been on a stable regimen of HES therapy for 4 weeks prior to randomization and were to maintain this stable dose throughout the study's treatment phase. Adjustment of the standard therapy was allowed only as part of flare treatment in case of symptom deterioration.

For 74% of comparator arm patients, standard therapy at baseline comprised oral corticosteroids (OCS) or cytotoxic/immunosuppressant therapies (see Table 13 in Appendix B of dossier assessment A21-152 [1]). In addition, 35% of comparator arm participants received other HES therapies at baseline, including drugs used in clinical practice in case of involvement of specific organ systems (e.g. in pulmonary, dermatological, or gastrointestinal manifestations). According to information provided in written comments [3] and the discussion in the oral hearing [9], it is possible for patients with specific organ involvement to forego systemic therapy with OCS or cytotoxic/immunosuppressant therapies and instead receive therapy with drugs targeting specific organ systems. The commenting procedure additionally revealed that in the clinical care of HES patients, the overall goal is to substantially reduce long-term therapy with OCS or cytotoxic/immunosuppressant therapies, particularly in patients where a particular organ system is primarily involved, e.g. In patients exhibiting pronounced pulmonary symptoms which can also be treated with inhaled corticosteroids. Also, in clinical practice, patients who suffer from uncontrolled disease but are in stable condition do not receive optimization of standard therapy; instead, treatment is reduced where possible to prevent treatment-related side effects. For the 200622 study's participants receiving a stable dose of their HES therapy for 4 weeks prior to randomization, optimization of baseline standard therapy therefore fails to reflect clinical practice in the German healthcare context.

For the 200622 study, no information is available as to the number of patients who were candidates for foregoing systemic therapy due to specific organ involvement. Information on the symptoms experienced by the 200622 study's participants shows, e.g. that about 50% reported skin symptoms as burdensome HES-related symptoms at baseline (see Table 12 in Appendix B of dossier assessment A21-152 [1]). However, it remains unclear whether these patients simultaneously exhibited other symptoms and which therapy they received, potentially for treating symptoms in different organ systems as well. While at 91%, the majority of patients in the comparator arm received HES therapy at baseline, the available information does not show which therapy was administered to patients in the comparator arm who received neither OCS nor cytotoxic/immunosuppressant therapy at baseline (26% of comparator arm patients). However, specific therapy in accordance with particular organ involvement is assumed to have been sufficient for at least some of these patients. Yet the available information does not reveal the percentage of patients for whom this was the case. In addition, a small percentage of participants, 9% of comparator arm participants, received no baseline HES therapy.

In summary, it remains unclear whether the comparator treatment used in the 200622 study represents a full implementation of the ACT. The remaining uncertainties did not result in exclusion of the study, however. Instead, it was assumed that conclusions on the added benefit of mepolizumab in comparison with the ACT can be drawn on the basis of the study results. However, the uncertainties described were taken into account in the assessment of the certainty of conclusions of results (see Section 2.2.2).

Neither in its dossier nor with its comments did the company submit separate analyses based on the type of standard therapy received at baseline by the 200622 study's participants. Therefore, no analyses taking into account prior treatment type at baseline (OCS or cytotoxic/immunosuppressant therapy versus other HES therapy versus no HES therapy) are available for the present assessment.

The results for the 200622 study's overall population are described and assessed below. The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

The present addendum is structured as follows: Section 2.1 describes the characteristics of the 200622 study. Sections 2.2 and 2.3 present the results and the derivation of the overall conclusion on added benefit of mepolizumab in the present research question based on the 200622 study. A summary of the benefit assessment is found in Section 2.4.

2.1 Study characteristics

A detailed characterization of the 200622 study can be found in dossier assessment A21-152 [1] and its Appendix B.

Patient characteristics

The patient characteristics were largely comparable between the treatment groups of the 200622 study. Most patients were white, and the mean age was 46 years. The mean time from initial diagnosis to randomization was likewise comparable between treatment arms, at 5.6 years. No information is available on the organ systems affected by the disorder at baseline or the therapies administered for the various organ involvement types. Information is available only on the baseline HES-related symptoms which were rated most burdensome by patients. Said information shows that the most common symptoms were skin symptoms and breathing symptoms, each reported by about 50% of included patients. Information regarding the percentage of patients showing a combination of symptoms and, if so, which ones are not available for the 200622 study.

A detailed characterization of the study population as well as of baseline HES therapy can be found in dossier assessment A21-152 [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 + standard therapy versus placebo + standard therapy

Study	Adequate random sequence generation	Allocation concealment	Blinding		Nonselective reporting	Absence of other aspects	Risk of bias at study level
			Patients	Treatment providers			
200622	Yes	Yes	Yes	Yes	Yes	No	Low
RCT: randomized controlled trial							

The risk of bias at study level for the 200622 study was rated as low.

2.2 Results on added benefit

2.2.1 Outcomes included

The following patient-relevant outcomes were to be taken into account in the assessment:

- Mortality
  - all-cause mortality
- Morbidity
  - clinically manifested HES flares

  - fatigue surveyed using the Brief Fatigue Inventory (BFI)
  - severity of HES symptoms, surveyed using the HES Daily Symptoms (DS) electronic diary
  - patient-rated treatment response – Response to Therapy Score (RTS)
  - patient-rated severity of symptoms – Subject-Rated Symptom Severity (SSR)
  - activity impairment surveyed using question 6 of the Work Productivity and Activity Impairment questionnaire (WPAI question 6)
- Health-related quality of life
  - surveyed using the Short Form-36 Health Survey version 2 (SF-36v2)
- Side effects
  - serious adverse events (SAEs)
  - discontinuation due to adverse events (AEs)
  - further 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 C).

Table 2 shows the outcomes for which data were available in the included study.

