IQWiG Reports – Commission No. A21-150

Mepolizumab (chronic rhinosinusitis with nasal polyps) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Mepolizumab (chronische Rhinosinusitis mit Nasenpolypen) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 25 February 2022). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AERD	aspirin-exacerbated respiratory disease
ASA	acetylsalicylic acid
CRSwNP	chronic rhinosinusitis with nasal polyps
EPOS	European position paper on rhinosinusitis and nasal polyps
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
NSAID	nonsteroidal anti-inflammatory drugs
OCS	oral corticosteroids
PCS	Physical Component Summary
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SCS	systemic corticosteroids
SF-36v2	Short Form 36 – version 2 Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SNOT-22	22-item Sino-Nasal Outcome Test
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug mepolizumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 29 November 2021.

Research question

The aim of the present report is the assessment of the added benefit of mepolizumab as an add-on therapy with intranasal corticosteroids (INCS) in comparison with the appropriate comparator therapy (ACT) in adult patients with severe chronic rhinosinusitis with nasal polyps (CRSwNP) for whom therapy with systemic corticosteroids (SCS) and/or surgery do not provide adequate disease control.

The research question presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of mepolizumab

Therapeutic indication	**ACT**[a]
Add-on therapy for adults with severe CRSwNP that cannot be adequately controlled with systemic corticosteroids and/or surgery	Treatment with intranasal corticosteroids (budesonide or mometasone furoate)[b]
a. Presentation of the ACT specified by the G-BA. b. The G-BA specified that patients in both study arms should receive maintenance treatment with intranasal corticosteroids as well as further supportive measures (e.g. nasal douching) and an adequate, approval-compliant treatment of complications (if necessary, short-term antibiotics, short-term systemic corticosteroids as part of relapse therapy). It is also assumed that invasive treatment options are currently (at study entry) 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 assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks are used for the derivation of added benefit.

Study pool and study design

The study pool for the benefit assessment of mepolizumab in comparison with the ACT consists of the RCT SYNAPSE.

The SYNAPSE study is a randomized double-blind study comparing mepolizumab with placebo, each in addition to maintenance therapy with the intranasal corticosteroid mometasone furoate. It included adult patients with presence of at least 2 symptoms of chronic rhinosinusitis

for ≥ 12 weeks with recurrent bilateral nasal polyps and at least one previous nasal polyp surgery in the previous 10 years before study entry. In addition, patients had to have treatment with INCS for at least 8 weeks prior to screening.

Before randomization, there was a 4-week run-in phase, in which patients were placed on the maintenance therapy with 400 µg intranasal mometasone furoate daily (2 actuations of 50 µg in each nostril twice daily) if other INCS had previously been used for treatment or if the maximum dose of mometasone furoate had not been used by that time.

Following the run-in phase, only those patients were randomized to the treatment arms who, in addition to meeting the inclusion criteria, had a nasal polyp score of ≥ 5 (≥ 2 for each nostril) on a scale of 0 to 8 at screening and a visual analogue scale (VAS) score for total symptoms > 7 and for nasal obstruction > 5 over the last 7 days prior to randomization.

Administration of intranasal mometasone furoate at stable doses was continued in the treatment phase. Besides the study medication to be investigated and the maintenance therapy with intranasal mometasone furoate, treatment with saline nasal douching, systemic antibiotics, short courses of mainly oral systemic corticosteroids (OCS) and nasal polyp surgery were allowed if required.

In the SYNAPSE study, a total of 414 patients[3] were randomly assigned (1:1) to 52-week treatment with mepolizumab (N = 206) or placebo (N = 201).

Primary outcomes were the mean change in nasal obstruction VAS in weeks 49 to 52 and the change in nasal polyp score at week 52. Patient-relevant outcomes of the outcome categories of morbidity, health-related quality of life and side effects were additionally recorded.

Limitations of the study

The SYNAPSE study has the following limitations: Firstly, there is uncertainty as to whether (necessary) surgery may have been delayed for some patients due to their inclusion in the study. Secondly, there are concerns as to whether all patients with aspirin-exacerbated respiratory disease (AERD) were adequately treated before and during the SYNAPSE study. These limitations of the study lead to an overall reduced certainty of conclusions (see below).

Risk of bias and certainty of conclusions

The risk of bias across outcomes for the SYNAPSE study is rated as low.

The risk of bias for the included outcomes of mortality and SAEs is rated as low. There is a high risk of bias for the results of the outcome category of morbidity. The reason for this is the high proportion of imputed values, which differs between the study arms (intervention arm 19% versus placebo arm 32%), which is mainly due to the imputation strategy chosen by the company, in which recorded values are imputed. The results on health-related quality of life,

[3] Of the 414 randomized patients, 7 were randomized in error and subsequently excluded.

recorded with the Short Form 36 – version 2 Health Survey (SF-36v2), are not usable. Therefore, the risk of bias is not assessed for this outcome. The certainty of results for the outcome of discontinuation due to adverse events (AEs) is limited despite a low risk of bias.

The limitations of the study described above overall lead to a reduced certainty of conclusions. 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.

Results

For the outcomes on morbidity and health-related quality of life, the company chose an imputation strategy in which patients who had undergone nasal polyp surgery or sinuplasty were assigned their worst observed score prior to the intervention. However, after nasal polyp surgery, patients continued to be treated with the study medication and data on symptoms and health-related quality of life continued to be recorded until week 52. These data are relevant for the benefit assessment, but were not included in the presented analyses of the outcomes on morbidity and health-related quality of life. In the present situation, the analyses with the described imputation strategy presented by the company are used for the assessment of the added benefit. However, as it is unclear how the data after nasal polyp surgery imputed by the company affect the effects, statistically significant effects are non-quantifiable in the present assessment.

Mortality

All-cause mortality

No deaths occurred in the SYNAPSE study. 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 is therefore not proven.

Morbidity

Nasal obstruction, nasal discharge, mucus in the throat, facial pain/pressure, loss of smell

For the outcomes of nasal obstruction, nasal discharge, mucus in the throat, facial pain/pressure, and loss of smell, each recorded with a VAS, there was a statistically significant difference in favour of mepolizumab + mometasone furoate in comparison with placebo + mometasone furoate in the proportion of patients with an improvement of ≥ 1.5 points. This results in a hint of an added benefit of mepolizumab as an add-on therapy with INCS in comparison with INCS therapy for each of these outcomes.

22-item Sino-Nasal Outcome Test (SNOT-22; symptoms and social/emotional consequences of rhinosinusitis)

For the outcome of SNOT-22, there was a statistically significant difference in favour of mepolizumab + mometasone furoate in comparison with placebo + mometasone furoate in the proportion of patients with an improvement of the overall score by ≥ 16.5 points. This results

in a hint of an added benefit of mepolizumab as an add-on therapy with INCS in comparison with INCS therapy.

