IQWiG Reports – Commission No. A19-96

Dupilumab (chronic rhinosinusitis with nasal polyposis) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Dupilumab (*Chronische Rhinosinusitis mit Nasenpolypen*) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 27 February 2020). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Dupilumab (chronic rhinosinusitis with nasal polyposis) – Benefit assessment according to §35a Social Code Book V

Commissioning agency

Federal Joint Committee

Commission awarded on

21 November 2019

Internal Commission No.

A19-96

Address of publisher

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

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Keywords: Dupilumab, Sinusitis, Benefit Assessment, NCT02912468, NCT02898454

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSACI	British Society of Allergy and Clinical Immunology
CI	confidence interval
CRSwNP	chronic rhinosinusitis with nasal polyposis
EPOS	European Position Paper on Rhinosinusitis and Nasal Polyps
EQ-5D	European Quality of Life-5 Dimensions
ERD	exacerbated respiratory disease
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)
LABA	long-acting beta agonists
LAMA	long-acting muscarinic receptor antagonists
NSAID	nonsteroidal anti-inflammatory drug
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SCS	systemic corticosteroids
SGB	Sozialgesetzbuch (Social Code Book)
SNOT-22	22-Item Sino-Nasal Outcome Test
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug dupilumab. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 21 November 2019.

Research question

Aim of the present report is the assessment of the added benefit of dupilumab as add-on therapy with intranasal corticosteroids (INCS) in comparison with the appropriate comparator therapy (ACT) in adult patients with severe chronic rhinosinusitis with nasal polyposis (CRSwNP) which cannot be adequately controlled with systemic corticosteroids (SCS) and/or surgery.

The specification of the ACT by the G-BA resulted in the research question presented in Table 2 for the present benefit assessment.

Table 2: Research question of the benefit assessment of dupilumab

Therapeutic indication	**ACT[a]**
Adult patients with severe CRSwNP which cannot be adequately controlled with SCS and/or surgery[b, c]	Treatment with topical corticosteroids (budesonide or mometasone furoate)[c, d]

a. Presentation of the ACT specified by the G-BA. The G-BA's ACT refers to the planned therapeutic indication of dupilumab at the time of the consultation: adult patients with severe CRSwNP in whom previous therapies with SCS and/or surgery failed or in whom such treatment is unsuitable due to intolerance or contraindication.
b. It is assumed that the deviation of the designation of the final therapeutic indication from the therapeutic indication planned at the time of the consultation neither challenges the research question of the present assessment nor the ACT. The benefit assessment refers to the approved therapeutic indication.
c. The G-BA specified that patients in both study arms should receive maintenance treatment with topical corticosteroids as well as further supportive measures (e.g. nasal rinsing) and an adequate, approval-compliant treatment of complications. It is also assumed that invasive treatment options are currently not indicated for patients for whom treatment with dupilumab is suitable.
d. According to the G-BA for patients for whom drug treatment is an option.

ACT: appropriate comparator therapy; CRSwNP: chronic rhinosinusitis with nasal polyposis; G-BA: Federal Joint Committee; SCS: systemic corticosteroid

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 the added benefit.

Results

Study pool

The study pool for the benefit assessment of dupilumab in comparison with the ACT consisted of the RCTs SINUS-24 und SINUS-52.

Study characteristics

The studies SINUS-24 and SINUS-52 are randomized, double-blind phase 3 studies on the comparison of dupilumab versus placebo each in addition to maintenance treatment with intranasal mometasone furoate. Both studies included adult patients with bilateral nasal polyposis who despite treatment with SCS within the past 2 years and/or contraindication/ intolerance to SCS and/or at least one prior sino-nasal surgery had a nasal polyp score of ≥ 5 and < 8 as well as at least two persistent symptoms of chronic rhinosinusitis since ≥ 8 weeks before the run-in-phase.

Prior to randomisation, both studies had a 4-week run-in phase in which the suitability of the patients for inclusion in the study was assessed and maintenance treatment was started with 400 µg intranasal mometasone furoate daily (2 shots of 50 µg each per nasal opening twice daily).

Following the run-in phase, only those patients could be randomly assigned to the treatment arms who, in addition to meeting the inclusion criteria, had at least 2 symptoms for a total of at least 12 weeks (at least 8 weeks before and 4 weeks during the run-in phase) (including nasal congestion/obstruction with moderate or severe severity and, for instance, loss of smell or anterior/posterior rhinorrhoea). During the treatment phase, administration of intranasal mometasone furoate at stable doses was continued in both studies. In addition to the study medication to be investigated and the maintenance therapy with intranasal mometasone furoate, emergency treatment was allowed in case of worsening of (endoscopic/radiological) signs and (SINUS-24, SINUS-52) /or (SINUS-52) symptoms.

The treatment phase was followed by a follow-up observation phase (SINUS-24: 24 weeks; SINUS-52: 12 weeks), during which the treatment with intranasal mometasone furoate could be continued at stable doses or treatment could be switched at the investigator’s discretion.

In the SINUS-24 study, a total of 276 patients were randomly assigned to 24-week treatment with 300 mg dupilumab every 2 weeks (N = 143) or with placebo (N = 133). In the SINUS-52 study, a total of 448 patients were randomly assigned to 3 treatment arms. Patients received either 300 mg dupilumab every 2 weeks for 52 weeks (N = 150) or 300 mg dupilumab every 2 weeks for 24 weeks and subsequently 300 mg dupilumab every 4 weeks until week 52 (N = 145) or placebo for 52 weeks (N = 153).

Primary outcomes in both studies were changes in the nasal congestion/obstruction and the nasal polyp score each at week 24. Further patient-relevant outcomes were all-cause mortality as well as outcomes of the outcome category “morbidity” and “side effects”.

Due to the similarity of the studies, all treatment arms of both studies at week 24 were considered for a meta-analysis for the present benefit assessment.

Risk of bias

The risk of bias across outcomes was rated as low both for the SINUS-24 study and for the SINUS-52 study.

The outcome-specific risk of bias for each of the results of the outcomes in the outcome categories "mortality" and "morbidity" was rated as low. Outcomes of the outcome category "health-related quality of life" were not recorded in the studies SINUS-24 and SINUS-52.

Mortality

All-cause mortality

Until week 24, no deaths occurred in the studies SINUS-24 and SINUS-52. For the outcome "all-cause mortality", the meta-analysis of the studies SINUS-24 and SINUS-52 thus showed no significant difference of dupilumab + mometasone furoate versus placebo + mometasone furoate at week 24. This resulted in no hint of an added benefit of dupilumab as add-on therapy with INCS in comparison with a treatment with topical corticosteroids; an added benefit is therefore not proven.

Morbidity

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

For the outcome "SNOT-22", the meta-analysis of the SINUS-24 and SINUS-52 studies showed a statistically significant difference in favour of dupilumab + mometasone furoate over placebo + mometasone furoate for the proportion of patients with an improvement of the overall score by ≥ 8.9 points at week 24. This resulted in proof of added benefit of dupilumab as add-on therapy with INCS in comparison with treatment with topical corticosteroids.

Nasal congestion/obstruction, loss of smell, rhinorrhoea (anterior/posterior), visual analogue scale (VAS) rhinosinusitis, health status (European Quality of Life-5 Dimensions [EQ-5D VAS])

At week 24, the meta-analysis of the studies SINUS-24 and SINUS-52 showed a statistically significant difference in favour of dupilumab + mometasone furoate versus placebo + mometasone furoate on the basis of the mean change for each of the outcomes "nasal congestion/obstruction", "loss of smell", "rhinorrhoea (anterior/posterior)", "VAS rhinosinusitis" and "health status (EQ-5D VAS)". The 95% confidence interval (CI) of the standardized mean difference (Hedges' g) is fully outside the irrelevance range of −0.2 to 0.2. This was interpreted to be a relevant effect. In each case, this resulted in proof of added benefit of dupilumab as add-on therapy with INCS in comparison with treatment with topical corticosteroids.

Health-related quality of life

Outcomes of the outcome category "health-related quality of life" were not recorded in the studies SINUS-24 and SINUS-52. This resulted in no hint of an added benefit of dupilumab as add-on therapy with INCS in comparison with a treatment with topical corticosteroids; an added benefit is therefore not proven.

Side effects

The present analyses on adverse events (AEs) also comprise events that can be assigned to both side effects of the therapy and symptoms of the disease. As this refers to a large proportion of patients, the data on AEs cannot be used for the derivation of the added benefit.

Serious adverse events (SAEs), discontinuation due to AEs

Usable data for the outcomes "SAEs" and "discontinuation due to AEs" are neither available from SINUS-24 nor from SINUS-52. In each case, this resulted in no hint of greater or lesser harm from dupilumab as add-on therapy with INCS in comparison with a treatment with topical corticosteroids; greater or lesser harm is therefore not proven.

Specific AEs

All specific AEs identified in the studies SINUS-24 and SINUS-52 can be assigned both to side effects and the symptoms of the disease. Therefore, no specific AEs were selected. This resulted in no hint of greater or lesser harm from dupilumab as add-on therapy with INCS in comparison with a treatment with topical corticosteroids; greater or lesser harm is therefore not proven.