Table 2: Matrix of the outcomes – RCT, direct comparison: mepolizumab + standard therapy versus placebo + standard therapy

Study	Outcomes											
	All-cause mortality	Clinically manifested HES flares[a]	Worst fatigue (BFI item 3)	Fatigue intensity / impairment by fatigue (BFI total score)	Severity of HES symptoms (HES-DS)[b]	Patient-rated treatment response (RTS)	Patient-rated symptom severity (SSR)	Activity impairment (WPAI question 6)	Health-related quality of life (SF-36v2)	SAEs	Discontinuation due to AEs	Specific AEs
200622	Yes	Yes	Yes	Yes	Yes	No[c]	No[c]	Yes	Yes	Yes	Yes	No[d]

a. Defined as clinical manifestation of HES as surveyed via physician-documented changes in clinical signs or symptoms (using a standardized assessment) which renders one of the following measures necessary: increase of OCS maintenance dose by at least 10 mg/day for 5 days or increase or addition of cytotoxic or immunosuppressant HES therapy.
b. Worst extent was surveyed via an NRS for each of the following symptoms: muscle/joint pain, chills/sweats, abdominal pain/bloating, breathing symptoms, nasal/sinus symptoms, skin symptoms.
c. No usable data available; see Section 2.2.1 of the addendum for reasoning.
d. No specific AEs were identified based on the AEs which occurred in the relevant study.

AE: adverse event; BFI: Brief Fatigue Inventory; HES: hypereosinophilic syndrome; HES-DS: HES Daily Symptoms; NRS: numeric rating scale; RCT: randomized controlled trial; RTS: Response to Therapy Score; SAE: serious adverse event; SF-36v2: Short Form-36 Health Survey version 2; SSR: Subject-Rated Symptom Severity; WPAI: Work Productivity and Activity Impairment

Unusable analyses for the outcomes of patient-rated treatment response and patient-rated symptom severity

In the 200622 study, patients assessed the treatment response and symptom severity.

For the outcome of patient-rated treatment response (RTS), the 200622 study's participants each rated, from their perspective, their responses to therapy compared to baseline every 4 weeks from Week 4 to Week 32. Patients were to choose from 7 response categories, each assigned a value ranging from 1 to 7 (significant improvement [1], moderate improvement [2], minor improvement [3], no change [4], mild deterioration [5], moderate deterioration [6], and significant deterioration [7]). In Module 4 C of its dossier, the company presents responder analyses for improvement by ≥ 1 category at Week 32 as well as analyses of overall response to therapy at Week 32 by means of ordinal logistical regression analysis. This regression analysis includes all categories of improvement, no change, and deterioration, but the effect estimate allows drawing conclusions only on changes from one response category to the next. Additionally, the company did not submit any information on the extent to which changes over

the course of the study were taken into account in the analysis. While responder analyses of the percentage of patients with improvement are meaningful in the present situation, the dossier provides these analyses only for the physician-rated surveys. For the benefit assessment, however, analyses based on ratings from the patient perspective would be relevant. For the outcome of patient-rated treatment response, no usable analyses are therefore available.

For the outcome of patient-rated symptom severity (SSR), patients rated the severity of their HES symptoms at baseline on a scale of 0 to 4 (none [0], mild [1], moderate [2], severe [3], and very severe [4] symptoms). They subsequently rated their symptoms on this scale every 4 weeks until Week 32. For the analyses of this outcome, the study protocol provides for patients being categorized as follows based on symptom change from baseline: from -4 points (improvement by 4 points) to 0 points (no change) and +4 points (deterioration by 4 points). The company's dossier presents analyses of change in symptom severity using an ordinal logistic regression analysis based on these categories. The company describes the approach as analogous to the above-described regression analysis for the outcome of patient-rated treatment response (RTS). As explained above for said outcome, the analyses are unusable for the present benefit assessment. Regarding the outcome of patient-rated symptom severity, no usable analyses are therefore available for the benefit assessment. Regarding the severity of individual HES symptoms, however, continuous analyses are both available and being used in the present benefit assessment.

Comments on further outcomes from the morbidity category

Patient Reported Outcome Measurement Information System (PROMIS)

The 200622 study used PROMIS to survey physical functioning and sleep. PROMIS is a valid, generic system consisting of domain-specific instruments for the self-reported and proxy-reported assessment of physical, mental, and social health. In general, the PROMIS system allows generating user-defined short forms for each domain by selecting items from the PROMIS item database.

In the 200622 study, the company utilized user-defined short forms for surveying physical functioning and for surveying sleep. However, no information is available as to whether the company conducted a validation for its item selection. In its description of methods underlying these outcomes, the company merely cites a publication by Reeve from 2007 [10], describing a validation method for the PROMIS item database. The study documents likewise contain no information on the manner in which the items were selected from the item database for the short forms used by the company or on the version of the item database used for the selection. Furthermore, the study documents contain discrepant information on the number of items used to survey physical functioning in the short form (14 items according to the study protocol versus 12 items according to the statistical analysis plan). Module 4 C additionally shows that scoring departed from the PROMIS recommendation in that raw values were not transformed into T-values. Due to the described uncertainties, the analyses presented by the company on physical functioning and sleep using PROMIS are unusable for the present benefit assessment.

Modified MSAS-SF

The 200622 study surveyed symptom burden via a modified form of the Memorial Symptom Assessment Scale-Short Form (MSAS-SF) questionnaire, which was originally developed by Chang et al. [11] for surveying symptoms in patients with various oncological indications. While Module 4 C of the company's dossier and the study documents indicate that the modified version was developed by means of qualitative interviews with 26 patients with HES, the company did not provide any information on the adjustments made on this basis. The questionnaire version used in the study comprises 20 items for which the frequency of symptom occurrence and the extent of symptom burden were surveyed. The MSAS-SF developed by Chang et al. contains a total of 32 items on symptoms; for 28 of these items, only the extent of symptom burden was rated, and for 4 items, only the frequency of occurrence.

The company did not present any information on the validation of the questionnaire's modified version. On the basis of the information submitted by the company, it therefore remains unclear which items are included in each of the presented analyses on the global stress index or physical or psychological symptoms, or the extent to which the frequency of occurrence of symptoms or symptom burden were taken into account. The analyses of the modified MSAS-SF presented by the company are therefore unsuitable for the present benefit assessment.

