

Tezepelumab (chronic rhinosinusitis with nasal polyps)

Addendum to Project A25-145
(dossier assessment)¹

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
CRSwNP	chronic rhinosinusitis with nasal polyps
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
INCS	intranasal corticosteroids
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LOCF	last observation carried forward
MCS	Mental Component Summary
mFAS	modified full analysis set
NRS	numeric rating scale
PCS	Physical Component Summary
RCT	randomized controlled trial
SAE	serious adverse event
SCS	systemic corticosteroids
SF-36v2	Short Form 36-version 2 Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SNOT-22	22-item Sino-Nasal Outcome Test
VAS	visual analogue scales
WPAI	Work Productivity and Activity Impairment
WPS	worst possible score

1 Background

On 24 March 2026, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A25-145 (Tezepelumab – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprised the assessment of the analyses presented by the pharmaceutical company (hereinafter referred to as the ‘company’) in the commenting procedure [2], taking into account the relevant information in the company’s dossier [3]:

- Re-evaluation of the data subsequently submitted by the company relating to the modified full analysis set (mFAS) on treatment and study discontinuations; data on return rates; sensitivity analyses for the symptoms outcomes; data on the facial pain outcome; and data on the decision to undergo surgery for nasal polyps

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

2 Assessment

For the benefit assessment of tezepelumab as an add-on therapy for adults 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 company submitted an adjusted indirect comparison. On the intervention side, it drew on the results from a subpopulation of the WAYPOINT study, while on the comparator side, on the results of the SYNAPSE study. A detailed description of the studies can be found in the benefit assessment on commission A25-145 [1].

Within the commenting procedure, the company submitted further data regarding the relevant subpopulation from WAYPOINT, as well as 2 sensitivity analyses for the indirect comparison. These data included analysable results for the adjusted indirect comparison for the outcomes on morbidity and health-related quality of life. The individual aspects are described below.

It was described in benefit assessment A25-145 that in both studies, the uncertainty regarding the need for nasal polyp surgery at baseline led to a reduced certainty of conclusions (see A25-145, 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. During the commenting procedure and the oral hearing [4], it also became apparent that it is unclear whether, in the German health care context, patients who have already experienced a deterioration following surgery for nasal polyps would undergo a further operation for nasal polyps if they do not respond to treatment, or whether other options – such as switching to a different biologic agent – would instead be preferred. It is also unclear whether the availability of other (subsequent) treatment options, such as biologic agents, might have influenced the selected therapeutic strategy in WAYPOINT and SYNAPSE (see Section 2.1 for further details). It should be noted that, in SYNAPSE, undergoing nasal polyp surgery had no impact on the planned 52-week duration of treatment with the study medication; in WAYPOINT, however, nasal polyp surgery resulted directly in premature treatment discontinuation (see Section 2.1).

These uncertainties did not call into question the requirements for the certainty of results when conducting an adjusted indirect comparison; however, they did contribute to a reduced certainty of conclusions and were taken into account for the derivation of the overall conclusion on added benefit (see Section 2.5.2).

2.1 Data submitted subsequently by the company during the commenting procedure

Data on study and treatment discontinuations, and follow-up in WAYPOINT

As described in assessment A25-145, there were minor differences between the treatment arms of SYNAPSE in terms of the proportion of treatment discontinuations [1]. For the WAYPOINT study, no data on treatment or study discontinuations were available for the

relevant subpopulation. These data are generally necessary for the assessment of study results. In this indirect comparison, however, these were particularly important because of the differences in study design in terms of follow-up between the studies included:

Whilst in SYNAPSE, 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 WAYPOINT, 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, of being contacted by telephone at monthly intervals and continuing to complete the electronic diary, or of only being contacted in Week 52 (follow-up options 1 to 3, see Table 1 for definition). If patients did not agree to follow-up contact, this resulted in study discontinuation in accordance with the study protocol.

Within the commenting procedure, the company provided detailed information on treatment and study discontinuations amongst patients in the relevant subpopulation of WAYPOINT. Furthermore, it provided detailed information on further follow-up for patients who discontinued treatment prematurely during the course of the study.

Table 1 summarizes the data on treatment and study discontinuations, as well as follow-up after treatment discontinuation, for WAYPOINT.

Table 1: Study/treatment discontinuation, follow-up after treatment discontinuation – RCT, direct comparison: tezepelumab + INCS vs. placebo + INCS (WAYPOINT study)

Characteristic Category	tezepelumab + INCS N = 144	placebo + INCS N = 147
Randomized patients in the relevant subpopulation	144	147
Treatment discontinuation, n (%) ^a	8 (6)	44 (30)
AEs	1 (< 1)	2 (1)
Lost to follow-up	0 (0)	1 (< 1)
Protocol violation	1 (< 1)	0 (0)
Patient request	4 (3)	28 (19)
Other	2 (1)	13 (9)
Treatment discontinuation with follow-up until study end, n (%)	5 (3)	30 (20)
Option 1 ^b	2 (1)	16 (11)
Option 2 ^c	1 (< 1)	2 (1)
Option 3 ^d	2 (1)	12 (8)
Study discontinuation, n (%) ^e	8 (6)	23 (16)
Patients who underwent NP surgery during the course of the study	N = 0	N = 20
Treatment discontinuation with follow-up until study end, n (%)	0 (0)	19 (95)
Option 1 ^b	0 (0)	13 (65)
Option 2 ^c	0 (0)	1 (5)
Option 3 ^d	0 (0)	5 (25)
Study discontinuation, n (%) ^f	0 (0)	1 (5)
a. All patients received the treatment. 136 (94%) vs. 103 (70%) of the patients completed treatment as planned. b. The patients attended all scheduled clinic visits and underwent all planned examinations (with the exception of the administration of the study medication) up to the end-of-treatment visit in Week 52. c. The patients were offered the option of continuing to be followed up by telephone on a monthly basis until the end-of-treatment visit in Week 52, whilst the recording of PROs at home via the electronic diary continued. d. The patients were contacted by the investigator only in Week 52 following randomization. Prior to this contact, no study examinations had been conducted and no PROs had been recorded in the electronic diary. e. Common reasons for study discontinuation in the intervention vs. control arm were (percentages refer to randomized patients): patient request (4% vs. 12%). f. Common reasons for study discontinuation in the intervention arm vs. control arm were: patient request (0 vs. 1 patient). AE: adverse event; INCS: intranasal corticosteroids; n: number of patients in the category; N: number of randomized patients; NP: nasal polyps; PRO: patient-reported outcome; RCT: randomized controlled trial		