Conclusion on side effect-related outcomes

If the respective patients with events that can also be assigned to the symptoms are subtracted from the total rates of SAEs and AEs resulting in treatment discontinuation, increased rates of SAEs and AEs resulting in treatment discontinuation are still not shown for dupilumab as add-on therapy with INCS compared to treatment with topical corticosteroids.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

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

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

The overall consideration shows positive effects only for dupilumab + mometasone furoate versus placebo + mometasone furoate. These positive effects comprise a proof of considerable added benefit in the total score of the 22-Item Sino-Nasal Outcome Test (SNOT-22) as well as proof of a non-quantifiable added benefit for each of the outcomes "loss of smell", "VAS rhinosinusitis", "nasal congestion/obstruction", "rhinorrhoea (anterior/posterior)" and "health status", recorded using the EQ-5D VAS. In the present situation, greater harm from dupilumab in comparison with the comparator therapy can be ruled out.

In summary, there is proof of a non-quantifiable, at least considerable added benefit of dupilumab as add-on therapy with INCS compared to the ACT for adult patients with severe CRSwNP that cannot be adequately controlled with SCS and/or surgery.

The 52-week data of the SINUS-52 study presented as supplementary information show similar results for all used outcomes and confirm the results of the meta-analysis of the studies SINUS-24 and SINUS-52 at week 24.

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

Table 3: Dupilumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with CRSwNP which cannot be adequately controlled with SCS and/or surgery[b, c]	Treatment with topical corticosteroids (budesonide or mometasone furoate)[c, d]	Proof of added benefit, extent: non-quantifiable, at least considerable

a. Presentation of the ACT specified by the G-BA. The G-BA's ACT refers to the planned therapeutic indication of dupilumab at the time of the consultation: adult patients with severe CRSwNP in whom previous therapies with SCS and/or surgery failed or in whom such treatment is unsuitable due to intolerance or contraindication.
b. It is assumed that the deviation of the designation of the final therapeutic indication from the therapeutic indication planned at the time of the consultation neither challenges the research question of the present assessment nor the ACT. The benefit assessment refers to the approved therapeutic indication.
c. The G-BA specified that patients in both study arms should receive maintenance treatment with topical corticosteroids as well as further supportive measures (e.g. nasal rinsing) and an adequate, approval-compliant treatment of complications. It is also assumed that invasive treatment options are currently not indicated for patients for whom treatment with dupilumab is suitable.
d. According to the G-BA for patients for whom drug treatment is an option.

ACT: appropriate comparator therapy; CRSwNP: chronic rhinosinusitis with nasal polyposis; G-BA: Federal Joint Committee; SCS: systemic corticosteroid

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

2.2 Research question

Aim of the present report is the assessment of the added benefit of dupilumab as add-on therapy with INCS in comparison with the ACT in adult patients with severe CRSwNP which cannot be adequately controlled with SCS and/or surgery.

The specification of the ACT by the G-BA resulted in the research question presented in Table 4 for the present benefit assessment.

Table 4: Research question on the benefit assessment of dupilumab

Therapeutic indication	**ACT**[a]
Adult patients with severe Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP) which cannot be adequately controlled with systemic corticosteroids (SCS) and/or surgery[b, c]	Treatment with topical corticosteroids (budesonide or mometasone furoate)[c, d]
a. Presentation of the ACT specified by the G-BA. The G-BA's ACT refers to the planned therapeutic indication of dupilumab at the time of the consultation: adult patients with severe CRSwNP in whom previous therapies with SCS and/or surgery failed or in whom such treatment is unsuitable due to intolerance or contraindication. b. It is assumed that the deviation of the designation of the final therapeutic indication from the therapeutic indication planned at the time of the consultation neither challenges the research question of the present assessment nor the ACT. The benefit assessment refers to the approved therapeutic indication. c. The G-BA specified that patients in both study arms should receive maintenance treatment with topical corticosteroids as well as further supportive measures (e.g. nasal rinsing) and an adequate, approval-compliant treatment of complications. It is also assumed that invasive treatment options are currently not indicated for patients for whom treatment with dupilumab is suitable. d. According to the G-BA for patients for whom drug treatment is an option. ACT: appropriate comparator therapy; CRSwNP: chronic rhinosinusitis with nasal polyposis; G-BA: Federal Joint Committee; SCS: systemic corticosteroid	

The company followed the G-BA's specification and cited treatment with topical corticosteroids (budesonide or mometasone furoate) as ACT.

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

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on dupilumab (status: 1 October 2019)
- bibliographical literature search on dupilumab (last search on 23 September 2019)
- search in trial registries for studies on dupilumab (last search on 23 September 2019)

To check the completeness of the study pool:

- search in trial registries for studies on dupilumab (last search on 3 September 2019)

No additional relevant study was identified from the check.

2.3.1 Studies included

The studies listed in the following Table 5 were included in the benefit assessment.

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

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	**Sponsored study[a] (yes/no)**	**Third-party study (yes/no)**
SINUS-24[b] (EFC14146)	Yes	Yes	No
SINUS-52[b] (EFC14280)	Yes	Yes	No

a. Study for which the company was sponsor.
b. In the following tables, the study is referred to with this abbreviated form.
RCT: randomized controlled trial; vs.: versus

The study pool for the benefit assessment of dupilumab in comparison with the ACT comprises the RCTs SINUS-24 and SINUS-52 and concurs with that of the company.

Section 2.6 contains a reference list for the studies included.

2.3.2 Study characteristics

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

Table 6: Characteristics of the studies included – RCT, direct comparison: dupilumab + mometasone furoate vs. placebo + mometasone furoate (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
SINUS-24	RCT, double-blind	Adult patients (≥ 18 years) with bilateral nasal polyps and persistent rhinosinusitis symptoms despite treatment with SCS within the past 2 years and/or contraindication/intolerance to SCS and/or at least one prior sino-nasal surgery	▪ Dupilumab Q2W + mometasone furoate (N = 143) ▪ placebo + mometasone furoate (N = 133)	▪ Run-in: ▪ 4 weeks ▪ treatment: ▪ 24 weeks ▪ follow-up observation: ▪ 24 weeks	67 study centres in: Bulgaria, Czech Republic, France, Germany, Hungary, Italy, Netherlands, Poland, Romania, Russia, Ukraine, United Kingdom, USA 12/2016–07/2018[b]	Primary: ▪ Changes NC and NPS each at week 24 Secondary: ▪ Mortality ▪ Morbidity ▪ AEs
SINUS-52	RCT, double-blind	Adult patients (≥ 18 years) with bilateral nasal polyps and persistent rhinosinusitis symptoms despite treatment with SCS within the past 2 years and/or one contraindication/intolerance to SCS and/or at least one prior sino-nasal surgery	▪ Arm A: dupilumab Q2W + mometasone furoate until week 52 (N = 150) ▪ arm B: dupilumab Q2W + mometasone furoate until week 24, then dupilumab Q4W[c] + mometasone furoate until week 52 (N = 145) ▪ arm C: placebo + mometasone furoate (N = 153)	▪ Run-in: ▪ 4 weeks ▪ treatment: ▪ 52 weeks ▪ follow-up observation: ▪ 12 weeks	117 study centres in: Argentina, Australia, Belgium, Canada, Chile, Israel, Japan, Mexico, Portugal, Russia, Sweden, Spain, Turkey, USA 11/2016–11/2018[d]	Primary: ▪ Changes NC and NPS each at week 24 Secondary: ▪ Mortality ▪ Morbidity ▪ AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. According to the company, last patient with last treatment; information on the date of study end are not available.
c. To maintain blinding, dupilumab was administered alternately with placebo Q2W after week 24. Administration of dupilumab Q4W does not correspond to the approval [3].
d. Designated as “end of the study” in the addendum to the study report; according to the information provided by the company in Module 4 D, the last patient received the last treatment on 29 August 2018.

AE: adverse event; N: number of randomized patients; NC: nasal congestion/obstruction; NPS: nasal polyp score; Q2W: once every 2 weeks; Q4W: once every 4 weeks; RCT: randomized controlled study; SCS: systemic corticosteroid; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: dupilumab + mometasone furoate vs. placebo + mometasone furoate (multipage table)

Study	Intervention	Comparison
SINUS-24	Week −4 to 0: maintenance treatment with intranasal mometasone furoate[a]	Week −4 to 0: maintenance treatment with intranasal mometasone furoate[a]
	week 0–24: dupilumab 300 mg SC Q2W	week 0–24: placebo SC Q2W
	+ continuation of the maintenance treatment with intranasal mometasone furoate at stable doses[b]	
	Concomitant treatment ▪ <u>Emergency treatment</u>: during the randomized treatment phase and the follow-up observation, the following treatment was allowed at the investigator's discretion if endoscopic/radiological indications and clinical symptoms worsened: ▫ nasal rinsing with saline solution and/or systemic antibiotics (up to 2 weeks in case of acute infections)[c] ▫ short-term treatment (≤ 2 weeks) with SCS (prednisone or prednisolone)[c] ▫ sino-nasal surgery for the treatment of nasal polyps (NP)[d] ▪ <u>further concomitant treatment besides the maintenance and emergency treatments</u>: ▫ oral corticosteroids (for the short-term treatment of e.g. asthma exacerbation) and inhaled corticosteroids ▫ nasal rinsing with saline solution (initiation from V2 was assigned to emergency treatment[e]) ▫ antibiotics (< 2 weeks), short-acting and long-acting beta agonists (LABA), long-acting muscarinic receptor antagonists (LAMA) and systemic antihistamines ▫ methylxanthine (e.g.: theophylline, aminophylline) ▫ decongestives (e.g.: oxymetazoline hydrochloride) as well as anaesthetics (e.g.: lidocaine) in topical form before endoscopic examination **Prohibited prior and concomitant treatment** ▪ biological therapies/systemic immunosuppressants within 2 months before V1 or within 5 half-lives (whichever is longer) ▪ investigational monoclonal antibodies within 5 half-lives or, if unknown, within 6 months before V1 ▪ anti-immunoglobulin E(IgE) therapy (omalizumab) within 130 days before V1 ▪ mepolizumab, reslizumab[e] ▪ leukotriene antagonists/modifiers at the time of V1, except for continuation of ongoing treatment (≥ 30 days before V1) ▪ initiation of an allergen immunotherapy within 3 months before V1 or a dose change of an ongoing allergen immunotherapy within the run-in or the randomized treatment phase ▪ intranasal and/or sinus surgery (including polypectomy) within 6 months prior to V1; sino-nasal or sinus surgery that altered the structure of the lateral wall and thus prevented recording of the nasal polyp score (NPS) ▪ intranasal corticosteroid droplets within the run-in phase or the randomized treatment phase ▪ systemic steroids (> 2 weeks) within the run-in phase or the randomized treatment phase	