2.2.2 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 + standard therapy versus placebo + standard therapy

Study		Outcomes											
	Study level	All-cause mortality	Clinically manifested HES flares[a]	Worst fatigue (BFI Item 3)	Fatigue intensity / impairment by fatigue (BFI total score)	Severity of HES symptoms (HES-DS)[b]	Patient-rated treatment response (RTS)	Patient-rated symptom severity (SSR)	Activity impairment (WPAI question 6)	Health-related quality of life (SF-36v2)	SAEs	Discontinuation due to AEs	Specific AEs
200622	L	L	L	H[c]	H[d]	L	–[e]	–[e]	H[f]	L	L	L	–[g]

a. Defined as clinical manifestation of HES as surveyed via physician-documented changes in clinical signs or symptoms (using a standardized assessment) necessitating one of the following interventions: increase of OCS maintenance dose by at least 10 mg/day for 5 days or increase or addition of cytotoxic or immunosuppressant HES therapy.
b. Worst extent was surveyed via an NRS for each of the following symptoms: muscle/joint pain, chills/sweats, abdominal pain/bloating, breathing symptoms, nasal/sinus symptoms, skin symptoms.
c. Treatment groups contain differing percentage of patients replaced as nonresponders (> 5 percentage points).
d. High percentage (> 10%) of missing values replaced as nonresponders.
e. No usable data available; see Section 2.2.1 of the addendum for reasoning.
f. Decreasing questionnaire return rate over the course of the study and hence high percentage of missing values at the end of the analysis period (> 20%).
g. No specific AEs identified based on the AEs occurring in the relevant study.

AE: adverse event; BFI: Brief Fatigue Inventory; H: high; HES: hypereosinophilic syndrome; HES-DS: HES Daily Symptoms; L: low; RCT: randomized controlled trial; RTS: Response to Therapy Score; SAE: serious adverse event; SF-36v2: Short Form-36 Health Survey Version 2; SSR: Subject-Rated Symptom Severity; WPAI: Work Productivity and Activity Impairment

The risk of bias is rated as low for the results of the included outcomes, except for fatigue and activity impairment outcomes.

For the results on the fatigue outcomes, surveyed by BFI, there is a high risk of bias due to the differing percentages of missing values replaced as nonresponders (BFI item 3) as well as due to the large total percentage of missing values replaced as nonresponders (BFI total score). For the results of the outcome of activity impairment, surveyed by means of WPAI question 6, there is a high risk of bias due to decreasing questionnaire return rates, resulting in a high percentage (> 20%) of missing values at the end of the analysis period.

Summary assessment of the certainty of conclusions

For the present benefit assessment, it remains unclear whether the comparator therapy used in the 200622 study represents a full implementation of the ACT. This evaluation stems, in

particular, from the fact that for patients who had received neither OCS nor cytotoxic/immunosuppressant therapy at baseline (26% of patients in the comparator arm), no information is available as to whether baseline HES therapy was appropriate for the underlying organ involvement. In addition, a small percentage of participants, 9% of comparator arm participants, received no baseline HES therapy. The certainty of conclusions of the study results for the present research question is therefore reduced. Based on the 200622 study, at most hints, e.g. of an added benefit, can be determined for all presented outcomes (for reasoning, see Section 2).

2.2.3 Results

Table 4 and Table 5 summarize the results for the comparison of mepolizumab as add-on treatment versus the ACT for adult patients with inadequately controlled HES without an identifiable non-haematologic secondary cause. Where necessary, IQWiG calculations are provided in addition to data from the company's dossier.

For assessing clinical relevance, the standardized mean difference (SMD) is used, provided the mean difference (MD) is statistically significant. The company presents the corresponding calculations in Appendix 4 G. Since no description of calculation methods was provided, results were checked by IQWiG calculations. For this purpose, SMD was determined using the MD estimated from the analysis of a mixed model repeated measurement (MMRM), the associated 95% confidence interval (CI), and the respective sample size.

While the results differed from those of the company's calculation, said differences were deemed minor. Therefore, the company's calculations were used for the assessment.

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

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

Study Outcome category Outcome	Mepolizumab + standard therapy		Placebo + standard therapy		Mepolizumab + standard therapy vs. placebo + standard therapy
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
200622 (Week 32)					
Mortality					
All-cause mortality	54	1 (2)	54	0 (0)	–[a]; 0.528[b]
Morbidity					
Clinically manifested HES flares[c]	54	13 (24)	54	25 (46)	0.52 [0.28; 0.94]; 0.016[d]
Worst fatigue (BFI item 3)[e, f]	54	18 (33)	54	11 (20)	0.61 [0.30; 1.17]; 0.149[g,h]
Fatigue intensity / impairment by fatigue (BFI total score)[f, i]	54	17 (31)	54	10 (19)	0.59 [0.28; 1.16]; 0.131[g,h]
Patient-rated treatment response (RTS)	No usable data				
Patient-rated symptom severity (SSR)	No usable data				
Health-related quality of life					
SF-36v2					
Physical Component Summary (PCS)[f, j]	54	16 (39)	54	4 (7)	0.25 [0.07; 0.69]; 0.003[g,h]
Mental Component Summary (MCS)[f, k]	54	14 (26)	54	6 (11)	0.43 [0.13; 1.03]; 0.051[g,h]
Side effects					
AEs (supplementary information)	54	48 (89)	54	47 (87)	–
SAEs[l]	54	9 (17)	54	8 (15)	1.13 [0.45; 3.22]; 0.870[g]
Discontinuation due to AEs	54	0 (0)	54	2 (4)	0.2 [0.01; 4.07]; 0.209[d]

