IQWiG Reports – Commission No. A22-42

Mepolizumab (chronic rhinosinusitis with nasal polyposis) –

Addendum to Commission A21-150[1]

Addendum

Commission: A22-42
Version: 1.0
Status: 28 April 2022

[1] Translation of addendum A22-42 *Mepolizumab (chronische Rhinosinusitis mit Nasenpolypen) – Addendum zum Auftrag A21-150* (Version 1.0; Status: 28 April 2022). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Mepolizumab (chronic rhinosinusitis with nasal polyposis) – Addendum to Commission A21-150

Commissioning agency
Federal Joint Committee

Commission awarded on
12 April 2022

Internal Commission No.
A22-42

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Keywords: Mepolizumab, Sinusitis, Benefit Assessment, NCT03085797

Table of contents

List of tables

Page

List of abbreviations

Abbreviation	Meaning
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
INCS	intranasal corticosteroids
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MCS	Mental Component Summary
MID	minimally important difference
PCS	Physical Component Summary
RCT	randomized controlled trial
SF-36v2	Short Form 36-Item Health Survey
SNOT-22	22-item Sino-Nasal Outcome Test
VAS	visual analogue scale
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 A21-150 (Mepolizumab – benefit assessment according to §35a Social Code Book V) [1]. The benefit assessment of mepolizumab included the randomized controlled trial (RCT) SYNAPSE comparing mepolizumab + mometasone furoate with placebo + mometasone furoate.

The G-BA commissioned IQWiG with assessing the following analyses from the SYNAPSE study, taking into account the information provided in the dossier [2]:

- Short Form 36-Item Health Survey (SF-36) (responder analyses using the 15% threshold as well as the minimally important difference [MID] of 5 points)
- nasal polyp surgery
- Work Productivity and Activity Impairment [WPAI] question 6 (activity impairment)
- subsequently submitted analyses performed by the pharmaceutical company (hereinafter referred to as “company”) on morbidity and quality of life outcomes without imputation of missing values, taking into account the data which actually continued to be surveyed [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 Assessment

2.1 Relevance rating of the outcomes/analyses evaluated in the addendum

Replacement strategy for outcomes of the categories of morbidity and health-related quality of life

For outcomes of the morbidity category (surveyed via visual analogue scales [VAS], the 22-item Sino-Nasal Outcome Test [SNOT-22], and the WPAI) and the health-related quality of life category (surveyed with the SF-36v2), the company's dossier contained analyses in which patients who had undergone nasal polyp surgery (see dossier assessment A21-150 for a definition) or sinuplasty were allocated the worst value observed prior to the procedure despite the fact that these patients did not discontinue treatment and data continued to be surveyed in the subsequent visits. The analyses presented by the company were used in dossier assessment A21-150. How the data the company imputed after nasal polyp surgery impact the effects was described as unclear, however; therefore, statistically significant effects were non-quantifiable in the present assessment.

As part of the commenting procedure, the company subsequently submitted analyses without the described imputation strategy for outcomes of the morbidity category (VAS SNOT-22) and the health-related quality of life category (SF-36v2) [3]. These results are relevant for the benefit assessment since nasal polyp surgery does not represent the end of all therapies in the therapeutic indication but instead is part of a treatment strategy. The Summaries of Product Characteristics (SPCs) [4,5] likewise do not specify for mepolizumab treatment to end after surgery, and studies investigate the effect of mepolizumab treatment on the risk of haemorrhage and postoperative wound healing [6]. Therefore, data on symptoms and quality of life after nasal polyp surgery are therefore both patient relevant and assessment relevant. Based on these data, the added benefit on the outcome level can now be quantified. For the above-cited outcomes, the results without imputation (of the values of patients who underwent nasal polyp surgery) are presented below; the corresponding results with imputation are presented as supplementary information. Where possible, the added benefit of mepolizumab on the outcome level is assessed and quantified on the basis of results without imputation.