For the relevant subpopulation of WAYPOINT, the proportion of treatment discontinuations was 6% in the tezepelumab arm and 30% in the placebo arm. The data subsequently submitted by the company showed that, for approximately two-thirds of the total of 8 and 44 patients in the tezepelumab and placebo arms respectively – who had discontinued treatment

prematurely for various reasons – data on outcomes up to the end of the study (of varying scope) were subsequently recorded as part of follow-up options 1 to 3. A similar picture emerged among patients in the placebo arm who discontinued treatment due to surgery for nasal polyps: Of the 20 patients, the majority remained in the study and were followed up until Week 52 in accordance with the various options listed in Table 1. For a total of 6 patients (5 patients in option 3 and one patient who discontinued the study following surgery for nasal polyps), data were missing for the collection and analysis of patient-reported outcomes due to treatment or study discontinuation following surgery for nasal polyps.

For the relevant subpopulation of WAYPOINT, the overall proportion of study discontinuations in the placebo arm was 16%, which was higher than in the tezepelumab arm (6%) and in both treatment arms of SYNAPSE (8%; see Table 9 in [1]). These differences were also reflected in the proportions of imputed values (see the discussion in the following sections).

Return rates for patient-reported outcomes

The benefit assessment noted that, on the intervention side, the return rates for the completed questionnaires in WAYPOINT showed a relevant proportion of missing values for the outcomes on symptoms and health-related quality of life, with this proportion varying between the treatment arms, resulting in a high risk of bias for these outcomes. Within the commenting procedure, the company corrected the data on the return rates in WAYPOINT for the symptoms outcomes (nasal congestion/obstruction, reduction/loss of smell, nasal discharge, mucus in the throat, facial pain). However, the data submitted subsequently for the symptoms outcomes also showed a relevant proportion of missing values for the various individual symptoms at Week 52, which differed between the treatment arms: 5.6% in the intervention arm compared with 20.4% in the placebo arm. For the outcomes for the SNOT-22 total score and the outcomes for health-related quality of life, it could also be derived from the supplementary data that there was a relevant proportion of missing values in each case, varying between the treatment arms. The risk of bias was therefore still considered high for all the outcomes concerned in WAYPOINT (see also Section 2.2).

Sensitivity analyses for imputing missing values for outcomes in the morbidity and health-related quality of life categories

In Module 4, the company presented responder analyses for the outcomes from the morbidity and health-related quality of life categories, and conducted adjusted indirect comparisons using 2 different analysis strategies. The 2 analysis strategies differed in terms of how they handled values observed following surgery for nasal polyps. In analysis strategy 1 (referred to as estimand 1 by the company), following surgery for nasal polyps, all subsequent values were imputed using the worst possible score (WPS; which corresponds to non-responders in responder analyses), whilst for patients undergoing SCS or (additional) biological therapy, as well as those who discontinued treatment, the observed values were used. In analysis strategy

2 (referred to by the company as estimand 2), the observed values were also used following surgery for nasal polyps (see benefit assessment A25-145 [1]). This was the only difference between the 2 analysis strategies. In both of the analysis strategies presented, the company imputed the missing values that were missing independent of nasal polyp surgery using the non-responder imputation method. Patients with missing baseline values were excluded from the analyses.

In the benefit assessment, the analyses submitted by the company on the basis of analysis strategy 2 (without imputation of the observed values following nasal polyp surgery) were used. For these analyses, missing values were imputed using non-responder imputation. Due to a high risk of bias arising from a relevant proportion of missing values in WAYPOINT, which differed between the treatment arms, it was not possible to conduct an indirect comparison for all the outcomes concerned, particularly as no sensitivity analyses were available using alternative imputation strategies that would more accurately represent the therapeutic strategy than the non-responder imputation method employed. Consequently, in its comments the company presented 2 sensitivity analyses employing different approaches to handling missing values, both based on analysis strategy 2, for the outcomes in the categories morbidity and health-related quality of life.

The first sensitivity analysis presented the results of a tipping-point analysis in which gradual responder imputation was performed for a total of 6 patients (symptoms outcomes) and 9 patients (SNOT-22 and SF-36v2) with missing values following surgery for nasal polyps. The second sensitivity analysis was a combined last observation carried forward (LOCF)/responder imputation. For this, missing values for patients who had not undergone nasal polyp surgery were imputed using the LOCF method, combined with responder imputation for patients with missing values following nasal polyp surgery. In doing so, for the symptoms outcomes (nasal congestion/obstruction, reduction/loss of smell, nasal discharge, mucus in the throat, facial pain), missing values for 6 patients who had undergone nasal polyp surgery were imputed using responder imputation. For the SNOT-22 outcome (total score) and the health-related quality of life outcomes (SF-36v2 PCS and MCS), missing values for 9 patients who had undergone nasal polyp surgery were imputed using responder imputation. Missing values for patients who had not undergone nasal polyp surgery were imputed using the LOCF method. With regard to the symptoms outcomes, there were 8 (5.6%) patients in the tezepelumab arm and 23 (15.8%) patients in the placebo arm of WAYPOINT (see Table 1). For the SNOT-22 outcome (total score) and the health-related quality of life outcomes (SF-36v2 PCS and MCS), missing values for 17 (11.8%) patients in the tezepelumab arm and 30 (20.4%) patients in the placebo arm were imputed using LOCF imputation. The 3 analyses – that is, analysis strategy 2, including both sensitivity analyses – made it possible to reach the assessment that the observed effects for the patient-reported outcomes were sufficiently robust and remained unchanged. Therefore, despite a high risk of bias regarding these outcomes in WAYPOINT (see

Section 2.2 and the section above), it was assumed that the results of an adjusted indirect comparison were sufficiently reliable.

Analyses using combined LOCF/responder imputation, based on analysis strategy 2, were considered the most appropriate for representing the treatment context in the given therapeutic indication, and were used for all relevant outcomes for the adjusted indirect comparison. The analyses from analysis strategy 2 and from the sensitivity analysis using the tipping-point method are presented as supplementary information in Appendix B.

