

Tezepelumab (chronic rhinosinusitis with nasal polyps)

Benefit assessment according to §35a SGB V¹

A decorative horizontal bar composed of 18 squares of varying shades of blue and grey. The word 'EXTRACT' is centered in white text on a dark blue rectangular background that spans most of the width of the bar.

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Siegburger Str. 237
50679 Köln
Germany

Phone: +49 221 35685-0

Fax: +49 221 35685-1

Email: info@iqwig.de

Internet: www.iqwig.de

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Medical and scientific advice

- Leif Erik Walther, HNO-Gemeinschaftspraxis (ENT practice), Main Taunus Zentrum, D-65843 Sulzbach (Taunus), Germany

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Patient and family involvement

No feedback was received within the framework of this dossier assessment.

IQWiG employees involved in the dossier assessment

- Annette Christoph
- Nadia Abu Rajab-Conrads
- Simone Heß
- Lisa Junge
- Mattea Patt
- Snjezana Petzler
- Daniela Preukschat
- Min Ripoll
- Veronika Schneck

Part I: Benefit assessment

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I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AERD	aspirin-exacerbated respiratory disease
CRSwNP	chronic rhinosinusitis with nasal polyps
CTCAE	Common Terminology Criteria for Adverse Events
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)
NCS	nasal congestion score
NPS	nasal polyp score
NPSD	nasal polyposis symptom diary
NRI	non-responder imputation
NRS	numeric rating scale
OCS	oral corticosteroids
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)
SmPC	summary of product characteristics
SNOT-22	Sino-Nasal Outcome Test (22 items)
VAS	visual analogue scale
WPAI	Work Productivity and Activity Impairment
WPS	worst possible score

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book 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 tezepelumab. 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 17 November 2025.

Research question

The aim of this report is the assessment of the added benefit of tezepelumab 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 shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of tezepelumab

Therapeutic indication	ACT ^a
Add-on therapy for adults with severe CRSwNP for whom therapy with SCS, and/or surgery do not provide adequate disease control	▪ dupilumab or ▪ omalizumab or ▪ mepolizumab in each case in combination with intranasal corticosteroids (budesonide or mometasone furoate)^b
a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 Section 4.2.2 is printed in bold. 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 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 tezepelumab is an option. ACT: appropriate comparator therapy; CRSwNP: chronic rhinosinusitis with nasal polyposis; G-BA: Federal Joint Committee; SCS: systemic corticosteroid	

In addressing the research question, the company followed the G-BA's specification of the ACT. For the derivation of the added benefit on the basis of an adjusted indirect comparison, the company selected mepolizumab from the various options for the ACT.

The assessment was 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 were used for the derivation of added benefit.

Study pool and study design

The review of the completeness of the study pool did not identify any studies for a direct comparison of tezepelumab as an add-on therapy with INCS versus the ACT for the given research question.

The company therefore presented an adjusted indirect comparison according to Bucher for the assessment of tezepelumab in combination with INCS versus the ACT using the common comparator placebo. For the intervention, it drew on the WAYPOINT study, and for the comparator mepolizumab, the SYNAPSE study.

WAYPOINT study

The WAYPOINT study is a double-blind RCT comparing tezepelumab with placebo, both administered in addition to maintenance therapy with INCS over 52 weeks. The study included adult patients who, despite previous documented SCS treatment and/or surgery for nasal polyps, or in cases where there were contraindications to or intolerance of both treatments, were suffering from CRSwNP that had been diagnosed at least 12 months prior to baseline. At the time of screening, patients had to have a nasal polyp score (NPS) of ≥ 5 (≥ 2 for each nostril) on a scale of 0 to 8, as well as a nasal congestion score (NCS) of ≥ 2 on a scale of 0 to 3, and CRSwNP symptoms such as nasal discharge and/or reduction or loss of smell for ≥ 8 weeks. The total score on the 22-item Sino-Nasal Outcome Test (SNOT-22) had to be ≥ 30 . Patients also had to have received standard of care for treatment of CRSwNP, at a stable dose, for at least 30 days prior to screening.

Prior to randomization, there was a 5-week run-in phase during which patients were treated with standardized INCS maintenance therapy (400 µg mometasone furoate or equivalent) and were instructed on how to record the severity of their symptoms daily in an electronic symptom diary.

Following the run-in phase, only those patients were randomized to the treatment arms who, in addition to meeting the inclusion criteria, had an NPS of ≥ 5 (≥ 2 for each nostril) on a scale of 0 to 8 at screening. In addition, over the 14 days prior to randomization, a mean NCS of ≥ 2 on a scale of 0 to 3 had to have been recorded in the symptom diary, and the SNOT-22 total score at the time of randomization had to have been ≥ 30 .

Treatment with tezepelumab was in compliance with the summary of product characteristics (SmPC). Administration of INCS at stable doses was continued in the treatment phase. In addition to the study medication under investigation and INCS maintenance therapy, short-

term treatment with SCS or antibiotics was permitted as needed to treat nasal polyps. A total of 410 patients were randomized in a 1:1 ratio to receive either tezepelumab (N = 204) or placebo (N = 206), and of these, 408 patients were treated with tezepelumab (N = 203) or placebo (N = 205).

The primary outcomes were the change in the NPS at Week 52 and the change in bi-weekly mean NCS at Week 52. In addition, further patient-relevant outcomes in the outcome categories of morbidity, health-related quality of life and side effects were recorded.

For the adjusted indirect comparison, the company presented the results for a subpopulation of patients whose medical history already included at least one documented operation for nasal polyps. This subpopulation comprises 144 patients in the intervention arm and 147 patients in the comparator arm.

SYNAPSE study

The SYNAPSE study is a double-blind RCT comparing mepolizumab with placebo, both administered in addition to maintenance therapy with the intranasal corticosteroid mometasone furoate over 52 weeks. The study 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.

Prior to randomization, there was a 4-week run-in phase during which patients were instructed on how to record the severity of their symptoms daily in an electronic symptom diary. During this phase, patients were also switched to maintenance therapy with 400 µg of intranasal mometasone furoate daily if they had previously been treated with another INCS or had not yet reached the maximum dose of mometasone furoate at that point.

Following the run-in phase, only those patients were to be 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 in the symptom diary.

Treatment with mepolizumab was in compliance with the SmPC. 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 corticosteroids or alternative administration of SCS was allowed as required. Surgery for the treatment of nasal polyps was also permitted.

A total of 407 patients were allocated in a 1:1 ratio to treatment with mepolizumab (N = 206) or placebo (N = 201).

The primary outcomes were the change in the mean VAS score for nasal obstruction in Weeks 49 to 52 and the change in the NPS at Week 52. In addition, other patient-relevant outcomes in the outcome categories of morbidity, health-related quality of life and side effects were recorded.

Limitations of the studies

The WAYPOINT and the SYNAPSE studies have 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 studies. Furthermore, for the WAYPOINT study, it is unclear whether necessary nasal polyp operations at baseline were delayed for patients in the relevant subpopulation, as – unlike in the SYNAPSE study – undergoing surgery resulted in treatment discontinuation. The uncertainties described contributed to a reduced certainty of conclusions at study level for both studies. However, this alone did not call into question the requirements for the certainty of results when carrying out an adjusted indirect comparison.

Similarities of the studies for the indirect comparison

Overall, there were some differences between the WAYPOINT and SYNAPSE studies in terms of study and patient characteristics; however, none of these differences fundamentally called into question the sufficient level of similarity required to conduct an adjusted indirect comparison using placebo as the common comparator, taking into account both the WAYPOINT and SYNAPSE studies.

Risk of bias and certainty of conclusions

There was one RCT on each side of the available adjusted indirect comparison. Consequently, there was no need to assess homogeneity. As there was no study of direct comparison of tezepelumab versus the ACT, it was impossible to check the consistency of results. Therefore, the adjusted indirect comparisons had at most a low certainty of results. Hence, no more than hints, e.g. of an added benefit, could be derived on the basis of the data available from the adjusted indirect comparison. In both studies, the uncertainty regarding the need for surgery for nasal polyps at baseline led to a reduced certainty of conclusions. However, this alone did not mean that the requirements for the certainty of results needed to conduct an adjusted indirect comparison were not met.

The risk of bias across outcomes was rated as low for both studies. For SYNAPSE, the risk of bias in the results for all study outcomes was assessed as low. In WAYPOINT, there is a high risk of bias in the results for all outcomes, with the exception of the outcome discontinuation due to AEs. For the outcome category morbidity and health-related quality of life, this is due

to the large difference between the treatment groups in the proportion of values imputed using non-responder imputation (NRI). No sensitivity analyses were available for these outcomes to assess whether the effects identified remain robust when other imputation methods are used that more accurately represent the therapeutic strategy. For the outcomes based on the recording of side effects, including deaths, the high risk of bias stems from the high and, between study arms, differing proportions of patients with incomplete follow-up. Consequently, the requirements for certainty of results needed to conduct an adjusted indirect comparison were not met, and the indirect comparison of the individual outcomes was not used for the benefit assessment. The latter also applied to the outcome discontinuation due to AEs, for which, despite the low risk of bias, the certainty of results was considered to be limited in both studies.

In summary, data with sufficient certainty of results, which would allow an informative adjusted indirect comparison to be conducted, were not available for any of the outcomes of either study.

Results

Mortality

Overall survival

Due to insufficient certainty of the results in the WAYPOINT study (incomplete observations for potentially informative reasons), it was not possible to conduct an adjusted indirect comparison for the results for the outcome all-cause mortality. There is therefore no hint of an added benefit of tezepelumab + INCS in comparison with mepolizumab + INCS; an added benefit is therefore not proven.

Morbidity

Nasal congestion/obstruction, facial pain

No suitable data were available for the results for the symptom outcomes nasal congestion/obstruction and facial pain. With regard to the outcome nasal congestion, this was due to the fact that WAYPOINT reported more responders than patients with a completed questionnaire at Week 52. For the outcome facial pain it was assumed that, on the intervention side, results from WAYPOINT relating to facial pressure were included, whilst on the comparator side, results from SYNAPSE relating to facial pain were included. There is therefore in each case no hint of an added benefit of tezepelumab + INCS in comparison with mepolizumab + INCS; an added benefit is therefore not proven.

Reduction/loss of smell, nasal discharge, mucus in the throat, SNOT-22 and activity impairment

Due to insufficient certainty of results in the WAYPOINT study (large difference between the treatment groups in the proportion of values imputed using NRI), it was not possible to

conduct an adjusted indirect comparison for the results for the symptom outcomes reduction/loss of smell, nasal discharge, mucus in the throat, and the SNOT-22 and activity impairment outcomes. There is therefore in each case no hint of an added benefit of tezepelumab + INCS in comparison with mepolizumab + INCS; an added benefit is therefore not proven.

Health-related quality of life

SF-36v2

With regard to the results for the SF-36v2 outcome, it was not possible to conduct an adjusted indirect comparison due to insufficient certainty of results in the WAYPOINT study (large difference between the treatment groups in the proportion of values imputed using NRI). There is therefore no hint of an added benefit of tezepelumab + INCS in comparison with mepolizumab + INCS; an added benefit is therefore not proven.

Side effects

SAEs and discontinuation due to AEs

Due to insufficient certainty of the results in the WAYPOINT study, it was not possible to conduct an adjusted indirect comparison for the outcomes SAEs and discontinuation due to AEs. For the outcome SAEs this was due to incomplete observations for potentially informative reasons. For the outcome discontinuation due to AEs, there was limited certainty of the results in both studies, despite the low risk of bias, due to treatment discontinuations for reasons other than AEs. Hence for these outcomes, there was in each case no hint of greater or lesser harm of tezepelumab + INCS in comparison with mepolizumab + INCS; greater or lesser harm for these outcomes is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit³

On the basis of the results presented, the probability and extent of the added benefit of the drug tezepelumab versus the ACT was assessed as follows:

For the individual outcomes within the various outcome categories, there were no results available that meet the requirements for certainty of results necessary to conduct an adjusted

³ 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 lesser benefit). For further details see [1,2].

indirect comparison, or the indirect comparison could not be conducted because no suitable results were available for at least one side of the indirect comparison.

In summary, for patients with severe CRSwNP for whom therapy with SCS, and/or surgery do not provide adequate disease control, there is no hint of an added benefit of tezepelumab + INCS versus mepolizumab + INCS.

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

Table 3: Tezepelumab – probability and extent of added benefit

Therapeutic indication	ACT ^a	Probability and extent of added benefit
Add-on therapy for adults with severe CRSwNP for whom therapy with SCS, and/or surgery do not provide adequate disease control	▪ dupilumab or ▪ omalizumab or ▪ mepolizumab in each case in combination with intranasal corticosteroids (budesonide or mometasone furoate) ^b	Added benefit not proven
a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 Section 4.2.2 is printed in bold. 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 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 tezepelumab is an option. ACT: appropriate comparator therapy; CRSwNP: chronic rhinosinusitis with nasal polyposis; G-BA: Federal Joint Committee; SCS: systemic corticosteroid		

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

I 2 Research question

The aim of this report is the assessment of the added benefit of tezepelumab 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 shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of tezepelumab

Therapeutic indication	ACT ^a
Add-on therapy for adults with severe CRSwNP for whom therapy with SCS, and/or surgery do not provide adequate disease control	▪ dupilumab or ▪ omalizumab or ▪ mepolizumab in each case in combination with intranasal corticosteroids (budesonide or mometasone furoate) ^b
a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 Section 4.2.2 is printed in bold. 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 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 tezepelumab is an option. ACT: appropriate comparator therapy; CRSwNP: chronic rhinosinusitis with nasal polyposis; G-BA: Federal Joint Committee; SCS: systemic corticosteroid	

In addressing the research question, the company followed the G-BA's specification of the ACT. For the derivation of the added benefit on the basis of an adjusted indirect comparison, the company selected mepolizumab from the various options for the ACT (see Chapter I 3).