Morbidity

WPAI question 6 (activity impairment)

The WPAI is an instrument for measuring the impairment of work productivity and activities within the prior 7 days [7]. The questionnaire comprises 6 questions; as commissioned, the impairment of daily activities (question 6) was presented. The outcome is deemed patient relevant and taken into account in the benefit assessment. For this outcome, the company presents continuous analyses at Week 52 with imputation.

Nasal polyp surgery

In the SYNAPSE study, nasal polyp surgery was defined as any procedure involving instruments leading to an incision and removal of tissue from the paranasal sinus

(polypectomy). Hence, procedures only dilating the airway without tissue removal (e.g. balloon sinuplasty) were not included in this outcome. At each visit, patients were asked whether nasal polyp surgery had been performed, and their answer was documented. Any measures performed on the same day were deemed 1 single surgical procedure.

As done in dossier assessment A21-150, the outcome of nasal polyp surgery was disregarded in the assessment. The results for the outcome were presented as supplementary information in Appendix A as commissioned by the G-BA.

Health-related quality of life
(SF-35v2 responder analyses)

For health-related quality of life, the company's dossier presented responder analyses of SF-36v2. For the responder analyses, the company presented results for the response criterion of 15%, corresponding to an improvement by ≥ 9.4 points (Physical Component Summary [PCS]) or ≥ 9.6 points (Mental Component Summary [MCS]). For deriving added benefit, the company used the responder analyses of the MID for an improvement by ≥ 5 points in both summary scores. However, the company did not address the necessary normalization of the scale range from 100 to 63 (PCS) or to 64 (MCS), which is the prerequisite for applying the response criteria of 15% or MID ≥ 5. Due to these uncertainties, the SF-36v2 data were unusable for the benefit assessment. As part of the commenting procedure [8], the company transparently clarified that for the analysis, the necessary normalization of the scale range from 100 to 63 (PCS) or 64 (MCS) was conducted. In addition, the company reported that the continuous analyses of SF-36v2 presented in the dossier erroneously included the subscales of physical functioning and mental health instead of PCS and MCS. For the responder analyses, however, the PCS and MCS data were reportedly used. In the present addendum, the analyses for the response criterion of 15% are therefore used for the benefit assessment. As explained in the IQWiG *General Methods* [9], for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to at least 15% of the scale range of an instrument if prespecified and exactly 15% of the scale range in post-hoc analyses.

The SF-36v2 results presented by the company for the response criterion of ≥ 5 points (without imputation) are presented as supplementary information in Appendix A as commissioned by the G-BA.

2.2 Risk of bias

The risk of bias is rated as low for the results of the subsequently submitted and included outcomes on morbidity (surveyed via VAS symptom scales and SNOT-22) and health-related quality of life (SF-36v2, improvement by ≥ 9.4 points [PCS] or by ≥ 9.6 points [MCS]).

For the subsequently submitted analyses without imputation (of the values of patients who have undergone nasal polyp surgery), no data on questionnaire return rates after surgery are available. Hence, it remains unclear which percentage, if any, of patients who underwent nasal polyp surgery (intervention arm: 9%; placebo arm: 23%) discontinued the study in the further

course or had missing data on individual questionnaires. On the basis of the information on study discontinuation (about 7%) and missing values (about 3%) among patients without nasal polyp surgery, however, the percentage of imputed values in the overall population is assumed to be low; therefore, the risk of bias of results is not high.

For the results of the outcome of activity impairment (surveyed with WPAI question 6), the risk of bias is presumably high. This is due to the percentage of imputed values being high and differing between study arms, primarily after nasal polyp surgery (intervention arm: 9%; placebo arm: 23%).

Summary assessment of certainty of results

As described in dossier assessment A21-150, uncertainties result for the SYNAPSE study regarding the need for nasal polyp surgery at baseline and the (prior) treatment of aspirin-exacerbated respiratory disorders, which overall lead to reduced certainty of results. On the basis of the effects shown in the SYNAPSE study, at most hints, e.g. of an added benefit, can therefore be derived for all outcomes.

