

Single Technology Appraisal

Dupilumab for treating severe chronic rhinosinusitis with nasal polyposis [ID6480]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Dupilumab for treating severe chronic rhinosinusitis with nasal polyposis [ID6480]

Contents:

The following documents are made available to stakeholders:

Access the [final scope](#) and [final stakeholder list](#) on the NICE website.

1. **Company submission from Sanofi:**
 - a. Full submission
 - b. Summary of Information for Patients (SIP)
2. **Clarification questions and company responses**
3. **Patient group, professional group, and NHS organisation submissions** from:
 - a. Fifth Sense
 - b. Fifth Sense appendix
 - c. Sinus UK
 - d. Sinus UK appendix
 - e. Association of Respiratory Nurse Specialists
4. **Expert personal perspectives** from:
 - a. Professor Claire Hopkins – clinical expert, nominated by Sanofi
 - b. Professor Carl Philpott – clinical expert, nominated by Sanofi
 - c. Sophie Dodworth – patient expert, nominated by Fifth Sense
 - d. Andrew Knill - patient expert, nominated by Sinus UK
5. **External Assessment Report** prepared by BMJ Technology Assessment Group
6. **External Assessment Report – factual accuracy check**

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Dupilumab for treating chronic rhinosinusitis with nasal polyposis [ID6480]

Company evidence submission

File name	Version	Contains confidential information	Date
ID6480_Dupilumab_Company evidence submission_14022025_CIC	Final	NO REDACTED	14/02/2025

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1 Decision problem, description of the technology and clinical care pathway

Disease overview and burden

- Chronic rhinosinusitis (CRS) refers to inflammation of the paranasal sinuses and nasal cavity, with symptoms that persist beyond 12 weeks.^{1,2} There are two broad CRS subtypes defined by the presence or absence of nasal polyps which are non-cancerous soft tissue growths within the sinonasal passages or sinuses.¹
- CRS with nasal polyps (CRSwNP) is the result of a chronic type 2 inflammatory phenotype, driven by the cytokines interleukin [IL]-4 and IL-13.² The estimated prevalence of CRSwNP among adults living in the UK in 2013 was 1.6/100,000 (0.16%).³
- People with uncontrolled CRSwNP suffer from significant and debilitating symptoms including loss of sense of smell and taste, sinonasal obstruction, chronic infections and facial pain.^{2,4} These persistent symptoms have a substantial adverse impact on the health-related quality of life (HRQoL) of patients, affecting sleep quality, mood and activities of daily living.⁵⁻⁷ CRSwNP is associated with a high rate of polyp recurrence despite surgical intervention and revision surgery is common (~15% of patients within 5 years).^{2,8}
- Treatment of CRSwNP is associated with important healthcare resource utilisation (HCRU); in England between 2010 and 2020, CRSwNP-related costs totalled £86.3 million (cost year unavailable).⁹ The burden of sinonasal surgery for CRSwNP was £174 million during this time, including £66.7 million attributable to revision surgeries.⁹

Clinical pathway of care

- Established clinical management (ECM) for people with uncontrolled CRSwNP consists of maintenance therapy with intranasal corticosteroids (INCS) combined with saline rinses, in addition to short-term use of systemic corticosteroids (SCS; for the treatment of exacerbations) and endoscopic sinonasal surgery (ESS).^{1,10}

Unmet need

- ECM does not target the underlying aetiology of CRSwNP (type 2 inflammation), meaning the clinical benefits of ECM are limited and diminish over time:^{10,11}
 - Recurrence following ESS is common, with a 5-year revision rate of ~15%, which increases among people who had one or more previous surgeries.⁸ The clinical benefits of revision surgery are not only temporary but may also be unsatisfactory, with no assurance that sense of smell will return, and limited gains in HRQoL.^{5,12}
 - Extensive (cumulative courses >300 mg within one year) use of SCS is associated with adverse events such as osteoporosis, hypertension and glaucoma,^{10,12,13} while ESS carries a risk of potentially serious post-operative complications.^{10,14,15} For patients requiring revision surgery, the risk of complications increases with each subsequent surgery.^{8,16}
- National Health Service (NHS) waiting lists for ESS (50% of which represent revision surgery) range from 6 months up to 3 years following specialist referral.¹² This long waiting time negatively impacts people with uncontrolled CRSwNP who, as a result of persistent type 2 inflammation, experience worsening of their disease and prolonged loss of smell and use of SCS.¹²