Health-related quality of life

SF-36v2

There are no usable data for the outcome category of health-related quality of life, recorded with the SF-36v2. 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.

Side effects

Serious AEs (SAEs), discontinuations due to AEs

There was no statistically significant difference between the treatment arms for either of the outcomes of SAEs and discontinuation due to AEs. In each case, this results in no hint of greater or lesser harm from mepolizumab as an add-on therapy with INCS in comparison with INCS therapy; greater or lesser harm is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[4]

Based on the results presented, the probability and extent of added benefit of the drug mepolizumab in comparison with the ACT are assessed as follows:

Overall, only positive effects are shown in the outcome categories of serious/severe symptoms/late complications and non-serious/non-severe symptoms/late complications, each with non-quantifiable extent. There are no usable data on health-related quality of life.

In summary, there is a hint of a non-quantifiable added benefit of mepolizumab as an add-on therapy with INCS in comparison with INCS therapy for patients with severe CRSwNP for whom therapy with SCS and/or surgery do not provide adequate disease control.

Table 3 shows a summary of the probability and extent of added benefit of mepolizumab.

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

Table 3: Mepolizumab – probability and extent of added benefit

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

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

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is the assessment of the added benefit of mepolizumab as an add-on therapy with INCS in comparison with the ACT in adult patients with severe CRSwNP for whom therapy with SCS and/or surgery do not provide adequate disease control.

The research question presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of mepolizumab

Therapeutic indication	**ACT**[a]
Add-on therapy for adults with severe CRSwNP that cannot be adequately controlled with systemic corticosteroids and/or surgery	Treatment with intranasal corticosteroids (budesonide or mometasone furoate)[b]

a. Presentation of the ACT specified by the G-BA.
b. The G-BA specified that patients in both study arms should receive maintenance treatment with intranasal corticosteroids as well as further supportive measures (e.g. nasal douching) and an adequate, approval-compliant treatment of complications (if necessary, short-term antibiotics, short-term systemic corticosteroids as part of relapse therapy). It is also assumed that invasive treatment options are currently (at study entry) 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 company followed the specification of the G-BA by designating therapy with INCS (budesonide or mometasone furoate) as the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks are used for the derivation of added benefit. This concurs with the company's inclusion criteria.

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on mepolizumab (status: 5 October 2021)
- bibliographical literature search on mepolizumab (last search on 5 October 2021)
- search in trial registries/trial results databases for studies on mepolizumab (last search on 5 October 2021)
- search on the G-BA website for mepolizumab (last search on 5 October 2021)

To check the completeness of the study pool:

- search in trial registries for studies on mepolizumab (last search on 13 December 2021); for search strategies, see Appendix A of the full dossier assessment

The check did not identify any additional relevant studies.

2.3.1 Studies included

The study presented in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: mepolizumab + mometasone furoate vs. placebo + mometasone furoate

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no citation)	Registry entries[b] (yes/no citation)	Publication and other sources (yes/no citation)
205687 (SYNAPSE[d])	Yes	Yes	No	Yes [3]	Yes [4,5]	Yes [6-8]

a. Study for which the company was sponsor.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. Other sources: CRSwNP Consolidated Response Document and EPAR.
d. In the following tables, the study is referred to by this acronym.

CRSwNP: chronic rhinosinusitis with nasal polyps; EPAR: European Public Assessment Report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool consists of study 205687 (hereinafter referred to as “SYNAPSE”) and concurs with that of the company.

2.3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: mepolizumab + mometasone furoate vs. placebo + mometasone furoate

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
SYNAPSE	RCT, double-blind, parallel	Adults (≥ 18 years) with recurrent chronic rhinosinusitis with recurrent bilateral nasal polyps and with: ▪ VAS for nasal obstruction > 5[b] ▪ overall VAS symptom score > 7[b] ▪ NPS ≥ 5 (≥ 2 for each nostril)[c] ▪ ≥ 1 surgery[d] in the previous 10 years for the removal of nasal polyps	Mepolizumab + mometasone furoate (N = 206) Placebo + mometasone furoate (N = 201)	Run-in: 4 weeks[e] Treatment: 52 weeks Follow-up: 24 weeks[f]	86 centres in Argentina, Australia, Canada, Germany, Korea, Netherlands, Romania, Russia, Sweden, United Kingdom, USA 5/2017–12/2019	Primary: change in NPS at week 52 mean change in nasal obstruction VAS in weeks 49–52 Secondary: morbidity, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Scale range 0 to 10.
c. Required criterion for randomization; in deviation from this, a total of 18% of patients (17% in the mepolizumab arm and 20% in the placebo arm) had a nasal polyp score < 5 at the time of randomization. The scale ranges from 0 to 8 (a higher score indicates worse status).
d. Nasal polyp surgery was defined as any procedure involving instruments with resulting incision and removal of tissue from the paranasal sinus (polypectomy).
e. If the patient had a cold during run-in, then run-in could be extended by 2 weeks to a maximum of 6 weeks.
f. Only for the first up to 200 randomized patients participating in the 24-week follow-up phase without study medication.

AE: adverse event; N: number of randomized patients; NPS: nasal polyp score; RCT: randomized controlled trial; VAS: visual analogue scale

Table 7: Characteristics of the intervention – RCT, direct comparison: mepolizumab + mometasone furoate vs. placebo + mometasone furoate

Study	Intervention	Comparison
SYNAPSE	Mepolizumab 100 mg/mL, SC, every 4 weeks + continuation of the maintenance treatment with intranasal mometasone furoate in stable dosage[a]	Placebo, SC, every 4 weeks
	Required pretreatment ▪ INCS in stable dosage for at least 8 weeks before screening[b] ▪ at least one nasal polyp surgery[c] in the previous 10 years before screening **Permitted concomitant treatment** ▪ short courses of high doses of OCS ▪ antibiotic treatment for nasal polyps ▪ saline nasal douching ▪ nasal polyp surgery[c] ▪ ongoing asthma treatment ▪ analgesics **Prohibited prior and concomitant treatment** ▪ investigational drugs or therapies or radiotherapy within 3 months or 5 half-lives (whichever is longer) before screening ▪ investigational anti-inflammatory drugs (non-biologics) within 3 months before screening ▪ biologics or immunosuppressants (except omalizumab) within 5 half-lives before screening ▪ omalizumab within 130 days before screening ▪ SCS (including OCS) within 4 weeks before screening or administration during the double-blind treatment phase planned at study entry ▪ corticosteroid injection into the nasal polyps within 6 months before screening ▪ methotrexate, troleandomycin, ciclosporin, azathioprine within 4 weeks before screening ▪ oral gold compounds within 3 months before screening ▪ chemotherapy (except for asthma) within 12 months ▪ participation in previous studies with mepolizumab, reslizumab, dupilumab, benralizumab ▪ intranasal non-surgical interventions (e.g. balloon dilatation/sinuplasty or insertion of any nasal stents) 6 months before screening ▪ commencement or change of dose of ongoing leukotriene antagonist treatment within 30 days before screening until end of study ▪ commencement or change of dose of ongoing allergen immunotherapy within 3 months before screening until end of study	

a. During the entire study (run-in, treatment and follow-up phase), all patients received maintenance treatment consisting of daily administration of intranasal mometasone furoate; 2 actuations (50 µg/actuation) in each nostril twice daily, i.e. 400 µg daily; for patients who were intolerant to this daily dose, a lower daily dose of 200 µg mometasone furoate was allowed.
b. Then: 4-week run-in phase with 400 µg intranasal mometasone furoate.
c. Nasal polyp surgery was defined as any procedure involving instruments with resulting incision and removal of tissue from the paranasal sinus (polypectomy).