Uncertainties associated with analysis strategy 2

As described above, in the analyses based on analysis strategy 2, the observed values following nasal polyp surgery were used without imputation. Such an approach was representative of the therapeutic strategy and did not involve any uncertainties associated with value imputation. Nevertheless, for analyses that incorporated values following nasal polyp surgery to a relevant extent, uncertainty arose around the question of how long-lasting the effect of repeated nasal polyp surgery is. An investigation by Smith in 2019 showed that the lasting effect on symptoms diminishes as the number of operations increases. For some patients, this is even seen in the notably shorter intervals between necessary nasal polyp operations, in some cases of less than 12 months [5]. It was therefore unclear whether the effect estimate, based on the values observed at the end of the study (Week 52), would allow any conclusions to be drawn about the long-term status of the symptoms.

It should be noted, however, that when analysis strategy 1 was applied – in which, following nasal polyp surgery, all subsequent values were imputed using WPS (which corresponds to non-responders in responder analyses) – no differences relevant to the conclusion emerged in comparison with the results from analysis strategy 2 (but also note that the necessary sensitivity analyses were not available for analysis strategy 1).

Corrected results for the outcome nasal congestion/obstruction

The benefit assessment A25-145 stated that, in Module 4 A of the dossier, the number of responders was higher than the number of patients with an analysed questionnaire at Week 52. For this reason the data provided were not usable. As described above, the company corrected the information on the return rates for the symptoms outcomes in its comments and provided data on patients with observed or missing values. The information provided was plausible. Based on these data, it was possible to perform an assessment of the outcome.

Data on facial pain outcome corrected

For the outcome facial pain, the issue with the dossier submitted was that, on the intervention side, results from WAYPOINT on facial pressure were included, whilst on the comparator side, results on facial pain from SYNAPSE were used. The results presented were therefore

fundamentally unsuitable for an adjusted indirect comparison. Within its comments, the company provided analyses for WAYPOINT for analysis strategy 2, including the 2 sensitivity analyses for facial pain. Based on these data, it was possible to perform an assessment of the outcome facial pain.

Information provided on the decision to undergo nasal polyp surgery

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. The outcome ‘nasal polyp surgery’ was changed during the course of the study to ‘decision to undergo nasal polyp surgery’ due to COVID-19-related delays in scheduling. Module 4 A of the dossier contained data on performed nasal polyp operations. Within its comments, the company also provided additional data regarding the decision to undergo nasal polyp surgery, both for the relevant subpopulation of the WAYPOINT study and for the SYNAPSE study. The results of this operationalization of the outcome are, as in assessment A25-145, presented as supplementary information in Appendix A (see Table 8).

As described above, there was some uncertainty regarding the role of nasal polyp surgery within the therapeutic strategy. During the commenting procedure and the oral hearing [4], it emerged that it is unclear in which cases, for patients with severe CRSwNP and multiple recurrent nasal polyps, performing a further nasal polyp operation as subsequent therapy represents the optimal therapeutic strategy. It is particularly unclear whether within the German health care context, patients who have already experienced a deterioration following nasal polyp surgery would undergo a further operation for nasal polyps if they do not respond to treatment, or whether other options – such as switching to a different biologic agent – would instead be preferred.

Furthermore, it is unclear what criteria were used in the studies to establish the indication for nasal polyp surgery. The respective study documents did not set out any specific criteria for performing nasal polyp surgery during the course of the study. The inclusion criteria for the 2 studies used did specify the need for nasal polyp surgery at baseline, and the definition of this was sufficiently similar between the studies (see benefit assessment A25-145 [1]). It was, however, unclear whether these criteria were applied consistently in the 2 global studies for performing nasal polyp surgery during the course of the study, or whether the availability of other (subsequent) treatment options, such as biologic agents, may instead have influenced the therapeutic strategy. The 2020 European Position Paper on Rhinosinusitis and Nasal Polyps points to differences in the rates of nasal polyp surgery across various countries in Europe and North America, citing access to health care and differing patient preferences, amongst other things, as possible reasons [6]. Where studies are conducted outside of Europe or North America, the differences in health care may be even more pronounced. For example, the company's data from the dossier on prior and subsequent therapies in the global

WAYPOINT study indicated that only a total of 6 patients in the total population had received a biologic agent (dupilumab, mepolizumab) as subsequent therapy, even though only a few (n = 15, corresponding to 3.7% of the total WAYPOINT study population) had previously received biological therapy. This could possibly be due, amongst other things, to the unavailability of these drugs outside the German health care system. It was therefore unclear overall whether the approach taken in the studies regarding nasal polyp surgery was transferable to the German health care context. This was taken into account when deriving the overall conclusion on the added benefit (see Section 2.5.2).

Overview of the outcomes in the indirect comparison

Table 2 shows for which outcomes, taking into account the subsequently submitted data, data were available in the included studies (yes/no) and whether an adjusted indirect comparison was feasible based on the available data (yes/no).

Table 2: 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	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No ^d
mepolizumab + INCS vs. placebo + INCS												
SYNAPSE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No ^e
Indirect comparison feasible	No ^f	Yes ^g	Yes ^g	Yes ^g	Yes ^g	Yes ^g	Yes ^g	No ^f	Yes ^g	No ^f	No ^f	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 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 benefit assessment A25-145 Section I 4.2 [1]). e. No specific AEs were identified based on the AEs occurring in the study. f. Requirement for the certainty of results to perform an adjusted indirect comparison is not met (see Section 2.2). g. The requirements for the certainty of results for conducting an adjusted indirect comparison are not fulfilled (see Section 2.2); however, sensitivity analyses are available which allow the assessment that the effects used are sufficiently robust – even when using imputation methods that more accurately represent the therapeutic strategy – to assume that an adjusted indirect comparison can yield a reliable result. 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												

2.2 Risk of bias

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

Table 3: Risk of bias across outcomes and outcome-specific risk of bias – RCT, 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	H ^e	H ^e	H ^e	H ^e	H ^e	H ^e	H ^f	H ^e	H ^d	L ^g	–
mepolizumab + INCS vs. placebo + INCS													
SYNAPSE	L	L	L	L	L	L	L	L	L	L	L	L ^g	–
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. Large difference between the treatment groups (> 10 percentage points) regarding the proportion of values imputed.													
f. Large difference between the treatment groups (> 10 percentage points) regarding the proportion of values for which the worst possible value was imputed.													
g. Despite the low risk of bias, the certainty of the results is considered to be limited (see also benefit assessment A25-145 [1]).													
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

The risk of bias was considered to be high for the results of the subsequently submitted and included outcomes on morbidity and health-related quality of life (recorded using the NRS

symptom scales, SNOT-22 and SF-36v2) in the WAYPOINT study. This is due to the large difference between the treatment groups (> 10 percentage points) in terms of the proportion of values imputed. Within the commenting procedure, the company submitted sensitivity analyses for these outcomes, which allowed the assessment that the effects used are sufficiently robust – even when using imputation methods that more accurately represent the therapeutic strategy – to assume that an adjusted indirect comparison can yield a reliable result.