Proposed population for dupilumab

- It is anticipated that dupilumab will be used in line with its licensed indication, as an add-on therapy with INCS for the treatment of adults with severe CRSwNP for whom therapy with SCS and/or surgery do not provide adequate disease control.^{17,18}
- In alignment with phase 3 clinical trials for dupilumab, the population considered in this submission is people with uncontrolled CRSwNP following one (or more) surgeries.

1.1 *Decision problem*

This technology appraisal evaluates the clinical- and cost-effectiveness of dupilumab as a treatment for people with uncontrolled CRSwNP. Dupilumab (Dupixent®) is indicated in the United Kingdom (UK) 'as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.'^{17,18}

The final scope for dupilumab in uncontrolled CRSwNP was issued by the National Institute for Health and Care Excellence (NICE) in November 2024. The key evidence in this submission is based on the results of SINUS-24 and SINUS-52 which are two replicate phase III randomised controlled trials (RCTs) that evaluated the efficacy and safety of dupilumab as an add-on to intranasal corticosteroids (INCS) versus INCS alone in adults with uncontrolled chronic rhinosinusitis with nasal polyps (CRSwNP). The decision problem addressed in this submission is summarised in Table 1.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with previously treated severe chronic rhinosinusitis with nasal polyps.	The base case focuses on adults with uncontrolled CRSwNP following one or more surgeries.	The CRSwNP indication is: ‘Dupixent is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.’ The scope population encompasses the indicated population but whilst implicit, does not formally stipulate the failure of, or intolerance to, previous treatments. Currently, ECM for people with uncontrolled CRSwNP includes INCS with saline rinses, SCS for exacerbations and, for patients whose disease remains uncontrolled (defined as per EPOS 2020 guidelines; Section <u>1.2.1.2</u>), surgery. The experts that we have consulted (see Appendix R for the full HCP Consultancy Report) stated that surgery should be recommended first because surgery does work for some people.¹² However, patients who require revision surgery following a successful sinus surgery should have access to biologic therapy, which would be an add-on to ECM, while further revision surgery should be avoided where possible.¹² Therefore, our base case population includes people with uncontrolled disease following one (or more) surgeries.
Intervention	Dupilumab as an add on to maintenance treatment.	Dupilumab as an add on to maintenance treatment with INCS. ^{17,18}	n/a
Comparator(s)	ECM without dupilumab, including surgery	Per NICE scope	n/a
Outcomes	The outcome measures to be considered include: - Nasal congestion and/or obstruction - Sense of smell	Per NICE scope	n/a

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Sinus opacifications • Need for surgery • Need for SCS • AE of treatment • HRQoL		
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	Per NICE scope	n/a
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • People who have asthma • People who are ineligible for surgery • People who are ineligible for SCS • People with NSAID-ERD	The subgroups considered in this submission are: • People who have had one (or more) surgery • People with any prior type 2 medical history (including asthma/NSAID-ERD) • People who have had one (or more) surgery AND with any prior type 2 medical history (including asthma/NSAID-ERD)	We do not believe it is appropriate to provide subgroup analyses for people with CRSwNP ineligible for surgery or for SCS. The rationale for the two subgroups is presented below: 1. People ineligible for surgery In line with clinical advice, the base case focuses on patients who have had one (or more) prior surgeries and who remain uncontrolled following reoccurrence of their nasal polyps. By definition this population includes patients who may be ineligible for revision surgery. However, in the SINUS studies only 23.74% of patients were ineligible for revision surgery. The proportion who had had NO prior surgery AND who were ineligible for surgery was 0%. This means that