Table 7: Characteristics of the intervention – RCT, direct comparison: dupilumab + mometasone furoate vs. placebo + mometasone furoate (multipage table)

Study	Intervention		Comparison
SINUS-52	Arm A: week −4 to 0: maintenance treatment with intranasal mometasone furoate[a] week 0–52: dupilumab 300 mg SC Q2W	Arm B: week −4 to 0: maintenance treatment with intranasal mometasone furoate[a] week 0–24: dupilumab 300 mg SC Q2W week 24–52: dupilumab 300 mg SC Q4W[f]	Arm C: week −4 to 0: maintenance treatment with intranasal mometasone furoate[a] week 0–52: placebo SC Q2W
	+ continuation of the maintenance treatment with intranasal mometasone furoate at stable doses[b]		
	Prior and concomitant treatment ▪ see information on SINUS-24[g]		

a. 2 shots of 50 µg into each nostril twice daily; corresponds to a daily dose of 400 µg; a lower daily dose of 200 µg mometasone furoate was allowed if patients did not tolerate this daily dose.
b. During the treatment phase, patients further received the mometasone furoate dose determined in the run-in phase from V2, unless adverse events required a dose adjustment. After the treatment phase, maintenance treatment with mometasone furoate could be continued at the stable dose determined during the treatment phase until the end of the study, or the treatment could be switched at the investigator's discretion.
c. Patients who received emergency treatment other than sino-nasal surgery should continue the study medication unless the investigator decided that the study medication should be discontinued. Before a patient started treatment with SCS, she/he was examined (including endoscopy and PRO recording) in the study centre. According to Amendment 1 of the respective study protocols (17 May 2017), only oral corticosteroids were intended for emergency treatment with SCS.
d. According to the study protocols, 8-week treatment with the study medication is recommended before sino-nasal surgery. Patients who underwent sino-nasal surgery during the study received no further study medication after surgery (maintenance therapy with mometasone furoate was continued). This should be followed by the examinations planned for the end of treatment and other examinations specified in the protocol.
e. According to Amendment 1 of the respective study protocols (17 May 2017).
f. To maintain blinding, dupilumab was administered alternately with placebo Q2W after week 24. Dosage of dupilumab 300 mg Q4W does not correspond to the approval [3].
g. Deviating from the SINUS-24 study, the SINUS-52 study defined the requirement for emergency treatment as a worsening of signs and/or symptoms at the investigator's discretion.

NP: nasal polyps; NPS: nasal polyp score; PRO: patient-reported outcome; Q2W: once every 2 weeks; Q4W: once every 4 weeks; RCT: randomized controlled trial; SC: subcutaneous; SCS: systemic corticosteroid; V1: study visit 1 (start of run-in phase); V2: study visit 2 (start of randomized treatment phase); vs.: versus

Study design

The studies SINUS-24 and SINUS-52 have a similar study design and are therefore, if possible, hereinafter described jointly.

The studies SINUS-24 and SINUS-52 are randomized, double-blind phase 3 studies on the comparison of dupilumab versus placebo each in addition to maintenance treatment with intranasal mometasone furoate. Both studies included adult patients with bilateral nasal polyposis who despite treatment with SCS within the past 2 years and/or contraindication/ intolerance to SCS and/or at least one prior sino-nasal surgery had a nasal polyp score of ≥ 5

and < 8 as well as at least two persistent symptoms of chronic rhinosinusitis since ≥ 8 weeks before the run-in-phase.

Prior to randomisation, both studies had a 4-week run-in phase in which the suitability of the patients for inclusion in the study was assessed and maintenance treatment was started with 400 µg intranasal mometasone furoate daily (2 shots of 50 µg each per nasal opening twice daily). This does not correspond to the initial daily dose of 200 µg according to the Summary of Product Characteristics (SPC), but to a dose which, in case of inadequate symptom control, can only be administered in the later course of treatment [4]. However, this treatment regimen is considered adequate for the majority of patients and has no impact on the present assessment (see Section 2.7.4.1). Depending on the tolerance, dose reduction of mometasone furoate to one daily administration (a total of 200 µg) was possible.

Following the run-in phase, only those patients could be randomly assigned to the treatment arms who, in addition to meeting the inclusion criteria, had at least 2 symptoms for a total of at least 12 weeks (at least 8 weeks before and 4 weeks during the run-in phase) (including mandatory nasal congestion/obstruction with moderate or severe severity and, for instance, loss of smell or anterior/posterior rhinorrhoea). During the treatment phase, administration of intranasal mometasone furoate at stable doses was continued in both studies in all study arms. In addition to the study medication to be investigated and the maintenance therapy with intranasal mometasone furoate, emergency treatment was allowed in case of worsening of (endoscopic/radiological) signs and (SINUS-24, SINUS-52) /or (SINUS-52) symptoms. Nasal rinsing with saline solution, systemic antibiotics, short-term treatment with SCS and sino-nasal surgery were offered for the treatment of nasal polyps. If patients underwent sino-nasal surgery as part of their emergency treatment, they received no further study medication (dupilumab or placebo).

Stratification in both studies was based on the presence of asthma and/or analgesic intolerance syndrome (nonsteroidal anti-inflammatory drug [NSAID]-exacerbated respiratory disease [ERD]) (yes, no), past sino-nasal surgery (yes, no) and country (SINUS-24: Eastern Europe, Western countries or SINUS-52: Asia, Latin America, Eastern Europe, Western countries).

The treatment phase was followed by a follow-up observation phase (SINUS-24: 24 weeks; SINUS-52: 12 weeks), during which the treatment with intranasal mometasone furoate could be continued at stable doses or treatment could be switched at the investigator's discretion. The study documents provide no information on the subsequent therapies.

In the SINUS-24 study, a total of 276 patients were randomly assigned (1:1) to 24-week treatment with 300 mg dupilumab every 2 weeks (N = 143) or with placebo (N = 133). In the SINUS-52 study, a total of 448 patients were randomly assigned to the treatment arms (1:1:1). Patients received either 300 mg dupilumab every 2 weeks for 52 weeks (N = 150) or 300 mg dupilumab every 2 weeks for 24 weeks and subsequently 300 mg dupilumab every 4 weeks

until week 52 (N = 145) or placebo for 52 weeks (N = 153). Administration of 300 mg dupilumab every 2 weeks corresponds to the approval [3].

Primary outcomes in both studies were changes in the nasal congestion/obstruction and the nasal polyp score each at week 24. Further patient-relevant outcomes were all-cause mortality as well as outcomes of the outcome category "morbidity" and "side effects".

Selection of the applicable treatment period and the relevant treatment arms for conducting the meta-analysis

The company submitted the two relevant RCTs SINUS-24 and SINUS-52 for the present benefit assessment. Both studies were planned and conducted almost identically, and the primary and other patient-relevant outcomes were also defined identically. Moreover, the same emergency treatment was offered in both studies.

The studies differ chiefly in the maximum treatment duration (SINUS-24: 24 weeks; SINUS-52: 52 weeks). In the SINUS-52 study, analyses at week 24 were planned a priori in addition to analyses at the end of treatment. Due to the similarity of the studies, all treatment arms of both studies at week 24 were considered for a meta-analysis for the present benefit assessment. These are the following arms or patient numbers:

- Intervention: dupilumab 300 mg once every 2 weeks + mometasone furoate
  - SINUS-24: N = 143
  - SINUS-52, arm A: N = 150
  - SINUS-52, arm B: N = 145
- Comparison: placebo + mometasone furoate
  - SINUS-24: N = 133
  - SINUS-52: N = 153

Results of the study SINUS-52 at week 52 on the comparison of dupilumab + mometasone furoate administered in compliance with the approval (arm A) versus placebo + mometasone furoate illustrate long-term symptom changes and are presented in Appendix A of the full dossier assessment.

Imputation strategy applied in the benefit assessment

The results presented in Module 4 D of the dossier are based on an imputation strategy that was defined in the study report as sensitivity analysis planned a priori for the prespecified primary imputation strategy on the primary outcomes. Concurring with the company, these data were used for the benefit assessment (see Section 2.7.4.3.1 of the full dossier assessment).

Patient characteristics

Table 8 shows the characteristics of the patients in the studies included.