As described in detail in benefit assessment A25-145, the risk of bias in the results of WAYPOINT was assessed as high for the outcomes all-cause mortality and SAEs, and as low with limited certainty of results for the outcome discontinuation due to AEs [1]. For the morbidity outcome activity impairment (WPAI, question 6), too, the benefit assessment had already described a high risk of bias due to a large difference between the treatment groups (> 10 percentage points) in the proportion of values for which the worst possible value was imputed [1].

SYNAPSE

For the results of all outcomes of the study SYNAPSE, the risk of bias was assessed as low. For the outcome discontinuation due to AEs, the certainty of conclusions was limited despite a low risk of bias (see benefit assessment A25-145 [1]).

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.

Consequently, in both studies, there were no data of sufficient certainty of results regarding the outcomes in the categories of mortality and side effects – which are based on the recording of adverse events – or regarding the morbidity outcome activity impairment, that would allow for a meaningful adjusted indirect comparison.

In view of the sensitivity analyses submitted subsequently for outcomes in the categories of morbidity and health-related quality of life, it was assumed – despite the high risk of bias on the intervention side in each case – that an adjusted indirect comparison would yield sufficiently reliable results for these outcomes.

2.3 Results

Table 4 summarizes the results of the comparison of tezepelumab + intranasal corticosteroids (INCS) versus mepolizumab + INCS in adult patients with severe CRSwNP for whom therapy with SCS, and/or surgery do not provide adequate disease control. For the outcomes in the morbidity and health-related quality of life categories, sensitivity analyses based on analysis

strategy 2, using a combination of LOCF/responder imputation, were used. In addition, analyses of the outcomes from the morbidity and health-related quality of life categories, based on analysis strategy 2, as well as the sensitivity analysis using the tipping-point method submitted by the company within the commenting procedure, are presented in Table 9 in Appendix B.

As described in benefit assessment A25-145 [1], an adjusted indirect comparison for the results relating to the outcome activity impairment (WPAI, question 6) was not feasible due to the insufficient certainty of results in WAYPOINT (a large difference between the treatment groups [> 10 percentage points] in the proportion of values for which the worst-possible value was imputed). The results of the analysis of the continuous data on the outcome activity impairment are presented in detail in Table 14 of benefit assessment A25-145 [1] and are not represented again in this assessment.

Table 4: 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	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Comparison Study					
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					
					–

Table 4: 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	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Comparison Study					
Morbidity (Week 52)^e					
Nasal congestion/obstruction					
tezepelumab + INCS vs. placebo + INCS					
WAYPOINT (NPSD [NRS]) ^f	144	134 (93.1)	147	97 (66.0)	0.71 [0.63; 0.81] ^g ; < 0.001 ^h
mepolizumab + INCS vs. placebo + INCS					
SYNAPSE (VAS) ⁱ	206	155 (75.0)	201	132 (66.0)	0.87 [0.76; 0.99] ^g ; 0.037 ^j
Indirect comparison using common comparators^d:					
tezepelumab + INCS vs. mepolizumab + INCS					0.82 [0.69; 0.98] ^g ; 0.032
Reduction/loss of smell					
tezepelumab + INCS vs. placebo + INCS					
WAYPOINT (NPSD [NRS]) ^f	144	94 (65.3)	147	40 (27.2)	0.41 [0.31; 0.54] ^g ; < 0.001 ^h
mepolizumab + INCS vs. placebo + INCS					
SYNAPSE (VAS) ⁱ	206	100 (49.0)	201	71 (35.0)	0.73 [0.57; 0.95] ^g ; 0.007 ^j
Indirect comparison using common comparators^d:					
tezepelumab + INCS vs. mepolizumab + INCS					0.56 [0.38; 0.82] ^g ; 0.003
Nasal discharge					
tezepelumab + INCS vs. placebo + INCS					
WAYPOINT (NPSD [NRS]) ^f	144	126 (87.5)	147	83 (56.5)	0.65 [0.56; 0.76] ^g ; < 0.001 ^h
mepolizumab + INCS vs. placebo + INCS					
SYNAPSE (VAS) ⁱ	206	155 (75.0)	201	132 (66.0)	0.87 [0.76; 0.99] ^g ; 0.037 ^j
Indirect comparison using common comparators^d:					
tezepelumab + INCS vs. mepolizumab + INCS					0.75 [0.61; 0.92] ^g ; 0.005
Mucus in the throat					
tezepelumab + INCS vs. placebo + INCS					
WAYPOINT (NPSD [NRS]) ^f	144	103 (71.5)	147	85 (57.8)	0.81 [0.69; 0.97] ^g ; 0.019 ^h
mepolizumab + INCS vs. placebo + INCS					
SYNAPSE (VAS) ⁱ	206	148 (72.0)	201	130 (65.0)	0.90 [0.78; 1.03] ^g ; 0.129 ^j
Indirect comparison using common comparators^d:					
tezepelumab + INCS vs. mepolizumab + INCS					0.90 [0.73; 1.13] ^g ; 0.373