The assessment was 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 were used for the derivation of added benefit. This concurred with the company's inclusion criteria.

I 3 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study list on tezepelumab (status: 1 October 2025)
- Bibliographical literature search on tezepelumab (last search on 2 October 2025)
- Search of trial registries / trial results databases for studies on tezepelumab (last search on 17 October 2025)
- Search on the G-BA website for tezepelumab (last search on 10 October 2025)
- Bibliographical literature search on mepolizumab (last search on 2 October 2025)
- Search of trial registries / trial results databases for studies on mepolizumab (last search on 20 October 2025)
- Search on the G-BA website for mepolizumab (last search on 10 October 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on tezepelumab (last search on 20 November 2025); for search strategies, see I Appendix A of the full dossier assessment
- Search of trial registries for studies on mepolizumab (last search on 21 November 2025); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company's findings, the review of the completeness of the study pool did not identify any studies for a direct comparison of tezepelumab as an add-on therapy with INCS versus the ACT for the given research question.

The company therefore presented an adjusted indirect comparison according to Bucher [3] for the assessment of tezepelumab in combination with INCS versus the ACT mepolizumab using the common comparator placebo. For the intervention, it drew on the WAYPOINT study, and for the comparator, the SYNAPSE study (see Section I 3.1).

In addition to the SYNAPSE study on mepolizumab, the MERIT study was identified as a further relevant study, in line with the company's findings [4,5]. The company did not use the study, but did not give any specific reasons for this. It merely stated that the MERIT study was designed for the purpose of marketing authorization in Japan and China, and that, in its view, the SYNAPSE study represented the best available evidence for an indirect comparison. Concurring with the company, the MERIT study was not included in the adjusted indirect comparison. The reasons for this are provided below.

MERIT study

MERIT is a randomized, double-blind study comparing mepolizumab with placebo. The study included adult patients with bilateral nasal polyps, a blood eosinophil count $> 2\%$ and symptoms of chronic rhinosinusitis that had persisted for ≥ 12 weeks, including nasal obstruction with a score > 5 on a visual analogue scale (VAS). Patients' medical history had to include treatment for nasal polyps by means of surgery and/or SCS on at least 3 consecutive days within the preceding 2 years, unless there was a contraindication to or intolerance of SCS. Existing maintenance treatment with INCS was not a prerequisite for inclusion in the study; patients were not permitted to start treatment with INCS during the screening phase. 74% of the randomized patients were receiving maintenance therapy with INCS at baseline. For an adjusted indirect comparison in accordance with the marketing authorization for tezepelumab [6], fundamentally relevant is the subpopulation of patients who have undergone surgery for nasal polyps and/or received SCS treatment in the past, or who have an existing contraindication or intolerance to both treatments, and who were receiving INCS maintenance therapy at baseline. The adjusted indirect comparison versus the SYNAPSE study, as presented by the company, included only patients who had previously undergone surgery for nasal polyps, as per the study's inclusion criteria (see Section I 3.2). MERIT included 35% of patients who had not previously undergone surgery for nasal polyps. No analyses were available for the subpopulation meeting the criteria of having undergone previous surgery for nasal polyps and receiving INCS maintenance therapy at baseline. The total population of MERIT was not suitable for the adjusted indirect comparison. Furthermore, no information was available regarding the type, dosage and route of administration of the drugs used in the INCS therapy continued in the study. The relevant subpopulation would be that of patients receiving maintenance therapy with mometasone furoate or budesonide, in accordance with the ACT (see Table 4).

I 3.1 Studies included

The studies listed in the following table were included in the benefit assessment.

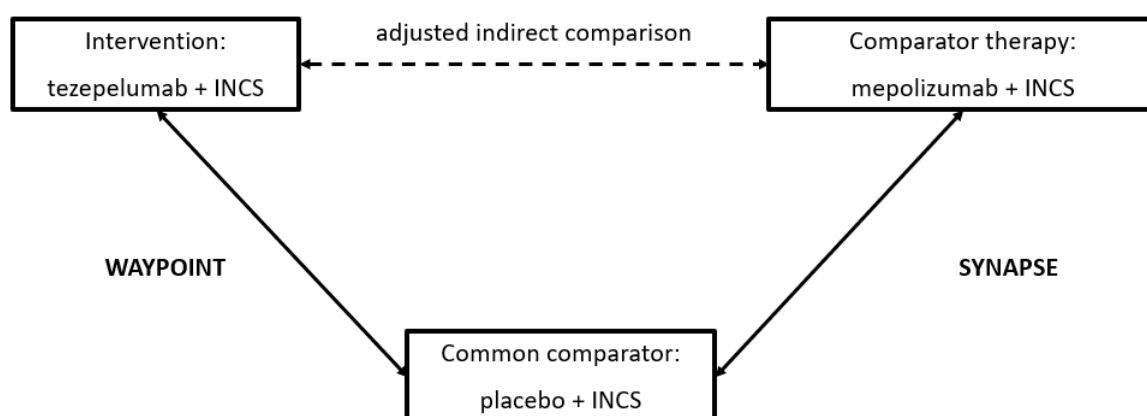
Table 5: Study pool – RCT, indirect comparison: tezepelumab + INCS vs. mepolizumab + INCS

Study	Study category			Available sources		
	Study for the marketing authorization 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 ^c (yes/no [citation])
D5242C00001 (WAYPOINT ^d)	Yes	Yes	No	Yes [7,8]	Yes [9,10]	Yes [11]
205687 (SYNAPSE ^d)	No	No	Yes	No	Yes [12,13]	Yes [14-18]

a. Study sponsored by the company.
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: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to by this acronym.
CSR: clinical study report; G-BA: Federal Joint Committee; INCS: intranasal corticosteroids; RCT: randomized controlled trial

The study pool for the benefit assessment concurred with that of the company. On the intervention side, it included the WAYPOINT study. On the comparator side, it included the SYNAPSE study. SYNAPSE was already presented and assessed for a previous benefit assessment of mepolizumab [17,18].

Figure 1 is a schematic representation of the indirect comparison.



INCS: intranasal corticosteroids

Figure 1: Study pool for the adjusted indirect comparison between tezepelumab and mepolizumab each in combination with INCS via the common comparator placebo

I 3.2 Study characteristics

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

Table 6: Characteristics of the studies included – RCT, indirect comparison: tezepelumab + INCS vs. mepolizumab + INCS (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes ^a
tezepelumab + INCS vs. placebo + INCS						
WAYPOINT	RCT, double-blind, parallel	Adults (≥ 18 years) with chronic rhinosinusitis with nasal polyps (CRSwNP) and with: ▪ NPS ≥ 5 (≥ 2 for each nostril)^b ▪ NCS score ≥ 2^c ▪ Acute nasal polyps symptoms (> 8 weeks) ▪ SNOT-22 total score ≥ 30^d ▪ Previous treatment with corticosteroids^e and/or surgery to remove nasal polyps ▪ Standard of care for treatment^f of CRSwNP at a stable dose (≥ 30 days)	tezepelumab + INCS (N = 204) placebo + INCS (N = 206) Relevant subpopulation thereof^g: tezepelumab + INCS (n = 144) placebo + INCS (n = 147)	Run-in: 5 weeks Treatment: 52 weeks Follow-up: 24 weeks^h	112 centres in Canada, China, Denmark, Germany, Hungary, Japan, Poland, Spain, United Kingdom and United States 4/2021–12/2024 Data cuts: 23 September 2024ⁱ 23 January 2025^j	Coprimary: change in NPS at Week 52 change in bi-weekly mean NCS at Week 52 Secondary: morbidity, health-related quality of life, AEs

Table 6: Characteristics of the studies included – RCT, indirect comparison: tezepelumab + INCS vs. mepolizumab + INCS (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes ^a
mepolizumab + INCS vs. placebo + INCS						
SYNAPSE	RCT, double-blind, parallel	Adults (≥ 18 years) with recurrent chronic rhinosinusitis with recurrent bilateral nasal polyps and with: ▪ VAS for nasal obstruction > 5^k ▪ VAS symptom total score > 7^k ▪ NPS ≥ 5 (≥ 2 for each nostril)^l ▪ ≥ 1 surgery^m in the previous 10 years for the removal of nasal polyps ▪ Prior treatment with INCS at a stable dose (≥ 8 weeks)	mepolizumab + INCS (N = 206) placebo + INCS (N = 201)	Run-in: 4 weeks ⁿ Treatment: 52 weeks Follow-up: 24 weeks ^g	86 centres in Argentina, Australia, Canada, Germany, Korea, Netherlands, Romania, Russia, Sweden, United Kingdom, United States 5/2017–12/2019	Coprimary: change in NPS at Week 52 change in the mean nasal obstruction VAS score during Weeks 49–52 Secondary: morbidity, health-related quality of life, AEs

Table 6: Characteristics of the studies included – RCT, indirect comparison: tezepelumab + INCS vs. mepolizumab + INCS (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes ^a
a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment. b. The scale ranges from 0 to 8 (a higher score indicates worse status). c. At screening (Visit 1) and at the time of randomization (Visit 3). Under amendment 3 to the study protocol dated 28 January 2022, a mean NCS of ≥ 2, calculated from study days -13 to 0, was required at the time of randomization. Scale range: 0 to 3. d. Scale range: 0 to 110. e. Systemic treatment on ≥ 3 consecutive days or 1 intramuscular depot injection (or contraindication/intolerance) < 12 to ≥ 3 months prior to screening (Visit 1). f. In particular INCS. g. Relevant subpopulation for the adjusted indirect comparison presented; patients with at least one documented operation for nasal polyps before baseline. Nasal polyp surgery was defined as any procedure involving instruments with resulting incision and removal of tissue from the paranasal sinus (e.g. polypectomy, sinus surgery). h. 24 weeks' follow-up only for the first 200 randomized patients; the remaining patients were followed up for a period of 12 weeks after the end of treatment. i. Prespecified primary analysis after all patients had completed Week 52. j. Date of the final database lock; prespecified final analysis once all patients had completed the follow-up period (Week 76 for the first 200 patients and Week 64 for all other patients). k. Scale range: 0 to 10. l. 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). m. Nasal polyp surgery was defined as any procedure involving instruments with resulting incision and removal of tissue from the paranasal sinus (polypectomy). n. If the patient had a cold during run-in, then run-in could be extended by 2 weeks to a maximum of 6 weeks. AE: adverse event; CRSwNP: chronic rhinosinusitis with nasal polyps; INCS: intranasal corticosteroids; n: relevant subpopulation; N: number of randomized patients; NCS: nasal congestion score; NPS: nasal polyp score; RCT: randomized controlled trial; SNOT-22: SinoNasal Outcome Test 22-item; VAS: visual analogue scale						

Table 7: Characteristics of the intervention – RCT, indirect comparison: tezepelumab + INCS vs. mepolizumab + INCS (multipage table)

Study	Intervention	Comparison
tezepelumab + INCS vs. placebo + INCS		
WAYPOINT	tezepelumab 210 mg, SC, every 4 weeks + continuation of the maintenance treatment with intranasal mometasone furoate (or equivalent INCS) at a stable dose ^a	placebo, SC, every 4 weeks
Required prior treatment - Standard of care for treatment of CRSwNP at a stable dose (≥ 30 days prior to screening)^b - SCS^c on ≥ 3 consecutive days or 1 intramuscular depot injection < 12 to ≥ 3 months prior to screening and/or a history of ≥ 1 surgery^c to remove nasal polyps Allowed concomitant treatment - Short-term treatment with SCS^d - Antibiotic treatment for nasal polyps Disallowed prior and concomitant treatment - Nasal polyp surgery^{e, f} during the course of the study - Biologics (e.g. mepolizumab, reslizumab, dupilumab, benralizumab, omalizumab) ≤ 4 months or 5 half-lives (whichever period is longer) prior to screening and following the last dose of the study medication - Initiation of allergen immunotherapy, or dose modification to ongoing treatment, within 30 days before screening until end of study - Regular use of decongestants (topical or systemic) at the time of screening and throughout the course of the study, with the exception of use for endoscopic procedures - Intranasal drugs, with the exception of standardized INCS maintenance therapy - Immunosuppressants: ≤ 3 months prior to screening until 3 months or 5 half-lives (whichever period is longer) after the last dose of the study medication - Corticosteroid-eluting intranasal stents ≤ 6 months prior to screening until the end of the study - Receipt of immunoglobulins or blood products ≤ 30 days prior to screening until 4 weeks after the last dose of the study medication - Investigational nonbiologics ≤ 30 days or 5 half-lives prior to the date of informed consent, whichever is longer - Aspirin desensitization ≤ 6 months prior to baseline (any other use of aspirin was permitted) - Live vaccines ≤ 30 days to 16 weeks / 5 half-lives after the last dose of study medication - Sinus surgery (≤ 6 months prior to screening) / sinus surgery in the past which changed the lateral wall of the nose		

Table 7: Characteristics of the intervention – RCT, indirect comparison: tezepelumab + INCS vs. mepolizumab + INCS (multipage table)

Study	Intervention	Comparison
mepolizumab + INCS vs. placebo + INCS		
SYNAPSE	mepolizumab 100 mg/mL, SC, every 4 weeks + continuation of the maintenance treatment with intranasal mometasone furoate at a stable dose^a Required prior treatment ▪ INCS at a stable dose for at least 8 weeks before screening^b ▪ At least one nasal polyp surgery^e in the previous 10 years before screening Allowed concomitant treatment ▪ Short courses of high doses of OCS ▪ Antibiotic treatment for nasal polyps ▪ Saline nasal douching ▪ Nasal polyp surgery^e ▪ Ongoing asthma treatment ▪ Analgesics Disallowed 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 (nonbiologics) 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 before screening ▪ Participation in previous studies with mepolizumab, reslizumab, dupilumab, benralizumab ▪ Intranasal nonsurgical interventions (e.g. balloon dilatation/sinuplasty or insertion of any nasal stents) 6 months before screening ▪ Initiation or dose modification of ongoing leukotriene antagonist treatment within 30 days before screening until end of study ▪ Initiation of allergen immunotherapy, or dose modification to ongoing treatment, within 3 months before screening until end of study	placebo, SC, every 4 weeks