Table 8: Characteristics of the study populations – RCT, direct comparison: dupilumab + mometasone furoate vs. placebo + mometasone furoate (multipage table)

Study Characteristics Category	SINUS-24		SINUS-52		
	Dupilumab Q2W + mometasone furoate	Placebo + mometasone furoate	Dupilumab Q2W + mometasone furoate	Dupilumab Q2W/Q4W + mometasone furoate	Placebo + mometasone furoate
	N[a] = 143	N[a] = 133	N[a] = 150	N[a] = 145	N[a] = 153
Age [years], mean (SD)	50 (14)	51 (13)	52 (12)	52 (13)	52 (13)
Sex [F/M], %	38/62	47/53	35/65	40/60	38/72
Region, n (%)					
North America	18 (12.6)	16 (12.0)	30 (20.0)	30 (20.7)	29 (19.0)
European Union	92 (64.3)	85 (63.9)	28 (18.7)	29 (20.0)	30 (19.6)
Rest of the world	33 (23.1)	32 (24.1)	92 (61.3)	86 (59.3)	94 (61.4)
Family origin, n (%)					
White	138 (96.5)	126 (94.7)	124 (82.7)	120 (82.8)	128 (83.7)
Black	2 (1.4)	7 (5.3)	2 (1.3)	2 (1.4)	3 (2.0)
Asian	1 (0.7)	0 (0)	17 (11.3)	19 (13.1)	18 (11.8)
Other[b]	1 (0.7)	0 (0)	7 (4.7)	4 (2.8)[c]	4 (2.6)[c]
Unknown	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)
Time since first diagnosis of NP [years], mean (SD)	11.4 (9.7)	10.8 (8.6)	11.3 (10.4)	10.7 (9.1)	10.9 (9.4)
sino-nasal surgery and/or SCS therapy within the past 2 years, n (%)	141 (98.6)	130 (97.7)	146 (97.3)	140 (96.6)	148 (96.7)
At least one prior sino-nasal surgery due to NP, n (%)	99 (69.2)	99 (74.4)	88 (58.7)	85 (58.6)	88 (57.5)
SCS therapy within the past 2 years, n (%)	92 (64.3)	87 (65.4)	121 (80.7)	116 (80.0)	122 (79.7)
At least 2 rhinosinusitis symptoms[d] 8 week before screening n (%)	141 (98.6)	133 (100)	146 (97.3)	144 (99.3)	151 (98.7)
Asthma and/or NSAID-ERD at baseline, n (%)	83 (58.0)	79 (59.4)	88 (58.7)	89 (61.4)	92 (60.1)
Nasal congestion/obstruction, score at baseline (0–3), median [Q1; Q3]	2.0 [2.0; 3.0]	2.6 [2.0; 3.0]	2.9 [2.0; 3.0]	2.6 [2.0; 3.0]	2.3 [2.0; 3.0]
Loss of smell, score at baseline (0–3), median [Q1; Q3]	3.0 [2.6; 3.0]	3.0 [2.5; 3.0]	3.0 [3.0; 3.0]	3.0 [2.9; 3.0]	3.0 [2.7; 3.0]
Rhinorrhoea (anterior/posterior), score at baseline (0–3), median [Q1; Q3]	2.0 [1.4; 2.1]	2.0 [1.8; 2.7]	2.0 [1.6; 2.6]	2.1 [1.8; 2.7]	2.0 [1.4; 2.5]
VAS rhinosinusitis at baseline, median [Q1; Q3]	7.6 [6.6; 9.0]	8.4 [6.8; 9.8]	8.8 [7.3; 9.7]	8.1 [6.8; 9.7]	8.7 [7.0; 9.7]

Table 8: Characteristics of the study populations – RCT, direct comparison: dupilumab + mometasone furoate vs. placebo + mometasone furoate (multipage table)

Study Characteristics Category	SINUS-24		SINUS-52		
	Dupilumab Q2W + mometasone furoate	Placebo + mometasone furoate	Dupilumab Q2W + mometasone furoate	Dupilumab Q2W/Q4W + mometasone furoate	Placebo + mometasone furoate
	N[a] = 143	N[a] = 133	N[a] = 150	N[a] = 145	N[a] = 153
Treatment discontinuation, n (%)				Until week 24:	
	5 (3.5)	7 (5.3)	7 (4.7[c])	3 (2.1[c])	19 (12.4)
				Until week 52:	
			13 (8.7[c])	5 (3.4[c])	31 (20.3[c])
Study discontinuation, n (%)				Until week 24:	
	1 (0.7)	3 (2.3)	3 (2[c])	1 (0.7[c])	5 (3.3)
				Until week 52:	
			4 (2.7[c])	3 (2.1[c])	14 (9.2[c])[e]

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Native Americans and Alaskans, Hawaiians and other Pacific Islanders, multiple family origin.
c. Institute's calculation.
d. For randomization, there had to be two persistent symptoms of the following four symptoms: nasal congestion (NC), deterioration/loss of smell, anterior rhinorrhea and posterior rhinorrhea.
e. A patient in the placebo group discontinued the study on day 362 and thus before week 52; no reason for the early discontinuation of the study was given for this patient.

F: female; M: male; n: number of patients in the category; N: number of randomized patients; NC: nasal congestion/obstruction; NP: nasal polyps; NSAID-ERD: analgesic intolerance syndrome; Q1: first quartile; Q2W: once every 2 weeks; Q3: third quartile; Q4W: once every 4 weeks; RCT: randomized controlled trial; SCS: systemic corticosteroid; SD: standard deviation; VAS: visual analogue scale; vs.: versus

The patient characteristics are sufficiently similar both between the treatment groups of the individual studies and between the studies. The mean age of the patients was approx. 50 years, and most of them were male.

Nearly all patients received at least one sino-nasal surgery and/or treatment with SCS during the two years preceding the study and had at least two moderate to severe rhinosinusitis symptoms that had been persisting for 12 weeks at the time of randomization. About 60% of the included patients were characterized by comorbidity with asthma and/or NSAID-ERD. In both studies, only few patients discontinued treatment or the study.

However, differences between the two studies are shown for the characteristic "family origin" and "region". SINUS-24 only included one patient with Asian family origin (intervention arm: 0.7%), in the SINUS-52 study, the proportions of patients with Asian family origin was approx. 11 to 13%. The majority of the patients from the European Union were included in the SINUS-24 study, whereas SINUS-52 included more patients from the countries that were assigned to

"rest of the world". The imbalance in these characteristics does not call into question the similarity of the patient populations.

Assessment of the severity of the disease of the patients included in the studies

According to the approval, dupilumab is indicated for patients with severe CRSwNP [3]. The various guidelines provide no or no uniform definition of the severities of the disease [5-8]. For instance, the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) and the guideline of the British Society of Allergy and Clinical Immunology (BSACI) use a VAS to differentiate the severity of the disease, but with different threshold values and categories (VAS > 7: severe disease [7]; VAS > 4: moderate to severe disease [8]). The German S2k guideline on rhinosinusitis includes no classification of the severity of the disease Deutsche Gesellschaft für Hals-Nasen-Ohren-Heilkunde, 2017 #40}. Thus, generally applicable criteria suitable to assess the severity of the chronic rhinosinusitis cannot be identified. In Module 3 D, the company also states that there is currently no uniform classification of the severity of the CRSwNP.

The inclusion criteria of the studies SINUS-24 and SINUS-52 comprised no explicit definition of the severity. However, it can be assumed that the study populations are suitable to answer the present research question. This is explained below:

In the studies SINUS-24 and SINUS-52, almost all patients included (> 96%) had received prior treatment with SCS and/or sino-nasal surgery. According to the S2k guideline, administration of SCS can only be considered in individual cases. Moreover, sino-nasal surgery is only indicated in chronic rhinosinusitis if the symptoms have not improved after sufficient drug therapy [9]. EPOS lists both oral corticosteroids and surgery as treatment alternatives exclusively in patients with severe CRSwNP, whereby surgery should only be performed if the other treatment options have not improved the symptoms [7].

Although the patients included in the studies had received prior therapy in compliance with the guidelines (first, INCS before the start of the study in > 80% of the patients; second, SCS and/or sino-nasal surgery in > 96% of the patients), they showed different symptoms. According to the S2k guideline, typical symptoms include e.g. nasal breathing obstruction, anterior and/or posterior secretion and smell disorder. The patient characteristics at baseline, for instance, show that approx. 75% of the patients included in the studies showed severe loss of smell or a VAS rhinosinusitis > 7 (see also Section 2.5.1). Another aspect that characterizes a severe disease is comorbidity with other type 2 inflammatory diseases and/or hypersensitivity to analgesics. About 60% of the patients in the included studies had asthma and/or NSAID-ERD besides their chronic rhinosinusitis (Table 8). The company presented no information on how many patients had severe symptoms. However, based on the described aspects it is assumed that this proportion was low.

Considering the prior therapies, the existing symptoms and the high proportion of comorbid patients, it is assumed that the study populations of SINUS-24 and SINUS-52 were suitable for answering the research question of the present benefit assessment.

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: dupilumab + mometasone furoate vs. placebo + mometasone furoate

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
SINUS-24	Yes	Yes	Yes	Yes	Yes	Yes	Low
SINUS-52	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias across outcomes was rated as low both for the SINUS-24 study and for the SINUS-52 study. This concurs with the company's assessment.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.4.3.2 of the full dossier assessment):

- Mortality
  - All-cause mortality
- Morbidity
  - 22-Item Sino-Nasal Outcome Test (SNOT-22; total score)
  - Nasal congestion/obstruction
  - Rhinorrhoea (anterior/posterior)
  - VAS rhinosinusitis
  - health status (EQ-5D VAS)
- Health-related quality of life

- Side effects
  - SAEs
  - Discontinuation due to AEs
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 D) (see Section 2.7.4.3 of the full dossier assessment).