Table 4: 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	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Comparison					
Study					
Facial pain					
tezepelumab + INCS vs. placebo + INCS					
WAYPOINT (NPSD [NRS]) ^f	144	90 (62.5)	147	76 (51.7)	0.83 [0.68; 1.02] ^g ; 0.074 ^h
mepolizumab + INCS vs. placebo + INCS					
SYNAPSE (VAS) ⁱ	206	141 (68.0)	201	119 (59.0)	0.86 [0.74; 1.00] ^g ; 0.054 ^j
Indirect comparison using common comparators^d:					
tezepelumab + INCS vs. mepolizumab + INCS					0.97 [0.75; 1.25] ^g ; 0.802
SNOT-22 total score ^k					
tezepelumab + INCS vs. placebo + INCS					
WAYPOINT	144	129 (89.6)	147	97 (66.0)	0.74 [0.65; 0.84] ^g ; < 0.001 ^h
mepolizumab + INCS vs. placebo + INCS					
SYNAPSE	205	157 (76.6)	198	122 (61.6)	0.80 [0.69; 0.93] ^g ; 0.001 ^j
Indirect comparison using common comparators^d:					
tezepelumab + INCS vs. mepolizumab + INCS					0.92 [0.76; 1.12] ^g ; 0.412
Health-related quality of life (Week 52)^e					
SF-36v2					
Physical Component Summary (PCS) ^l					
tezepelumab + INCS vs. placebo + INCS					
WAYPOINT	144	69 (47.9)	147	49 (33.3)	0.70 [0.52; 0.93] ^g ; 0.013 ^h
mepolizumab + INCS vs. placebo + INCS					
SYNAPSE	205	86 (42.0)	198	46 (23.2)	0.55 [0.39; 0.76] ^g ; < 0.001 ^j
Indirect comparison using common comparators^d:					
tezepelumab + INCS vs. mepolizumab + INCS					1.27 [0.82; 1.96] ^g ; 0.294
Mental Component Summary (MCS) ^m					
tezepelumab + INCS vs. placebo + INCS					
WAYPOINT	144	48 (33.3)	147	46 (31.3)	0.94 [0.67; 1.31] ^g ; 0.710 ^h
mepolizumab + INCS vs. placebo + INCS					
SYNAPSE	205	62 (30.2)	198	41 (20.7)	0.68 [0.47; 0.99] ^g ; 0.030 ^j
Indirect comparison using common comparators^d:					
tezepelumab + INCS vs. mepolizumab + INCS					1.38 [0.84; 2.28] ^g ; 0.206

Table 4: 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	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Comparison					
Study					
Side effects					
AEs ⁿ					
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 ^o					
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					
– ^p					
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					
– ^p					

Table 4: 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	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Comparison Study					
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 [7]. e. Responder imputation for patients with missing values following NP surgery, and LOCF imputation for patients with missing values without NP surgery f. 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). g. The data are based on a comparison of placebo + INCS versus tezepelumab + INCS for the WAYPOINT study, placebo + INCS versus mepolizumab + INCS for the SYNAPSE study, and mepolizumab + INCS versus tezepelumab + INCS for the indirect comparison. h. 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. i. 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). j. 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 [8]). k. 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). l. 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 [9]). m. 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 [9]). n. Includes disease-related events. o. Without deaths. p. Requirements for the certainty of results to perform an adjusted indirect comparison are not met (see Table 3 and Section 2.2).					

Table 4: 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	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Comparison Study					
AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; 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					

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. The uncertainties regarding nasal polyp surgery described above contributed to a reduced certainty of conclusions and were taken into account when deriving the overall conclusion on added benefit (see Section 2.5.2).

Mortality

All-cause mortality

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, reduction/loss of smell, nasal discharge

For the symptom outcomes of nasal congestion/obstruction, reduction/loss of smell and nasal discharge, the adjusted indirect comparison showed a statistically significant difference in favour of tezepelumab + INCS versus mepolizumab + INCS in the proportion of patients with an improvement of 15% of the scale range for each outcome. There is a hint of an added benefit of tezepelumab + INCS in comparison with mepolizumab + INCS for each of these outcomes.

Mucus in the throat, facial pain and SNOT-22

For the results for the symptoms outcomes mucus in the throat and facial pain, and for the SNOT-22 outcomes, there was no statistically significant difference between tezepelumab + INCS and mepolizumab + INCS in the proportion of patients with an improvement of 15% of the scale range. 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.

Activity impairment (WPAI, question 6)

As described in benefit assessment A25-145 [1], an adjusted indirect comparison for the results on the outcome activity impairment (WPAI, question 6) is not feasible. There is therefore 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

For the results for the outcome SF-36v2, there was no statistically significant difference between tezepelumab + INCS and mepolizumab + INCS in the proportion of patients with an improvement of 15% of the scale range. 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.

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.

2.4 Subgroups and other effect modifiers

The company did not provide any subgroup analyses for the subsequently submitted results relevant to the assessment.

2.5 Probability and extent of added benefit

2.5.1 Assessment of added benefit at outcome level

The extent of the added benefit at outcome level (see Table 5) was assessed based on the results presented in Section 2.3 and the findings of dossier assessment A25-145.

Determination of the outcome category for symptom outcomes

The rating of outcomes in terms of the outcome category ‘serious/severe’ or ‘non-serious/non-severe’ depends on the patients’ baseline situation, in particular on the severity and degree of impairment caused by their symptoms. In line with the benefit assessment of mepolizumab in this therapeutic indication [10,11], which also drew on the SYNAPSE study, the outcomes on symptoms (nasal congestion/obstruction, reduction/loss of smell, nasal discharge) were classified in the outcome category ‘serious/severe symptoms / late complications’. The company did not explicitly comment on the classification of the outcomes with regard to the outcome category, but also assumed a severe manifestation at baseline.

Table 5: Extent of added benefit at outcome level^a: tezepelumab + INCS vs. mepolizumab + INCS (multipage table)

Outcome category Outcome	tezepelumab + INCS vs. mepolizumab + INCS Proportion of events (%) Effect estimation [95% CI]; p-value Probability ^b	Derivation of extent ^c
Mortality		
All-cause mortality	No suitable data ^d	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	93.1% vs. 75.0% 0.82 [0.69; 0.98]; p = 0.032 Probability: hint	Outcome category: serious/severe symptoms / late complications $0.90 \leq Cl_u < 1.00$ Added benefit, extent: minor
Reduction/loss of smell Improvement at Weeks 49 to 52 of 0.45 (NPSD [NRS]) and 1.5 points (VAS) respectively	65.3% vs. 49.0% 0.56 [0.38; 0.82]; p = 0.003 Probability: hint	Outcome category: serious/severe symptoms / late complications $0.75 \leq Cl_u < 0.90$ Added benefit, extent: considerable

Table 5: Extent of added benefit at outcome level^a: tezepelumab + INCS vs. mepolizumab + INCS (multipage table)