Table 7: Characteristics of the intervention – RCT, indirect comparison: tezepelumab + INCS vs. mepolizumab + INCS (multipage table)

Study	Intervention	Comparison
a. During the entire study (run-in, treatment and follow-up period), 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 was allowed. In the WAYPOINT study, equivalent INCS could be administered in place of mometasone furoate; the equivalent dose was defined as the highest on-label INCS dose for CRSwNP in the respective country; for these alternative INCS, a reduction in the daily dose was also permitted as needed. b. Thereafter: ≥ 4-week run-in phase with standardized INCS maintenance therapy. c. Unless a contraindication or intolerance was present. d. Treatment with SCS for ≥ 3 consecutive days or 1 intramuscular depot injection as part of emergency treatment in the event of a worsening of nasal polyp symptoms, asthma attacks or another indication. If the interval between 2 treatment episodes was < 7 days, this was considered continuous therapy. e. Nasal polyp surgery was defined as any procedure involving instruments with resulting incision and removal of tissue from the paranasal sinus (polypectomy). f. Although surgery for nasal polyps was generally permitted in the WAYPOINT study, it resulted in the permanent discontinuation of treatment with the study medication. Following randomization, no surgery for nasal polyps was to be scheduled for within the first 3 months, unless deemed necessary in the investigator's opinion. CRSwNP: chronic rhinosinusitis with nasal polyps; INCS: intranasal corticosteroids; OCS: oral corticosteroids; RCT: randomized controlled trial; SC: subcutaneous; SCS: systemic corticosteroids		

Study design

WAYPOINT (study for tezepelumab in combination with INCS)

The WAYPOINT study is a double-blind RCT comparing tezepelumab with placebo, both administered in addition to maintenance therapy with INCS over 52 weeks. The study included adult patients who, despite previous documented SCS treatment and/or surgery for nasal polyps, or in cases where there were contraindications to or intolerance of both treatments, were suffering from CRSwNP that had been diagnosed at least 12 months prior to baseline. At the time of screening, patients had to have a nasal polyp score (NPS) of ≥ 5 (≥ 2 for each nostril) on a scale of 0 to 8, as well as a nasal congestion score (NCS) of ≥ 2 on a scale of 0 to 3, and CRSwNP symptoms such as nasal discharge and/or reduction or loss of smell for ≥ 8 weeks. The total score on the 22-item Sino-Nasal Outcome Test (SNOT-22) had to be ≥ 30 (scale range: 0 to 110). Patients also had to have received standard of care for treatment of CRSwNP, at a stable dose, for at least 30 days prior to screening. For the study participants, this consisted primarily of INCS such as mometasone, budesonide or fluticasone.

Prior to randomization, there was a 5-week run-in phase during which patients were treated with standardized INCS maintenance therapy and were asked to record the severity of their symptoms daily (nasal blockage, nasal congestion, nasal discharge, reduction or loss of smell, mucus in the throat, headache, facial pressure and facial pain) in an electronic symptom diary. The standardized INCS maintenance therapy consisted of 400 µg of intranasal mometasone

furoate daily (2 actuations of 50 µg per nostril twice daily) or an equivalent INCS, with the equivalent dose defined as the maximum permitted INCS dose for CRSwNP in the respective country. In exceptional cases, a reduction in the dose was possible, subject to the patient's tolerability and at the discretion of the investigator.

Following the run-in phase, only those patients were randomized to the treatment arms who, in addition to meeting the inclusion criteria, had an NPS of ≥ 5 (≥ 2 for each nostril) on a scale of 0 to 8 at screening. In addition, over the 14 days prior to randomization (Day -13 to Day 0), a mean NCS of ≥ 2 on a scale of 0 to 3 had to have been recorded in the symptom diary, and the SNOT-22 total score at the time of randomization had to have been ≥ 30 .

Administration of INCS at stable doses was continued in the treatment phase. In addition to the study medication under investigation and INCS maintenance therapy, short-term treatment with SCS or antibiotics was permitted as needed to treat nasal polyps. Additional measures (such as nasal douching) were not explicitly excluded in the study protocol. Following randomization, no surgery for nasal polyps was to be scheduled for within the first 3 months of the study, unless deemed necessary in the investigator's opinion. In WAYPOINT, surgery for nasal polyps led to the permanent discontinuation of treatment with the study drug.

A total of 410 patients were randomized in a 1:1 ratio to receive either tezepelumab (N = 204) or placebo (N = 206), and of these, 408 patients were treated with tezepelumab (N = 203) or placebo (N = 205). Randomization was stratified by region (China versus Japan versus the rest of the world), previous surgery for nasal polyps, and comorbid asthma / aspirin-exacerbated respiratory disease (AERD) / non-steroidal anti-inflammatory drug-exacerbated respiratory disease.

Treatment with tezepelumab was in compliance with the summary of product characteristics (SmPC) [6]. After the 52-week treatment phase, a 24-week follow-up period was planned for the first 200 randomized patients. The follow-up period for all other patients was 12 weeks.

The primary outcomes were the change in the NPS at Week 52 and the change in bi-weekly mean NCS at Week 52. In addition, further patient-relevant outcomes in the outcome categories of morbidity, health-related quality of life and side effects were recorded.

Subpopulation used for the adjusted indirect comparison

For the adjusted indirect comparison, the company presented the results for a subpopulation of patients whose medical history already included at least one documented operation for nasal polyps. This subpopulation comprised 144 patients in the intervention arm and 147 patients in the comparator arm. The company justified the inclusion of this subpopulation on the grounds that the SYNAPSE study exclusively included patients with nasal polyp surgery

in their medical history, and that this approach would ensure the best possible comparability between the populations of the 2 studies, WAYPOINT and SYNAPSE. The company's approach is comprehensible. In the following, only the WAYPOINT subpopulation who had previously undergone surgery for nasal polyps are considered.

SYNAPSE (study for mepolizumab in combination with INCS)

The SYNAPSE study is a double-blind RCT comparing mepolizumab with placebo, both administered in addition to maintenance therapy with the intranasal corticosteroid mometasone furoate over 52 weeks. The study was already described in detail in dossier assessment A21-150 [18]. The study 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.

Prior to randomization, there was a 4-week run-in phase during which patients were instructed to record the severity of their symptoms (nasal obstruction, nasal discharge, loss of smell, mucus in the throat, facial pain, overall symptom score) on a daily basis in an electronic symptom diary (see details in the study protocol [19]). During this phase, patients were also switched to maintenance therapy with 400 μg of intranasal mometasone furoate daily (2 50- μg actuations into each nostril twice daily) if they had previously been treated with another INCS or had not yet reached the maximum dose of mometasone furoate at that point. Depending on tolerance, dose reduction of mometasone furoate to one daily administration (a total of 200 μg) was an option.

Following the run-in phase, randomization to the treatment arms was only to occur for those patients who, in addition to meeting the inclusion criteria at screening, scored an NPS of ≥ 5 (≥ 2 for each nostril) on a scale of 0 to 8, and who, in their symptom diary covering the 7 days prior to randomization, had a VAS score for total symptoms > 7 and for nasal obstruction > 5 . Contrary to this, at the time of randomization, a total of 18% of patients (17% in the mepolizumab arm and 20% in the placebo arm) had a nasal polyp score of < 5 . This discrepancy did not affect this assessment, as the study population as a whole was considered to be sufficiently severely affected for the given 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 oral corticosteroids or alternative administration of SCS was allowed as required. Surgery for the treatment of nasal polyps was also permitted.

A total of 407 patients were allocated in a 1:1 ratio to treatment with mepolizumab (N = 206) or placebo (N = 201). Randomization was carried out separately for each country. Treatment

with mepolizumab was in compliance with the SmPC [20]. After the 52-week treatment phase, a 24-week follow-up period was planned for the first up to 200 randomized patients.

The primary outcomes were the change in the mean VAS score for nasal obstruction in Weeks 49 to 52 and the change in the NPS at Week 52. In addition, other patient-relevant outcomes in the outcome categories of morbidity, health-related quality of life and side effects were recorded.

Planned duration of follow-up

Table 8 shows the planned duration of patient follow-up for the individual outcomes in the studies WAYPOINT and SYNAPSE.

Table 8: Planned duration of follow-up– RCT, indirect comparison: tezepelumab + INCS vs. mepolizumab + INCS (multipage table)

Comparison Study Outcome category Outcome	Planned follow-up
tezepelumab + INCS vs. placebo + INCS	
WAYPOINT	
Mortality All-cause mortality ^a	Until end of study ^b , study discontinuation or, in case of treatment discontinuation, until at least 4 weeks ± 5 days ^{c, d} after the last dose of study medication
Morbidity Symptoms (NPSD ^e , SNOT-22) Activity impairment (WPAI, question 6)	Until end of study ^b , study discontinuation or, in case of treatment discontinuation, until at least 4 weeks ± 5 days ^c after the last dose of study medication Until Week 52, study discontinuation or, in case of treatment discontinuation, until at least 4 weeks ± 5 days ^c after the last dose of study medication
Health-related quality of life SF-36v2	Until Week 52, study discontinuation or, in case of treatment discontinuation, until at least 4 weeks ± 5 days ^c after the last dose of study medication
Side effects All outcomes in the side effects category	Until end of study ^b , study discontinuation or, in case of treatment discontinuation, until at least 4 weeks ± 5 days ^{c, d} after the last dose of study medication
mepolizumab + INCS vs. placebo + INCS	
SYNAPSE	
Mortality All-cause mortality ^a	Until end of study ^f or, in case of study discontinuation, until 4 weeks after the last dose of study medication
Morbidity Symptoms (VAS ^g , SNOT-22), activity impairment (WPAI, question 6)	Until end of study ^f 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 ^f or, in case of study discontinuation, until 4 weeks after the last dose of study medication
Side effects All outcomes in the side effects category	Until end of study ^f or, in case of study discontinuation, until 4 weeks after the last dose of study medication

Table 8: Planned duration of follow-up– RCT, indirect comparison: tezepelumab + INCS vs. mepolizumab + INCS (multipage table)

Comparison Study Outcome category Outcome	Planned follow-up
	a. The results on all-cause mortality are based on the information on fatal AEs. b. A total of 163 patients (73 from the placebo arm and 90 from the tezepelumab arm) took part in a 24-week follow-up period after the end of the double-blind treatment phase and were followed up until Week 76. All other patients were followed up during a 12-week follow-up period up to Week 64. c. In the event of a permanent discontinuation of study medication due to surgery for nasal polyps, the visit to discuss treatment discontinuation should take place before the operation and as close as possible to the scheduled date. Patients who discontinued the study medication were encouraged to continue attending the scheduled study visits beyond the 4-week follow-up, up to Week 52 (Option 1). Alternatively, following treatment discontinuation, patients could be contacted by telephone at monthly intervals up to Week 52 and continue to complete the electronic diary for the recording of PROs (Option 2). If patients did not wish to do either, they were contacted by telephone by the investigator at Week 52 (Option 3). If patients chose none of the 3 options, this led to study discontinuation in accordance with the study protocol. d. For AEs, the company provides in Module 4 A only analyses covering the period up to 33 days after treatment discontinuation. e. The following symptoms were recorded using the NPSD: nasal congestion, reduction or loss of smell, nasal discharge, mucus in the throat, facial pain. f. 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. g. The following symptoms were recorded using a VAS: nasal obstruction, nasal discharge, mucus in the throat, facial pain, loss of smell. AE: adverse event; INCS: intranasal corticosteroids; NPSD: nasal polyposis symptom diary; PRO: patient-reported outcome; 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; WPAI: Work Productivity and Activity Impairment

In the WAYPOINT study, outcomes were recorded until the end of the study (all-cause mortality, symptom-related outcomes, side effects) or until Week 52 (activity impairment, health-related quality of life outcomes); for all outcomes, data were recorded until study discontinuation or, in the event of treatment discontinuation, for at least 4 weeks $\pm$ 5 days after the last dose of the study medication.

Patients who discontinued treatment with the study medication were encouraged, in line with the study documents, to continue attending the scheduled study visits beyond the 4-week follow-up, up to Week 52 (Option 1). Alternatively, following treatment discontinuation, they could be contacted by telephone at monthly intervals up to Week 52 and continue to complete the electronic diary for the recording of patient-reported outcomes (Option 2). If patients did not wish to choose either of the 2 options mentioned, they were contacted by telephone by the investigator at Week 52 so that information could be recorded on, amongst other things, adverse events (AEs) or serious adverse events (SAEs), concomitant medication and asthma exacerbations (Option 3). If patients did not agree to follow-up contact, this resulted in study

discontinuation in accordance with the study protocol. In the total population, a total of 46 patients opted for one of the options mentioned after the discontinuation of treatment (Option 1: 2 versus 20 patients; Option 2: 1 versus 2 patients; Option 3: 2 versus 19 patients [21]). Based on the information in the study protocol, it was assumed that patients who discontinued treatment and did not choose any of the 3 options (3 versus 22 patients) then discontinued the study. No data were available for the subpopulation of the WAYPOINT study used for the adjusted indirect comparison. For AEs (including deaths), the company only provided analyses in Module 4 A covering the period up to 33 days after treatment discontinuation. This might have led to differences in the follow-up periods for the AE outcomes. No information was provided on the follow-up period for the subpopulation used. Given this context, therefore, the treatment durations in the subpopulation were examined as an approximation. These averaged 364 days in the tezepelumab arm and 310 days in the placebo arm; a difference of around 15% in the average treatment duration. In the given situation, it was possible to analyse the relative risks of the AE outcomes presented. In order to draw a reliable conclusion over the total study period, it would be necessary to record all outcomes over the total study period. In the SYNAPSE study, all outcomes were recorded up to the end of the study or until study discontinuation occurred. This also applied in cases of treatment discontinuation or short-term therapy with oral corticosteroids (OCS) / SCS, and in cases of surgery to treat nasal polyps. No data were available on the duration of treatment and follow-up period for the outcomes of the SYNAPSE study.