Table 10 shows for which outcomes data were available in the studies included.

Table 10: Matrix of the outcomes – RCT, direct comparison: dupilumab + mometasone furoate vs. placebo + mometasone furoate

Study	Outcomes									
	All-cause mortality	SNOT-22 (total score)	Nasal congestion/obstruction	Loss of smell	Rhinorrhoea (anterior/posterior)	VAS rhinosinusitis	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Discontinuation due to AEs
SINUS-24	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[a]	No[b]	No[b]
SINUS-52	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[a]	No[b]	No[b]

a. Outcomes of this category were not recorded.
b. No usable data available; for reasons see Section 2.4.3 as well as Section 2.7.4.3.2 of the full dossier assessment.

AE: adverse event; EQ-5D: European Quality of Life-5 Dimensions; RCT: randomized controlled trial; SAE: serious adverse event; SNOT-22: 22-Item Sino-Nasal Outcome Test; VAS: visual analogue scale; vs.: versus

2.4.2 Risk of bias

Table 11 describes the risk of bias for the results of the relevant outcomes.

Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: dupilumab + mometasone furoate vs. placebo + mometasone furoate

Study	Study level	Outcomes									
		All-cause mortality	SNOT-22 (total score)	Nasal congestion/obstruction	Loss of smell	Rhinorrhoea (anterior/posterior)	VAS rhinosinusitis	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Discontinuation due to AEs
SINUS-24	L	L	L	L	L	L	L	L	–[a]	–[b]	–[b]
SINUS-52	L	L	L	L	L	L	L	L	–[a]	–[b]	–[b]

a. Outcomes of this category were not recorded.
b. No usable data available; for reasons see Section 2.4.3 as well as Section 2.7.4.3.2 of the full dossier assessment.

AE: adverse event; EQ-5D: European Quality of Life-5 Dimensions; L: low; RCT: randomized controlled trial; SNOT-22: 22-Item Sino-Nasal Outcome Test; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

The outcome-specific risk of bias for each of the results of the outcomes in the outcome categories “mortality” and “morbidity” was rated as low. This concurs with the company’s assessment.

Outcomes of the outcome category “health-related quality of life” were not recorded in the studies SINUS-24 and SINUS-52. The data on SAEs, discontinuation due to AEs presented by the company were not usable (see Section 2.4.3 as well as Section 2.7.4.3.2 of the full dossier assessment). Therefore, the risk of bias was not assessed for these outcomes.

2.4.3 Results

Table 12 and Table 13 summarize the results of the meta-analysis of the 24-week data on the comparison of dupilumab + mometasone furoate with placebo + mometasone furoate in patients with severe CRSwNP that cannot be adequately controlled with SCS and/or surgery. Appendix A of the full dossier assessment presents the results of the 52-week data from the SINUS-52 study as supplementary information. Appendix B of the full dossier assessment shows the results on common AEs, SAEs and AEs that resulted in treatment discontinuation (SINUS-24: 24-week data; SINUS-52: 52-week data) The common SAEs from the SINUS-52 study are not listed, because there were no events at System Organ Class (SOC)/Preferred Term (PT) level that met the criteria for presentation (see explanation in Appendix B of the full

dossier assessment). Complete data on the common AEs at SOC/PT level at week 24 from the SINUS-52 study were not provided in the dossier.

Table 12: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous data) – RCT, direct comparison: dupilumab + mometasone furoate vs. placebo + mometasone furoate (24-week data) (multipage table)

Outcome category Outcome Study	Dupilumab Q2W + mometasone furoate[a]		Placebo + mometasone furoate		Dupilumab Q2W + mometasone furoate vs. placebo + mometasone furoate
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[b]
Mortality					
All-cause mortality					
SINUS-24	143	0 (0)	132	0 (0)	–
SINUS-52	297	0 (0)	150	0 (0)	–
Morbidity					
SNOT-22 total score (improvement ≥ 8.9 points)[c]					
SINUS-24	143	116 (81.1)	133	71 (53.4)	1.53 [1.28; 1.82]; < 0.001
SINUS-52	295	233 (79.0)	153	82 (53.6)	1.48 [1.26; 1.73]; < 0.001
Total					1.50 [1.33; 1.69]; < 0.001
Health-related quality of life	Outcomes of this category were not recorded				
Side effects					
AEs (supplementary information)					
SINUS-24	143	93 (65.0)	132	93 (70.5)	–
SINUS-52	297	221 (74.4)	150	122 (81.3)	–
SAEs					
SINUS-24	Not usable[d]				
SINUS-52					
Discontinuation due to AEs					
SINUS-24	Not usable[d]				
SINUS-52					

a. The treatment groups with dupilumab + mometasone furoate were pooled (arm A + B) for the analysis of the SINUS-52 study at week 24.
b. RR, 95% CI as well as the p-value from a generalized linear model with treatment arm, asthma/NSAID-ERD status, surgical history and region as covariables; study and study x treatment arm are additional covariates for the meta-analysis. Missing values after emergency surgery were imputed using WOCF.
c. Suitable data on single scores are not available for responder analyses. The MID of 8.9 points is only applicable and validated for the total score. The single scores are recorded on a scale from 0 to 5.
d. Data are not usable, as they contain a large proportion of patients with events that can be both side effects and symptoms of the disease.

AE: adverse event; CI: confidence interval; MID: minimally important difference; n: Number of patients with (at least one) event; N: Number of analysed patients; NSAID-ERD: analgesic intolerance syndrome; Q2W: once every 2 weeks; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SNOT-22: 22-Item Sino-Nasal Outcome Test, WOCF: worst observation carried forward; vs.: versus

Table 13: Results (morbidity, steady data) – RCT, direct comparison: dupilumab + mometasone furoate vs. placebo + mometasone furoate (24-week data) (multipage table)

Outcome category Outcome Study	Dupilumab Q2W + mometasone furoate[a]			Placebo + mometasone furoate			Dupilumab Q2W + mometasone furoate vs. placebo + mometasone furoate
	N[b]	Values at baseline mean (SD)	Change at end of study mean (SE)	N[b]	Values at baseline mean (SD)	Change at end of study mean (SE)	MD [95% CI]; p-value[c]
Morbidity							
Nasal congestion/obstruction[d]							
SINUS-24	140	2.26 (0.57)	−1.38 (0.07)	128	2.45 (0.55)	−0.56 (0.07)	−0.82 [−1.00; −0.65]; < 0.001
SINUS-52	289	2.46 (0.61)	−1.28 (0.06)	144	2.38 (0.54)	−0.48 (0.07)	−0.80 [−0.95; −0.64]; < 0.001
Total							−0.81 [−0.93; −0.70]; < 0.001 Hedges' g: −1.05 [−1.20; −0.90]
Loss of smell[d]							
SINUS-24	140	2.70 (0.57)	−1.44 (0.07)	128	2.73 (0.51)	−0.37 (0.08)	−1.07 [−1.26; −0.88]; < 0.001
SINUS-52	289	2.77 (0.53)	−1.24 (0.06)	144	2.72 (0.52)	−0.27 (0.08)	−0.98 [−1.15; −0.81]; < 0.001
Total							−1.02 [−1.15; −0.89]; < 0.001 Hedges' g: −1.20 [−1.35; −1.05]
Rhinorrhoea (anterior/posterior)[d]							
SINUS-24	140	1.87 (0.62)	−1.07 (0.06)	126	2.10 (0.67)	−0.49 (0.06)	−0.58 [−0.74; −0.42]; < 0.001
SINUS-52	289	2.07 (0.74)	−1.03 (0.05)	141	1.98 (0.72)	−0.49 (0.07)	−0.54 [−0.69; −0.39]; < 0.001
Total							−0.57 [−0.67; −0.46]; < 0.001 Hedges' g: −0.80 [−0.95; −0.65]
VAS rhinosinusitis[d]							
SINUS-24	134	7.42 (2.01)	−4.67 (0.23)	123	7.96 (2.06)	−1.59 (0.24)	−3.08 [−3.68; −2.47]; < 0.001
SINUS-52	277	8.01 (2.01)	−4.43 (0.18)	139	7.98 (2.22)	−1.88 (0.24)	−2.55 [−3.07; −2.03]; < 0.001
Total							−2.78 [−3.18; −2.39]; < 0.001 Hedges' g: −1.10 [−1.25; −0.94]

Table 13: Results (morbidity, steady data) – RCT, direct comparison: dupilumab + mometasone furoate vs. placebo + mometasone furoate (24-week data) (multipage table)

Outcome category Outcome Study	Dupilumab Q2W + mometasone furoate[a]			Placebo + mometasone furoate			Dupilumab Q2W + mometasone furoate vs. placebo + mometasone furoate
	N[b]	Values at baseline mean (SD)	Change at end of study mean (SE)	N[b]	Values at baseline mean (SD)	Change at end of study mean (SE)	MD [95% CI]; p-value[c]
Health status (EQ-5D VAS)[e]							
SINUS-24	133	66.10 (19.39)	11.81 (1.53)	127	65.98 (21.32)	3.43 (1.60)	8.38 [4.36; 12.39]; < 0.001
SINUS-52	277	65.70 (20.72)	11.06 (1.17)	140	63.89 (19.99)	3.45 (1.51)	7.62 [4.32; 10.91]; < 0.001
Total							7.90 [5.35; 10.45]; < 0.001 Hedges' g: 0.48 [0.33; 0.64]

a. The treatment groups with dupilumab + mometasone furoate were pooled (arm A + B) for the analysis of the SINUS-52 study at week 24.
b. Number of patients considered in the analysis for the calculation of the effect estimation; the values at baseline may be based on other patient numbers.
c. MD, 95% CI as well as the p-value from an ANCOVA model for the change at baseline with treatment arm, value at baseline, asthma/NSAID-ERD status, surgical history and region as covariables; study and study x treatment arm are additional covariates for the meta-analysis. Missing values after emergency surgery were imputed using WOCF.
d. Lower (decreasing) values mean an improvement; negative effects (dupilumab Q2W + mometasone furoate) – (placebo + mometasone furoate) mean an advantage for dupilumab Q2W + mometasone furoate.
e. Higher (decreasing) values mean an improvement; positive effects (dupilumab Q2W + mometasone furoate) – (placebo + mometasone furoate) mean an advantage for dupilumab Q2W + mometasone furoate.