Outcome category Outcome	tezepelumab + INCS vs. mepolizumab + INCS Proportion of events (%) Effect estimation [95% CI]; p-value Probability^b	Derivation of extent^c
Nasal discharge Improvement at Weeks 49 to 52 of 0.45 (NPSD [NRS]) and 1.5 points (VAS) respectively	87.5% vs. 75.0% 0.75 [0.61; 0.92]; p = 0.005 Probability: hint	Outcome category: serious/severe symptoms / late complications 0.90 ≤ Cl _u <1.00 Added benefit, extent: minor
Mucus in the throat Improvement at Weeks 49 to 52 of 0.45 (NPSD [NRS]) and 1.5 points (VAS) respectively	71.5% vs. 72.0% 0.90 [0.73; 1.13]; p = 0.373	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	62.5% vs. 68.0% 0.97 [0.74; 1.25]; p = 0.802	Lesser benefit not proven / added benefit not proven
SNOT-22 total score Improvement at Week 52 of 16.5 points	89.6% vs. 76.6% 0.92 [0.76; 1.12]; p = 0.412	Lesser benefit not proven / added benefit not proven
Activity impairment Improvement at Week 52	No suitable data ^{d, e}	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	47.9% vs. 42.0% 1.27 [0.82; 1.96]; p = 0.294	Lesser benefit not proven / added benefit not proven
Mental Component Summary (MCS) Improvement at Week 52 of 9.6 points	33.3% vs. 30.2% 1.38 [0.84; 2.28]; p = 0.206	Lesser benefit not proven / added benefit not proven
Side effects		
SAEs	No suitable data ^d	Lesser benefit not proven / added benefit not proven
Discontinuation due to AEs	No suitable data ^d	Lesser benefit not proven / added benefit not proven

Table 5: Extent of added benefit at outcome level^a: tezepelumab + INCS vs. mepolizumab + INCS (multipage table)

Outcome category Outcome	tezepelumab + INCS vs. mepolizumab + INCS Proportion of events (%) Effect estimation [95% CI]; p-value Probability ^b	Derivation of extent ^c
a. Based on the results of sensitivity analysis 2 (combined LOCF/responder imputation): Patients who had a missing post-baseline value at Week 52 and who had undergone nasal polyp surgery during the study were rated as responders. Missing post-baseline values at Week 52 for patients who did not undergo nasal polyp surgery during the study were imputed using the LOCF method. The responder status was then determined. b. Probability provided if statistically significant differences are present. c. Depending on the outcome category, estimations of effect size use different limits based on the upper limit of the confidence interval (CI_u). d. Requirements for the certainty of results to perform an adjusted indirect comparison are not met (see Table 3 and Section 2.2). e. A large difference between the treatment groups (> 10 percentage points) in terms of the proportion of values for which the worst possible value was imputed (see benefit assessment A25-145 [1]). 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		

2.5.2 Overall conclusion on added benefit

Table 6 summarizes the results taken into account for the overall conclusion on the extent of the added benefit.

Table 6: Positive and negative effects from the assessment of tezepelumab + INCS in comparison with mepolizumab + INCS

Positive effects	Negative effects
Serious/severe symptoms / late complications - Nasal congestion/obstruction: hint of an added benefit – extent: minor - Reduction/loss of smell: hint of an added benefit – extent: considerable - Nasal discharge: hint of an added benefit – extent: minor	–
No data suitable for the adjusted indirect comparison were available for the outcomes of the categories mortality and side effects or for the morbidity outcome activity impairment.	
INCS: intranasal corticosteroids	

Overall, only positive effects were shown for tezepelumab + INCS in comparison with mepolizumab + INCS. However, no usable data were available for the outcomes in the

categories of mortality and side effects, or for the morbidity outcome activity impairment, for the indirect comparison. For each of these outcomes, there is no hint of an added benefit or of any greater or lesser harm. In the morbidity outcome category, there are hints of an added benefit of minor or considerable extent.

The extent of the added benefit was assessed as non-quantifiable given the available data. This was due to the fact that there were a number of uncertainties associated with the performance of nasal polyp surgery (see Chapter 2 and Section 2.1). Furthermore, despite extensive recording – including, amongst other things, using the SNOT-22 instrument – the advantages in terms of morbidity were shown only for 3 symptom outcomes, each of which was assessed using 2 different study-specific instruments. In this context, the use of visual analogue scales (VAS) in the SYNAPSE study and 4-point numeric rating scales (NRS) in the WAYPOINT study allowed for a more or less detailed assessment of the severity of the respective symptoms, depending on the study (see also the benefit assessment for the commission [1]). By contrast, no effects were shown in the total SNOT-22 score or in the health-related quality of life outcomes. Furthermore, no results were available for outcomes in the side effects category for the adjusted indirect comparison; however, given the available data, it was not considered that the potential harm would entirely call into question the in part considerable added benefit for outcomes in the morbidity category.

In summary, for adult patients with CRSwNP for whom therapy with SCS, and/or surgery do not provide adequate disease control, there is a hint of a non-quantifiable added benefit of tezepelumab + INCS in comparison with the ACT.

2.6 Summary

The data submitted by the company during the commenting procedure alter the conclusion regarding the added benefit of tezepelumab set out in dossier assessment A25-145. Whilst the added benefit was not proven in dossier assessment A25-145, in this assessment there is a hint of a non-quantifiable added benefit.

The following Table 7 shows the result of the benefit assessment of tezepelumab, taking into account dossier assessment A25-145 and this addendum.

Table 7: 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	Hint of a non-quantifiable added benefit
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 G-BA decides on the added benefit.

3 References

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Appendix A Decision regarding nasal polyp surgery

Table 8: Results (morbidity, supplementary information) – RCT, indirect comparison: tezepelumab + INCS vs. mepolizumab + INCS

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 ^a
Morbidity					
Decision to undergo nasal polyp surgery					
tezepelumab + INCS vs. placebo + INCS					
WAYPOINT	144	1 (0.7)	147	30 (20.4)	0.03 [0.01; 0.25]; < 0.001
mepolizumab + INCS vs. placebo + INCS					
SYNAPSE	206	28 (13.6)	201	56 (27.9)	0.49 [0.32; 0.74]; < 0.001
Indirect comparison using common comparators^b:					
tezepelumab + INCS vs. mepolizumab + INCS					— ^c
a. RR unadjusted, CI and p-value from Wald test. b. Indirect comparison according to Bucher [7]. c. Undergoing nasal polyp surgery not used as an outcome for conducting an adjusted indirect comparison (see Section 2.1). CI: confidence interval; CRSwNP. Chronic rhinosinusitis with nasal polyps; INCS: intranasal corticosteroids; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk					