2.3 Results

Table 1 and Table 2 summarize the results of the comparison of mepolizumab + mometasone furoate with placebo + mometasone furoate in patients with severe chronic rhinosinusitis with nasal polyps which cannot be adequately controlled with systemic corticosteroids and/or surgery. Presented as supplementary information are the results of the outcomes on morbidity, surveyed by VAS symptom scales and SNOT-22, and on health-related quality of life (SF-36v2) with imputation strategy (for patients who underwent nasal polyp surgery or sinuplasty, the worst value observed prior to the procedure was used).

Table 1: Results (morbidity, health-related quality of life) – RCT, direct comparison: mepolizumab + mometasone furoate versus placebo + mometasone furoate (multipage table)

Study Outcome category Outcome	Mepolizumab + mometasone furoate		Placebo + mometasone furoate		Mepolizumab + mometasone furoate vs. placebo + mometasone furoate
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI][a]; p-value[b]
SYNAPSE					
Morbidity					
Overall symptom score (supplementary information)[c]					
With imputation[d] (presented as supplementary information)	*206*	*139 (67)*	*201*	*90 (45)*	*0.66 [0.55; 0.80][e]; < 0.001*
Without imputation[f]	206	154 (75)	201	129 (64)	0.86 [0.75; 0.98][e]; 0.022
VAS for nasal obstruction[c]					
With imputation[d] (presented as supplementary information)	*206*	*140 (68)*	*201*	*93 (46)*	*0.68 [0.56; 0.82][e]; < 0.001*
Without imputation[f]	206	155 (75)	201	132 (66)	0.87 [0.76; 0.99][e]; 0.037
VAS for nasal discharge[c]					
With imputation[d] (presented as supplementary information)	*206*	*140 (68)*	*201*	*93 (46)*	*0.68 [0.56; 0.82][e]; < 0.001*
Without imputation[f]	206	155 (75)	201	132 (66)	0.87 [0.76; 0.99][e]; 0.037
VAS for mucus in the throat[c]					
With imputation[d] (presented as supplementary information)	*206*	*133 (65)*	*201*	*92 (46)*	*0.71 [0.58; 0.86][e]; < 0.001*
Without imputation[f]	206	148 (72)	201	130 (65)	0.90 [0.78; 1.03][e]; 0.129
VAS for facial pain/pressure[c]					
With imputation[d] (presented as supplementary information)	*206*	*126 (61)*	*201*	*87 (43)*	*0.71 [0.58; 0.87][e]; < 0.001*
Without imputation[f]	206	141 (68)	201	119 (59)	0.86 [0.74; 1.00][e]; 0.054
VAS for loss of smell[c]					
With imputation[d] (presented as supplementary information)	*206*	*92 (45)*	*201*	*50 (25)*	*0.56 [0.40; 0.75][e]; < 0.001*
Without imputation[f]	206	100 (49)	201	71 (35)	0.73 [0.57; 0.95][e]; 0.007

Table 1: Results (morbidity, health-related quality of life) – RCT, direct comparison: mepolizumab + mometasone furoate versus placebo + mometasone furoate (multipage table)

Study Outcome category Outcome	Mepolizumab + mometasone furoate		Placebo + mometasone furoate		Mepolizumab + mometasone furoate vs. placebo + mometasone furoate
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI][a]; p-value[b]
SNOT-22 total score[g]					
With imputation[d] (presented as supplementary information)	*205*	*142 (69)*	*198*	*90 (45)*	*0.66 [0.54; 0.79][e]; < 0.001*
Without imputation[f]	205	157 (77)	198	122 (62)	0.80 [0.69; 0.93][e]; 0.001
Health-related quality of life					
SF-36v2					
Physical Component Summary (PCS)[h]					
With imputation[d] (presented as supplementary information)	*205*	*81 (40)*	*198*	*32 (16)*	*0.41 [0.27; 0.59][e]; < 0.001*
Without imputation[f]	205	86 (42)	198	46 (23)	0.55 [0.39; 0.76][e]; < 0.001
Mental Component Summary (MCS)[i]					
With imputation[d] (presented as supplementary information)	*205*	*59 (29)*	*198*	*27 (14)*	*0.47 [0.30; 0.72][e]; < 0.001*
Without imputation[f]	205	62 (30)	198	41 (21)	0.68 [0.47; 0.99][e]; 0.030