ANCOVA: analysis of covariance; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; IPD: individual patient data; MD: mean difference; N: number of analysed patients; NSAID-ERD: analgesic intolerance syndrome; Q2W: once every 2 weeks; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale; WOCF: worst observation carried forward; vs.: versus

Based on the available data, no more than proofs, e.g. of an added benefit, can be determined for all outcomes.

Mortality

All-cause mortality

Until week 24, no deaths occurred in the studies SINUS-24 and SINUS-52. For the outcome "all-cause mortality", the meta-analysis of the studies SINUS-24 and SINUS-52 thus showed no significant difference of dupilumab + mometasone furoate versus placebo + mometasone furoate at week 24. This resulted in no hint of an added benefit of dupilumab as add-on therapy with INCS in comparison with a treatment with topical corticosteroids; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

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

For the outcome "SNOT-22", the meta-analysis of the SINUS-24 and SINUS-52 studies showed a statistically significant difference in favour of dupilumab + mometasone furoate over placebo + mometasone furoate for the proportion of patients with an improvement of the overall score by ≥ 8.9 points at week 24. This resulted in proof of added benefit of dupilumab as add-on therapy with INCS in comparison with treatment with topical corticosteroids.

This concurs with the assessment of the company, which, however, in addition to the event rates, also used analyses on the mean change to derive the added benefit (see Section 2.7.4.3.2 of the full dossier assessment) and therewith came to the same result.

Nasal congestion/obstruction

At week 24, the meta-analysis of the studies SINUS-24 and SINUS-52 showed a statistically significant difference in favour of dupilumab + mometasone furoate over placebo + mometasone furoate based on the mean change for the outcome "nasal congestion/obstruction". The 95% CI of the standardized mean difference (Hedges' g) is fully outside the irrelevance range of −0.2 to 0.2. This was interpreted to be a relevant effect. This resulted in proof of added benefit of dupilumab as add-on therapy with INCS in comparison with treatment with topical corticosteroids.

This concurs with the assessment of the company, which, however, in addition to the mean change, also used responder analyses to derive the added benefit (see Section 2.7.4.3.2 of the full dossier assessment) and therewith came to the same result.

Loss of smell

At week 24, the meta-analysis of the studies SINUS-24 and SINUS-52 showed a statistically significant difference in favour of dupilumab + mometasone furoate over placebo + mometasone furoate based on the mean change for the outcome "loss of smell". The 95% CI of the standardized mean difference (Hedges' g) is fully outside the irrelevance range of −0.2 to 0.2. This was interpreted to be a relevant effect. This resulted in proof of added benefit of dupilumab as add-on therapy with INCS in comparison with treatment with topical corticosteroids.

This concurs with the assessment of the company, which, however, in addition to the mean change, also used responder analyses to derive the added benefit (see Section 2.7.4.3.2 of the full dossier assessment) and therewith came to the same result.

Rhinorrhoea (anterior/posterior)

At week 24, the meta-analysis of the studies SINUS-24 and SINUS-52 showed a statistically significant difference in favour of dupilumab + mometasone furoate over placebo +

mometasone furoate based on the mean change for the outcome "rhinorrhoea (anterior/ posterior)". The 95% CI of the standardized mean difference (Hedges' g) is fully outside the irrelevance range of −0.2 to 0.2. This was interpreted to be a relevant effect. This resulted in proof of added benefit of dupilumab as add-on therapy with INCS in comparison with treatment with topical corticosteroids.

This concurs with the assessment of the company, which, however, in addition to the mean change, also used responder analyses to derive the added benefit (see Section 2.7.4.3.2 of the full dossier assessment) and therewith came to the same result.

VAS rhinosinusitis

At week 24, the meta-analysis of the studies SINUS-24 and SINUS-52 showed a statistically significant difference in favour of dupilumab + mometasone furoate over placebo + mometasone furoate based on the mean change for the outcome "VAS rhinosinusitis". The 95% CI of the standardized mean difference (Hedges' g) is fully outside the irrelevance range of −0.2 to 0.2. This was interpreted to be a relevant effect. This resulted in proof of added benefit of dupilumab as add-on therapy with INCS in comparison with treatment with topical corticosteroids.

This concurs with the assessment of the company, which, however, in addition to the mean change, also used responder analyses for a subset of patients of the included patients to derive the added benefit (see Section 2.7.4.3.2 of the full dossier assessment) and therewith came to the same result.

Health status (EQ-5D VAS)

At week 24, the meta-analysis of the studies SINUS-24 and SINUS-52 showed a statistically significant difference in favour of dupilumab + mometasone furoate over placebo + mometasone furoate for the outcome "health status (EQ-5D VAS)". The 95% CI of the standardized mean difference (Hedges' g) is fully outside the irrelevance range of −0.2 to 0.2. This was interpreted to be a relevant effect. This resulted in proof of added benefit of dupilumab as add-on therapy with INCS in comparison with treatment with topical corticosteroids.

This concurs with the company's assessment.

Health-related quality of life

Outcomes of the outcome category "health-related quality of life" were not recorded in the studies SINUS-24 and SINUS-52. This resulted in no hint of an added benefit of dupilumab as add-on therapy with INCS in comparison with a treatment with topical corticosteroids; an added benefit is therefore not proven.

This deviates from the company's approach, which considered individual items of the SNOT-22 for the outcome category "health-related quality of life", but did not use them to derive an added benefit of dupilumab (see Section 2.7.4.3.2 of the full dossier assessment). Altogether,

the company did not consider the outcome category "health-related quality of life" when deriving the added benefit.

Side effects

The available analyses on AEs also include events that can be ascribed to both side effects and symptoms of the disease (for the presentation of the events on common AEs see Appendix A of the full dossier assessment). As this refers to a large proportion of patients, the data on AEs cannot be used for the derivation of the added benefit. The company also did not use the outcomes for the derivation of the added benefit. It justified this with the fact that the majority of AEs are represented in morbidity outcomes (see Section 2.7.4.3.2 of the full dossier assessment).

SAEs

Usable data for the outcome "SAEs" are neither available from SINUS-24 nor from SINUS-52. This resulted in no hint of greater or lesser harm from dupilumab as add-on therapy with INCS in comparison with a treatment with topical corticosteroids; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

Usable data for the outcome "discontinuation due to AEs" are neither available from SINUS-24 nor from SINUS-52. This resulted in no hint of greater or lesser harm from dupilumab as add-on therapy with INCS in comparison with a treatment with topical corticosteroids; greater or lesser harm is therefore not proven.

Specific AEs

Deviating from all other outcomes, the selection of the specific AEs was based on the individual studies because the company provided no complete list of common AEs at SOC and PT level for the relevant period of week 24 for the SINUS-52 study. Relevant data are only available on week 52 (see Appendix B of the full dossier assessment). All specific AEs identified in the studies SINUS-24 and SINUS-52 can be assigned both to side effects and the symptoms of the disease. Therefore, no specific AEs were selected. This resulted in no hint of greater or lesser harm from dupilumab + mometasone furoate in comparison with placebo + mometasone furoate; greater or lesser harm is therefore not proven.

Basically, this concurs with the company's assessment, which, however, does not consider its selection of specific AEs for the derivation of the additional benefit, because no results with a difference ≥ 5% between treatment groups occurred.

Conclusion on side effect-related outcomes

The complete list of SAEs at SOC/PT level in the respective study reports shows that only one event per patient occurred in the majority of patients in whom SAEs occurred. For AEs that led to treatment discontinuation, also one event was usually recorded per patient. If the respective

patients with events that can also be assigned to the symptoms are subtracted from the total rates of SAEs and AEs resulting in treatment discontinuation, increased rates of SAEs and AEs resulting in treatment discontinuation are still not shown for dupilumab as add-on therapy with INCS compared to treatment with topical corticosteroids. Therefore, greater harm from dupilumab as add-on therapy with INCS can be ruled out for the outcomes "SAEs" and "discontinuations due to AEs".

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics were relevant for the present benefit assessment:

- Age (< 65 years, ≥ 65 years)
- Sex (male, female)
- Region (North America, European Union, rest of the world)
- Family origin (white, black, Asian, others)
- Treatment with SCS within the last two years before screening (yes, no)
- Sino-nasal surgery in the past (yes, no)
- VAS rhinosinusitis at baseline (≤ 7, > 7)

Interaction tests were performed if at least 10 patients per subgroup were included in the analysis. For binary data, there had to be 10 events in at least one subgroup.

Only 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 were only presented if there was a statistically significant and relevant effect in at least one subgroup.