Appendix B Outcomes in the category morbidity and health-related quality of life – estimand 2 analysis without/with responder imputation of missing values

Table 9: Results (morbidity, health-related quality of life, dichotomous, supplementary information) – 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
Morbidity (Week 52)					
Nasal congestion/obstruction					
tezepelumab + INCS vs. placebo + INCS					
WAYPOINT (NPSD [NRS]) ^a	144	128 (88.9)	147	83 (56.5)	0.64 [0.55; 0.75] ^b ; < 0.001 ^c
mepolizumab + INCS vs. placebo + INCS					
SYNAPSE (VAS) ^d	206	155 (75.0)	201	132 (66.0)	0.87 [0.76; 0.99] ^b ; 0.037 ^e
Indirect comparison using common comparators^f:					
tezepelumab + INCS vs. mepolizumab + INCS					0.74 [0.60; 0.90] ^b ; 0.003
<i>Sensitivity analysis 1^g</i>					
tezepelumab + INCS vs. placebo + INCS					
WAYPOINT (NPSD [NRS]) ^a	144	128 (88.9)	147	89 (60.5) ^h	ND
mepolizumab + INCS vs. placebo + INCS					
SYNAPSE (VAS) ^d	206	155 (75.0)	201	132 (66.0)	0.87 [0.76; 0.99] ^b ; 0.037 ^e
Indirect comparison using common comparators^f:					
tezepelumab + INCS vs. mepolizumab + INCS					0.79 [0.65; 0.96] ^b ; 0.016
Reduction/loss of smell					
tezepelumab + INCS vs. placebo + INCS					
WAYPOINT (NPSD [NRS]) ^a	144	90 (62.5)	147	32 (21.8)	0.34 [0.25; 0.48] ^b ; < 0.001 ^c
mepolizumab + INCS vs. placebo + INCS					
SYNAPSE (VAS) ^d	206	100 (49.0)	201	71 (35.0)	0.73 [0.57; 0.95] ^b ; 0.007 ^e
Indirect comparison using common comparators^f:					
tezepelumab + INCS vs. mepolizumab + INCS					0.47 [0.31; 0.71] ^b ; < 0.001

Table 9: Results (morbidity, health-related quality of life, dichotomous, supplementary information) – RCT, indirect comparison: tezepelumab + INCS vs. mepolizumab + INCS (multipage table)

Outcome category	tezepelumab + INCS or mepolizumab + INCS		placebo + INCS		Group difference
Outcome	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Comparison					
Study					
<i>Sensitivity analysis 1^g</i>					
<i>tezepelumab + INCS vs. placebo + INCS</i>					
WAYPOINT (NPSD [NRS]) ^a	144	90 (62.5)	147	38 (25.9) ^h	ND
<i>mepolizumab + INCS vs. placebo + INCS</i>					
SYNAPSE (VAS) ^d	206	100 (49.0)	201	71 (35.0)	0.73 [0.57; 0.95] ^b ; 0.007 ^e
Indirect comparison using common comparators^f:					
tezepelumab + INCS vs. mepolizumab + INCS					0.55 [0.37; 0.82] ^b ; 0.003
Nasal discharge					
<i>tezepelumab + INCS vs. placebo + INCS</i>					
WAYPOINT (NPSD [NRS]) ^a	144	119 (82.6)	147	71 (48.3)	0.59 [0.49; 0.71] ^b ; < 0.001 ^c
<i>mepolizumab + INCS vs. placebo + INCS</i>					
SYNAPSE (VAS) ^d	206	155 (75.0)	201	132 (66.0)	0.87 [0.76; 0.99] ^b ; 0.037 ^e
Indirect comparison using common comparators^f:					
tezepelumab + INCS vs. mepolizumab + INCS					0.68 [0.54; 0.85] ^b ; < 0.001
<i>Sensitivity analysis 1^g</i>					
<i>tezepelumab + INCS vs. placebo + INCS</i>					
WAYPOINT (NPSD [NRS]) ^a	144	119 (82.6)	147	77 (52.4) ^h	ND
<i>mepolizumab + INCS vs. placebo + INCS</i>					
SYNAPSE (VAS) ^d	206	155 (75.0)	201	132 (66.0)	0.87 [0.76; 0.99] ^b ; 0.037 ^e
Indirect comparison using common comparators^f:					
tezepelumab + INCS vs. mepolizumab + INCS					0.73 [0.59; 0.91] ^b ; 0.005
Mucus in the throat					
<i>tezepelumab + INCS vs. placebo + INCS</i>					
WAYPOINT (NPSD [NRS]) ^a	144	101 (70.1)	147	74 (50.3)	0.72 [0.60; 0.88] ^b ; < 0.001 ^c
<i>mepolizumab + INCS vs. placebo + INCS</i>					
SYNAPSE (VAS) ^d	206	148 (72.0)	201	130 (65.0)	0.90 [0.78; 1.03] ^b ; 0.129 ^e
Indirect comparison using common comparators^f:					
tezepelumab + INCS vs. mepolizumab + INCS					0.80 [0.63; 1.02] ^b ; 0.070

Table 9: Results (morbidity, health-related quality of life, dichotomous, supplementary information) – RCT, indirect comparison: tezepelumab + INCS vs. mepolizumab + INCS (multipage table)