Patient characteristics

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

Table 9: Characteristics of the study populations as well as study/treatment discontinuation – RCT, indirect comparison: tezepelumab + INCS vs. mepolizumab + INCS (multipage table)

Study Characteristic Category	tezepelumab + INCS vs. placebo + INCS		mepolizumab + INCS vs. placebo + INCS	
	WAYPOINT		SYNAPSE	
	tezepelumab + INCS	placebo + INCS	mepolizumab + INCS	placebo + INCS
	N ^a = 144	N ^a = 147	N ^a = 206	N ^a = 201
Age [years], mean (SD)	50 (14)	49 (13)	49 (14)	49 (12)
Sex [F/M], %	38/62	31/69	33/67	38/62
Family origin, n (%)				
White	110 (76)	109 (74)	192 (93)	187 (93)
Asian	30 (21)	33 (22)	9 (4)	9 (4)
Black or African American	1 (< 1)	3 (2)	4 (2)	5 (2)
Other ^b	3 (2)	2 (1)	1 (< 1)	0 (0)
Duration of disease: duration of CRSwNP [years], mean (SD)	14.8 (10.5)	14.6 (10.4)	11.4 (8.5)	11.5 (8.3)
Nasal polyp surgery, n (%)				
Within the past 2 years	ND	ND	56 (27)	63 (31)
< 3 years	32 (22)	33 (22)	ND	ND
Number of previous NP operations ^c , n (%)				
1	73 (51)	77 (52)	108 (52)	81 (40)
2	37 (26)	27 (18)	47 (23)	47 (23)
3	20 (14)	21 (14)	27 (13)	35 (17)
4	7 (5)	17 (12)	13 (6)	12 (6)
5	3 (2)	3 (2)	4 (2)	15 (7)
> 5	4 (3)	2 (1)	7 (3)	11 (5)
Time since the last nasal polyp surgery [years], mean (SD)	7.7 (6.5)	7.7 (6.2)	ND	ND
OCS treatments in the past 12 months, n (%)				
0	71 (49) ^d	82 (56) ^d	100 (49)	110 (55)
1	47 (33) ^d	42 (29) ^d	64 (31)	47 (23)
≥ 2	12 (8) ^d	16 (11) ^d	42 (20) ^e	44 (22) ^e
Nasal polyp score (NPS) ^f , mean (SD)	6.0 (1.2)	6.1 (1.2)	5.4 (1.2)	5.6 (1.4)
Total symptom score (NPSD) ^g , mean (SD)	16.1 (4.5)	16.9 (4.7)	Not recorded	
VAS symptom total score ^h , mean (SD)	Not recorded		9.0 (0.8)	9.1 (0.7)

Table 9: Characteristics of the study populations as well as study/treatment discontinuation – RCT, indirect comparison: tezepelumab + INCS vs. mepolizumab + INCS (multipage table)

Study Characteristic Category	tezepelumab + INCS vs. placebo + INCS		mepolizumab + INCS vs. placebo + INCS	
	WAYPOINT		SYNAPSE	
	tezepelumab + INCS	placebo + INCS	mepolizumab + INCS	placebo + INCS
	N ^a = 144	N ^a = 147	N ^a = 206	N ^a = 201
NCS (NPSD) ^g , mean (SD)	2.6 (0.5)	2.6 (0.6)	Not recorded	
Nasal obstruction (VAS) ^h , mean (SD)	Not recorded		8.9 (0.8)	9.0 (0.8)
Reduction or loss of smell (NPSD) ^g , mean (SD)	2.9 (0.4)	2.9 (0.3)	Not recorded	
Loss of smell (VAS) ^h , mean (SD)	Not recorded		9.6 (0.8)	9.7 (0.6)
Nasal discharge (NPSD) ^g , mean (SD)	2.0 (0.7)	2.1 (0.8)	Not recorded	
Nasal discharge (VAS) ^h , mean (SD)	Not recorded		8.8 (1.1)	8.8 (1.3)
Mucus in the throat (NPSD) ^g , mean (SD)	1.9 (0.8)	2.0 (0.8)	Not recorded	
Mucus in the throat (VAS) ^h , mean (SD)	Not recorded		8.5 (1.6)	8.6 (1.6)
Facial pressure/pain (NPSD) ^{g, i} , mean (SD)	1.6 (0.9)	1.7 (0.9)	Not recorded	
Facial pain (VAS) ^{h, j} , mean (SD)	Not recorded		7.8 (2.5)	7.8 (2.7)
SNOT-22 total score ^h , mean (SD)	66.5 (18.0) ^k	70.3 (18.6) ^k	63.7 (17.6)	64.4 (19.0)
AERD	25 (17)	31 (21)	45 (22) ^l	63 (31) ^l
Asthma	88 (61)	92 (63)	140 (68) ^l	149 (74) ^l
Treatment discontinuation, n (%)	ND ^m	ND ^m	23 (11) ⁿ	34 (17) ⁿ
Study discontinuation, n (%)	ND ^o	ND ^o	17 (8) ^p	17 (8) ^p
a. Number of randomized patients who received at least one dose of the respective treatment. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant. b. SYNAPSE study: American Indian / Alaska Native. c. The WAYPOINT study took into account any previous NP operations in the patients' medical history. In the SYNAPSE study, the relevant period covers the 10 years prior to enrolment in the study. d. Data are available for only 130 out of 144 (90.3%) versus 140 out of 147 (95.3%) patients in the relevant subpopulation. e. Institute's calculation. f. Higher values indicate greater disease severity. The NPS can take a value between 0 and 4 for each nostril, with the NPS being calculated as the sum of the scores for both nostrils (total range 0 to 8). g. Higher values indicate greater disease severity. In the WAYPOINT study, all individual NPSD items were recorded on a scale of 0 to 3. The NPSD total symptom score is composed of the 8 scores for the following individual items: nasal blockage, nasal congestion, nasal discharge, mucus in the throat, headache, facial pressure, facial pain and reduction of smell; range 0 to 24. h. Higher values indicate greater disease severity.				

Table 9: Characteristics of the study populations as well as study/treatment discontinuation – RCT, indirect comparison: tezepelumab + INCS vs. mepolizumab + INCS (multipage table)

Study Characteristic Category	tezepelumab + INCS vs. placebo + INCS		mepolizumab + INCS vs. placebo + INCS	
	WAYPOINT		SYNAPSE	
	tezepelumab + INCS	placebo + INCS	mepolizumab + INCS	placebo + INCS
	N ^a = 144	N ^a = 147	N ^a = 206	N ^a = 201
i. Based on the data in the study documentation relating to the total population, it can be assumed that, in accordance with the approach described by the company, only data relating to facial pressure were included in the analysis. j. The outcome referred to as 'VAS for facial pain/pressure' in Module 4 A for the drug mepolizumab in the current therapeutic indication [22], in dossier assessment A21-150 [18] and in addendum A22-42 [17] was recorded using a 'facial pain' VAS; thus, only pain in the facial region was recorded during the course of the study. k. Inconsistent information in Module 4 A, Section 4.3.2.1.2.1, and Module 4 A, Appendix 4-G; the information shown is taken from Appendix 4-G. l. Institute's calculation(see dossier assessment A21-150 [18]). m. No data is available for the relevant subpopulation for the data cut from 23 September 2024. In the tezepelumab arm versus the placebo arm of the total population, 8 (4%) vs. 63 (31%) patients discontinued treatment (Institute's calculation of the percentages based on 204 vs. 206 of the randomized patients). Common reasons for study discontinuation were: patient request 4 (2%) vs. 43 (21%), other reasons: 2 (1%) vs. 14 (7%). Conflicting information regarding the reasons for treatment discontinuation is documented in [11]. In addition, 1 (< 1%) vs. 1 (< 1%) of the randomized patients never started treatment. 195 (96%) vs. 142 (69%) of the patients completed treatment as planned. n. 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%). Absolute frequencies are not available. o. No data is available for the relevant subpopulation for the data cut from 23 September 2024. In the tezepelumab arm versus the placebo arm of the total population, 10 (5%) vs. 31 (15%) discontinued the study (Institute's calculation of the percentages based on 204 vs. 206 of the randomized patients). The most common reason for study discontinuation was: patient withdrawal of informed consent – 8 (4%) vs. 23 (11%). p. Reasons for study discontinuation in the mepolizumab arm vs. placebo arm were: patient request (8% vs. 8%), lost to follow-up (0% vs. 1%). Absolute frequencies are not available. AERD: aspirin-exacerbated respiratory disease; CRSwNP: chronic rhinosinusitis with nasal polyps; F: female; INCS: intranasal corticosteroids; M: male; n: number of patients in the category; N: number of randomized patients; NCS: nasal congestion score; ND: no data; NP: nasal polyps; NPS: nasal polyp score; NPSD: nasal polyposis symptom diary; OCS: oral corticosteroids; RCT: randomized controlled trial; SD: standard deviation; SNOT-22: 22-item Sino-Nasal Outcome Test; VAS: visual analogue scale				

The patient characteristics of the relevant subpopulation from the WAYPOINT study and the SYNAPSE study population were largely balanced across the arms of the 2 studies. The mean patient age in both studies was just under 50 years; the majority were male and white. The mean disease duration before the start of the study was between a good 11 and just under 15 years. At 22%, the proportion of patients with Asian family origin in the WAYPOINT study was higher than in the SYNAPSE study (4%). All patients in the WAYPOINT subpopulation used and the SYNAPSE study had undergone at least one operation for nasal polyps in the years prior to study start, and more than 40% had required SCS therapy in the 12 months prior to

study start. The patients were suffering from CRSwNP with a mean NPS of around 6 at baseline and persistent and generally severe symptoms despite standard treatment (WAYPOINT study), which consisted primarily of INCS therapy, or despite ongoing INCS therapy (SYNAPSE study).

A good 60 to 70% of patients also suffered from comorbid asthma. Approximately 20% of the patient population had AERD.

In the SYNAPSE study, there were minor differences between the treatment arms regarding the proportion of patients who discontinued treatment. For the WAYPOINT study, no data on treatment discontinuations were available for the relevant subpopulation. In the total population, the proportion of patients who discontinued treatment was 4% in the tezepelumab arm and 31% in the placebo arm. The most common reason given for treatment discontinuation was 'patient request', at 2% compared with 21%. It should be noted that, according to the study documentation, in cases of treatment discontinuation due to surgery for nasal polyps, the reason recorded was 'patient request'. No data on study discontinuations were available for the relevant WAYPOINT subpopulation either. In the placebo arm of the total WAYPOINT population, the proportion of study discontinuations was 15%, which is higher than in the tezepelumab arm (5%) and in both treatment arms of the SYNAPSE study (8%). This may also be attributable to the WAYPOINT approach in cases of surgery for nasal polyps, which was performed much more frequently in the placebo arm (see detailed description in Section I 3.2).

Assessment of the severity of the disease of the included patients

According to the marketing authorization, both tezepelumab and mepolizumab are indicated for patients with severe CRSwNP [6,20]. The various guidelines provide no or no uniform definition of the severity grades of the disease [23-25]. According to the update to the chapter 'Treatment of chronic rhinosinusitis with nasal polyposis (CRSwNP) using monoclonal antibodies (biologics)' in the S2k guideline, the individual burden of disease of each patient should be taken into account in all cases [23]. The documentation form for assessing the eligibility criteria for the on-label use of biologics in CRSwNP specifies the presence of 'severe CRSwNP'; however, it does not describe the criteria on the basis of which the severity is to be determined. Modified indication criteria, or those which may be applied optionally in line with the inclusion criteria of the approval studies, include: intranasal steroids for 8 weeks at the recommended dosage, NPS ≥ 2 per side and a total of ≥ 5 , recurrent polyposis following surgery (paranasal sinus surgery) within the last 10 years, treatment with SCS within the last 2 years (or a contraindication), persistent symptoms (≥ 2 , for ≥ 3 months): nasal breathing obstruction, anterior rhinorrhoea / postnasal drip, facial pressure/pain, reduced sense of smell, overall 'nasal symptoms' score (VAS) > 5 (maximum 10), SNOT-22 score ≥ 20 ; for omalizumab: total IgE 30–1 500 IU/mL and suitable for dosing (based on body weight). The

final criterion was not relevant for this benefit assessment. In addition, comorbidities (e.g. signs of type 2 inflammation), further information on previous treatments (e.g. the occurrence of recurrent polyposis less than 2 years after surgery for nasal polyps) and eosinophilia may be used to support the case that treatment with a biologic agent is indicated. Based on the baseline characteristics of the patients in the WAYPOINT and SYNAPSE studies, it was generally assumed that the disease severity was high, even though not all the optional indication criteria set out in the documentation form recommended in the S2k guideline were met in the WAYPOINT study. Overall, however, it was assumed that both the WAYPOINT and the SYNAPSE patient populations used were suitable for addressing the research question at hand. This is explained below with regard to the WAYPOINT subpopulation used. The suitability of the study population from the SYNAPSE study for the given research question was already described in detail in dossier assessment A21-150 [18]. Following the update of the S2k guideline, this suitability remains valid, even when taking into account the specified optional indication criteria for treatment with a biologic agent [23].