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			an analysis of the surgery ineligible subgroup only is likely to be highly uncertain and unsuitable for decision making. 2. People ineligible for SCS This population was very small (5.25%) in the SINUS studies and thus, meaningful subgroup analysis is not possible. According to clinical opinions we have received, this subgroup is rarely seen in clinical practice. Providing a subgroup analysis for people with type 2 inflammatory disease including asthma and NSAID-ERD seems appropriate for the following reasons: NSAID-ERD is defined as the presence of CRSwNP with asthma and NSAID sensitivity. CRSwNP is also predominantly a type 2 inflammatory disease. Thus, the NSAID-ERD subgroup, which is also associated with type 2 inflammation and asthma, is a clinically relevant subgroup. It is recognised that up to 60% of patients with CRSwNP suffer from comorbid asthma and frequently present with NSAID-ERD given the strong underlying linkage to the type 2 pathophysiology. Given the high prevalence of comorbid asthma and NSAID-ERD in people with CRSwNP and the increased surgery burden in people with vs. those without these comorbidities,⁹ we have therefore provided an analysis for the subgroup “people with any prior type 2 medical history”.

AE = adverse events; CRSwNP = chronic rhinosinusitis with nasal polyps; ECM = established clinical management; HRQoL = health-related quality-of-life; INCS = intranasal corticosteroids; n/a = not applicable; NHS = National Health Service; NSAID-ERD = non-steroidal anti-inflammatory drug exacerbated respiratory disease; PSS = Personal Social Services; QALY = quality-adjusted life year; SCS = systemic corticosteroids

Sources: Dupixent® (dupilumab) SmPC;^{17,18} Hopkins 2022;⁹ Sanofi data on file, 2024

1.1 Description of the technology being evaluated

Dupilumab, the technology being appraised, is described in [Table 2](#). The Summary of Product Characteristics (SmPC) for dupilumab in CRSwNP can be found in [Appendix C](#).^{17,18}

Table 2. Technology being evaluated

UK approved name and brand name	Dupilumab (Dupixent®)
Mechanism of action	Dupilumab is a recombinant human IgG4 monoclonal antibody that inhibits IL-4 and IL-13 signalling. Dupilumab inhibits IL-4 signalling via the Type I receptor (IL-4Rα/γ c), and both IL-4 and IL-13 signalling through the Type II receptor (IL-4Rα/IL-13Rα). IL-4 and IL-13 are major drivers of human type 2 inflammatory disease, such as AD, asthma, COPD, CRSwNP, EoE and PN. Blocking the IL-4/IL-13 pathway with dupilumab in patients decreases many of the mediators of type 2 inflammation.
Marketing authorisation/CE mark status	EMA centralised marketing authorisation approval for dupilumab in adults with severe CRSwNP was received on 24 October 2019. UK marketing approval was granted by the MHRA on 1 January 2021 following a submission through the European Commission Decision Reliance Procedure.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Dupilumab is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.
Method of administration and dosage	The recommended dose of dupilumab for adult patients is 300 mg given every other week. Dupilumab is self-administered by subcutaneous injection into the thigh or abdomen, except for the 5 cm around the navel, using a single-use pre-filled syringe or pen. If the injection is being administered by somebody else, the upper arm can also be used.
Additional tests or investigations	No additional tests or monitoring beyond those already recommended for patients with CRSwNP are required.
List price and average cost of a course of treatment	£1,264.89 per pack of 2 pre-filled pens or pre-filled syringes. £16,500 PPPY.
Patient access scheme (if applicable)	The current PAS is a simple discount of [REDACTED] representing [REDACTED] per pack or [REDACTED] PPPY. In addition to the simple discount PAS, dupilumab is eligible for VPAG payments. This represents an additional 23.5% (DHSC's estimate as of January 2025) rebate on net sales of the product in 2025.

AD = atopic dermatitis; COPD = chronic obstructive pulmonary disease; CRSwNP = chronic rhinosinusitis with nasal polyps; DHSC = Department of Health and Social Care; EMA = European Medicines Agency; EoE = eosinophilic esophagitis; HCP = healthcare professional; Ig = immunoglobulin; IL = interleukin; MHRA = Medicines and Healthcare products Regulatory Agency; PAS = patient access scheme; PN = prurigo nodularis; PPPY = per patient per year; VPAG = voluntary scheme for branded medicines pricing, access and growth
Sources: Dupixent® (dupilumab) SmPC.^{17,18}