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

Study Outcome category Outcome	Mepolizumab + standard therapy		Placebo + standard therapy		Mepolizumab + standard therapy vs. placebo + standard therapy
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value

a. Effect estimate and 95% CI not meaningfully interpretable.
b. p-value: IQWiG calculation (unconditional exact test, CSZ method according to [12]).
c. Patients with ≥ 1 HES flare or premature study discontinuation; discrepant information provided in Module 4 C, designating them as patients with ≥ 1 HES flare or premature treatment discontinuation. In deviation from the information provided in Module 4 C of the company's dossier, study documents indicate that Module 4 C presents analyses on patients with ≥ 1 HES flare or premature study discontinuation. Including patients without HES flare who discontinued the study prematurely does not, overall, affect results in a relevant manner due to the small number of affected patients (n = 1 in the intervention arm and n = 2 in the control arm).
d. IQWiG calculation of CI (asymptotic); where 1 study arm had 0 events, the calculation of effect and CI used the correction factor 0.5 in both study arms; p-value: IQWiG calculation, unconditional exact test (CSZ method according to [12]).
e. Percentage of patients with improvement: decrease by ≥ 1.5 points (corresponds to ≥ 15% of the scale range from 0 to 10) for worst fatigue in the prior 24 hours (BFI item 3) at Week 32.
f. The company replaced missing values as nonresponders.
g. Exact unconditional CI, calculated by inversion of 2 separate one-sided tests on the basis of the score statistics; p-value: IQWiG calculation, unconditional exact test (CSZ method according to [12]).
h. Information based on the comparison of placebo + standard therapy versus mepolizumab + standard therapy.
i. Percentage of patients with improvement: decrease by ≥ 1.5 points (corresponds to ≥ 15% of the scale range from 0 to 10) in total BFI score at Week 32.
j. Percentage of patients with improvement: increase in PCS score by ≥ 9.4 points at Week 32 compared to baseline (corresponds to 15% of the scale range; normalized scale with a minimum of approx. 7 and a maximum of approx. 70); no data available on the SF-36 subscales.
k. Percentage of patients with improvement: increase in MCS score by ≥ 9.6 points at Week 32 compared to study start (corresponds to 15% of the scale range; normalized scale with a minimum of approx. 6 and a maximum of approx. 70); no data available on the SF-36v2 subscales.
l. Excluding deaths.

AE: adverse event; BFI: Brief Fatigue Inventory; CI: confidence interval; CSZ: convexity, symmetry, z-score; HES: hypereosinophilic syndrome; HES-DS: HES-Daily Symptoms; MCS: Mental Component Summary; n: number of patients with (at least 1) event; N: number of analysed patients; OCS: oral corticosteroid; PCS: Physical Component Summary; RCT: randomized controlled trial; RR: relative risk; RTS: Response to Therapy Score; SAE: serious adverse event; SF-36v2: Short Form-36 Health Survey Version 2; SSR: Subject-Rated Symptom Severity

Table 5: Results (morbidity, continuous) – RCT, direct comparison: mepolizumab + standard therapy versus placebo + standard therapy

Study Outcome category Outcome	Mepolizumab + standard therapy			Placebo + standard therapy			Mepolizumab + standard therapy vs. placebo + standard therapy
	N[a]	Values at baseline mean (SD)	Change at Week 32 mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change at Week 32 mean[b] (SE)	MD [95% CI][b]; p-value
200622 (Week 32)							
Morbidity							
Severity of HES symptoms (HES-DS)[c]							
Muscle/joint pain	ND	3.86 (2.49)	-1.03 (0.27)	ND	3.08 (2.68)	-0.27 (0.27)	-0.76 [-1.52; 0.01]; 0.052
Chills/sweats	ND	2.65 (2.82)	-1.19 (0.24)	ND	1.98 (2.37)	-0.41 (0.25)	-0.78 [-1.47; -0.09]; 0.026 SMD: -0.46 [-0.86; -0.05]
Abdominal pain/bloating	ND	3.12 (2.84)	-0.75 (0.24)	ND	2.63 (2.41)	-0.05 (0.25)	-0.70 [-1.39; 0.00]; 0.049 SMD: -0.40 [-0.81; 0.00]
Breathing symptoms	ND	4.08 (3.22)	-1.73 (0.27)	ND	3.23 (2.80)	-0.82 (0.28)	-0.91 [-1.68; -0.13]; 0.022 SMD: -0.47 [-0.88; -0.07]
Nasal/sinus symptoms	ND	3.51 (3.04)	-1.07 (0.27)	ND	2.90 (2.83)	-0.32 (0.28)	-0.75 [-1.53; 0.03]; 0.059
Skin symptoms	ND	2.94 (2.80)	-0.66 (0.28)	ND	3.37 (3.14)	-0.41 (0.28)	-0.25 [-1.04; 0.53]; 0.522
Activity impairment (WPAI question 6) (%)[d]	ND	46.3 (30.49)	-20.20 (3.47)	ND	40.4 (28.61)	-3.61 (3.46)	-16.59 [-26.39; -6.80]; 0.001 SMD: -0.74 [-1.18; -0.29]

a. Number of patients taken into account in the analysis for calculating the effect estimator.
b. MMRM baseline value, OCS dose at baseline, region, treatment group and visit as well as the interaction terms for visit and baseline value as well as visit and treatment group; the effect represents the difference in changes between treatment groups from study start to Week 32.
c. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus control) indicate an advantage for the intervention (scale range of 0 to 10).
d. Percent impairment; lower percentages indicate less activity impairment; negative effects (intervention minus control) indicate an advantage for the intervention (scale range of 0 to 100).

CI: confidence interval; HES: hypereosinophilic syndrome; HES-DS: ; 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; SMD: standardized mean difference; WPAI: Work Productivity and Activity Impairment

Based on the available data, at most hints, e.g. of an added benefit, can be determined for all outcomes (see Section 2.2.2).

Mortality

All-cause mortality

There was no statistically significant difference between treatment groups for the outcome of all-cause mortality. This results in no hint of added benefit of mepolizumab as add-on treatment in comparison with treatment according to physician's choice; an added benefit is therefore not proven.