At the time of screening, patients in the WAYPOINT study had been suffering persistent CRSwNP symptoms for ≥ 8 weeks. All patients in the subpopulation used for the adjusted indirect comparison had undergone at least one operation for nasal polyps before study begin, with around 20% of these having taken place within the previous 3 years. For half of the study population, more than one previous operation for nasal polyps was reported. About half of the patients had received SCS therapy within the 12 months before study begin (see Table 9). During the course of the study, at least 16.3% of patients in the placebo arm required a treatment escalation in the form of short-term SCS treatment. During the 52-week treatment duration, a total of 20 out of 147 patients in the placebo arm (13.6%) also underwent surgery for nasal polyps (see also Table 18 of the full dossier assessment). The European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA) 2023 identifies both SCS and nasal polyp surgery as treatment options for patients with severe CRSwNP, noting that the first nasal polyp surgery should only be performed if symptoms have not improved following 1 to 2 courses of treatment with oral corticosteroids within the past 2 years, as well as treatment with INCS [24]. In the WAYPOINT study, patients had been receiving stable standard treatment (consisting primarily of INCS) for at least 30 days prior to study start, and had a history of at least one operation for nasal polyps and, where applicable, SCS therapy. From the run-in phase at the latest, all patients were then given mometasone furoate at the maximum daily dose as per the marketing authorization or an equivalent (see Table 7), provided that symptoms of a defined severity were still present at the time of randomization (see Table 6). Patient-reported symptoms were assessed at baseline (defined as the mean over the 14 days prior to the day of randomization) using a 4-point numeric rating scale (NRS) (0 – none to 3 – severe symptoms) for various symptoms typical of CRSwNP (nasal congestion, reduction/loss of smell, nasal discharge, mucus in the throat, headache, facial pressure and facial pain) by the patients in an electronic symptom diary (nasal polyposis symptom diary,

NPSD). On average, the symptoms at baseline were assessed as at least moderate, with the exception of those relating to facial pressure/pain. In particular, the reduction or loss of smell – one of the key symptoms in the therapeutic indication [25,26] – was assessed on average as 2.9 on a scale of 0 to 3 (see Table 9). In addition, patients reported the severity of their sinonasal condition using the SNOT-22 questionnaire. The total score at baseline was between 66 and 70 out of a possible 110 points, which was slightly higher than the baseline value in the SYNAPSE study. The recommended SNOT-22 threshold values for the use of biologics range from 20 (S2k guideline) to 40 (EPOS2020) [23,27]. Another aspect that characterizes severe disease is comorbidity with other type 2 inflammatory diseases. In the WAYPOINT study, around 60% of patients had asthma and around 20% had AERD as a comorbid condition.

This meant that the WAYPOINT study, just like the SYNAPSE study, revealed a pronounced set of symptoms overall.

Taking into account prior therapies and the severity of the existing symptoms, the study populations of the WAYPOINT and SYNAPSE studies were generally considered suitable for answering the research question of this benefit assessment.

Limitations of the WAYPOINT and SYNAPSE studies

As described above, the WAYPOINT and SYNAPSE studies were used for the benefit assessment. However, there were limitations, which are described below.

Need for nasal polyp surgery unclear at baseline

In addition to the presence of persistent CRSwNP symptoms (WAYPOINT study: ≥ 8 weeks prior to screening; SYNAPSE study: ≥ 12 weeks prior to screening), an inclusion criterion for both studies was a severity of the condition that would generally warrant surgery for nasal polyps (described in the study protocols as ‘severity consistent with need for surgery’). In both study protocols, this was operationalized using the criterion NPS ≥ 5 (≥ 2 for each nostril); in the SYNAPSE study, it was additionally operationalized using a VAS score for total symptoms > 7 at baseline. However, to be included in the SYNAPSE study, patients were not allowed to be on a waiting list for nasal polyp surgery and planned operations had to be cancelled. In the WAYPOINT study, too, at the time of screening surgery for nasal polyps was not allowed to be scheduled for during the study.

In both studies, it was generally permitted for surgery for nasal polyps to be performed during the course of the study, albeit with different implications for subsequent treatment with the study medication (see Section I 3.3). Nasal polyp surgery was defined in both studies as any procedure involving instruments with resulting incision and removal of tissue from the paranasal sinus (see Table 6). During the course of the study, nasal polyp surgery was reported for a total of 20 patients from the relevant subpopulation of the WAYPOINT study and 64 patients from the SYNAPSE study. Of these, 20 (14%) patients were from the placebo arm

of the WAYPOINT study and 46 (23%) from the placebo arm of the SYNAPSE study (see also the supplementary table in I Appendix B.1, Table 18, of the full dossier assessment). In the tezepelumab arm of the WAYPOINT study, one patient was also scheduled to undergo surgery for nasal polyps during the treatment period, but the operation was not performed. This proportion of patients does not suggest an acutely necessary surgical intervention at study entry for either study.

However, for the SYNAPSE study it was unknown how many patients were taken off a waiting list for nasal polyp surgery at the beginning of the study and how many planned surgeries were cancelled, so that there remained uncertainty as to whether (necessary) surgery may have been delayed for some patients due to their inclusion in the studies. The same applies, in principle, to the WAYPOINT study as well.

Furthermore, for the WAYPOINT study, it is unclear whether necessary nasal polyp operations at baseline were delayed for patients in the relevant subpopulation, as surgery resulted in treatment discontinuation – and this could have led to study discontinuation if patients did not want to choose an option for follow-up. In the WAYPOINT study, in principle, no surgery for nasal polyps should be scheduled within the first 3 months following randomization, unless the investigator deemed it necessary.

The uncertainties described contributed to a reduced certainty of conclusions at study level for both studies. However, this alone did not call into question the requirements for the certainty of results when carrying out an adjusted indirect comparison.

Adequate (pre-) treatment of AERD unclear

Both studies included patients with AERD (see Table 9). In the WAYPOINT study, this applied to 25 patients in the tezepelumab arm (17%) and 31 patients in the placebo arm (21%); in the SYNAPSE study, it applied to 45 patients in the mepolizumab arm (22%) and 63 patients in the placebo arm (31%). For patients with proven analgesic intolerance syndrome, there is in principle the therapeutic option of adaptive deactivation. This adaptive deactivation with acetylsalicylic acid can achieve a reduction in inflammation or polyp growth and a prolongation of the intervals between necessary revision operations [24]. The available documentation for both studies did not provide any information on the reasons for the lack of response or the unsuitability of (pre-)treatment for AERD. In the WAYPOINT study, participants were also not allowed to have had adaptive deactivation with acetylsalicylic acid for at least 6 months prior to enrolment in the study. As the updated S2k guideline no longer contains any explicit recommendations for adaptive deactivation with acetylsalicylic acid [23], this had no implications for this benefit assessment.

I 3.3 Similarities of the studies for the indirect comparison

The following text discusses key aspects of the similarity of the studies for conducting an adjusted indirect comparison beyond the study characteristics described in Section I 3.2.

Similarities in study conduct

The 2 studies presented for an adjusted indirect comparison are multicentre, double-blind RCTs with largely comparable study designs, which included patients with severe CRSwNP. For the adjusted indirect comparison, the company used only the subpopulation of the WAYPOINT study with a history of nasal polyp surgery; the SYNAPSE study only included patients with a history of nasal polyp surgery.

The outcomes relating to morbidity, health-related quality of life and side effects, including the recording of deaths, were recorded and analysed in both studies over the course of a 52-week placebo-controlled treatment phase.

Whilst in the SYNAPSE study, nasal polyp surgery could be conducted at any point during the study course and had no impact on the planned 52-week course of treatment with the study medication, in the WAYPOINT study, nasal polyp surgery resulted directly in premature treatment discontinuation. The outcomes were then monitored for at least a further 4 weeks $\pm$ 5 days. However, all patients who discontinued treatment with the study medication for any reason (including surgery for nasal polyps) had the option of continuing to attend the scheduled study visits beyond the planned 4-week follow-up period up to Week 52, or of being contacted by telephone at monthly intervals and continuing to complete the electronic diary. However, it is unclear how many patients in the relevant subpopulation of the WAYPOINT study made use of this option following permanent treatment discontinuation (see detailed description in Section I 3.2). A total of 20 out of 147 patients in the placebo arm (13.6%) of the WAYPOINT subpopulation underwent surgery for nasal polyps (see also Table 18 of the full dossier assessment). The differences described in the management of nasal polyps surgery with regard to the administration of the study medication did not call into question the comparability of the 2 studies for the purpose of an adjusted indirect comparison when considering the total number of cases that occurred in WAYPOINT. No data were available on the overall number of patients who discontinued treatment or withdrew from the study within the relevant subpopulation of the WAYPOINT study.

Although there is a difference of a few years between the periods in which the studies were conducted, this did not call into question the comparability of the studies for the adjusted indirect comparison. Whilst the SYNAPSE study on the comparator side was conducted between 2017 and 2019, the WAYPOINT study on the intervention side was conducted between 2021 and 2024.

Similarities between instruments used for the recording of individual symptoms

Another difference between the studies of the adjusted indirect comparison presented for this benefit assessment lies in the instruments used to record various symptoms. Both instruments were electronic symptom diaries in which patients recorded, every morning, the most severe level of a range of predefined symptoms experienced over the previous 24 hours. In the WAYPOINT study, patients assessed their symptoms in the NPSD using a 4-point scale ranging from 0 – none, to 1 – mild, to 2 – moderate, to 3 – severe. In the SYNAPSE study, however, a visual analogue scale (VAS, ranging from 0 to 100) was used.

The company used various individual symptoms for the adjusted indirect comparison (see Section I 4.1). Despite marginal differences in the wording of the 2 instruments, they represented the same symptoms. For the purposes of this benefit assessment, it was further assumed that it is, in principle, possible to perform the recording of symptoms using the various instruments employed, i.e. the NRS from the NPSD on the intervention side and the VAS on the comparator side. It should however be noted that this meant that in the WAYPOINT study patients had a 4-point NRS for assessing the severity of their symptoms, which is a much coarser scale compared to the VAS (0 to 100) used in the SYNAPSE study.

Similarities in the patient populations

An eligibility criterion for participation in the WAYPOINT study was documented treatment of nasal polyp exacerbation with any history of nasal polyp surgery and/or SCS (one intramuscular depo-injectable dose on at least 3 consecutive days) within the 12 months prior to screening, but not within the 3 months prior to screening, or contraindications or intolerances to either treatment. Furthermore, in both studies, the severity of the condition had to be such that surgery for nasal polyps would, in principle, appear necessary. In both studies, an NPS of ≥ 5 (≥ 2 for each nostril) was required for this, and in the SYNAPSE study, the VAS total symptom score also had to be > 7 at baseline. In the WAYPOINT study, although the severity of the condition which in principle would make surgery for nasal polyps necessary was not defined in terms of specific existing symptoms, participants were required to have symptoms ($NCS \geq 2$ and $SNOT-22 \geq 30$) in order to be included in the study. In order to present comparability with the SYNAPSE study, the company formed a subpopulation for the adjusted indirect comparison with those patients who had already undergone at least one previous operation for nasal polyps. This subpopulation was used for the adjusted indirect comparison (see Section I 3.2).

Details of the patient characteristics of the relevant subpopulation in the WAYPOINT study (intervention side) and of the SYNAPSE study (comparison side) can be found in Section I 3.2. The demographic and clinical characteristics of the study populations used were largely comparable between the 2 studies.

A relevant difference between the 2 studies included in this benefit assessment was the proportion of Asian patients, which was approximately 20% in the WAYPOINT study versus 4% in the SYNAPSE study, as the WAYPOINT study also involved centres in China and Japan. However, this difference had no bearing on this benefit assessment, as there was no indication of any effect modification by the region characteristic.

In both studies, there was uncertainty regarding the need for surgery for nasal polyps at baseline (see Section I 3.2).

The 2 studies differed marginally in terms of the required prior treatment with INCS before study begin. Whilst in the SYNAPSE study, at least 8 weeks' treatment with INCS was a prerequisite for participation, in the WAYPOINT study, participants were required to have received prior standard treatment for CRSwNP at a stable dose for at least 30 days prior to study begin. The study documents showed that a maximum of 22 out of 291 (max. 8%) patients in the relevant subpopulation had not received treatment with INCS before the study started and only received INCS maintenance therapy during the 5-week run-in phase of the study [7]. The 2 studies also showed minor differences in the use of INCS as a concomitant treatment. Whilst in the SYNAPSE study the concomitant treatment throughout the study consisted of mometasone furoate for all patients, in the WAYPOINT study a total of 24 (8.6%) patients (tezepelumab arm: 5 [approx. 2%], placebo arm 19 [6.5%]) received INCS other than the drugs mometasone furoate and budesonide, which had been specified by the G-BA as the ACT. One patient in the tezepelumab arm received no concomitant treatment with INCS. The differences mentioned had no bearing on this benefit assessment.

Although, when viewed as a whole, both study populations were pronouncedly symptomatic for CRSwNP (see Section I 3.2) – and sufficient similarity to allow for an adjusted indirect comparison was therefore assumed – the patients nevertheless differed in some respects in their assessment of the severity of individual symptoms at baseline, as measured using the NRS of the NPSD in WAYPOINT and the VAS in the SYNAPSE study. The symptoms of nasal discharge and mucus in the throat were reported by patients in the WAYPOINT study on the NRS as being, on average, moderate (mean score over the 14 days prior to randomization: 1.9 to 2.1). By contrast, the baseline values for these symptoms in the SYNAPSE study were, on average, rated as severe on the VAS, ranging from 8.5 to 8.8 out of 10 (maximum conceivable discomfort). With regard to the individual symptom of facial pain, it was not possible to compare the study populations used (for reasons, see Section I 4.1).

Similarities in the common comparator

The common comparator in the presented adjusted indirect comparison was placebo + INCS. For the placebo + INCS common comparator arm, there were some differences between the 2 studies.

Additional concomitant drug therapies for the treatment of acute symptoms caused by nasal polyps, including short-term treatment with SCS, were permitted in both studies. However, over the course of the study, fewer SCS treatments were administered in the placebo arm of the WAYPOINT study than in the placebo arm of the SYNAPSE study (16.3% vs. 37%).