Outcome category	tezepelumab + INCS or mepolizumab + INCS		placebo + INCS		Group difference
Outcome	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Comparison					
Study					
<i>Sensitivity analysis 1^g</i>					
<i>tezepelumab + INCS vs. placebo + INCS</i>					
WAYPOINT (NPSD [NRS]) ^a	144	101 (70.1)	147	80 (54.4) ^h	ND
<i>mepolizumab + INCS vs. placebo + INCS</i>					
SYNAPSE (VAS) ^d	206	148 (72.0)	201	130 (65.0)	0.90 [0.78; 1.03] ^b ; 0.129 ^e
Indirect comparison using common comparators^f:					
tezepelumab + INCS vs. mepolizumab + INCS					0.87 [0.69; 1.09] ^b ; 0.226
Facial pain					
<i>tezepelumab + INCS vs. placebo + INCS</i>					
WAYPOINT (NPSD [NRS]) ^a	144	84 (58.3)	147	66 (44.9)	0.78 [0.62; 0.97] ^b ; 0.027 ^c
<i>mepolizumab + INCS vs. placebo + INCS</i>					
SYNAPSE (VAS) ^d	206	141 (68.0)	201	119 (59.0)	0.86 [0.74; 1.00] ^b ; 0.054 ^e
Indirect comparison using common comparators^f:					
tezepelumab + INCS vs. mepolizumab + INCS					0.90 [0.69; 1.18] ^b ; 0.450
<i>Sensitivity analysis 1^g</i>					
<i>tezepelumab + INCS vs. placebo + INCS</i>					
WAYPOINT (NPSD [NRS]) ^a	144	84 (58.3)	147	72 (49.0) ^h	ND
<i>mepolizumab + INCS vs. placebo + INCS</i>					
SYNAPSE (VAS) ^d	206	141 (68.0)	201	119 (59.0)	0.86 [0.74; 1.00] ^b ; 0.054 ^e
Indirect comparison using common comparators^f:					
tezepelumab + INCS vs. mepolizumab + INCS					0.98 [0.76; 1.28] ^b ; 0.898
SNOT-22 total score ⁱ					
<i>tezepelumab + INCS vs. placebo + INCS</i>					
WAYPOINT	144	117 (81.2)	147	74 (50.3)	0.62 [0.52; 0.74] ^b ; < 0.001 ^c
<i>mepolizumab + INCS vs. placebo + INCS</i>					
SYNAPSE	205	157 (76.6)	198	122 (61.6)	0.80 [0.69; 0.93] ^b ; 0.001 ^e
Indirect comparison using common comparators^f:					
tezepelumab + INCS vs. mepolizumab + INCS					0.77 [0.61; 0.98] ^b ; 0.031

Table 9: Results (morbidity, health-related quality of life, dichotomous, supplementary information) – RCT, indirect comparison: tezepelumab + INCS vs. mepolizumab + INCS (multipage table)

Outcome category	tezepelumab + INCS or mepolizumab + INCS		placebo + INCS		Group difference
Outcome	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Comparison					
Study					
<i>Sensitivity analysis 1^g</i>					
<i>tezepelumab + INCS vs. placebo + INCS</i>					
WAYPOINT	144	117 (81.2)	147	83 (56.5) ^h	ND
<i>mepolizumab + INCS vs. placebo + INCS</i>					
SYNAPSE	205	157 (76.6)	198	122 (61.6)	0.80 [0.69; 0.93] ^b ; 0.001 ^e
Indirect comparison using common comparators^f:					
tezepelumab + INCS vs. mepolizumab + INCS					0.87 [0.70; 1.08] ^b ; 0.211
Health-related quality of life (Week 52)					
SF-36v2					
Physical Component Summary (PCS) ^j					
<i>tezepelumab + INCS vs. placebo + INCS</i>					
WAYPOINT	144	60 (41.7)	147	36 (24.5)	0.59 [0.42; 0.83] ^b ; 0.002 ^c
<i>mepolizumab + INCS vs. placebo + INCS</i>					
SYNAPSE	205	86 (42.0)	198	46 (23.2)	0.55 [0.39; 0.76] ^b ; < 0.001 ^e
Indirect comparison using common comparators^f:					
tezepelumab + INCS vs. mepolizumab + INCS					1.07 [0.66; 1.73] ^b ; 0.786
<i>Sensitivity analysis 1^g</i>					
<i>tezepelumab + INCS vs. placebo + INCS</i>					
WAYPOINT	144	60 (41.7)	147	45 (30.6) ^h	ND
<i>mepolizumab + INCS vs. placebo + INCS</i>					
SYNAPSE	205	86 (42.0)	198	46 (23.2)	0.55 [0.39; 0.76] ^b ; < 0.001 ^e
Indirect comparison using common comparators^f:					
tezepelumab + INCS vs. mepolizumab + INCS					1.34 [0.85; 2.11] ^b ; 0.213
Mental Component Summary (MCS) ^k					
<i>tezepelumab + INCS vs. placebo + INCS</i>					
WAYPOINT	144	40 (27.8)	147	33 (22.4)	0.81 [0.54; 1.21] ^b ; 0.296 ^c
<i>mepolizumab + INCS vs. placebo + INCS</i>					
SYNAPSE	205	62 (30.2)	198	41 (20.7)	0.68 [0.47; 0.99] ^b ; 0.030 ^e
Indirect comparison using common comparators^f:					
tezepelumab + INCS vs. mepolizumab + INCS					1.19 [0.69; 2.05] ^b ; 0.536

Table 9: Results (morbidity, health-related quality of life, dichotomous, supplementary information) – RCT, indirect comparison: tezepelumab + INCS vs. mepolizumab + INCS (multipage table)

Outcome category	tezepelumab + INCS or mepolizumab + INCS		placebo + INCS		Group difference
Outcome					
Comparison	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Study					
<i>Sensitivity analysis 1^g</i>					
<i>tezepelumab + INCS vs. placebo + INCS</i>					
WAYPOINT	144	40 (27.8)	147	42 (28.6) ^h	ND
<i>mepolizumab + INCS vs. placebo + INCS</i>					
SYNAPSE	205	62 (30.2)	198	41 (20.7)	0.68 [0.47; 0.99] ^b ; 0.030 ^e
Indirect comparison using common comparators^f:					
tezepelumab + INCS vs. mepolizumab + INCS					1.51 [0.90; 2.55] ^b ; 0.121
a. 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). b. The data are based on a comparison of placebo + INCS versus tezepelumab + INCS for the WAYPOINT study, placebo + INCS versus mepolizumab + INCS for the SYNAPSE study, and mepolizumab + INCS versus tezepelumab + INCS for the indirect comparison. c. 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. d. 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). e. 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 [8]). f. Indirect comparison according to Bucher [7]. g. Responder imputation for patients with missing values following NP surgery. h. Institute's calculation. i. 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). j. 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 [9]). k. 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 [9]).					

Table 9: Results (morbidity, health-related quality of life, dichotomous, supplementary information) – RCT, indirect comparison: tezepelumab + INCS vs. mepolizumab + INCS (multipage table)

Outcome category	tezepelumab + INCS or mepolizumab + INCS		placebo + INCS		Group difference
Outcome	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Comparison Study					
AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; INCS: intranasal corticosteroids; MCS: Mental Component Summary; n: number of patients with (at least one) event; N: number of analysed patients; NP: nasal polyps; 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					