Morbidity

Clinically manifested HES flares

Operationalization

The 200622 study surveyed HES flares both on the basis of clinical manifestations and independently of symptoms following 2 or more cycles of blinded, active OCS treatment during the study's treatment phase. Clinically manifested flares were defined as HES-caused clinical manifestation based on a physician-documented change in clinical signs or symptoms (with the aid of standardized assessment) which necessitates one of the following measures:

- increase in OCS maintenance dose by at least 10 mg/day for 5 days or
- increase in or additional administration of cytotoxic or immunosuppressant HES therapy.

The study provided for blinded OCS treatment according to a predefined dosing regimen in case of doubling of the blood eosinophil count or an increase by 2500 cells/µL, each from baseline, in patients without any treatment adjustments due to symptom deterioration within the prior 2 weeks. Where 2 or more cycles of said OCS treatment were administered within the study's treatment phase, this was rated as an HES flare (symptom-independent).

In the dossier's Module 4 C, the company submits various analyses of HES flares. Firstly, the company presents both time-to-event analyses and analyses of the percentage of patients with flares, each for all HES flares (clinically manifested and symptom-independent) and for clinically manifested flares. Secondly, the company submitted analyses of the annualized flare rate.

For the present benefit assessment, analyses of the percentage of patients with ≥ 1 clinically manifested HES flare are used because these events are associated with patient-noticeable symptoms. Analyses of all HES flares, in contrast, include events based merely on changes in laboratory values. Therefore, analyses of the percentage of patients with ≥ 1 HES flare recorded after clinical manifestation or blinded, active OCS therapy during study treatment as well as analyses of the adjusted annualized rate of all HES flares are unsuitable for the present benefit assessment. Table 12 and Table 13 in Appendix B offer a supplementary presentation of these analyses.

Results

For the outcome of clinically manifested HES flares, a statistically significant effect was found in favour of mepolizumab + standard therapy in comparison with placebo + standard therapy. However, the effect for this outcome of the category non-serious/non-severe symptoms / late complications is no more than marginal. For the outcome of clinically manifested HES flares, this results in no hint of added benefit of mepolizumab as add-on treatment in comparison with treatment according to physician's choice; an added benefit is therefore not proven.

Fatigue (surveyed using BFI)

For both worst level of fatigue, surveyed using BFI item 3, and fatigue intensity or impairment by fatigue, surveyed using the BFI total score, no statistically significant difference between treatment groups was found on the basis of the responder analyses presented by the company. This results in no hint of added benefit of mepolizumab as add-on treatment in comparison with treatment according to physician's choice for either of them; an added benefit is therefore not proven.

Severity of HES symptoms (HES-DS)

Operationalization

The 200622 study surveyed the severity of symptoms for various organ systems using an electronic diary (HES-DS). In this diary, patients rated worst symptom experience over the previous 24 hours every day for each of the following symptoms: muscle/joint pain, chills/sweats, abdominal pain/bloating, breathing symptoms, nasal/sinus symptoms, skin symptoms. Worst symptom experience was rated, in each case, on a scale from 0 to 10 (0 for "not present" and 10 for "worst imaginable"). At randomization, patients were also asked to report up to 3 symptoms which were most burdensome for them.

Regarding the severity of HES symptoms surveyed by HES-DS, the study protocol provided for various analyses. First, change in symptom severity from baseline to Week 32 was to be analysed for each individual symptom. Second, this analysis of change from baseline to Week 32 was also planned for the most burdensome symptoms. In Module 4 C of its dossier, the company presented both continuous analyses and responder analyses, reporting that each of them are based on the most burdensome symptoms. A comparison with the study documents, however, shows that the responder analyses are based on the most burdensome symptoms, while the continuous analyses are based on worst symptom experience for the individual symptoms.

The continuous analyses of the individual symptoms were used for the present benefit assessment. The responder analyses of the most burdensome symptoms are unsuitable for the benefit assessment because patients selecting up to 3 most burdensome symptoms at baseline means that the analyses did not include all patients with all symptoms. The continuous analyses of the individual symptoms, in contrast, include the surveys of all patients, whether or not they reported the symptom as burdensome at baseline.

Results

Muscle/joint pain; nasal/sinus symptoms; skin symptoms

On the basis of analysed mean differences, no statistically significant difference between treatment groups was found for any of the listed symptoms outcomes. For these outcomes, this results in no hint of added benefit of mepolizumab as add-on treatment in comparison with treatment according to physician's choice for either of them; an added benefit is therefore not proven.

Chills/sweats; abdominal pain/bloating; breathing symptoms

On the basis of analyses of mean differences, a statistically significant difference between treatment groups in favour of mepolizumab + standard therapy in comparison with placebo + standard therapy was found for each of the listed symptoms outcomes. The SMD was analysed to examine the relevance of the result. The 95% CI of the SMD was not completely outside the irrelevance range of -0.2 to 0.2 for each of them. The observed effect can therefore not be inferred to be relevant. This results in no hint of added benefit of mepolizumab as add-on treatment in comparison with treatment according to physician's choice for either of them; an added benefit is therefore not proven for any of them.

Patient-rated treatment response (RTS)

No usable data are available for the outcome of patient-rated treatment response (see Section 2.2.1). This results in no hint of added benefit of mepolizumab as add-on treatment in comparison with treatment according to physician's choice; an added benefit is therefore not proven.

Patient-rated symptom severity (SSR)

No usable data are available for the outcome of patient-rated symptom severity (see Section 2.2.1). This results in no hint of added benefit of mepolizumab as add-on treatment in comparison with treatment according to physician's choice; an added benefit is therefore not proven.

Activity impairment (WPAI question 6)

The analyses presented by the company based on mean differences show a statistically significant difference in favour of mepolizumab + standard therapy versus placebo + standard therapy for the outcome of activity impairment, surveyed by WPAI question 6. The 95% CI of the SMD was fully outside the irrelevance range of -0.2 to 0.2. This was interpreted to be a relevant effect. For the outcome of activity impairment, this results in a hint of added benefit of mepolizumab as add-on treatment in comparison with treatment according to physician's choice.