As already described in the section on similarities in study design, surgery for nasal polyps was permitted in both studies, albeit with different implications for subsequent treatment with the study medication. In the WAYPOINT study, with protocol version 5 dated 17 October 2022, the outcome 'nasal polyp surgery' was changed to 'decision to undergo nasal polyp surgery' due to COVID-19-related delays in scheduling. The clinical study report analysed both the decision to undergo nasal polyp surgery and the operations for nasal polyps that were actually performed during the course of the study. For the adjusted indirect comparison, the company used the operations actually performed in the WAYPOINT study. Over the course of the study, fewer actual operations for nasal polyps were recorded in the relevant subpopulation from the WAYPOINT study than in the SYNAPSE study (see Table 18 of the full dossier assessment). It cannot be ruled out that, had there not been potential delays to operations due to the COVID-19 pandemic, more nasal polyp operations would have been performed in the placebo arm during the double-blind treatment phase. In the total population of the WAYPOINT study, the decision to undergo surgery for nasal polyps was made in 1 versus 42 patients during the course of the study; and, over the treatment period with the study medication, such surgery was actually conducted in 27 patients, all of whom were in the placebo arm. In the total population, a relevant proportion of patients opted for surgery for nasal polyps during the final weeks of the double-blind treatment period. No data were available on the decision to undergo surgery for nasal polyps, either for the relevant WAYPOINT subpopulation or for the SYNAPSE study.

In the WAYPOINT subpopulation used, 20 (13.6%) of the patients in the placebo arm underwent surgery for nasal polyps during the course of the study, compared with 46 (23.0%) in the SYNAPSE study.

Furthermore, over the course of the study, more responders to the SNOT-22 were identified in the placebo arm of the SYNAPSE study than in the placebo arm of the WAYPOINT study (50% vs. 62%). Furthermore, with regard to impairment of daily activities as assessed by question 6 of the Work Productivity and Activity Impairment (WPAI; scale range 0 to 100), impairment among patients in the placebo arm of the SYNAPSE study was slightly greater at baseline (53.2) than in the WAYPOINT study (41.3). These differences had no implications for this benefit assessment.

Summary of the similarities

Overall, there were some differences between the WAYPOINT and SYNAPSE studies in terms of study and patient characteristics; however, none of these differences fundamentally called into question the sufficient level of similarity required to conduct an adjusted indirect comparison using placebo as the common comparator, taking into account both the WAYPOINT and SYNAPSE studies.

I 3.4 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, indirect comparison: tezepelumab + INCS vs. mepolizumab + INCS

Comparison Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
tezepelumab + INCS vs. placebo + INCS							
WAYPOINT	Yes	Yes	Yes	Yes	Yes	Yes	Low
mepolizumab + INCS vs. placebo + INCS							
SYNAPSE	Yes	Yes	Yes	Yes	Yes	Yes	Low
INCS: inhaled corticosteroids; RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for both studies.

Transferability of the study results to the German health care context

From the company's perspective, the results of the WAYPOINT and SYNAPSE studies were transferable to the German health care context, given the comparability of the study populations and patients in Germany. According to the company, the age and sex distribution of the patients were similar to those of the German reference population, and the proportion of patients with comorbid asthma in the 2 studies was comparable to the data collected for patients with severe, uncontrolled CRSwNP as part of an analysis of health insurance data carried out in Germany. The company added that, in both studies, the patients presented with severe CRSwNP despite having previously undergone SCS therapy and/or surgery for nasal polyps, and that, in accordance with the recommendations of the German S2k guideline, treatment with biologics was indicated for these patients.

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

I 4 Results on added benefit

I 4.1 Outcomes included

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

- Mortality
 - All-cause mortality
- Morbidity
 - Nasal congestion/obstruction, recorded using the NRS in the NPSD in WAYPOINT and the VAS in SYNAPSE
 - Reduction/loss of smell, recorded using the NRS in the NPSD in WAYPOINT and the VAS in SYNAPSE
 - Nasal discharge, recorded using the NRS in the NPSD in WAYPOINT and the VAS in SYNAPSE
 - Mucus in the throat, recorded using the NRS in the NPSD in WAYPOINT and the VAS in SYNAPSE
 - Facial pain, recorded using the NRS in the NPSD in WAYPOINT and the VAS in SYNAPSE
 - SNOT-22; total score
 - Impairment of daily activities, recorded using question 6 of the WPAI
- Health-related quality of life
 - Short Form 36-version 2 Health Survey (SF-36v2)
- Side effects
 - SAEs
 - Discontinuation due to AEs

The selection of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A).

Table 11 shows for which outcomes data were available in the included studies (yes/no) and whether an adjusted indirect comparison was possible based on the available data (yes/no).

Table 11: Matrix of outcomes – RCT, indirect comparison: tezepelumab + INCS vs. mepolizumab + INCS

Comparison Study	Outcomes											
	All-cause mortality ^a	Nasal congestion/obstruction ^b	Reduction/loss of smell ^b	Nasal discharge ^b	Mucus in the throat ^b	Facial pain ^b	SNOT-22 (total score)	Activity impairment (WPAI, question 6)	Health-related quality of life (SF-36v2)	SAEs ^c	Discontinuation due to AEs	Specific AEs
tezepelumab + INCS vs. placebo + INCS												
WAYPOINT	Yes	No ^d	Yes	Yes	Yes	No ^d	Yes	Yes	Yes	Yes	Yes	No ^e
mepolizumab + INCS vs. placebo + INCS												
SYNAPSE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No ^f
Indirect comparison feasible	No ^g	No ^h	No ^g	No ^g	No ^g	No ^h	No ^g	No ^g	No ^g	No ^g	No ^g	No
a. The results on all-cause mortality are based on the information on fatal AEs. b. The patients recorded their symptoms daily in an electronic symptom diary. The most severe symptoms experienced in the last 24 hours were to be recorded in each instance. In WAYPOINT, the individual symptoms in the NPSD were assessed on a 4-point scale. In SYNAPSE, the assessment of the individual symptoms was performed using a VAS. c. Without deaths. d. No suitable data available; for reasoning, see the following text in Section I 4.1 of this dossier assessment. e. No specific AEs were selected based on the AEs that occurred in the relevant study, as the requirements for the certainty of results for conducting an unadjusted indirect comparison were not met for any of the AE outcomes (see Section I 4.2). f. No specific AEs were identified based on the AEs occurring in the study. g. The requirements for the certainty of results to perform an adjusted indirect comparison were not met (see following text, Table 12 and Section I 4.2). h. Indirect comparison not feasible because no suitable data are available for at least one side of the indirect comparison. AE: adverse event; INCS: intranasal corticosteroids; NCS: nasal congestion score; NPSD: nasal polyposis symptom diary; 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; WPAI: Work Productivity and Activity Impairment												

Period of analysis

In this assessment, the results from both studies at the end of the double-blind treatment phase (Week 52) were considered, as both tezepelumab and mepolizumab have marketing authorizations for long-term treatment and, according to the SmPCs, treatment is not intended to be discontinued after 52 weeks [6,20]. Furthermore, in both WAYPOINT and SYNAPSE, only a small proportion of patients progressed following the double-blind treatment period to the treatment-free (regarding study medication) follow-up phase until Week 76 (see Section I 3.2).

Outcomes on morbidity and health-related quality of life

Note on the selection of the analysis used

The company conducted adjusted indirect comparisons for the included morbidity outcomes, based on both continuous analyses and (with the exception of the 'activity impairment' outcome) responder analyses on improvement. Continuous analyses were prespecified in both studies; the responder analyses were conducted post hoc. The company used an improvement of at least 15% of the respective scale range of the instrument as the response criterion. This meets the requirements for response criteria for reflecting with sufficient certainty a change that is perceivable for patients, as described in the IQWiG General Methods [28]. For the quality of life outcomes, the company presented only post-hoc responder analyses using the threshold value mentioned above. The responder analyses were used for the derivation of the added benefit for the patient-reported outcomes in the categories of morbidity (with the exception of the 'activity impairment' outcome) and health-related quality of life.

Imputation strategies

The company presented adjusted indirect comparisons using 2 different imputation strategies. Whilst results were available for both imputation strategies for the binary analyses of the outcomes included in the benefit assessment, given the data available from the SYNAPSE study, only imputation strategy 1 (referred to by the company as estimand 1) was applicable for continuous analyses, with the exception of the activity impairment outcome. For the activity impairment outcome, only analyses using imputation strategy 2 (referred to as estimand 2 by the company) were available. Under imputation strategy 1 (with imputation), missing data were imputed as follows: for all continuous outcomes, missing values were imputed using the worst possible score (WPS). For the responder analyses, patients with missing values were categorized as non-responders. Patients with missing baseline values were excluded from the analyses. With regard to intercurrent events, imputation was carried out in accordance with the WPS following surgery for nasal polyps, whereas the observed values were used following SCS or (additional) biologic therapy, as well as in cases of treatment discontinuation. Imputation strategy 2 (no imputation) differed from imputation

strategy 1 in terms of how it dealt with surgery for nasal polyps. Following surgery for nasal polyps, the observed values were used for imputation strategy 2 (no imputation). To derive the added benefit, the company used the results for imputation strategy 2 (no imputation) for the outcomes included in this benefit assessment.

On the comparator side, for the SYNAPSE study this benefit assessment drew on the results for imputation strategy 2 (no imputation) already presented in A22-42 [17] for the adjusted indirect comparison.

On the intervention side, the return rates for the completed questionnaires in the WAYPOINT study show a relevant proportion of missing values for the outcomes relating to symptoms and health-related quality of life, with variations between the treatment arms. As described above, the company conducted non-responder imputation (NRI) for missing values. It was assumed that the difference in the proportion of missing usable questionnaires, for example, for the various individual symptoms in the NPSD at Week 52, with 12.5% in the intervention arm compared with 29.3% in the placebo arm, was attributable to a relevant extent to the nasal polyp operations carried out during the study (1 planned nasal polyp operation in the tezepelumab arm versus 20 patients in the placebo arm who underwent nasal polyp surgery [13.6%], see Table 18 of the full dossier assessment), as these resulted in premature discontinuation of treatment with the study drug. It was also assumed that this resulted in a shorter observation period for some patients (see Section I 3.2).

However, surgery for nasal polyps in the therapeutic indication of severe CRSwNP, like treatment with SCS, forms part of the therapeutic strategy and is sometimes conducted repeatedly, also whilst medication is continued. For this reason, NRI for missing values does not constitute appropriate imputation.

The analyses presented in the dossier regarding the adjusted indirect comparison of the outcome categories for morbidity and health-related quality of life did not include any sensitivity analyses applying alternative imputation strategies for outcomes with a relevant proportion of missing values, differing between the treatment arms, in the WAYPOINT study. For this reason, it could not be assumed that the effects used by the company to derive the added benefit would be retained with the application of other imputation methods that more accurately represent the therapeutic strategy. As such a robust effect was not tested or verified, it was not possible to conduct an indirect comparison for all the outcomes affected. Appropriate sensitivity analyses would need to be available for this purpose.

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

In both studies, patients recorded daily the most severe level of a range of predefined symptoms experienced over the previous 24 hours. In the WAYPOINT study, patients assessed

their symptoms in the NPSD on a 4-point scale ranging from 0 – none, to 1 – mild, to 2 – moderate, to 3 – severe, for a total of 8 symptoms (nasal blockage, nasal congestion, reduction/loss of smell, nasal discharge, mucus in the throat, headache, facial pressure and facial pain). In the SYNAPSE study, a VAS (on a scale of 0 to 100) was used to record the symptoms of nasal obstruction, nasal discharge, mucus in the throat, facial pain and loss of smell. The VAS scores recorded in the electronic diary were divided by 10, reported to one decimal place, and therefore ranged from 0 (no symptoms) to 10 ('as bad as you can imagine').

The company used the individual symptoms of nasal congestion/obstruction, reduction/loss of smell, nasal discharge, mucus in the throat and facial pain for the adjusted indirect comparison. The company aligned the analysis of symptoms for the WAYPOINT study with the operationalization of the SYNAPSE study, in order to ensure the best possible comparability for conducting the indirect comparison.

As already described in Section I 3.3, the various individual symptoms used represent the same symptoms in both instruments, despite marginal differences in their wording. It was also assumed that, in the given context, it is in principle possible to carry out the recording of symptoms using the various instruments employed, namely the NRS in the NPSD on the intervention side and the VAS on the comparator side.

This assessment used the responder analyses on the mean for Weeks 49 to 52 compared with baseline (defined as the mean over the last 14 days in the WAYPOINT study or the last 7 days in the SYNAPSE study prior to the day of randomization) presented by the company. For the responder analyses, the company selected a response criterion of 15%, which corresponds to an improvement of ≥ 0.45 points (on a scale of 0 to 3) in WAYPOINT and an improvement of ≥ 1.5 points (on a scale of 0 to 10) in SYNAPSE. This benefit assessment included the outcomes of nasal congestion/obstruction, reduction/loss of smell, nasal discharge, mucus in the throat, and facial pain, as these represent the differentiated characteristic symptoms of severe CRSwNP.

Nasal congestion/obstruction

For the outcome nasal congestion/obstruction (referred to as 'nasal congestion' by the company in Module 4 A), the NPSD item NCS was used on the intervention side and the VAS item nasal obstruction was used on the comparator side. It seems possible to consider both symptom items together, particularly as it has been reported that many patients find it difficult to distinguish between nasal congestion, and nasal blockage as a physical obstruction of the nasal cavity, or do not consider such a distinction to be meaningful [29].

In the data available for WAYPOINT, the issue with the NCS outcome in the tezepelumab arm is that the number of responders is higher than the number of patients with a completed

questionnaire at Week 52. For this reason, the data provided were not usable, and it was unclear which data the analysis was based on.