a. Exact unconditional CI calculated by inverting 2 separate one-sided tests based on the score statistic.
b. IQWiG calculation, unconditional exact test (CSZ method according to [10]).
c. Proportion of patients with a score decrease by ≥ 1.5 points of the mean from week 49 to 52 from baseline (7 days before randomization), at a scale range of 0 to 10. Lower (decreasing) values indicate an improvement of symptoms.
d. For patients who had undergone nasal polyp surgery or sinuplasty, the worst value observed prior to surgery was used.
e. Data based on the comparison of placebo + mometasone furoate vs. mepolizumab + mometasone furoate.
f. Based on the imputation strategy cited in footnote d. The analysis may include imputations of values missing for other reasons (e.g. study discontinuation).
g. Proportion of patients with a ≥ 16.5-point decrease in total score from baseline (randomization) to Week 52, on a scale range of 0 to 110. Lower (decreasing) values indicate an improvement in symptoms.
h. Proportion of patients with a ≥ 9.4-point PCS score increase from baseline (randomization) to Week 52, measured on a standardized scale with a minimum of about 7 and a maximum of about 70. Higher (increasing) values indicate an improvement in health-related quality of life.
i. Proportion of patients with a ≥ 9.6-point increase in MCS score from baseline (randomization) to Week 52, measured on a standardized scale with a minimum of about 6 and a maximum of about 70. Higher (increasing) values indicate an improvement in health-related quality of life.

CI: confidence interval; CSZ: convexity, symmetry, z-score; IQWiG: Institute for Quality and Efficiency in Health Care; MCS: Mental Component Summary; n: number of patients with (at least 1) event; N: number of analysed patients; PCS: Physical Component Summary; RCT: randomized controlled trial; RR: relative risk; SF-36v2: Short Form 36 Health Survey version 2; SNOT-22: 22-item Sino-Nasal Outcome Test; VAS: visual analogue scale

Table 2: Results (morbidity, continuous) – RCT, direct comparison: mepolizumab + mometasone furoate versus placebo + mometasone furoate

Study Outcome category Outcome	Mepolizumab + mometasone furoate			Placebo + mometasone furoate			Mepolizumab + mometasone furoate vs. placebo + mometasone furoate
	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]
SYNAPSE							
Morbidity							
Activity impairment[c] [%][d]	ND	53.4 (28.0)	-33.1 (1.74)	ND	53.2 (29.1)	-25.3 (1.77)	-7.8 [-12.67; -2.93]; 0.002 SMD: -0.33 [-0.54; -0.12]

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 group, baseline WPAI, region, log(e) baseline blood eosinophil count, and visit as well as interaction terms for visit and baseline WPAI and visit and treatment group.
c. With imputation of missing values; missing values were presumably replaced by the patient's worst previously observed value, including values after nasal polyp surgery, as done by the company in Module 4 A for the other outcomes of the morbidity and health-related quality of life categories.
d. Lower percentages indicate less impairment of daily activity; negative effects (intervention minus control) indicate an advantage for the intervention (scale range of 0 to 100).

CI: confidence interval; MD: mean difference; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; SMD: standardized mean difference; WPAI: Work Productivity and Activity Impairment

Morbidity

Nasal obstruction, nasal discharge, loss of smell

For the outcomes of nasal obstruction, nasal discharge, and loss of smell, each recorded with a VAS, a statistically significant difference was found in favour of mepolizumab + mometasone furoate in comparison with placebo + mometasone furoate in the proportion of patients with an improvement by ≥ 1.5 points. This results in a hint of an added benefit of mepolizumab as an add-on therapy with intranasal corticosteroids (INCS) in comparison with INCS therapy for each of these outcomes.

Mucus in the throat, facial pain/pressure

For the outcomes of mucus in the throat and facial pain/pressure, each recorded with a VAS, no statistically significant difference between treatment arms was found in the proportion of patients with an improvement by ≥ 1.5 points. This results in no hint of an added benefit of mepolizumab as an add-on therapy with INCS in comparison with INCS therapy; an added benefit for these outcomes is not proven.