Health-related quality of life

SF-36v2 – Physical and Mental Component Summary

Operationalization

For the SF-36v2 PCS and MCS, Module 4 C of the company's dossier presents both continuous analyses and responder analyses of improvement, using both a response threshold of 15% of the scale range, corresponding to an improvement by ≥ 9.4 points (PCS) or ≥ 9.6 points (MCS), and improvement by a minimal important difference (MID) of ≥ 5 points.

The present assessment used the analyses of improvement by 15% of the scale range at Week 32. A supplementary presentation of the analyses of improvement by ≥ 5 points at Week 32 can be found in Table 12 in Appendix B.

Results

For the SF-36v2 PCS, there was a statistically significant difference in favour of mepolizumab + standard therapy in comparison with placebo + standard therapy on the basis of the responder analysis of improvement by ≥ 9.4 points. This results in a hint of added benefit of mepolizumab as add-on treatment in comparison with treatment according to physician's choice.

For the SF-36v2 MCS, there is no statistically significant difference between treatment groups on the basis of the responder analysis of improvement by ≥ 9.6 points. This results in no hint of added benefit of mepolizumab as add-on treatment in comparison with treatment according to physician's choice; an added benefit is therefore not proven.

Side effects

SAEs, discontinuation due to AEs

There was no statistically significant difference between treatment groups for either of the outcomes of SAEs and discontinuation due to AEs. For each of these outcomes, this results in no hint of greater or lesser harm from mepolizumab as add-on treatment in comparison with treatment according to physician's choice; greater or lesser harm is therefore not proven for these outcomes.

2.2.4 Subgroups and other effect modifiers

The following effect modifiers were deemed relevant for the present benefit assessment:

- age (2 to < 18 years / 18 to 64 years / ≥ 65 years)
- sex (female/male)

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

On the basis of the information provided by the company, the subgroup analyses of fatigue, surveyed using BFI, can be assumed to be based on continuous analyses. The present benefit

assessment, however, uses responder analyses of improvement by 15% of the scale range (corresponding to ≥ 1.5 points) (see Section 2.2.3).

For severity of HES symptoms, surveyed using HES-DS, the company did not carry out any subgroup analyses regarding the worst symptom experience for the individual symptoms. The company submitted subgroup analyses only for the symptoms patients reported at baseline as being most burdensome in the HES-DS survey. These analyses are not relevant for the present benefit assessment (see Section 2.2.3).

The company presented subgroup analyses of health-related quality of life, surveyed with the SF36v2-36v2 PCS and MCS, only for the responder analyses of improvement by a MID of ≥ 5 points. However, these analyses are irrelevant for the present benefit assessment (see Section 2.2.3). The company has not presented any subgroup analyses for the responder analyses relevant for the present benefit assessment, 15% of the scale range (≥ 9.4 points for PCS or ≥ 9.6 points for MCS).

Furthermore, Module 4 C of the company's dossier does not identify the methods generally used for calculating subgroup results and performing the interaction testing.

In addition, the company failed to report the effect measure on which the interaction tests are based for the subgroup analyses of the outcomes of clinically manifested HES flares, health-related quality of life, and side effects. Presumably, the odds ratio (OR) was used for interaction testing. What would be required, however, is a test for subgroup effects regarding the effect measure of relative risk (RR). The 2 effect measures can produce different results in the evaluation of an effect modification.

2.3 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG General Methods [13].

2.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.2 (see Table 6).

Determination of the outcome category for the morbidity outcomes

For the morbidity outcomes below, it cannot be inferred from the dossier whether they are serious/severe or non-serious/non-severe. The allocation of these outcomes is explained below.

Baseline data are used for assessing the severity of the individual HES symptoms, surveyed by HES-DS, as well as the outcome of activity impairment, surveyed by WPAI (question 6). For each of these outcomes, the means, both at baseline and over the course of the study, were in the low to moderate range, with lower values indicating better symptoms or less impairment.

The outcomes are assigned to the category of non-serious/non-severe symptoms / late complications.

The outcome of clinically manifested HES flares is assigned to the category of non-serious/non-severe symptoms / late complications because the available information is insufficient for rating them as serious/severe.

Table 6: Extent of added benefit at outcome level: mepolizumab + standard therapy versus standard therapy (multipage table)

Outcome category **Outcome**	**Mepolizumab + standard therapy vs. placebo + standard therapy** **Event rate (%) or mean** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality	2% vs. 0% RR: − p = 0.528	Lesser/added benefit not proven
Morbidity		
Clinically manifested HES flares	24% vs. 46% RR: 0.52 [0.28; 0.94]; p = 0.016	Outcome category: non-serious/non-severe symptoms / late complications $0.90 \leq CI_o < 1.00$ Lesser/added benefit not proven[c]
Fatigue (BFI item 3) Improvement by ≥ 1.5 points	33% vs. 20% RR: 0.61 [0.30; 1.17]; p = 0.149	Lesser/added benefit not proven
Fatigue (BFI total score) Improvement by ≥ 1.5 points	31% vs. 19% RR: 0.59 [0.28; 1.16]; p = 0.131	Lesser/added benefit not proven
Patient-rated treatment response (RTS)	No usable data	Lesser/added benefit not proven
Patient-rated symptom severity (SSR)	No usable data	Lesser/added benefit not proven
HES symptoms (HES-DS)		
Muscle/joint pain	Mean: -1.03 vs. -0.27 MD: -0.76 [-1.52; 0.01]; p = 0.052	Lesser/added benefit not proven
Chills/sweats	Mean: -1.19 vs. -0.41 MD: -0.78 [-1.47; -0.09]; p = 0.026 SMD: -0.46 [-0.86; -0.05][d]	Lesser/added benefit not proven
Abdominal pain/bloating	Mean: -0.75 vs. -0.05 MD: -0.70 [-1.39; 0.00]; p = 0.049 SMD: -0.40 [-0.81; 0.00][d]	Lesser/added benefit not proven
Respiratory symptoms	Mean: -1.73 vs. -0.82 MD: -0.91 [-1.68; -0.13]; p = 0.022 SMD: -0.47 [-0.88; -0.07][d]	Lesser/added benefit not proven
Nasal/sinus symptoms	Mean: -1.07 vs. -0.32 MD: -0.75 [-1.53; 0.03]; p = 0.059	Lesser/added benefit not proven