Overall, therefore, there were no suitable data available for the outcome of nasal congestion/obstruction to allow for an adjusted indirect comparison of the WAYPOINT and SYNAPSE studies.

Facial pain

To enable a comparison with the SYNAPSE study outcome referred to as 'VAS for facial pain/pressure' in the benefit assessment of mepolizumab [17,18] on the comparator side, the company conducted analyses on the intervention side of the adjusted indirect comparison in which it evaluated the symptoms of facial pain/pressure – which were recorded separately in the WAYPOINT study – jointly. To this end, the company used the higher (i.e. worse) of the 2 values for each item in its analyses. Based on the data for the total population, it was assumed that, according to the approach described by the company, almost exclusively the data on facial pressure were included in the analysis. No separate data on the 2 symptoms were available for the relevant subpopulation. By contrast, on the comparator side, the SYNAPSE study protocol stipulated that only the assessment of the severity of facial pain using the VAS was to be recorded (see details in the study protocol [19]) and, contrary to what is stated in A21-150 and the associated addendum A22-42, facial pressure/pain was not assessed. In the analyses provided for the adjusted indirect comparison of the outcome facial pressure/pain, which was named by the company in accordance with the benefit assessment procedure for mepolizumab, it was therefore assumed that, on the intervention side, the results relate to facial pressure, whilst on the comparator side they relate to facial pain. The results for the outcome of facial pain for the WAYPOINT study were therefore not suitable for the adjusted indirect comparison.

Overall, therefore, there were no suitable data available for the outcome facial pain to allow for an adjusted indirect comparison of the WAYPOINT and SYNAPSE studies.

I 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, indirect comparison: tezepelumab + INCS vs. mepolizumab + INCS

Comparison Study	Study level	Outcomes											
		All-cause mortality ^a	Nasal congestion/obstruction ^b	Reduction/loss of smell ^b	Nasal discharge ^b	Mucus in the throat ^b	Facial pain ^b	SNOT-22 (total score)	Activity impairment (WPAI, question 6)	Health-related quality of life (SF-36v2)	SAEs ^c	Discontinuation due to AEs	Specific AEs
tezepelumab + INCS vs. placebo + INCS													
WAYPOINT	L	H ^d	– ^e	H ^f	H ^f	H ^f	– ^e	H ^f	H ^g	H ^f	H ^d	L ^h	–
mepolizumab + INCS vs. placebo + INCS													
SYNAPSE	L	L	L	L	L	L	L	L	L	L	L	L ^h	–
a. The results on all-cause mortality are based on the information on fatal AEs. b. The patients recorded their symptoms daily in an electronic symptom diary. The most severe symptoms experienced in the last 24 hours were to be recorded in each instance. In WAYPOINT, the individual symptoms in the NPSD were assessed on a 4-point scale. In SYNAPSE, the assessment of the individual symptoms was performed using a VAS. c. Without deaths. d. Incomplete observations for potentially informative reasons. e. No suitable data available; for justification see Section I 4.1 of this dossier assessment. f. Large difference between the treatment groups (> 10 percentage points) regarding the proportion of values imputed using NRI. g. Large difference between the treatment groups (> 10 percentage points) regarding the proportion of values for which the worst possible value was imputed. h. Despite low risk of bias, limited certainty of results is assumed (see running text). AE: adverse event; H: high; INCS: intranasal corticosteroids; L: low; NPSD: nasal polyposis symptom diary; 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; WPAI: Work Productivity and Activity Impairment													

WAYPOINT

For the results on morbidity and health-related quality of life, as recorded via the outcomes of reduction/loss of smell (NPSD [NRS]), nasal discharge (NPSD [NRS]), mucus in the throat (NPSD [NRS]), SNOT-22 (total score), activity impairment (WPAI, question 6) and SF-36v2, the risk of bias was assessed as high. This is due to the large difference between the treatment

groups (> 10 percentage points) in terms of the proportion of values imputed. The company conducted an NRI for missing values. As described in Section I 4.1, this did not constitute appropriate imputation in the given context. Furthermore, the analyses presented for these outcomes did not include any sensitivity analyses to ensure that the effects used would remain robust even if other imputation methods would be used that more accurately represent the therapeutic strategy.

For the results relating to the outcome of all-cause mortality, based on deaths as part of side effect recording, and for the results relating to the SAE outcome, the risk of bias was assessed as high. This was due to the high number of incompletely observed patients, which differed between the study arms. These findings were due to the fact that the recording of side effects was linked to the end of the study treatment, and that nasal polyp operations carried out during the course of the study led directly to the premature discontinuation of treatment with the study medication and, consequently, to a shortened observation period of 33 days after the last dose of the study medication (see Section I 3.3).

Although the risk of bias for the outcome discontinuation due to AEs was low, the certainty of results for this outcome was limited. Premature treatment discontinuation for reasons other than AEs (e.g. due to nasal polyp surgery) is a competing event for the outcome discontinuation due to AEs to be recorded. This means that, although AEs that would have led to discontinuation of therapy may occur after discontinuation for other reasons, the criterion discontinuation is no longer applicable to them. It was impossible to estimate how many AEs this affected.

The risk of bias was not assessed for the other included outcomes nasal congestion/obstruction and facial pain, as no suitable analyses for the benefit assessment were available.

SYNAPSE

For the results of all outcomes of the study, the risk of bias was assessed as low. For the outcome discontinuation due to AEs, as with the WAYPOINT study, the certainty of conclusions was limited despite a low risk of bias (see above).

Consequences for the indirect comparison

If only one study is available on one side of an indirect comparison and results of individual outcomes of this study have a high risk of bias, the certainty of results required to conduct an adjusted indirect comparison is insufficient.

In summary, data with sufficient certainty of results, which would allow an informative adjusted indirect comparison to be conducted, were not available for any of the outcomes of either study.

Certainty of conclusions

In both studies, the uncertainty regarding the need for surgery for nasal polyps at baseline led to a reduced certainty of conclusions (see Section I 3.2). However, this alone did not mean that the requirements for the certainty of results needed to conduct an adjusted indirect comparison were not met.

I 4.3 Results

Table 13 and Table 14 summarize the results of the comparison of tezepelumab + INCS versus mepolizumab + INCS in adult 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 showing common AEs, common SAEs and discontinuations due to AEs for the WAYPOINT and SYNAPSE studies are contained in I Appendix C of the full dossier assessment.

Table 13: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, indirect comparison: tezepelumab + INCS vs. mepolizumab + INCS (multipage table)

Outcome category Outcome Comparison Study	tezepelumab + INCS or mepolizumab + INCS		placebo + INCS		Group difference
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Mortality (Week 52)					
All-cause mortality ^a					
tezepelumab + INCS vs. placebo + INCS					
WAYPOINT	144	0 (0)	147	1 (0.7)	– ^b ; > 0.999 ^c
mepolizumab + INCS vs. placebo + INCS					
SYNAPSE	206	0 (0)	201	0 (0)	–
Indirect comparison using common comparators^d:					
tezepelumab + INCS vs. mepolizumab + INCS					–
Morbidity (Week 52)					
Nasal congestion/obstruction					
tezepelumab + INCS vs. placebo + INCS					
WAYPOINT (NPSD [NRS]) ^e				No suitable data ^f	
mepolizumab + INCS vs. placebo + INCS					
SYNAPSE (VAS) ^g	206	155 (75.0)	201	132 (66.0)	0.87 [0.76; 0.99] ^h ; 0.037 ⁱ
Indirect comparison using common comparators^d:					
tezepelumab + INCS vs. mepolizumab + INCS					– ^f
Reduction/loss of smell					
tezepelumab + INCS vs. placebo + INCS					
WAYPOINT (NPSD [NRS]) ^e	144	90 (62.5)	147	32 (21.8)	0.34 [0.25; 0.48] ^h ; < 0.001 ^j
mepolizumab + INCS vs. placebo + INCS					
SYNAPSE (VAS) ^g	206	100 (49.0)	201	71 (35.0)	0.73 [0.57; 0.95] ^h ; 0.007 ⁱ
Indirect comparison using common comparators^d:					
tezepelumab + INCS vs. mepolizumab + INCS					– ^k

Table 13: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, indirect comparison: tezepelumab + INCS vs. mepolizumab + INCS (multipage table)

Outcome category Outcome Comparison Study	tezepelumab + INCS or mepolizumab + INCS		placebo + INCS		Group difference
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Nasal discharge					
tezepelumab + INCS vs. placebo + INCS					
WAYPOINT (NPSD [NRS]) ^e	144	119 (82.6)	147	71 (48.3)	0.59 [0.49; 0.71] ^h ; < 0.001 ^j
mepolizumab + INCS vs. placebo + INCS					
SYNAPSE (VAS) ^g	206	155 (75.0)	201	132 (66.0)	0.87 [0.76; 0.99] ^h ; 0.037 ⁱ
Indirect comparison using common comparators ^d : tezepelumab + INCS vs. mepolizumab + INCS					— ^k
Mucus in the throat					
tezepelumab + INCS vs. placebo + INCS					
WAYPOINT (NPSD [NRS]) ^e	144	101 (70.1)	147	74 (50.3)	0.72 [0.60; 0.88] ^h ; < 0.001 ^j
mepolizumab + INCS vs. placebo + INCS					
SYNAPSE (VAS) ^g	206	148 (72.0)	201	130 (65.0)	0.90 [0.78; 1.03] ^h ; 0.129 ⁱ
Indirect comparison using common comparators ^d : tezepelumab + INCS vs. mepolizumab + INCS					— ^k
Facial pain					
tezepelumab + INCS vs. placebo + INCS					
WAYPOINT (NPSD [NRS]) ^e			No suitable data ^f		
mepolizumab + INCS vs. placebo + INCS					
SYNAPSE (VAS) ^g	206	141 (68.0)	201	119 (59.0)	0.86 [0.74; 1.00] ^h ; 0.054 ⁱ
Indirect comparison using common comparators ^d : tezepelumab + INCS vs. mepolizumab + INCS					— ^f
SNOT-22 total score					
tezepelumab + INCS vs. placebo + INCS					
WAYPOINT	144	117 (81.2)	147	74 (50.3)	0.62 [0.52; 0.74] ^h ; < 0.001 ^j
mepolizumab + INCS vs. placebo + INCS					
SYNAPSE	205	157 (77)	198	122 (62)	0.80 [0.69; 0.93] ^h ; 0.001 ⁱ
Indirect comparison using common comparators ^d : tezepelumab + INCS vs. mepolizumab + INCS					— ^k

Table 13: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, indirect comparison: tezepelumab + INCS vs. mepolizumab + INCS (multipage table)

Outcome category	tezepelumab + INCS or mepolizumab + INCS		placebo + INCS		Group difference
Outcome					
Comparison					
Study	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Health-related quality of life (Week 52)					
SF-36v2					
Physical Component Summary (PCS) ^m					
tezepelumab + INCS vs. placebo + INCS					
WAYPOINT	144	60 (41.7)	147	36 (24.5)	0.59 [0.42; 0.83] ^h ; 0.002 ^j
mepolizumab + INCS vs. placebo + INCS					
SYNAPSE	205	86 (42)	198	46 (23)	0.55 [0.39; 0.76] ^h ; < 0.001 ⁱ
Indirect comparison using common comparators ^d :					
tezepelumab + INCS vs. mepolizumab + INCS					— ^k
Mental Component Summary (MCS) ⁿ					
tezepelumab + INCS vs. placebo + INCS					
WAYPOINT	144	40 (27.8)	147	33 (22.4)	0.81 [0.54; 1.21] ^h ; 0.296 ^j
mepolizumab + INCS vs. placebo + INCS					
SYNAPSE	205	62 (30)	198	41 (20)	0.68 [0.47; 0.99] ^h ; 0.030 ⁱ
Indirect comparison using common comparators ^d :					
tezepelumab + INCS vs. mepolizumab + INCS					— ^k
Side effects					
AEs ^o					
tezepelumab + INCS vs. placebo + INCS					
WAYPOINT	144	113 (78.5)	147	111 (75.5)	—
mepolizumab + INCS vs. placebo + INCS					
SYNAPSE	206	169 (82.0)	201	168 (83.6)	—
SAEs ^p					
tezepelumab + INCS vs. placebo + INCS					
WAYPOINT	144	8 (5.6)	147	10 (6.8)	0.82 [0.33; 2.01]; 0.809 ^c
mepolizumab + INCS vs. placebo + INCS					
SYNAPSE	206	12 (5.8)	201	13 (6.5)	0.90 [0.42; 1.93]; 0.839 ^c
Indirect comparison using common comparators ^d :					
tezepelumab + INCS vs. mepolizumab + INCS					— ^k

Table 13: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, indirect comparison: tezepelumab + INCS vs. mepolizumab + INCS (multipage table)

Outcome category Outcome Comparison Study	tezepelumab + INCS or mepolizumab + INCS		placebo + INCS		Group difference
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Discontinuation due to AEs					
tezepelumab + INCS vs. placebo + INCS					
WAYPOINT	144	1 (0.7)	147	2 (1.4)	0.51 [0.05; 5.57]; > 0.999 ^c
mepolizumab + INCS vs. placebo + INCS					
SYNAPSE	206	4 (1.9)	201	4 (2.0)	0.98 [0.25; 3.85]; > 0.999 ^c
Indirect comparison using common comparators^d:					
tezepelumab + INCS vs. mepolizumab + INCS					— ^k
a. The results on all-cause mortality are based on the information on fatal AEs. b. No presentation of effect estimation and CI, as these are not informative. c. RR unadjusted, CI from the Wald test, p-value from Fisher's exact test. In case of zero events in one study arm, the correction factor 0.5 was used for the calculation of effect in both study arms. d. Indirect comparison according to Bucher [3]. e. Proportion of patients with a reduction in score of ≥ 0.45 points in the mean value from Weeks 49 to 52 compared with baseline (mean value for the last 14 days prior to randomization). An NPSD NRS score decrease of ≥ 0.45 points in comparison with baseline is considered a clinically relevant improvement (scale range: 0 to 3). f. No suitable data available; for the reasoning, see Section I 3.4 of this dossier assessment. g. Proportion of patients with a reduction in score of ≥ 1.5 points in the mean value from Weeks 49 to 52 compared with baseline (mean value for the last 7 days prior to randomization). A decrease in the VAS score of ≥ 1.5 points in comparison with baseline is considered a clinically relevant improvement (scale range: 0 to 10). h. The data are based on a comparison of placebo + INCS versus tezepelumab + INCS for the WAYPOINT study, and placebo + INCS versus mepolizumab + INCS for the SYNAPSE study. i. Exact unconditional CI, calculated by inverting 2 separate one-sided tests based on the score statistic. p-value from the unconditional exact test (CSZ method according to [30]). j. Binomial regression model with the following terms: treatment arm, region, baseline value and log(e) baseline value of the eosinophil count in the blood. The log link function was used for the RR. 95% CI and p-value from Wald test. k. Requirements for the certainty of results to perform an adjusted indirect comparison are not met (see Table 12 and Section I 4.2). l. Proportion of patients with a reduction in the SNOT-22 total score of ≥ 16.5 points at Week 52 compared with baseline. A decrease in the SNOT-22 total score of ≥ 16.5 points in comparison with baseline is considered a clinically relevant improvement (scale range: 0 to 110).					