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

For the outcome of SNOT-22, a statistically significant difference was found in favour of mepolizumab + mometasone furoate in comparison with placebo + mometasone furoate in the proportion of patients with an improvement in overall score by ≥ 16.5 points. This difference was no more than marginal, however. This results in no hint of an added benefit of mepolizumab as an add-on therapy with INCS in comparison with INCS therapy; an added benefit for this outcome is not proven.

Activity impairment (WPAI question 6)

For the outcome of activity impairment (WPAI question 6), the continuous analysis of change from baseline shows a statistically significant difference in favour or mepolizumab + mometasone furoate in comparison with placebo+ mometasone furoate. However, the 95% CI of the standardized mean difference is not fully outside the irrelevance range of -0.2 to 0.2. It can therefore not be inferred that the observed effect was relevant. This results in no hint of an added benefit of mepolizumab as an add-on therapy with INCS in comparison with INCS therapy; an added benefit for this outcome is not proven.

Health-related quality of life (SF-36v2)

For the outcome of health-related quality of life (SF-36v2), responder analyses of improvement by ≥ 9.4 points are used for the Physical Component Summary and responder analyses of improvement by ≥ 9.6 points for the Mental Component Summary.

For the Physical Component Summary as well as the Mental Component Summary, there is a statistically significant difference in favour of mepolizumab + mometasone furoate in comparison with placebo + mometasone furoate. This results in a hint of added benefit of mepolizumab + mometasone furoate in comparison with placebo + mometasone furoate.

2.4 Subgroups and other effect modifiers

For the subsequently submitted results which are relevant for the assessment, the company has not presented any subgroup analyses. Regarding the analyses used in dossier assessment A21-150, likewise, no subgroup analyses at all are available for the analyses with imputation, and no suitable ones are available for the side effects analyses.

In its comments, the company further specified the methods it used for conducting subgroup analyses in continuous outcome operationalizations. The approach used by the company for this purpose is appropriate. For the outcome of activity impairment (WPAI question 6), there is no relevant effect modification for the subgroup characteristics of age, sex, and disease severity.

2.5 Probability and extent of added benefit

2.5.1 Assessment of the added benefit at outcome level

On the basis of the results presented in Section 2.3 and the results of dossier assessment A21-150, the extent of added benefit was estimated at outcome level (see Table 3).

Determination of the outcome category for the outcome of SNOT-22 (symptoms and social/emotional consequences of rhinosinusitis)

In its comments, the company allocates the outcome of SNOT-22 to the outcome category of serious/severe symptoms / late complications. The company bases this allocation on the research of Toma and Hopkins [11], who investigated patients with chronic rhinosinusitis irrespective of the presence of nasal polyps. The research does not show how many, if any, patients with nasal polyps were examined. Since it is unclear whether the severity threshold differs between chronic rhinosinusitis patients without nasal polyps versus those with nasal polyps, there is still no information available regarding a threshold for the SNOT-22 total score which would be suitable for rating the severity of SNOT-22-surveyed symptoms at baseline as serious or severe. Therefore, the outcome of SNOT-22 remains allocated to the outcome category of non-serious/non-severe symptoms / late complications.

See A21-150 regarding the determination of the outcome category for the outcome of symptoms (nasal obstruction, nasal discharge, mucus in the throat, facial pain/pressure, and loss of smell).

Table 3: Extent of added benefit at outcome level: mepolizumab + mometasone furoate versus mometasone furoate (multipage table)