Table 14 summarizes the subgroup results of the meta-analysis of SINUS-24 and SINUS-52 at week 24 on the comparison of dupilumab + mometasone furoate with placebo + mometasone furoate.

Table 14: Results (morbidity) – RCT, direct comparison: dupilumab + mometasone furoate vs. placebo + mometasone furoate (24-week data) (multipage table)

Outcome Characteristic Study Subgroup	Dupilumab Q2W + mometasone furoate[a]			Placebo + mometasone furoate			Dupilumab Q2W + mometasone furoate vs. placebo + mometasone furoate
	N[b]	Values at baseline mean (SD)	Change at end of study mean (SE)	N[b]	Values at baseline mean (SD)	Change at end of study mean (SE)	MD [95% CI]; p-value[c]
Loss of smell[d]							
Age							
SINUS-24							
< 65 years	118	2.71 (0.53)	−1.52 (0.08)	107	2.70 (0.54)	−0.37 (0.08)	−1.15 [−1.35; −0.95]; < 0.001
≥ 65 years	22	2.61 (0.78)	−1.17 (0.21)	21	2.85 (0.34)	−0.41 (0.22)	−0.76 [−1.30; −0.23]; 0.006
SINUS-52							
< 65 years	123	2.78 (0.51)	−1.34 (0.07)	121	2.72 (0.49)	−0.32 (0.09)	−1.02 [−1.21; −0.83]; < 0.001
≥ 65 years	56	2.70 (0.60)	−0.71 (0.16)	23	2.73 (0.67)	0.14 (0.22)	−0.85 [−1.26; −0.44]; < 0.001
Total						Interaction:	p-value = 0.043
< 65 years							−1.08 [−1.22; −0.94]; < 0.001 Hedges' g: −1.29 [−1.46; −1.13]
≥ 65 years							−0.74 [−1.06; −0.41]; < 0.001 Hedges' g: −0.87 [−1.25; −0.49]
Rhinorrhoea (anterior/posterior)[d]							
VAS rhinosinusitis at baseline							
SINUS-24							
≤ 7	51	1.66 (0.50)	−0.82 (0.08)	36	1.82 (0.51)	−0.38 (0.09)	−0.44 [−0.67; −0.22]; < 0.001
> 7	83	2.04 (0.64)	−1.20 (0.09)	88	2.22 (0.69)	−0.55 (0.08)	−0.65 [−0.86; −0.43]; < 0.001
SINUS-52							
≤ 7	66	1.73 (0.70)	−0.87 (0.09)	35	1.61 (0.57)	−0.57 (0.12)	−0.29 [−0.57; −0.02]; 0.035
> 7	218	2.18 (0.72)	−1.07 (0.06)	105	2.10 (0.72)	−0.45 (0.08)	−0.62 [−0.79; −0.45]; < 0.001

Table 14: Results (morbidity) – RCT, direct comparison: dupilumab + mometasone furoate vs. placebo + mometasone furoate (24-week data) (multipage table)

Outcome Characteristic Study Subgroup	Dupilumab Q2W + mometasone furoate[a]			Placebo + mometasone furoate			Dupilumab Q2W + mometasone furoate vs. placebo + mometasone furoate
	N[b]	Values at baseline mean (SD)	Change at end of study mean (SE)	N[b]	Values at baseline mean (SD)	Change at end of study mean (SE)	MD [95% CI]; p-value[c]
Total						Interaction:	p-value = 0.043
≤ 7							−0.36 [−0.54; −0.18]; < 0.001 Hedges' g: −0.60 [−0.90; −0.31]
> 7							−0.64 [−0.77; −0.50]; < 0.001 Hedges' g: −0.86 [−1.04; −0.68]
VAS rhinosinusitis[d]							
Age							
SINUS-24							
< 65 years	113	7.47 (1.97)	−5.01 (0.24)	103	8.08 (2.01)	−1.62 (0.25)	−3.39 [−4.03; −2.75]; < 0.001
≥ 65 years	21	7.11 (2.20)	−2.46 (0.64)	20	7.31 (2.23)	−0.78 (0.70)	−1.69 [−3.27; −0.11] 0.036
SINUS-52							
< 65 years	224	8.21 (1.73)	−4.59 (0.21)	117	8.04 (2.21)	−1.86 (0.26)	−2.73 [−3.32; −2.15] < 0.001
≥ 65 years	53	7.16 (2.76)	−3.97 (0.44)	22	7.64 (2.29)	−2.32 (0.61)	−1.64 [−2.78; −0.50]; 0.005
Total						Interaction:	p-value = 0.019
< 65 years							−3.02 [−3.46; −2.59]; < 0.001 Hedges' g: −1.19 [−1.36; −1.02]
≥ 65 years							−1.66 [−2.57; −0.74]; < 0.001 Hedges' g: −0.70 [−1.09; −0.31]

Table 14: Results (morbidity) – RCT, direct comparison: dupilumab + mometasone furoate vs. placebo + mometasone furoate (24-week data) (multipage table)

Outcome Characteristic Study Subgroup	Dupilumab Q2W + mometasone furoate[a]			Placebo + mometasone furoate			Dupilumab Q2W + mometasone furoate vs. placebo + mometasone furoate
	N[b]	Values at baseline mean (SD)	Change at end of study mean (SE)	N[b]	Values at baseline mean (SD)	Change at end of study mean (SE)	MD [95% CI]; p-value[c]
a. The treatment groups with dupilumab + mometasone furoate were pooled (arm A + B) for the analysis of the SINUS-52 study at week 24. b. Number of patients considered in the analysis for the calculation of the effect estimation; the values at baseline may be based on other patient numbers. c. MD, 95% CI as well as the p-value from an ANCOVA model for the change at baseline with treatment arm, value at baseline, asthma/NSAID-ERD status, surgical history and region as covariables; study and study x treatment arm are additional covariates for the meta-analysis. Missing values after emergency surgery were imputed using WOCF. d. Lower (decreasing) values mean an improvement; negative effects (dupilumab Q2W + mometasone furoate) – (placebo + mometasone furoate) mean an advantage for dupilumab Q2W + mometasone furoate. ANCOVA: analysis of covariance; CI: confidence interval; MD: mean difference; N: number of analysed patients; NSAID-ERD: analgesic intolerance syndrome; Q2W: once every 2 weeks; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale; WOCF: worst observation carried forward; vs.: versus							

Morbidity

Loss of smell

The meta-analysis at week 24 showed an effect modification by the characteristic "age" for the outcome "loss of smell". There is a statistically significant difference in favour of dupilumab + mometasone furoate over placebo + mometasone furoate for both patients < 65 years and patients ≥ 65 years. Thereby, the 95% CI of the standardized mean difference (Hedges' g) is completely outside the irrelevance range of −0.2 to 0.2 for both subgroups. This concurs with the result of the meta-analysis in the total population. The added benefit was therefore derived on the basis of the total population.

This approach concurs with that of the company.

Rhinorrhoea (anterior/posterior)

The meta-analysis at week 24 showed an effect modification by the characteristic "VAS rhinosinusitis at baseline" for the outcome "rhinorrhoea (anterior/posterior)". There is a statistically significant difference in favour of dupilumab + mometasone furoate over placebo + mometasone furoate for both patients with a value of < 7 and patients with a value ≥ 7. Thereby, the 95% CI of the standardized mean difference (Hedges' g) is completely outside the irrelevance range of −0.2 to 0.2 for both subgroups. This concurs with the result of the meta-analysis in the total population. The added benefit was therefore derived on the basis of the total population.

This approach concurs with that of the company.

VAS rhinosinusitis

At week 24, the meta-analysis showed an effect modification by the characteristic "age" for the outcome "VAS rhinosinusitis". There is a statistically significant difference in favour of dupilumab + mometasone furoate over placebo + mometasone furoate for both patients < 65 years and patients ≥ 65 years. Thereby, the 95% CI of the standardized mean difference (Hedges' g) is completely outside the irrelevance range of −0.2 to 0.2 for both subgroups. This concurs with the result of the meta-analysis in the total population. The added benefit was therefore derived on the basis of the total population.

This approach concurs with that of the company.

2.5 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below. taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

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

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 15).

Determination of the outcome category for the outcomes on symptoms

It cannot be inferred from the dossier for all outcomes considered in the present benefit assessment whether they were serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

As the results of the outcomes mentioned below had improved in all study arms during the course of the study, the values at baseline were relevant for the determination of the outcome category.

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

The outcome "nasal congestion/obstruction" was assigned to the outcome category "non-serious/non-severe symptoms/late complications", as more than half of the patients included in

the SINUS-24 and SINUS-52 studies had no severe symptoms at baseline (score < 3; see also Table 8).

The outcome "loss of smell" was assigned to the outcome category "serious/severe symptoms/ late complications", as about 75% of the patients included in the SINUS-24 and SINUS-52 studies had severe symptoms at baseline (score ≥ 2.5; see also Table 8).

The outcome "rhinorrhoea (anterior/posterior)" is assigned to the outcome category "non-serious/non-severe symptoms/late complications". The patients included in the studies had a median score of approx. 2 at baseline (corresponds to moderate symptoms; see also Table 8).

The outcome "VAS rhinosinusitis" was assigned to the outcome category "serious/severe symptoms/late complications", as more than 70% of the patients included in the SINUS-24 and SINUS-52 studies had a VAS > 7 at baseline. According to EPOS and Lim 2007 (among others), this cut-off value is defined for the description of a severe disease [7,10].