INCS: intranasal corticosteroids; OCS: oral corticosteroids; RCT: randomized controlled trial;
SC: subcutaneous; SCS: systemic corticosteroids

Study design

The SYNAPSE study is a randomized double-blind study comparing mepolizumab with placebo, each in addition to maintenance therapy with the intranasal corticosteroid mometasone furoate. It included adult patients with presence of at least 2 symptoms of chronic rhinosinusitis for ≥ 12 weeks with recurrent bilateral nasal polyps and at least one previous nasal polyp surgery in the previous 10 years before study entry. Nasal polyp surgery was defined as any procedure involving instruments with resulting incision and removal of tissue from the paranasal sinus (polypectomy). Dilatation of the nasal passage (e.g. balloon sinuplasty) was not considered nasal polyp surgery. In addition, patients had to have treatment with INCS for at least 8 weeks prior to screening.

Before randomization, there was a 4-week run-in phase, in which patients were placed on the maintenance therapy with 400 µg intranasal mometasone furoate daily (2 actuations of 50 µg in each nostril twice daily) if other INCS had previously been used for treatment or if the maximum dose of mometasone furoate had not been used by that time. The administered dose of mometasone furoate does not comply with the initial daily dose of 200 µg according to the Summary of Product Characteristics (SPC), but to a dose which, in case of inadequate symptom control, can only be administered in the later course of treatment [9]. This treatment regimen is nevertheless considered adequate for the included patient population (see below) and has no influence on the present assessment. Depending on the tolerance, dose reduction of mometasone furoate to one daily administration (a total of 200 µg) was possible.

Following the run-in phase, only those patients were randomized to the treatment arms who, in addition to meeting the inclusion criteria, had a nasal polyp score of ≥ 5 (≥ 2 for each nostril) on a scale of 0 to 8 at screening and a visual analogue scale (VAS) score for total symptoms > 7 and for nasal obstruction > 5 over the last 7 days prior to randomization (as of Amendment 2 of the study protocol [14 July 2017], a CT scan was no longer necessary in the study for recording the nasal polyp score). In deviation from this, a total of 18% of patients (17% in the mepolizumab arm and 20% in the placebo arm) had a nasal polyp score < 5 at the time of randomization. This deviation has no influence on the present assessment, as the disease severity of the study population overall is assessed to be sufficiently high for the present therapeutic indication (see below).

Administration of intranasal mometasone furoate at stable doses was continued in the treatment phase. Besides the study medication to be investigated and the maintenance therapy with intranasal mometasone furoate, treatment with saline nasal douching, systemic antibiotics, short courses of mainly OCS and nasal polyp surgery were allowed if required. An alternative application form of SCS was also allowed.

In the SYNAPSE study, a total of 414 patients[5] were randomly assigned (1:1) to 52-week treatment with mepolizumab (N = 206) or placebo (N = 201). Mepolizumab was administered

[5] Of the 414 randomized patients, 7 were randomized in error and subsequently excluded.

in compliance with the approval [10]. After the 52-week treatment phase, a 24-week follow-up phase was planned for the first up to 200 randomized patients. A total of 69 patients from the intervention arm and 65 patients from the comparator arm were followed up until week 76. Randomization was done separately for each country.

Primary outcomes were the mean change in nasal obstruction VAS in weeks 49 to 52 and the change in nasal polyp score at week 52. Patient-relevant outcomes of the outcome categories of morbidity, health-related quality of life and side effects were additionally recorded.

Table 8 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 8: Planned duration of follow-up observation – RCT, direct comparison: mepolizumab + mometasone furoate vs. placebo + mometasone furoate

Study **Outcome category** **Outcome**	**Planned follow-up observation**
SYNAPSE	
Mortality	
All-cause mortality[a]	until end of study[b] or, in case of study discontinuation, until 4 weeks after the last dose of study medication
Morbidity	
Symptoms (symptoms recorded with the VAS[c], SNOT-22)	until end of study[b] or, in case of study discontinuation, until 4 weeks after the last dose of study medication
Health-related quality of life (SF-36v2)	until end of study[b] or, in case of study discontinuation, until 4 weeks after the last dose of study medication
Side effects	
All outcomes in the category of side effects	until end of study[b] or, in case of study discontinuation, until 4 weeks after the last dose of study medication

a. Recorded within the framework of AEs.
b. Week 52; a total of 134 patients (65 from the placebo arm and 69 from the mepolizumab arm) participated in a 24-week follow-up period without study medication. These patients were followed up until week 76.
c. The following symptoms were recorded using a VAS: symptoms total, nasal obstruction, nasal discharge, mucus in the throat, facial pain/pressure, loss of smell.

AE: adverse event; RCT: randomized controlled trial; SF-36v2: Short Form 36 – version 2 Health Survey; SNOT-22: 22-item Sino-Nasal Outcome Test; VAS: visual analogue scale

All outcomes were recorded until the end of study or study discontinuation, this also applied to treatment discontinuations or treatment with short courses of OCS/SCS and nasal polyp surgery.

Patient characteristics

Table 9 shows the characteristics of the patients in the included study.