Table 6: Extent of added benefit at outcome level: mepolizumab + standard therapy versus standard therapy (multipage table)

Outcome category **Outcome**	**Mepolizumab + standard therapy vs. placebo + standard therapy** **Event rate (%) or mean** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Skin symptoms	Mean: -0.66 vs. -0.41 MD: -0.25 [-1.04; 0.53]; p = 0.522	Lesser/added benefit not proven
Activity impairment (WPAI question 6)	Mean: -20.20 vs. -3.61 MD: 16.59 [-26.39; -6.80]; p = 0.001 SMD: -0.74 [-1.18; -0.29] Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications Added benefit, extent: non-quantifiable
Health-related quality of life		
SF-36v2 PCS		
Improvement by ≥ 9.4 points	39% vs. 7% RR: 0.25 [0.07; 0.69]; p = 0.003 Probability: hint	Outcome category: health-related quality of life CI_u < 0.75, risk ≥ 5% Added benefit, extent: major
SF-36v2 MCS		
Improvement by ≥ 9.6 points	26% vs. 11% RR: 0.43 [0.13; 1.03]; p = 0.051	Lesser/added benefit not proven
Side effects		
SAEs	17% vs. 15% RR: 1.13 [0.45; 3.22]; p = 0.870	Greater/lesser harm not proven
Discontinuation due to AEs	0% vs. 2% RR: 0.2 [0.01; 4.07]; p = 0.209	Greater/lesser harm not proven

a. Probability is stated whenever a statistically significant and relevant effect is present.
b. Depending on the outcome category and the scale level of the outcome, effect size is estimated with different limits based on the upper or lower limit of the confidence interval (CI_u or CI_l).
c. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
d. If the CI for the SMD is fully outside the irrelevance range [-0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be inferred.

AE: adverse event; BFI: Brief Fatigue Inventory; CI: confidence interval; CI_l: lower limit of CI; CI_u: upper limit of CI; HES: hypereosinophilic syndrome; HES-DS: HES Daily Symptoms; MCS: Mental Component Summary; MD: mean difference; PCS: randomized controlled trial; RR: relative risk; RTS: Response to Therapy Score; SF-36v2: Short Form-36 Health Survey Version 2; SAE: serious adverse event; SSR: Subject-Rated Symptom Severity; WPAI: Work Productivity and Activity Impairment

2.3.2 Overall conclusion on added benefit

Table 7 summarizes the results taken into account in the overall conclusion of the extent of added benefit.

Table 7: Favourable and unfavourable effects from the assessment of mepolizumab + standard therapy in comparison with standard therapy

Favourable effects	**Unfavourable effects**
Non-serious/non-severe symptoms / late complications ▪ Activity impairment (WPAI question 6) – Hint of added benefit – extent: non-quantifiable	–
Health-related quality of life ▪ SF-36v2 PCS Hint of added benefit – extent: major	–
PCS: Physical Component Summary; SF-36v2: Short Form-36 Health Survey Version 2; WPAI: Work Productivity and Activity Impairment	

Overall, only favourable effects for mepolizumab were found, both in the outcome category of non-serious/non-severe symptoms / late complications and for health-related quality of life.

In summary, for adult patients with inadequately controlled HES without an identifiable non-haematological secondary cause, there is a hint of major added benefit of mepolizumab as add-on therapy in comparison with treatment according to physician's choice.

2.4 Summary

For this research question, the assessment of the 200622 study changes the conclusion on the added benefit of mepolizumab from dossier assessment A21-152 [1]. Table 8 below shows the result of the benefit assessment of mepolizumab taking into account dossier assessment A21-152 [1] and the present addendum.

Table 8: Mepolizumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Add-on therapy for adult patients with inadequately controlled HES without an identifiable non-haematological secondary cause[b]	Treatment according to physician's choice[c,d]	Hint of major added benefit

a. Presented is the respective ACT specified by the G-BA.
b. The clinical studies on mepolizumab did not investigate patients with FIP1L1-PDGFRα translocation. According to the G-BA, due to disease aetiology, patients with clonal hypereosinophilia are currently assumed not to be candidates for mepolizumab treatment. Therefore, this patient group was disregarded in the G-BA's specification of the ACT.
c. No approved drug therapies exist for treating HES without FIP1L1-PDGFRα translocation. Even the drugs listed in treatment recommendations are not approved for treatment. The following drugs may be suitable comparators within a study: corticosteroids and, if necessary, other immunosuppressants (azathioprine, interferon-α, or ciclosporin), or myelosuppressive therapy (hydroxycarbamide), or a treatment attempt with imatinib.
d. Unchanged continuation of an inadequate therapy does not constitute implementation of treatment according to physician's choice if at the time of enrolment, treatment adjustment options were still available to optimize treatment.

ACT: appropriate comparator therapy; FIP1L1-PDGFRα: FIP1-like1-Platelet-Derived Growth Factor Receptor α; G-BA: Federal Joint Committee; HES: hypereosinophilic syndrome

The G-BA decides on the added benefit.

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Appendix A Results on side effects

The tables below present events for MedDRA System Organ Classes (SOCs) and Preferred Terms (PTs) for the overall rates of AEs and SAEs, each on the basis of the following criteria:

- total rate of AEs (irrespective of severity): events which occurred in at least 10% of patients in 1 study arm
- SAEs: events which occurred in at least 5% of patients in 1 study arm
- Additionally, for all events irrespective of severity: events which occurred in at least 10 patients and at least 1% of patients in 1 study arm

For the outcome of discontinuation due to AEs, all events (SOCs/PTs) which resulted in discontinuation are completely presented.