Outcome category **Outcome**	**Mepolizumab + mometasone furoate vs. placebo + mometasone furoate** **Event rate (%) or change by Week 52** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality	0% vs. 0% RR: -	Lesser benefit/added benefit not proven
Morbidity		
VAS for nasal obstruction improvement by ≥ 1.5 points	75% vs. 66% RR: 0.87 [0.76; 0.99][c]; p = 0.037 Probability: hint	Outcome category: serious/severe symptoms / late complications $0.90 \leq CI_u < 1.00$ Added benefit, extent: minor
VAS for nasal discharge improvement by ≥ 1.5 points	75% vs. 66% RR: 0.87 [0.76; 0.99][c]; p = 0.037 Probability: hint	Outcome category: serious/severe symptoms / late complications $0.90 \leq CI_u < 1.00$ Added benefit, extent: minor
VAS for mucus in the throat improvement by ≥ 1.5 points	72% vs. 65% RR: 0.90 [0.78; 1.03][c]; p = 0.129	Lesser/added benefit not proven
VAS for facial pain/pressure improvement by ≥ 1.5 points	68% vs. 59% RR: 0.86 [0.74; 1.00][c]; p = 0.054	Lesser/added benefit not proven
VAS for loss of smell improvement by ≥ 1.5 points	49% vs. 35% RR: 0.73 [0.57; 0.95][c]; p = 0.007 Probability: hint	Outcome category: serious/severe symptoms / late complications $0.90 \leq CI_u < 1.00$ Added benefit, extent: minor
SNOT-22 total score improvement by ≥ 16.5 points	77% vs. 62% RR: 0.80 [0.69; 0.93][c]; p = 0.001	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser/added benefit not proven[d]
Activity impairment due to disease (WPAI question 6)	-33.1 vs. -25.3 MD: -7.8 [-12.67; -2.93]; p = 0.002 SMD: -0.33 [-0.54; -0.12][e]	Lesser/added benefit not proven

Table 3: Extent of added benefit at outcome level: mepolizumab + mometasone furoate versus mometasone furoate (multipage table)

Outcome category **Outcome**	**Mepolizumab + mometasone furoate vs. placebo + mometasone furoate** **Event rate (%) or change by Week 52** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Health-related quality of life		
SF-36v2		
Physical Component Summary (PCS) improvement by ≥ 9.4 points	42% vs. 23% RR: 0.55 [0.39; 0.76][c]; p < 0.001 Probability: hint	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ Added benefit, extent: considerable
Mental Component Summary (MCS) improvement by ≥ 9.6 points	30% vs. 21% RR: 0.68 [0.47; 0.99][c]; p = 0.030 Probability: hint	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Added benefit; extent: minor
Side effects		
SAEs	6% vs. 6% RR: 0.90 [0.38; 2.04]; p = 0.831	Greater/lesser harm not proven
Discontinuation due to AEs	2% vs. 2% RR: 0.98 [0.22; 4.33]; p > 0.999	Greater/lesser harm not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Data based on the comparison of placebo + mometasone furoate vs. mepolizumab + mometasone furoate.
d. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
e. 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 derived.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; MCS: Mental Component Summary; PCS: Physical Component Summary; RR: relative risk; SAE: serious adverse event; SF-36v2: Short Form 36 Health Survey version 2; SMD: standardized mean difference; SNOT-22: 22-item Sino-Nasal Outcome Test; VAS: visual analogue scale

2.5.2 Overall conclusion on added benefit

Table 4 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 4: Positive and negative effects from the assessment of mepolizumab + mometasone furoate in comparison with mometasone furoate

Positive effects	Negative effects
Serious/severe symptoms/late complications ▪ VAS for nasal obstruction, VAS for nasal discharge, VAS for loss of smell: each hint of added benefit – extent: minor Health-related quality of life (SF-36v2) ▪ Physical Component Summary (PCS): hint of an added benefit – extent: considerable ▪ Mental Component Summary (MCS): hint of an added benefit – extent: minor	-
MCS: Mental Component Summary; PCS: Physical Component Summary; SF-36v2: Short Form-36 Health Survey Version 2; VAS: visual analogue scale	

Overall, only positive effects were found. In the outcome category of serious/severe symptoms / late complications, they were of minor extent, while in the outcome category of health-related quality of life, they were of considerable extent.

In summary, there is a hint of considerable added benefit of mepolizumab as an add-on therapy with intranasal corticosteroids in comparison with the ACT for patients with severe chronic rhinosinusitis with nasal polyps which cannot be adequately controlled with systemic corticosteroids and/or surgery.

2.6 Summary

The data subsequently submitted by the company in the commenting procedure change the conclusion on the added benefit of mepolizumab drawn in dossier assessment A21-150: For patients with severe chronic rhinosinusitis with nasal polyps which cannot be adequately controlled with systemic corticosteroids and/or surgery, there is a hint of considerable added benefit.