Table 9: Characteristics of the study population – RCT, direct comparison: mepolizumab + mometasone furoate vs. placebo + mometasone furoate

Study Characteristic Category	Mepolizumab + mometasone furoate N = 206	Placebo + mometasone furoate N = 201
SYNAPSE		
Age [years], mean (SD)	49 (14)	49 (12)
Sex [F/M], %	33/67	38/62
Family origin n (%)		
White	192 (93)	187 (93)
Asian	9 (4)	9 (4)
Black or African American	4 (2)	5 (2)
Other[a]	1 (< 1)	0 (0)
Duration of disease [years], mean (SD)	11.4 (8.5)	11.5 (8.3)
Nasal polyp surgery, n (%)		
Within the past 2 years	56 (27)	63 (31)
Within the past 10 years	206 (100)[b]	201 (100)[b]
Number of previous NP surgeries in the past 10 years, n (%)		
1	108 (52)	81 (40)
2	47 (23)	47 (23)
3	27 (13)	35 (17)
≥ 4	24 (12)[b]	38 (19)[b]
OCS therapy in the past 12 months, n (%)	106 (51)[b]	91 (45)[b]
Nasal polyp score, mean (SD)[c]	5.4 (1.2)	5.6 (1.4)
Overall VAS symptom score, mean (SD)[c, d]	9 (0.8)	9.1 (0.7)
VAS for nasal obstruction, mean (SD)[c, d]	8.9 (0.8)	9 (0.8)
VAS for nasal discharge, mean (SD)[c, d]	8.8 (1.1)	8.8 (1.3)
VAS for mucus in the throat, mean (SD)[c, d]	8.5 (1.6)	8.6 (1.6)
VAS for facial pain/pressure, mean (SD)[c, d]	7.8 (2.5)	7.8 (2.7)
VAS for loss of smell, mean (SD)[c, d]	9.6 (0.8)	9.7 (0.6)
SNOT-22 score, mean (SD)[c, e]	63.7 (17.6)	64.4 (19)
AERD, n (%)	45 (22[b])	63 (31[b])
Asthma, n (%)	140 (68[b])	149 (74[b])
Treatment discontinuation, n (%)[f]	23 (11)	34 (17)
Study discontinuation, n (%)[g]	17 (8)	17 (8)

a. African American/African family origin and native Americans or native Alaskans
b. Institute's calculation.
c. At baseline (randomization); for outcomes recorded by VAS, the baseline value is the mean value of the last 7 days before randomization.
d. Scale range from 0 to 10.
e. Scale range from 0 to 110.
f. Common reasons for treatment discontinuation in the mepolizumab arm vs. placebo arm were: patient request (6% vs. 7%), lack of efficacy (2% vs. 5%), AEs (2% vs. 2%).
g. Reasons for study discontinuation in the mepolizumab arm vs. placebo arm were: patient request (8% vs. 8%), lost to follow-up (0% vs. 1%).

Table 9: Characteristics of the study population – RCT, direct comparison: mepolizumab + mometasone furoate vs. placebo + mometasone furoate

Study Characteristic Category	Mepolizumab + mometasone furoate N = 206	Placebo + mometasone furoate N = 201
AERD: aspirin-exacerbated respiratory disease; F: female; M: male; n: number of patients in the category, N: number of randomized patients; NP: nasal polyps; OCS: oral corticosteroids; RCT: randomized controlled trial; SD: standard deviation; SNOT-22: 22-item Sino-Nasal Outcome Test; VAS: visual analogue scale		

Patient characteristics were sufficiently similar between the treatment groups. This applies to both demographic and disease characteristics. The mean age of the patients was 49 years, and most of them were male and white. The mean disease duration before the start of the study was about 11 years. All patients had received at least one nasal polyp surgery in the previous 10 years before study entry, and approximately 48% had received OCS therapy in the previous 12 months.

There were differences between the treatment arms in the number of patients with AERD. In the mepolizumab arm, 22% of patients had AERD, compared with 31% in the placebo arm. This imbalance does not call into question the structural equality of the 2 treatment arms. Another difference can be seen in the number of treatment discontinuations. The proportion of treatment discontinuations was 11% in the mepolizumab arm and 17% in the placebo arm.

Assessment of the severity of the disease of the included patients

According to the approval, mepolizumab is indicated for patients with severe CRSwNP [10]. The various guidelines provide no or no uniform definition of the severity grades of the disease [11,12]. For example, the European position paper on rhinosinusitis and nasal polyps (EPOS) considers a VAS to classify severity (VAS > 7: severe disease [12]). The German S2k guideline on rhinosinusitis includes no classification of severity [11]. Thus, overall, no generally valid criteria can be identified that can be used to assess the severity of chronic rhinosinusitis. Nevertheless, it is assumed that the study population is suitable for answering the present research question. This is justified below.

All patients included in the SYNAPSE study had undergone at least one nasal polyp surgery in the previous 10 years; approximately 30% of the included patients had undergone at least one nasal polyp surgery within the 2-year period before screening. About half (approximately 48%) of the patients had received OCS therapy within the last 12 months before screening (see Table 9). During the course of the study, 51 (25%) patients in the mepolizumab arm and 74 (37%) patients in the placebo arm received SCS as conservative treatment escalation (for the use of surgery during the course of the study, see the following section). EPOS lists both OCS and surgery as treatment options for patients with severe CRSwNP, although surgery should only be performed if the other treatment options have failed to improve symptoms [12].

Although the patients had received corresponding guideline-compliant prior therapy before study entry (i.e. 1) INCS before study entry, 2) sinonasal surgery and SCS if necessary), they had various symptoms. According to the S2k guideline, typical symptoms include nasal obstruction, nasal discharge, mucus in the throat and loss of smell. The patient-reported symptoms at baseline (defined as the mean value over the last 7 days before the day of randomization), which were recorded by means of various VAS (nasal obstruction, nasal discharge, mucus in the throat, facial pain/pressure, loss of smell), were on average between 8 and 10 in the included patients on a scale of 0 (no complaints) to 10 (maximum imaginable complaints) (see Table 9). Thus, patients had pronounced symptoms. Another aspect that characterizes a severe disease is comorbidity with other type 2 inflammatory diseases and/or hypersensitivity to analgesics. In the SYNAPSE study, 71% of the patients had asthma in addition to their chronic rhinosinusitis (during treatment with the study medication, the patients had to maintain the asthma medication they were using at the time of randomization), 27% of the included patients had AERD.

Taking into account the prior therapies and the severity of the existing symptoms, the study population of the SYNAPSE study is generally considered suitable for answering the research question of the present benefit assessment.

Limitations of the SYNAPSE study

As described above, the SYNAPSE study is used for the benefit assessment. However, there are limitations, which are described below. Due to these limitations, only hints, e.g. of an added benefit, can be derived on the basis of the SYNAPSE study (see Section 2.4.2).

Need for nasal polyp surgery unclear at baseline

In addition to the presence of severe symptoms, the inclusion criteria for the study explicitly required a disease severity that would generally make nasal polyp surgery appear necessary (described in the study protocol as “severity consistent with a need for surgery”). This was operationalized in the study protocol with the criteria of an overall VAS symptom score > 7 and a nasal polyp score ≥ 5 (≥ 2 for each nostril). However, to be included in the study, patients were not allowed to be on a waiting list for nasal polyp surgery and preplanned surgery dates had to be cancelled. It is unclear how many patients were scheduled for nasal polyp surgery before study entry and how many patients were on a waiting list for surgery.

It should be noted in general that there are no clearly defined criteria for the indication of nasal polyp surgery, but that lack of improvement under treatment with conservative therapies as well as the patient’s wishes are decisive [11]. Since the patient population of the SYNAPSE study had received both long-term intranasal corticosteroid therapy (at least 8 weeks of INCS before screening) and at least one nasal polyp surgery within the last 10 years, as well as short-term therapies with OCS (48% of the patients in the last 12 months before study inclusion), it is assumed that, due to the predominant severe symptoms, nasal polyp surgery was generally an option for the included patients.