Table 9: Common AEs[a] – RCT, direct comparison: mepolizumab + standard therapy versus placebo + standard therapy

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**Mepolizumab + standard therapy N = 54**	**Placebo + standard therapy N = 54**
200622		
Overall AE rate	48 (89)	47 (87)
Infections and infestations	37 (69)	28 (52)
Bronchitis	8 (15)	10 (19)
Nasopharyngitis	7 (13)	7 (13)
Rhinitis	5 (9)	6 (11)
Upper respiratory tract infection	8 (15)	2 (4)
Gastrointestinal disorders	17 (31)	16 (30)
Diarrhoea	5 (9)	7 (13)
General disorders and administration site conditions	18 (33)	15 (28)
Musculoskeletal and connective tissue disorders	18 (33)	14 (26)
Pain in the extremities	6 (11)	2 (4)
Respiratory, thoracic, and mediastinal disorders	13 (24)	19 (35)
Nervous system disorders	17 (31)	13 (24)
Headache	7 (13)	7 (13)
Skin and subcutaneous tissue disorders	13 (24)	16 (30)
Pruritus	4 (7)	7 (13)
Injury, poisoning, and procedural complications	9 (17)	4 (7)
Reproductive system and breast disorders	6 (11)	3 (6)

a. Events which occurred in ≥ 10% of patients of at least 1 study arm.
b. MedDRA version 22.0; SOC and PT notation taken from Module 4 C.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 10: Common SAEs – RCT, direct comparison: mepolizumab + standard therapy versus placebo + standard therapy

Study	Patients with event n (%)	
	Mepolizumab + standard therapy N = 54	Placebo + standard therapy N = 54
Study 200622		
Total SAE rate[a]	9 (17)	8 (15)

a. Regarding SAEs, no MedDRA SOCs or PTs met the criterion for being presented (all events which occurred in ≥ 5% of patients in at least 1 study arm).

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 11: Discontinuation due to AEs – RCT, direct comparison: mepolizumab + standard therapy versus placebo + standard therapy

Study	Patients with event n (%)	
SOC[a] PT[a]	Mepolizumab + standard therapy N = 54	Placebo + standard therapy N = 54
Study 200622		
Total rate of discontinuations due to AEs	0 (0)	2 (4)
T-cell lymphoma	0 (0)	1 (2)
Malignant neoplasm at the lung	0 (0)	1 (2)[b]

a. MedDRA version 22.0; PT notation taken unmodified from Module 4 C.
b. The event occurred before treatment start but led to discontinuation after treatment start.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Appendix B Supplementary presentation of results on morbidity and health-related quality of life

Table 12: Results (morbidity, health-related quality of life, supplementary presentation) – RCT, direct comparison: mepolizumab + standard therapy versus placebo + standard therapy

Study Outcome category Outcome	Mepolizumab + standard therapy		Placebo + standard therapy		Mepolizumab + standard therapy vs. placebo + standard therapy
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
200622 (Week 32)					
Morbidity					
All HES flares[a]	54	15 (28)	54	30 (56)	0.50 [0.28; 0.85]; 0.004[b]
Health-related quality of life					
SF-36v2					
PCS[c,d]	54	23 (43)	54	20 (37)	0.87 [0.52; 1.43]; 0.603[e]
MCS[c,d]	54	25 (46)	54	17 (31)	0.68 [0.38; 1.11]; 0.126[e]

a. Patients with ≥ 1 HES flare or premature study discontinuation; flares were surveyed both based on clinical manifestation and based on 2 or more cycles of blinded, active OCS treatment. Discrepant information provided in Module 4 C, indicating patients with ≥ 1 HES flare or premature treatment discontinuation. In deviation from Module 4 C of the company's dossier, the study documents show that Module 4 C presents analyses on patients with ≥1 HES flare or premature study discontinuation. Due to the small number of affected patients (n = 1 in the intervention arm and n = 2 in the control arm), taking into account patients without HES flare who discontinued the study prematurely does not, overall, affect results in a relevant manner.

b. IQWiG calculation of CI (asymptotic); in case of 0 events in 1 study arm, the correction factor 0.5 was used for calculating effect and CI in both study arms; p-value: IQWiG calculation, unconditional exact test (CSZ method according to [12]).

c. Percentage of patients with increase in PCS or MCS score by ≥ 5 points at Week 32 compared to study start (normalized scale with a minimum of approx. 7 and a maximum of approx. 70).

d. The company replaced missing values as nonresponders.

e. Exact unconditional CI, calculated by inversion of 2 separate one-sided tests on the basis of the score statistics; p-value: IQWiG calculation, unconditional exact test (CSZ method according to [12]); information based on the comparison of placebo + standard therapy vs. mepolizumab + standard therapy.

CI: confidence interval; CSZ: convexity, symmetry, z-score; HES: hypereosinophilic syndrome; HES-DS: HES-Daily Symptoms; MCS: Mental Component Summary; n: number of patients with (at least 1) event; N: number of analysed patients; OCS: oral corticosteroid; PCS: Physical Component Summary; RCT: randomized controlled trial; RR: relative risk; SF-36v2: Short Form-36 Health Survey Version 2

Table 13: Results (morbidity, supplementary presentation) – RCT, direct comparison: mepolizumab + standard therapy versus placebo + standard therapy

Study **Outcome category** **Outcome**	**Mepolizumab + standard therapy**		**Placebo + standard therapy**		**Mepolizumab + standard therapy vs. placebo + standard therapy**
	N	**Number of events (annualized rate [95% CI][a,b])**	**N**	**Number of events (annualized rate [95% CI][a,b])**	**Rate ratio [95% CI]; p-value[b]**
200622					
Morbidity					
All HES flares[c]	54	17; (0.50 [ND])	54	48; (1.46 [ND])	0.34 [0.19; 0.63]; < 0.001

a. Adjusted mean annualized rate.
b. Negative binomial generalized linear model with baseline OCS dose, region, treatment group, and observed time (offset variable).
c. Flares were surveyed both based on clinical manifestation and based on 2 or more cycles of blinded active OCS treatment.

CI: confidence interval; HES: hypereosinophilic syndrome; N: number of analysed patients; ND: no data; OCS: oral corticosteroid; RCT: randomized controlled trial