1.2 Health condition and position of the technology in the treatment pathway

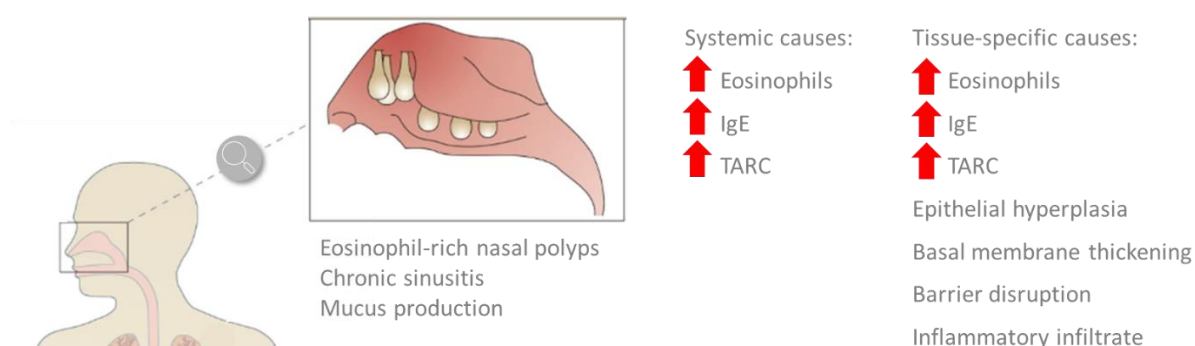
1.2.1 Disease overview

1.2.1.1 Pathophysiology of CRSwNP

Chronic rhinosinusitis (CRS) is defined as a symptomatic inflammation of tissues in the paranasal sinuses and nasal cavity; it may be localised (unilateral) or diffuse (bilateral) and is characterised by symptoms that persist beyond 12 weeks.^{1,2} CRS can be diagnosed with nasal polyps (CRSwNP) or without nasal polyps (CRSsNP), which are non-cancerous soft tissue growths that develop along the mucosal layer of the sinonasal passages or sinuses.^{1,19} Nasal polyps grow and protrude into the nasal cavities, causing partial or total obstruction.¹⁹

The underlying pathophysiology of CRSwNP is a type 2 inflammatory phenotype.^{1,2,20,21} Type 2 inflammation is driven by type 2 cytokines interleukin (IL)-4 and IL-13 which promote the infiltration of immune cells such as eosinophils into sinonasal tissue, and stimulate B-lymphocytes to produce immunoglobulin E (IgE) (Figure 2).^{1,2} The type 2 inflammatory environment in CRSwNP leads to sinonasal mucosal damage, overproduction of mucus and the remodelling of sinonasal tissue resulting in nasal polyp formation (Figure 1).^{1,2} Epithelial cells lining the sinonasal passages become more permeable, allowing foreign antigens and infectious agents to enter the submucosa.² This increased permeability, combined with deficiencies in mucociliary clearance, allows the accumulation of bacteria and fungi which can lead to chronic upper airway infection.²