For the outcome "health status", determined using the EQ-5D VAS, there is no information on a threshold value for the assessment of the severity. Therefore, the outcome "health status" is assigned to the outcome category "non-serious/non-serious symptoms/late complications".

The company did not assess the severity of individual morbidity outcomes, but stated that all outcomes of the disease-specific symptoms considered by it were classified as serious. In its documents, it provided no further information on the classification of the severity. The company's assessment deviates for the outcomes "SNOT-22 total score", "nasal congestion/ obstruction", "rhinorrhoea (anterior/posterior)" and "health status (EQ-5D VAS)".

Table 15: Extent of added benefit at outcome level: dupilumab + mometasone furoate vs. placebo + mometasone furoate (24-week data) (multipage table)

Outcome category **Outcome**	**Dupilumab + mometasone furoate vs. placebo + mometasone furoate** **proportion of events (%) or MD** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0% RR: –	Lesser benefit/added benefit not proven
Morbidity		
SNOT-22 total score[c]	79.0% to 81.1% vs. 53.4% to 53.6%[d] RR: 1.50 [1.33; 1.69]; RR: 0.67 [0.59; 0.75]; p < 0.001 probability: “proof”	Outcome category “non-serious/non-severe symptoms/late complications” CI_u < 0.80 added benefit, extent: “considerable”
Nasal congestion/obstruction[e]	−1.38 to −1.28 vs. −0.56 to −0.48[d] MD: −0.81 [−0.93; −0.70]; p < 0.001 Hedges’ g: −1.05 [−1.20; −0.90][f] probability: “proof”	Outcome category “non-serious/non-severe symptoms/late complications” added benefit, extent: “non-quantifiable”
Loss of smell[e]	−1.44 to −1.24 vs. −0.37 to −0.27[d] MD: −1.02 [−1.15; −0.89]; p < 0.001 Hedges’ g: −1.20 [−1.35; −1.05][f] probability: “proof”	Outcome category: serious/severe symptoms/late complications added benefit, extent: “non-quantifiable”
Rhinorrhoea (anterior/posterior)[e]	−1.07 to −1.03 vs. −0.49[d] MD: −0.57 [−0.67; −0.46]; p < 0.001 Hedges’ g: 0.80 [0.95; 0.65][f] probability: “proof”	Outcome category “non-serious/non-severe symptoms/late complications” added benefit, extent: “non-quantifiable”
VAS rhinosinusitis[e]	−4.67 to −4.43 vs. −1.88 to −1.59[d] MD: −2.78 [−3.18; −2.39]; p < 0.001 Hedges’ g: −1.10 [−1.25; −0.94][f] probability: “proof”	Outcome category: serious/severe symptoms/late complications added benefit, extent: “non-quantifiable”
Health status (EQ-5D VAS)[g]	11.06 to 11.81 vs. 3.43 to 3.45[d] MD: 7.90 [5.35; 10.45]; p < 0.001 Hedges’ g: 0.48 [0.33; 0.64][f] probability: “proof”	Outcome category “non-serious/non-severe symptoms/late complications” added benefit, extent: “non-quantifiable”
Health-related quality of life		
Outcomes of this category were not recorded		

Table 15: Extent of added benefit at outcome level: dupilumab + mometasone furoate vs. placebo + mometasone furoate (24-week data) (multipage table)

Outcome category **Outcome**	**Dupilumab + mometasone furoate vs. placebo + mometasone furoate** **proportion of events (%) or MD** **effect estimation [95% CI];** **p-value** **probability[a]**	**Derivation of extent[b]**
Side effects		
SAEs	Data not evaluable[c]	Greater/lesser harm not proven
Discontinuation due to AEs	Data not evaluable[c]	Greater/lesser harm not proven

a. Probability provided if statistically significant differences were present.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Patients with an improvement of the SNOT-22 total score of ≥ 8.9 points at week 24.
d. Minimum and maximum proportion of events or mean changes per treatment arm in the included studies.
e. Lower (decreasing) values mean an improvement; negative effects (dupilumab + mometasone furoate) – (placebo + mometasone furoate) mean an advantage for dupilumab + mometasone furoate.
f. If the CI of Hedges' g is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived.
d. Higher (increasing) values mean an improvement; positive effects (dupilumab + mometasone furoate) – (placebo + mometasone furoate) mean an advantage for dupilumab + mometasone furoate.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EQ-5D: European Quality of Life-5 Dimensions; MD: mean difference; RR: relative risk; randomized controlled trial; SAE: serious adverse event; SNOT-22: 22-Item Sino-Nasal Outcome Test; VAS: visual analogue scale; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 16 summarizes the results considered in the overall conclusion on the extent of the added benefit.

Table 16: Positive and negative effects from the assessment of dupilumab + mometasone furoate compared with placebo + mometasone furoate (24-week data)

Positive effects	**Negative effects**
Serious/severe symptoms/late complications ▪ loss of smell: proof of added benefit - extent: non-quantifiable ▪ VAS rhinosinusitis: proof of added benefit - extent: non-quantifiable	–
non-serious/non-severe symptoms/late complications ▪ SNOT-22 total score: proof of added benefit - extent: considerable ▪ nasal congestion/obstruction: proof of added benefit - rhinorrhoea (anterior/posterior): proof of added benefit - extent: non-quantifiable ▪ health status (EQ-5D VAS): proof of added benefit - extent: non-quantifiable	–

EQ-5D: European Quality of Life-5 Dimensions; SNOT-22: 22-Item Sino-Nasal Outcome Test; VAS: visual analogue scale

The overall consideration only shows positive effects for dupilumab + mometasone furoate versus placebo + mometasone furoate. These positive effects comprise a proof of considerable added benefit in the total score of SNOT-22 as well as proof of a non-quantifiable added benefit for each of the outcomes "loss of smell", "VAS rhinosinusitis", "nasal congestion/obstruction", "rhinorrhoea (anterior/posterior)" and "health status", recorded using the EQ-5D VAS. In the present situation, greater harm from dupilumab in comparison with the comparator therapy can be ruled out.

In summary, there is proof of a non-quantifiable, at least considerable added benefit of dupilumab as add-on therapy with INCS compared to the ACT for adult patients with severe CRSwNP that cannot be adequately controlled with SCS and/or surgery.

The 52-week data of the SINUS-52 study presented as supplementary information (see Appendix A of the full dossier assessment) illustrate a long-term change of the CRSwNP symptoms. The data presented show similar results for all used outcomes and confirm the results of the meta-analysis of the studies SINUS-24 and SINUS-52 at week 24.

The result of the assessment of the added benefit of dupilumab in comparison with the ACT is summarized in Table 17.

Table 17: Dupilumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with severe CRSwNP which cannot be adequately controlled with SCS and/or surgery[b, c]	Treatment with topical corticosteroids (budesonide or mometasone furoate)[c, d]	Proof of added benefit, extent: non-quantifiable, at least considerable

a. Presentation of the ACT specified by the G-BA. The G-BA's ACT refers to the planned therapeutic indication of dupilumab at the time of the consultation: adult patients with severe CRSwNP in whom previous therapies with SCS and/or surgery failed or in whom such treatment is not suitable due to intolerance or contraindication.
b. It is assumed that the deviation of the designation of the final therapeutic indication from the therapeutic indication planned at the time of the consultation neither challenges the research question of the present assessment nor the ACT. The benefit assessment refers to the approved therapeutic indication.
c. The G-BA specified that patients in both study arms should receive maintenance treatment with topical corticosteroids as well as further supportive measures (e.g. nasal rinsing) and an adequate, approval-compliant treatment of complications. It is also assumed that invasive treatment options are currently not indicated for patients for whom treatment with dupilumab is suitable.
d. According to the G-BA for patients for whom drug treatment 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 proof of major added benefit.

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

2.6 List of included studies

SINUS-24

Sanofi. A controlled clinical study of dupilumab in patients with bilateral nasal polyps (SINUS-24): study details [online]. In: ClinicalTrials.gov. 25.07.2019 [Accessed: 05.12.2019]. URL: https://ClinicalTrials.gov/show/NCT02912468.

Sanofi. A controlled clinical study of dupilumab in patients with bilateral nasal polyps (SINUS-24): study results [online]. In: ClinicalTrials.gov. 25.07.2019 [Accessed: 05.12.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT02912468.

Sanofi. A randomized, 24-week treatment, double-blind, placebo-controlled efficacy and safety study of dupilumab 300 mg every other week, in patients with bilateral nasal polyposis on a background therapy with intranasal corticosteroids: study EFC14146; clinical study report [unpublished]. 2018.

Sanofi. A randomized, 24-week treatment, double-blind, placebo-controlled efficacy and safety study of dupilumab 300 mg every other week, in patients with bilateral nasal polyposis on a background therapy with intranasal corticosteroids: study EFC14146; Zusatzanalysen [unpublished]. 2019.

Sanofi-Aventis Recherche et Developpement. A randomized, 24-week treatment, double-blind, placebo-controlled efficacy and safety study of dupilumab every other week, in patients with bilateral nasal polyposis on a background therapy with intranasal corticosteroids [online]. In: EU Clinical Trials Register. [Accessed: 05.12.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-003101-42.

Sanofi-Aventis Recherche et Developpement. A randomized, 24-week treatment, double-blind, placebo-controlled efficacy and safety study of dupilumab every other week, in patients with bilateral nasal polyposis on a background therapy with intranasal corticosteroids: clinical trial results [online]. In: EU Clinical Trials Register. 20.07.2019 [Accessed: 05.12.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-003101-42/results.

SINUS-52

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