Table 13: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, indirect comparison: tezepelumab + INCS vs. mepolizumab + INCS (multipage table)

Outcome category Outcome Comparison Study	tezepelumab + INCS or mepolizumab + INCS		placebo + INCS		Group difference
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
m. Proportion of patients with an increase in the PCS score of ≥ 9.4 points at Week 52 compared with baseline (at randomization in the SYNAPSE study; in the WAYPOINT study, it is unclear whether this was at randomization or at the start of the run-in phase in Week -2). An increase in PCS of ≥ 9.4 points in comparison with baseline is considered a clinically relevant improvement (scale range: 7.3 to 70.1; determined using the 2009 norm sample [31]). n. Proportion of patients with an increase in the MCS score of ≥ 9.6 points at Week 52 compared with baseline (at randomization in the SYNAPSE study; in the WAYPOINT study, it is unclear whether this was at randomization or at the start of the run-in phase in Week -2). An increase in MCS of ≥ 9.6 points in comparison with baseline is considered a clinically relevant improvement (scale range: 5.8 to approx. 69.9; determined using the 2009 norm sample [31]). o. Includes disease-related events. p. Excluding deaths. AE: adverse event; CI: confidence interval; INCS: intranasal corticosteroids; MCS: Mental Component Summary; n: number of patients with (at least one) event; N: number of analysed patients; NPSD: nasal polyposis symptom diary; NRS: numeric rating scale; 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					

Table 14: Results (morbidity, continuous) – RCT, indirect comparison: tezepelumab + INCS vs. mepolizumab + INCS

Outcome category	tezepelumab + INCS or mepolizumab + INCS			placebo + INCS			Group difference
Outcome	N ^a	Values at baseline mean (SD)	Change at Week 52 mean ^b (SE)	N ^a	Values at baseline mean (SD)	Change at Week 52 mean ^b (SE)	Mean difference ^b [95% CI]; p-value
Comparison Study							
Morbidity							
Activity impairment (WPAI, question 6) [%] ^c							
tezepelumab + INCS vs. placebo + INCS							
WAYPOINT	144	43.36 (22.89)	–22.32 (2.14)	147	41.30 (26.76)	–16.74 (2.36)	–5.59 [–10.98; –0.19]; 0.043 SMD: –0.23 [–0.48; 0.03]
mepolizumab + INCS vs. placebo + INCS							
SYNAPSE	ND	53.4 (27.99)	–33.10 (1.74)	ND	53.2 (29.07)	–25.30 (1.77)	–7.80 [–12.67; –2.93]; 0.002 SMD: –0.33 [–0.54; –0.12]
Indirect comparison using common comparators:							
tezepelumab + INCS vs. mepolizumab + INCS – ^d							
a. Number of patients taken into account in the effect estimation; baseline values (and values at Week 52) may be based on different patient numbers. Includes, for the WAYPOINT study, patients for whom the worst possible value was imputed due to missing data.							
b. MMRM with treatment group, WPAI at baseline, region, log(e) of the baseline blood eosinophil count and visit, as well as interaction terms for visit and WPAI at baseline and visit, and treatment group.							
c. Lower (decreasing) percentages mean less impairment of daily activities; negative effects (intervention minus comparator) mean an advantage for the intervention (scale range: 0 to 100).							
d. Requirements for the certainty of results to perform an adjusted indirect comparison are not met (see Table 12 and Section I 4.2).							
CI: confidence interval; INCS: intranasal corticosteroids; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SMD: standardized mean difference; WPAI: Work Productivity and Activity Impairment							

There was one RCT on each side of the available adjusted indirect comparison. Consequently, there was no need to assess homogeneity. As there was no study of direct comparison of tezepelumab versus the ACT, it was impossible to check the consistency of results. Therefore, the adjusted indirect comparisons had at most a low certainty of results. Hence, no more than hints, e.g. of an added benefit, could be derived on the basis of the data available from the adjusted indirect comparison. Whilst the uncertainty regarding the requirement for surgery

for nasal polyps at baseline, as described in Section I 3.2, also led to a reduced certainty of conclusions, this alone did not mean that the requirements for the certainty of results necessary to conduct an adjusted indirect comparison were not met.

Furthermore, the risk of bias was high for all results relating to the outcomes in the WAYPOINT study, with the exception of the outcome discontinuation due to AEs. Consequently, the requirements for the certainty of results needed to conduct an adjusted indirect comparison were not met, and the indirect comparison of the individual outcomes was not used for the benefit assessment. The latter also applies to the outcome discontinuation due to AEs, for which, despite the low risk of bias, the certainty of the results was considered to be limited (see Section I 4.2).

Mortality

All-cause mortality

Due to insufficient certainty of the results in the WAYPOINT study, it was not possible to conduct an adjusted indirect comparison for the results for the outcome all-cause mortality. There is therefore no hint of an added benefit of tezepelumab + INCS in comparison with mepolizumab + INCS; an added benefit is therefore not proven.

Morbidity

Nasal congestion/obstruction, facial pain

No suitable data were available for the results for the symptom outcomes nasal congestion/obstruction and facial pain. There is therefore in each case no hint of an added benefit of tezepelumab + INCS in comparison with mepolizumab + INCS; an added benefit is therefore not proven.

Reduction/loss of smell, nasal discharge, mucus in the throat, SNOT-22 and activity impairment

Due to insufficient certainty of results in the WAYPOINT study, it was not possible to conduct an adjusted indirect comparison for the results for the symptom outcomes reduction/loss of smell, nasal discharge, mucus in the throat, and the SNOT-22 and activity impairment outcomes. There is therefore in each case no hint of an added benefit of tezepelumab + INCS in comparison with mepolizumab + INCS; an added benefit is therefore not proven.

Health-related quality of life

SF-36v2

Due to insufficient certainty of the results in the WAYPOINT study, it was not possible to conduct an adjusted indirect comparison for the results for the outcome SF-36v2. There is therefore no hint of an added benefit of tezepelumab + INCS in comparison with mepolizumab + INCS; an added benefit is therefore not proven.

Side effects

SAEs and discontinuation due to AEs

Due to insufficient certainty of the results in the WAYPOINT study, it was not possible to conduct an adjusted indirect comparison for the outcomes SAEs and discontinuation due to AEs. Hence for these outcomes, there was in each case no hint of greater or lesser harm of tezepelumab + INCS in comparison with mepolizumab + INCS; greater or lesser harm for these outcomes is therefore not proven.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics were taken into account for this benefit assessment:

- Age (18 to < 40 years versus 40 to 64 years versus ≥ 65 years)
- Sex (female versus male)
- Disease severity (number of previous nasal polyp surgeries: 1 versus 2 versus > 2)

All the subgroup characteristics listed were prespecified for the primary outcomes in the WAYPOINT and SYNAPSE studies. The cut-off values used for age and disease severity corresponded to the prespecified cut-off values in the SYNAPSE study.

For this benefit assessment, subgroup analyses were available only for the outcome activity impairment (WPAI, question 6) in the operationalization used (see Section I 4.1) and for SAEs. For the other morbidity outcomes, only subgroup analyses for continuous analyses using imputation strategy 1 were available; these were not relevant to this benefit assessment (see Section I 4.1). Subgroup analyses were entirely absent for the health-related quality of life outcomes.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p -value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

Applying the methodology described above, no effect modifications relevant to the benefit assessment were identified for the outcomes for which suitable data are available. Overall, however, it was not possible to draw any conclusions regarding potential effect modifications based on the available data, as suitable subgroup analyses were available for only 2 outcomes.

I 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 IQWiG General Methods [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.

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Chapter I 4 (see Table 15).

Table 15: Extent of added benefit at outcome level: tezepelumab + INCS vs. mepolizumab + INCS (multipage table)

Outcome category Outcome	tezepelumab + INCS vs. mepolizumab + INCS mean value / mean change Effect estimation [95% CI]; p-value Probability^a	Derivation of extent^b
Mortality		
All-cause mortality	No suitable data ^c	Lesser benefit not proven / added benefit not proven
Morbidity		
Nasal congestion/obstruction Improvement at Weeks 49 to 52 of 0.45 (NPSD [NRS]) and 1.5 points (VAS) respectively	No suitable data ^d	Lesser benefit not proven / added benefit not proven
Reduction/loss of smell Improvement at Weeks 49 to 52 of 0.45 (NPSD [NRS]) and 1.5 points (VAS) respectively	No suitable data ^c	Lesser benefit not proven / added benefit not proven
Nasal discharge Improvement at Weeks 49 to 52 of 0.45 (NPSD [NRS]) and 1.5 points (VAS) respectively	No suitable data ^c	Lesser benefit not proven / added benefit not proven
Mucus in the throat Improvement at Weeks 49 to 52 of 0.45 (NPSD [NRS]) and 1.5 points (VAS) respectively	No suitable data ^c	Lesser benefit not proven / added benefit not proven
Facial pain Improvement at Weeks 49 to 52 of 0.45 (NPSD [NRS]) and 1.5 points (VAS) respectively	No suitable data ^d	Lesser benefit not proven / added benefit not proven
SNOT-22 total score Improvement at Week 52 of 16.5 points	No suitable data ^c	Lesser benefit not proven / added benefit not proven
Activity impairment Improvement at Week 52	No suitable data ^c	Lesser benefit not proven / added benefit not proven
Health-related quality of life		
SF-36v2		
Physical Component Summary (PCS) Improvement at Week 52 of 9.4 points	No suitable data ^c	Lesser benefit not proven / added benefit not proven

Table 15: Extent of added benefit at outcome level: tezepelumab + INCS vs. mepolizumab + INCS (multipage table)

Outcome category Outcome	tezepelumab + INCS vs. mepolizumab + INCS mean value / mean change Effect estimation [95% CI]; p-value Probability ^a	Derivation of extent ^b
Mental Component Summary (MCS) Improvement at Week 52 of 9.6 points	No suitable data ^c	Lesser benefit not proven / added benefit not proven
Side effects		
SAEs	No suitable data ^c	Lesser benefit not proven / added benefit not proven
Discontinuation due to AEs	No suitable data ^c	Lesser benefit not proven / added benefit not proven
a. Probability provided if statistically significant differences are present. b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u). c. Requirements for the certainty of results necessary to perform an adjusted indirect comparison are not met (see Table 12 and Section I 4.2). d. Indirect comparison not feasible because no suitable results are available for at least one side of the indirect comparison (see Section I 4.1 for reasons). AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; MCS: Mental Component Summary; NPSD: nasal polyposis symptom diary; NRS: numeric rating scale; PCS: Physical Component Summary; 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		

I 5.2 Overall conclusion on added benefit

Table 16 summarizes the results taken into account for the overall conclusion on the extent of the added benefit.

Table 16: Positive and negative effects from the assessment of tezepelumab + INCS in comparison with mepolizumab + INCS

Positive effects	Negative effects
No data suitable for the adjusted indirect comparison were available for the outcomes of the categories mortality, morbidity, health-related quality of life and side effects.	
INCS: intranasal corticosteroids	

For the individual outcomes within the various outcome categories, either there were no results available that meet the requirements for certainty of results necessary to conduct an adjusted indirect comparison, or the indirect comparison could not be conducted because no

suitable results were available for at least one side of the indirect comparison; for the reasoning behind this, see Section I 4.1.

In summary, for patients with severe CRSwNP for whom therapy with SCS, and/or surgery do not provide adequate disease control, there is no hint of an added benefit of tezepelumab + INCS versus mepolizumab + INCS.

Table 17 summarizes the result of the assessment of added benefit for tezepelumab in comparison with the ACT.

Table 17: Tezepelumab – probability and extent of added benefit

Therapeutic indication	ACT ^a	Probability and extent of added benefit
Add-on therapy for adults with severe CRSwNP for whom therapy with SCS, and/or surgery do not provide adequate disease control	▪ dupilumab or ▪ omalizumab or ▪ mepolizumab in each case in combination with intranasal corticosteroids (budesonide or mometasone furoate) ^b	Added benefit not proven
a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 Section 4.2.2 is printed in bold. 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 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 tezepelumab is an option. ACT: appropriate comparator therapy; CRSwNP: chronic rhinosinusitis with nasal polyposis; G-BA: Federal Joint Committee; SCS: systemic corticosteroid		

The assessment described above deviates from that of the company, which derived a hint of a considerable added benefit of tezepelumab in comparison with mepolizumab as the ACT.

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

I 6 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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