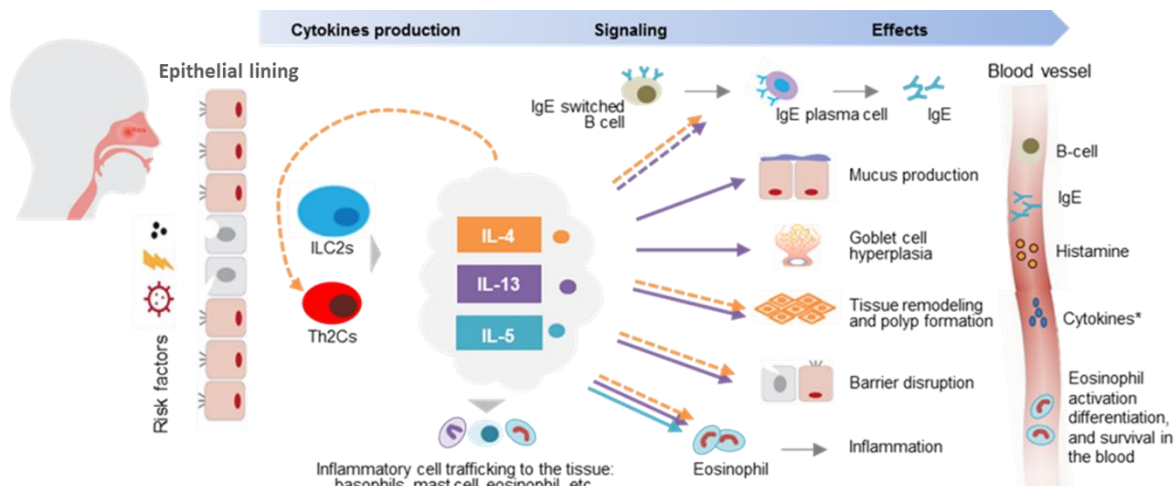
Figure 1. Pathophysiology of CRSwNP



CRSwNP = chronic rhinosinusitis with nasal polyps; IgE = immunoglobulin E; TARC = thymus- and activation-regulated chemokine.

Source: Adapted from Gandhi et al. 2015.²²

Figure 2. Role of type 2 inflammation in CRSwNP²



CRSwNP = chronic rhinosinusitis with nasal polyps; IL = interleukin; ILC2 = Group 2 innate lymphoid cell; IgE = immunoglobulin E; Th2C = T-helper 2 cell

*Type 2 cytokines recruit effector cells (e.g., basophils, mast cells, eosinophils) to the tissue and mediate B cell class switching to IgE upon exposure to antigen. These cytokines are central to inflammatory processes that result in mucus production and polyp formation. Cytokines IL-4 and IL-13 are the main effectors in this type 2 inflammatory response with IL-5 playing a more minor role in the disease pathway.

Source: Adapted from Hulse 2015.²

Type 2 inflammation is involved not only in the aetiology of CRSwNP, but also drives the pathophysiology of comorbidities associated with this disease.^{1,2,4,20} As discussed in [Section 1.2.1.4.2](#), asthma, allergies and non-steroidal anti-inflammatory drug-exacerbated respiratory disease (NSAID-ERD) are more common in people with CRSwNP than the general population, which is aligned with the concept of unified airway disease.^{23,24}

1.2.1.2 Presentation and diagnosis

CRSwNP is characterised by chronic inflammation which leads to epithelial damage, mucous membrane thickening and nasal polyp formation.¹ For the majority of people with CRSwNP, polyps occur bilaterally and most commonly arise in the ethmoid, maxillary and sphenoidal sinuses.¹⁹ Uncontrolled CRSwNP can have significant and debilitating symptoms that include:^{2,4,25,26}

- Loss of senses of smell and taste
- Sinonasal congestion/obstruction and discoloured discharge
- Impaired breathing
- Facial pain/pressure
- Fatigue and sleep disturbance
- Recurrent upper and lower respiratory infections
- Eustachian dysfunction and hearing impairment

- Post-nasal drip (possibly with bronchial aspiration and associated lower respiratory infection)

Initial patient presentation to a general practitioner (GP) is usually triggered by symptoms of sinonasal inflammation.⁴ Compared with the general population, people with CRSwNP produce greater amounts of sinonasal mucus, with sinonasal congestion and/or obstruction that lead to loss of both sense of smell and taste, fatigue and sleep disorders (such as sleep apnoea).^{1,2,4}

Diagnostic criteria for CRSwNP are described in the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) published in 2020 ([Table 3](#)).¹

Coexisting inflammatory disorders should also be considered during the diagnosis of CRSwNP.⁴ Nasal polyps develop as a result of the type 2 inflammatory process associated with these coexisting conditions, and therefore an assessment of nasal polyps is important for effective treatment choices.^{1,2,4}

Table 3. EPOS diagnostic criteria for CRS and CRSwNP¹

Diagnostic criteria
• ≥2 symptoms present for >12 weeks, one of which must be presence of sinonasal blockage/obstruction/congestion, or nasal discharge (i.e., anterior or posterior nasal drip): ○ Sinonasal blockage/obstruction/congestion and/or nasal discharge ○ ± Facial pain/pressure ○ ± Reduction or loss of smell • AND either endoscopic signs and/or CT changes: • Endoscopic signs: ○ Presence of nasal polyps (for CRSwNP) ○ Mucopurulent (containing mucus and pus) discharge primarily from the middle meatus ○ Oedema/mucosal obstruction primarily in the middle meatus • CT changes: ○ Mucosal changes within the ostiomeatal complex and/or sinuses

CRS = chronic rhinosinusitis; CRSwNP = chronic rhinosinusitis with nasal polyps; CT = computed tomography; EPOS = European Position Paper on Rhinosinusitis and Nasal Polyps.