The performance of nasal polyp surgery and other interventions such as sinuplasty was allowed at any time during the study (see Kaplan-Meier curves for time to first nasal polyp surgery in Appendix B of the full dossier assessment; first surgeries already took place in the first 8 weeks). The performance of nasal polyp surgery and other interventions (sinuplasty) was assessed and documented at each study visit. However, it is not clear from this whether surgery was recommended by the study staff or by the attending physician outside the study. At each study visit, it was also recorded whether the patient was waiting for an appointment for nasal polyp surgery.

During the 52-week treatment period, a total of 46 of 201 patients in the placebo arm (23%) and 18 patients in the mepolizumab arm (9%) underwent nasal polyp surgery. This proportion of patients does not suggest an acutely necessary surgical intervention at study entry. In addition, it is generally not assumed that necessary nasal polyp surgery was withheld from the patients, also because an operation did not result in the discontinuation of therapy or study, but therapy was continued. However, since it is unknown how many patients were on a waiting list for nasal polyp surgery at the beginning of the study and how many planned surgeries were cancelled, there is still uncertainty as to whether (necessary) surgery may have been delayed for some patients due to their inclusion in the study.

Adequate (pre)treatment of AERD unclear

In the SYNAPSE study, 45 patients with AERD were included in the mepolizumab arm (22%) and 63 in the placebo arm (31%) (see Table 9). For patients with proven analgesic intolerance syndrome, there is in principle the therapeutic option of adaptive deactivation. This adaptive deactivation with acetylsalicylic acid (ASA) can achieve a reduction in inflammation or polyp growth and a prolongation of the intervals between the necessary revision operations [11].

In the notes on the ACT, the G-BA points out that the dossier must describe which prior therapies patients with AERD had received before inclusion in the study [13]. In Module 4 A, the company listed which therapies the patient population with AERD received before and during the study. Only 4% of these patients had received ASA therapy before starting treatment. The company stated in Module 4 A that during mepolizumab treatment, 8 of the 45 patients (18%) in the mepolizumab arm and 11 of the 63 AERD patients (17%) in the placebo arm with received nonsteroidal anti-inflammatory drugs (NSAIDs). Only 2 patients with AERD in the placebo arm received ASA.

The dossier contained no information on the reasons for non-response or non-eligibility for (prior) therapy of AERD. Overall, concerns remain as to whether all patients with AERD were adequately treated before and during the SYNAPSE study.

Risk of bias across outcomes (study level)

Table 10 shows the risk of bias across outcomes (risk of bias at study level).

Table 10: Risk of bias across outcomes (study level) – RCT, direct comparison: mepolizumab + mometasone furoate vs. placebo + mometasone furoate

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
SYNAPSE	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low.

Transferability of the study results to the German health care context

The company assumed transferability of the study results to the German health care context. According to the company, mepolizumab was administered in compliance with the SPC [10], and the standard therapy received by patients in both arms was in line with the guideline-compliant standard therapy for CRSwNP [11]. Furthermore, the demographic characteristics such as age and sex distribution of the patients in the study corresponded to those in everyday German health care [14].

The company did not provide any further information on the transferability of the study results to the German health care context.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be considered in the assessment:

- Mortality
  - all-cause mortality
- Morbidity
  - VAS for nasal obstruction
  - VAS for nasal discharge
  - VAS for mucus in the throat
  - VAS for facial pain/pressure
  - VAS for loss of smell
  - SNOT-22 (total score)

- Health-related quality of life
  - SF-36v2
- Side effects
  - SAEs
  - discontinuation due to AEs

The choice of patient-relevant outcomes deviates from that made by the company, which used further outcomes in the dossier (Module 4 A).

Table 11 shows the outcomes for which data were available in the included study.

Table 11: Matrix of the outcomes – RCT, direct comparison: mepolizumab + mometasone furoate vs. placebo + mometasone furoate

Study	Outcomes										
	All-cause mortality	VAS for nasal obstruction	VAS for nasal discharge	VAS for mucus in the throat	VAS for facial pain/pressure	VAS for loss of smell	SNOT-22 (total score)	Health-related quality of life (SF-36v2)	SAEs	Discontinuation due to AEs	Specific AEs
SYNAPSE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[a]	Yes[b]	Yes	No[c]

a. No usable data; see running text for reasons.
b. Includes one event that can be both side effect and symptom of the disease (placebo arm "acute sinusitis").
c. No specific AEs were identified.

AE: adverse event; RCT: randomized controlled trial; SAE: serious adverse event; SF-36v2: Short Form 36 – version 2 Health Survey; SNOT-22: 22-item Sino-Nasal Outcome Test; VAS: visual analogue scale

Period of analysis

The company presented analyses for the end of the double-blind treatment phase (week 52) and the end of the follow-up phase (week 76). The present assessment only considers the results at the end of the double-blind treatment phase, as mepolizumab is approved for long-term therapy and ending treatment after 52 weeks is therefore not recommended according to the SPC [10]. In addition, only a small proportion of patients entered the follow-up phase without study medication until week 76 after the end of the double-blind treatment (see Section 2.3.2).

Outcomes on morbidity and health-related quality of life

Note on the choice of the relevant operationalization

For all included outcomes of morbidity and health-related quality of life, the company presented prespecified continuous analyses and post-hoc responder analyses with different response criteria. As explained in the *General Methods* of the Institute [1], 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, in post-hoc analyses exactly 15% of the scale range. The responder analyses are used for the derivation of the added benefit for the patient-reported outcomes in the categories of morbidity and health-related quality of life.

Imputation strategies

For the outcome of nasal obstruction (VAS), the company stated that patients who had undergone nasal polyp surgery (for definition see Section 2.3.2) or sinuplasty were assigned their worst observed score prior to the intervention, although these patients did not discontinue therapy and further data were recorded in subsequent visits. However, based on the information on the imputed values for the outcome of nasal obstruction (VAS), as well as on the proportions of events in the outcome of nasal polyp surgery, it can be assumed that there was no such imputation based on the performance of sinuplasty. Furthermore, patients with missing data were assigned their worst observed score prior to study discontinuation or missing visit. The imputation strategy of the company, which is to be understood as non-responder imputation, was prespecified.

Although the company did not comment on the other outcomes on morbidity or health-related quality of life with regard to the imputations made, it can be assumed that an identical procedure was chosen. This assumption is confirmed by the data on the outcomes of SNOT-22 and SF-36v2 presented in the appendix of Module 4 A. This shows that patients with nasal polyp surgery, with missing values or with study discontinuation were included in the analyses as non-responders.