Table 5 below shows the result of the benefit assessment of mepolizumab taking into account both dossier assessment A21-150 and the present addendum.

Table 5: Mepolizumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit[c]**
Add-on therapy for adults with severe CRSwNP which cannot be adequately controlled with systemic corticosteroids and/or surgery	Treatment with intranasal corticosteroids (budesonide or mometasone furoate)[b]	Hint of considerable added benefit

a. Presented is the ACT specified by the G-BA.
b. The G-BA specifies that the patients in both study arms were to receive maintenance therapy with intranasal corticosteroids as well as further supportive measures (e. g. nasal rinsing) and appropriate, approved therapy of complications (if necessary, short-term antibiotics, short-term systemic corticosteroids as part of flare treatment). It is also assumed that invasive treatment options are currently (at study enrolment) not indicated for patients for whom treatment with mepolizumab is an option.

ACT: appropriate comparator therapy; CRSwNP: chronic rhinosinusitis with nasal polyps; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

3 References

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Appendix A Supplementary presentation of the outcomes of nasal polyp surgery and responder analyses on health-related quality of life

Table 6: Results (morbidity, supplementary presentation) – RCT, direct comparison: mepolizumab + mometasone furoate versus placebo + mometasone furoate

Study Outcome category Outcome	Mepolizumab + mometasone furoate		Placebo + mometasone furoate		Mepolizumab + mometasone furoate vs. placebo + mometasone furoate
	N	Median time to event [95% CI] Patients with event n (%)	N	Median time to event [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
SYNAPSE					
Morbidity					
Nasal polyp surgery	206	ND 18 (9)	201	ND 46 (23)	0.43 [0.25; 0.76]; 0.003 RR: 0.38 [0.23; 0.64]; < 0.001[b]

a. Cox proportional hazards model with the covariates of geographic region, endoscopic nasal polyp score (centrally read) at baseline, VAS nasal obstruction at baseline, baseline blood eosinophil count log(e) and number of prior nasal polyp surgeries (1, 2, > 2).
b. IQWiG calculation of effect and CI (asymptotic): p-value unconditional exact test (CSZ method according to [10]).

CI: confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; IQWiG: Institute for Quality and Efficiency in Health Care; ND: no data; RCT: randomized controlled trial; RR: relative risk

Table 7: Results (health-related quality of life, supplementary presentation) – RCT, direct comparison: mepolizumab + mometasone furoate versus placebo + mometasone furoate

Study Outcome category Outcome	Mepolizumab + mometasone furoate		Placebo + mometasone furoate		Mepolizumab + mometasone furoate vs. placebo + mometasone furoate
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI][a]; p-value[b]
SYNAPSE					
Health-related quality of life					
SF-36v2[c]					
Physical Component Summary (PCS)[d]	205	109 (53)	198	49 (25)	0.47 [0.33; 0.61][e]; < 0.001
Mental Component Summary (MCS)[f]	205	81 (40)	198	54 (27)	0.69 [0.50; 0.95][e]; 0.010

a. Exact unconditional CI calculated by inverting 2 separate one-sided tests based on the score statistic.
b. IQWiG calculation, unconditional exact test (CSZ method according to [10]).
c. For the subscales, the company submitted only continuous analyses.
d. Percentage of patients with an increase by ≥ 5 points from baseline to Week 52, using a normalized scale range of 0 to 63. Higher (increasing) values indicate an improvement in health-related quality of life.
e. Data based on the comparison of placebo + mometasone furoate vs. mepolizumab + mometasone furoate.
f. Percentage of patients with an increase by ≥ 5 points from baseline to Week 52, using a normalized scale range of 0 to 64. Higher (increasing) values indicate an improvement in health-related quality of life.

CI: confidence interval; MCS: Mental Component Summary; n: number of patients with event; N: number of analysed patients; PCS: Physical Component Summary; RCT: randomized controlled trial; RR: relative risk; SF-36v2: Short Form 36-Item Health Survey version 2