Evidence of nasal polyps is required for a diagnosis of CRSwNP.

Source: Fokkens 2020.¹

The severity and duration of a person's symptoms are considered during diagnostic evaluation.¹ CRSwNP severity is currently reported utilising a Visual Analogue Scale (VAS) where patients are asked to rank the severity of their symptoms from 0 to 10, with ratings of 0 to 3, >3 to 7 and >7 to 10 indicating mild, moderate and severe symptoms, respectively.²⁷ A definition of disease severity in people with CRSwNP was published in the 2020 EPOS and is based on the level of disease control:¹

- **Controlled disease:** 'A disease state in which the patients do not have symptoms, or the symptoms do not adversely affect quality of life (QoL), if possible combined with a healthy or almost healthy mucosa and only need for local medication.'
- **Uncontrolled disease:** 'Partially or uncontrolled patients will have symptoms of nasal blockage, discharge, facial pain/pressure, reduced sense of smell and sleep disturbance of >5 in addition to nasal endoscopy findings and the need for rescue medication.'

A person with uncontrolled CRSwNP whose symptoms persist despite treatment may be referred to an Ear, Nose and Throat (ENT) or specialised Rhinology clinic for further investigation and treatment.¹² Persistent symptoms leading to referral can include loss of sense of smell, nasal obstruction and mucus that have not resolved with INCS or, in some cases, SCS (Section 1.2.2.1).¹² GP referral rates are variable, with some patients estimated to spend 2 to 3 years in primary care without satisfactory improvement before being referred to a specialist.¹²

1.2.1.3 Epidemiology

Epidemiological studies for CRSwNP are limited and prevalence estimates are impacted by the heterogeneity of CRS and the diagnostic criteria that are applied.²⁷ In 2013, analysis of Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES) data collected from over 700 primary care practices in the UK estimated the prevalence of CRSwNP in the adult population to be 1.6 per 100,000 individuals (0.16%).³

The peak incidence of CRSwNP occurs in working-age adults between 45 to 60 years.² The prevalence of CRSwNP in the UK is greater in males compared with females, and increases with age.³ In 2013, the prevalence of CRSwNP in the UK was highest among individuals aged 55 to 64 years (Table 4).³

Table 4 Prevalence of CRSwNP among adults in the UK by sex and age (2013)³

Age group (years)	Males (per 100,000)	Females (per 100,000)
18–24	1.13	1.11
25–34	1.80	1.34
35–44	2.20	1.54
45–54	2.64	1.55
55–64	3.54	1.98
65–74	3.30	1.40
75+	1.87	7.60

CRSwNP = chronic rhinosinusitis with nasal polyps
Source: Hopkins 2019.³

As described in Section 1.1, dupilumab is indicated in adults as add-on therapy with INCS for the treatment of adults with severe CRSwNP for whom therapy with SCS and/or surgery

do not provide adequate disease control.^{17,18} However, the proposed population eligible for dupilumab includes people with uncontrolled CRSwNP following one (or more) sinus surgeries. Thus, the estimated population eligible for dupilumab is estimated in a stepwise manner as described below and in [\(Figure 3\)](#).