Nasal polyp surgery in the therapeutic indication of severe CRSwNP is not the end of all therapies for the patient. Furthermore, given the disease severity in the patients included in the study, it can be assumed that the polyps will grow back quickly. The performance of nasal polyp surgery in the therapeutic indication is thus part of the therapeutic strategy. Drug treatments such as INCS as long-term treatment and OCS (if required as relapse therapy) and the (minimal-invasive) surgical removal of nasal polyps complement each other in the therapy concept, since, as described in Section 2.3.2, patients continued to be treated with the study medication after nasal polyp surgery and data on symptoms and health-related quality of life continued to be recorded until week 52. These data are relevant for the benefit assessment, but were not included in the presented analyses of the outcomes on morbidity and health-related quality of life. In the present situation, the analyses with the described imputation strategy presented by the company (see above) are used for the assessment of the added benefit. However, as it is

unclear how the data after nasal polyp surgery imputed by the company affect the effects, statistically significant effects are non-quantifiable in the present assessment.

Symptoms (nasal obstruction, nasal discharge, mucus in the throat, facial pain/pressure, loss of smell)

A VAS was used to record the symptoms of nasal obstruction, nasal discharge, mucus in the throat, facial pain/pressure and loss of smell. An overall symptom score (total symptom burden) was also recorded using a VAS. Symptoms and the total symptom burden were recorded daily with an electronic patient diary. Patients were asked to indicate on a VAS from 0 to 100 how distressing they felt the symptoms of their rhinosinusitis were. Here, a value of 0 means "no complaints at all" and a value of 100 means "as bad as you can imagine". The VAS scores were then transformed from 100 to 10 by the company.

The company stated that it presented the responder analyses for weeks 49 to 52 compared with baseline (defined as the mean value over the last 7 days before the day of randomization). It is unclear when a patient was considered a responder. It can be seen from the study documents that the company used the mean value of this 4-week period for the prespecified analysis of the change from baseline to weeks 49 to 52. The present benefit assessment assumes an identical procedure of the company for the responder analyses.

For the responder analyses, the company chose the response criterion of 15%, which corresponds to an improvement of ≥ 1.5 points at a scale range of 10. The present benefit assessment includes the symptom outcomes of nasal obstruction, nasal discharge, mucus in the throat, facial pain/pressure and loss of smell, as these represent the characteristic individual symptoms of severe CRSwNP in a more differentiated way than a total symptom score assessed by VAS.

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

The SNOT-22 is a disease-specific, patient-reported questionnaire with 22 individual questions to assess the severity and frequency of symptoms and social/emotional consequences of rhinosinusitis. Each question is answered on a scale from 0 (no problem) to 5 (problem as bad as it can be). A total score (0 to 110) is formed from the individual scores per question, with lower values corresponding to less impairment. Since this questionnaire is mainly used to assess impairments due to symptoms (e.g. blocked nose, runny nose, post nasal discharge, reduced sense of smell/taste), the questionnaire is assigned to morbidity.

For the responder analyses, the company's dossier presented both analyses for the response criterion of 15%, which corresponds to an improvement of ≥ 16.5 points on a scale range of 110, and a minimally important difference (MID) with an improvement of ≥ 8.9 points [15]. The company used the results on improvement by ≥ 8.9 points for the derivation of the added benefit.

The present assessment uses the analyses of the response criterion of 15%. Results for the improvement by ≥ 8.9 points are presented as supplementary information in Appendix C of the full dossier assessment.

SF-36v2

In Module 4 A, the company presented prespecified continuous analyses and post-hoc responder analyses for the Physical Component Summary (PCS) and the Mental Component Summary (MCS). For the responder analyses, the company presented results for the response criterion of 15%, corresponding to an improvement by ≥ 9.4 points (PCS) and 9.6 points (MCS). The company used the responder analyses on the MID for an improvement by ≥ 5 points for both sum scores for the derivation of the added benefit.

The company did not address the necessary standardization of the scale range from 100 to 63 (PCS) or 64 (MCS), which is the prerequisite for the application of the response criteria of 15% or the MID ≥ 5 [16]. In addition, the analyses of the continuous results presented in Module 4 A are not those on the MCS and PCS sum scores, but instead results on individual domains ("physical functioning" instead of the PCS and "mental health" instead of the MCS). It is thus unclear whether the results reported by the company on the SF-36v2 are actually based on the respective sum scores of the MCS and PCS or on their individual domains.

Due to these uncertainties, the data of the SF-36v2 are not usable and are therefore not used for the derivation of the added benefit.

Side effects

It is assumed that the company observed the side effects over the entire recording period for all patients, regardless of whether therapy was discontinued or nasal polyp surgery was performed (see Table 8). Thus, for all outcomes in the category of side effects, on the one hand, surgery-related AEs were included in recording of AEs. On the other hand, the analyses included AEs that occurred due to the therapy but only after the nasal polyp surgery. From the AEs that occurred in the SYNAPSE study, separated by System Organ Class (SOC) and Preferred Term (PT), it can be seen that no directly surgery-related events occurred for the outcome of SAEs and for the outcome of discontinuation due to AEs. Only in the AEs, there is a small proportion of potentially surgery-related AEs in the SOC of injury, poisoning and procedural complications.

Discontinuation due to AEs

Although the risk of bias for the outcome of discontinuation due to AEs is low (see Section 2.4.2), the certainty of results for this outcome is limited. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome of discontinuation due to AEs to be recorded. This means that, after discontinuation for other reasons, AEs that would have led to treatment discontinuation may have occurred, but that the criterion "discontinuation" can no longer be applied to them. It cannot be estimated how many AEs this concerns.

2.4.2 Risk of bias

Table 12 describes the risk of bias for the results of the relevant outcomes.

Table 12: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: mepolizumab + mometasone furoate vs. placebo + mometasone furoate

Study	Study level	Outcomes									
		All-cause mortality	VAS for nasal obstruction	VAS for nasal discharge	VAS for mucus in the throat	VAS for facial pain/pressure	VAS for loss of smell	SNOT-22 (total score)	Health-related quality of life (SF-36v2)	SAEs	Discontinuation due to AEs
SYNAPSE	L	L	H[a]	H[a]	H[a]	H[a]	H[a]	H[a]	-[b]	L	L[c]

a. High and varying proportion of values imputed in the course of study (see running text)
b. No usable data (see Section 2.4.1).
c. Despite low risk of bias, limited certainty of results is assumed (see Section 2.4.1).

AE: adverse event; H: high; L: low; RCT: randomized controlled trial; SAE: serious adverse event; SF-36v2: Short Form 36 – version 2 Health Survey; SNOT-22: 22-item Sino-Nasal Outcome Test; VAS: visual analogue scale

The risk of bias for the results of the included outcomes of mortality and SAEs is rated as low.

The results of the outcome category of morbidity assessed by VAS (nasal obstruction, nasal discharge, mucus in the throat, facial pain/pressure and loss of smell) and SNOT-22 show a high risk of bias. The reason for this is the high proportion of imputed values, which differs between the study arms (intervention arm 19% versus placebo arm 32%), which is mainly due to the imputation strategy chosen by the company, in which recorded values are imputed (see Section 2.4.1).

The results on health-related quality of life, recorded with the SF-36v2, are not usable (see Section 2.4.1). Therefore, the risk of bias is not assessed for this outcome. The certainty of results for the outcome of discontinuation due to AEs is limited despite low risk of bias (see Section 2.4.1).

Certainty of conclusions

There are uncertainties for the SYNAPSE study (see Section 2.3.2), which lead to an overall reduction in the certainty of conclusions. 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.

2.4.3 Results

Table 13 summarizes the results of the comparison of mepolizumab + mometasone furoate with placebo + mometasone furoate in patients with severe CRSwNP for whom therapy with SCS and/or surgery do not provide adequate disease control. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Tables on common AEs, SAEs and discontinuation due to AEs are presented in Appendix D of the full dossier assessment.

Table 13: Results (mortality, morbidity, side effects, health-related quality of life) – RCT, direct comparison: mepolizumab + mometasone furoate vs. 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					
Mortality					
All-cause mortality	206	0 (0)	201	0 (0)	-
Morbidity					
Overall symptom score (supplementary information)[c]	206	139 (67)	201	90 (45)	0.66 [0.55; 0.80][d]; < 0.001
VAS for nasal obstruction[c]	206	140 (68)	201	93 (46)	0.68 [0.56; 0.82][d]; < 0.001
VAS for nasal discharge[c]	206	140 (68)	201	93 (46)	0.68 [0.56; 0.82][d]; < 0.001
VAS for mucus in the throat[c]	206	133 (65)	201	92 (46)	0.71 [0.58; 0.86][d]; < 0.001
VAS for facial pain/pressure[c]	206	126 (61)	201	87 (43)	0.71 [0.58; 0.87][d]; < 0.001
VAS for loss of smell[c]	206	92 (45)	201	50 (25)	0.56 [0.40; 0.75][d]; < 0.001
SNOT-22 total score[e]	205	142 (69)	198	90 (45)	0.66 [0.54; 0.79][d]; < 0.001
Health-related quality of life					
SF-36v2					
Physical Component Summary (PCS)[f]	No usable data[h]				
Mental Component Summary (MCS)[g]	No usable data[h]				
Side effects					
AEs (supplementary information)[i]	206	169 (82)	201	168 (84)	-
SAEs[j]	206	12 (6)	201	13 (6)	0.90 [0.38; 2.04]; 0.831
Discontinuation due to AEs	206	4 (2)	201	4 (2)	0.98 [0.22; 4.33]; > 0.999

Table 13: Results (mortality, morbidity, side effects, health-related quality of life) – RCT, direct comparison: mepolizumab + mometasone furoate vs. 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]

a. Exact unconditional CI calculated by inverting 2 separate one-sided tests based on the score statistic.
b. Institute's calculation, unconditional exact test (CSZ method according to [17])
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. Data based on comparison of placebo + mometasone furoate vs. mepolizumab + mometasone furoate.
e. Proportion of patients with a total score decrease by ≥ 16.5 points at week 52 from baseline (randomization), at a scale range of 0 to 110. Lower (decreasing) values indicate an improvement of symptoms.
f. Proportion of patients with a PCS score increase by ≥ 9.4 points at week 52 from baseline (randomization), at a standardized scale with a minimum of about 7 and a maximum of about 70. Higher (increasing) values indicate an improvement of health-related quality of life.
g. Proportion of patients with a MCS score increase by ≥ 9.6 points at week 52 from baseline (randomization), at a standardized scale with a minimum of about 6 and a maximum of about 70. Higher (increasing) values indicate an improvement of health-related quality of life.
h. See Section 2.4.1of the present dossier assessment for the reasoning.
i: Events included that can be both side effects and symptoms of the underlying disease.
j. Includes one event that can be both side effect and symptom of the underlying disease (placebo arm "acute sinusitis").

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; MCS: Mental Component Summary; n: number of patients with (at least one) event; N: number of analysed patients; PCS: Physical Component Summary; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SF-36v2: Short Form 36 – version 2 Health Survey; SNOT-22: 22-item Sino-Nasal Outcome Test; VAS: visual analogue scale

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes (see Section 2.3.2).

Mortality

All-cause mortality

No deaths occurred in the SYNAPSE study. 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 is therefore not proven.

Morbidity

Nasal obstruction, nasal discharge, mucus in the throat, facial pain/pressure, loss of smell

For the outcomes of nasal obstruction, nasal discharge, mucus in the throat, facial pain/pressure, and loss of smell, each recorded with a VAS, there was a statistically significant difference in favour of mepolizumab + mometasone furoate in comparison with placebo + mometasone

furoate in the proportion of patients with an improvement of ≥ 1.5 points. This results in a hint of an added benefit of mepolizumab as an add-on therapy with INCS in comparison with INCS therapy for each of these outcomes.

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

For the outcome of SNOT-22, there was a statistically significant difference in favour of mepolizumab + mometasone furoate in comparison with placebo + mometasone furoate in the proportion of patients with an improvement of the overall score by ≥ 16.5 points. This results in a hint of an added benefit of mepolizumab as an add-on therapy with INCS in comparison with INCS therapy.

Health-related quality of life

SF-36v2

There are no usable data for the outcome category of health-related quality of life, recorded with the SF-36v2 (see Section 2.4.1). 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.

Side effects

SAEs

There was no statistically significant difference between the treatment arms for the outcome of SAEs. This results in no hint of greater or lesser harm from mepolizumab as an add-on therapy with INCS in comparison with INCS therapy; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

There was no statistically significant difference between the treatment arms for the outcome of discontinuation due to AEs. This results in no hint of greater or lesser harm from mepolizumab as an add-on therapy with INCS in comparison with INCS therapy; greater or lesser harm is therefore not proven.

2.4.4 Subgroups and other effect modifiers

The following effect modifiers were considered to be relevant for the present benefit assessment:

- age (18 to < 40 years/40 to 64 years/≥ 65 years)
- sex (female/male)
- disease severity (number of previous nasal polyp surgeries: 1, 2, > 2)

All mentioned subgroup characteristics and cut-off values had been prespecified for the primary outcomes.

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

For the morbidity outcomes of nasal obstruction, nasal discharge, mucus in the throat, facial pain/pressure and loss of smell, each recorded by means of a VAS, it can be assumed on the basis of the information provided by the company that the subgroup analyses were based on the continuous analyses. An analysis based on the responder analysis used with a response criterion of 15% (≥ 1.5 points) is relevant for the present benefit assessment, however (see Section 2.4.1).

The subgroup analyses on the morbidity outcome of SNOT-22 and on health-related quality of life (assessed via the SF-36v2) were based on responder analyses conducted on the basis of response criteria that are not used in the present benefit assessment. For SNOT-22, the company chose the MID ≥ 8.9 points as the basis for the analysis. However, subgroup analyses based on the response criterion of 15% (≥ 16.5 points) would be relevant for the benefit assessment. Such analyses were not presented by the company, however. For the PCS and MSC sum scores of the SF-36v2, the company chose the MID ≥ 5 points in each case. Again, an analysis based on the response criterion of 15% (≥ 9.4 points for the PCS or ≥ 9.6 points for the MCS) would be relevant.

Irrespective of this, however, the results on SF-36v2 are not usable (see Section 2.4.1).

Furthermore, it is not clear from the presentation of the company which methods were used to calculate the subgroup results and to conduct the interaction test. For the subgroup analyses for the outcomes of SNOT-22, SF-36v2 and side effects, the company also did not specify on which effect measure the interaction tests were based. It can be assumed that the odds ratio was used to conduct the interaction tests. What would be required, however, is a test for subgroup effects regarding the effect measure of relative riskPT. The 2 effect measures can lead to different results in the evaluation of an effect modification.

2.5 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 *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of the added benefit at outcome level

As described in Section 2.4.1, the comparison of mepolizumab (as an add-on therapy with INCS) with the ACT is influenced by the imputation strategy used for patients who underwent nasal polyp surgery during the treatment phase. Due to this limitation, the added benefit at outcome level is non-quantifiable (see Table 14).

Determination of the outcome category for symptom outcomes

For the symptoms outcomes below, it cannot be inferred from the dossier whether they are serious/severe or non-serious/non-severe. The classification for these outcomes is justified.

The assessment of the outcome category of the various symptom outcomes depends on the patients' baseline situation, particularly on the severity and degree of impairment caused by their symptoms. Therefore, the data at baseline are used.

Symptoms (nasal obstruction, nasal discharge, mucus in the throat, facial pain/pressure and loss of smell)

At baseline, the patients included in the study had a mean VAS score between 7.8 (facial pain/pressure) and 9.7 (loss of smell) at a scale range of 0 to 10. For the other symptoms assessed by VAS, the mean value at baseline was about 9. Although there is no reference for a severity classification for the symptoms assessed, the values were close to or on the upper limit of the scale, which means maximum symptom severity. For this reason, the outcomes of nasal obstruction, nasal discharge, mucus in the throat, facial pain/pressure and loss of smell are assigned to the outcome category of serious/severe symptoms/late complications.

The company did not explicitly comment on the classification of the outcomes with regard to the outcome category, but also assumed a severe symptom burden.

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

For the outcome of SNOT-22 total score, no information is available on a threshold value that would allow an assessment of the severity of the symptoms recorded by SNOT-22 as serious or severe at baseline. Therefore, the outcome of SNOT-22 is assigned to the outcome category of non-serious/non-severe symptoms/late complications.

The company did not make an assignment to the outcome category.

Table 14: Extent of added benefit at outcome level: mepolizumab + mometasone furoate vs. mometasone furoate (multipage table)

Outcome category **Outcome**	**Mepolizumab + mometasone furoate vs. placebo + mometasone furoate** **Proportion of events (%)** **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	68% vs. 46% RR: 0.68 [0.56; 0.82][c]; p < 0.001 Probability: "hint"	Outcome category: serious/severe symptoms/late complications Added benefit, extent: "non-quantifiable"
VAS for nasal discharge improvement by ≥ 1.5 points	68% vs. 46% RR: 0.68 [0.56; 0.82][c]; p < 0.001 Probability: "hint"	Outcome category: serious/severe symptoms/late complications Added benefit, extent: "non-quantifiable"
VAS for mucus in the throat improvement by ≥ 1.5 points	65% vs. 46% RR: 0.71 [0.58; 0.86][c]; p < 0.001 Probability: "hint"	Outcome category: serious/severe symptoms/late complications Added benefit, extent: "non-quantifiable"
VAS for facial pain/pressure improvement by ≥ 1.5 points	61% vs. 43% RR: 0.71 [0.58; 0.87][c]; p < 0.001 Probability: "hint"	Outcome category: serious/severe symptoms/late complications Added benefit, extent: "non-quantifiable"
VAS for loss of smell improvement by ≥ 1.5 points	45% vs. 25% RR: 0.56 [0.40; 0.75][c]; p < 0.001 Probability: "hint"	Outcome category: serious/severe symptoms/late complications Added benefit, extent: "non-quantifiable"
SNOT-22 total score improvement by ≥ 16.5 points	69% vs. 45% RR: 0.66 [0.54; 0.79][c]; p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications Added benefit, extent: "non-quantifiable"
Health-related quality of life		
SF-36v2		
Physical Component Summary (PCS) improvement by ≥ 9.4 points	No usable data	Lesser benefit/added benefit not proven
Mental Component Summary (MCS) improvement by ≥ 9.6 points	No usable data	Lesser benefit/added benefit not proven

Table 14: Extent of added benefit at outcome level: mepolizumab + mometasone furoate vs. mometasone furoate (multipage table)

Outcome category **Outcome**	**Mepolizumab + mometasone furoate vs. placebo + mometasone furoate** **Proportion of events (%)** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
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 comparison of placebo + mometasone furoate vs. mepolizumab + mometasone furoate.

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 – version 2 Health Survey; SNOT-22: 22-item Sino-Nasal Outcome Test; VAS: visual analogue scale

2.5.2 Overall conclusion on added benefit

Table 15 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 15: 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: hint of an added benefit – extent "non-quantifiable" ▪ VAS for nasal discharge: hint of an added benefit – extent "non-quantifiable" ▪ VAS for mucus in the throat: hint of an added benefit – extent "non-quantifiable" ▪ VAS for facial pain/pressure: hint of an added benefit – extent "non-quantifiable" ▪ VAS for loss of smell: hint of an added benefit – extent "non-quantifiable" Non-serious/non-severe symptoms/late complications ▪ SNOT-22 total score: hint of an added benefit – extent "non-quantifiable"	-
There are no usable data on health-related quality of life.	

SNOT-22: 22-item Sino-Nasal Outcome Test; VAS: visual analogue scale

Overall, only positive effects are shown in the outcome categories of serious/severe symptoms/late complications and non-serious/non-severe symptoms/late complications, each with non-quantifiable extent. There are no usable data on health-related quality of life.

In summary, due to the limitations described in Section 2.3.2 and Section 2.4.1, there is a hint of a non-quantifiable added benefit of mepolizumab as an add-on therapy with INCS in comparison with the ACT for patients with severe CRSwNP for whom therapy with SCS and/or surgery do not provide adequate disease control.

Table 16 summarizes the result of the assessment of added benefit of mepolizumab in comparison with the ACT.

Table 16: Mepolizumab – probability and extent of added benefit

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

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

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The assessment described above deviates from that of the company, which derived an indication of major added benefit.

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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