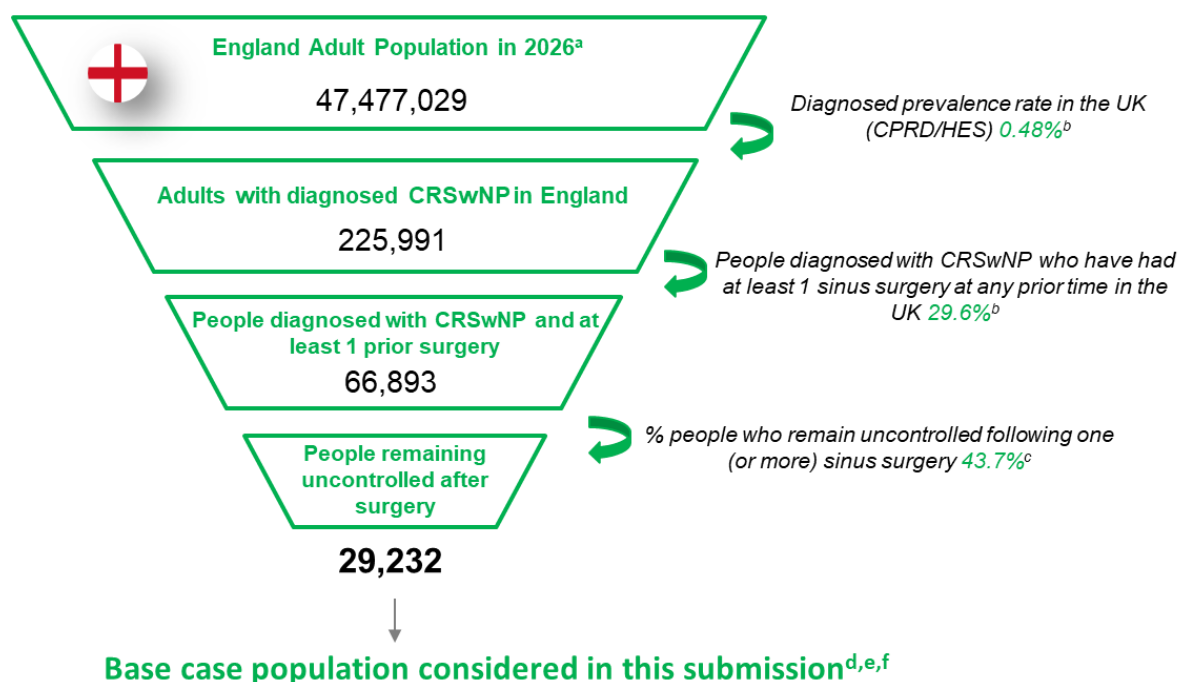
All patient numbers and percentages mentioned in the description below refer to the English adult population (>17 years old) and to 2026 (anticipated first full year of patient access), unless otherwise stated.

The adult population in England in 2026 (N=47,477,029) was estimated based on the mid-2023 population estimates for England (Office for National Statistics - ONS) and the cumulative annual growth rate from the 2022-based national population principal projections for England (ONS).²⁸

Benson et al. characterised the real-world burden of CRSwNP in the UK (analysis of CPRD and HES medical and prescribing records including 31,728 people with CRSwNP as of 31 December 2018, published in 2023) and reported the prevalence to be 0.476% of the population.¹⁶ To calculate the potential accessible number of CRSwNP adults anticipated to be eligible for treatment with dupilumab in England, this prevalence was applied to the adult English population. This equates to approximately 225,991 adults with diagnosed CRSwNP in England (0.476%; i.e., n = 225,991). Based on the same retrospective analysis of Benson et al. of medical and prescribing records in the UK (CPRD and HES), 29.6% of adults diagnosed with CRSwNP had ≥ 1 prior sinus surgery,¹⁶ which corresponds to a total of 66,893 people in England who have ever had a surgery for CRSwNP.

The proportion of patients with CRSwNP who remain uncontrolled despite prior sinus surgery is estimated based on the study by Van Der Veen et al. (2013-2014 survey of 389 adults with CRS who had undergone ESS in a tertiary referral centre in Belgium between 2008 and 2010, published in 2018), which reported that 43.7% of patients who had undergone ESS 3 to 5 years prior to the study were uncontrolled according to EPOS/EUFOREA criteria.²⁹ When applied to the population who had previously undergone sinus surgery, this results in a final population of 29,232 people eligible for treatment with dupilumab in the first full year of anticipated patient access (N=29,232). [\(Figure 3\)](#).

Figure 3. Population anticipated to be eligible for treatment with dupilumab in England in 2026



CRSwNP = chronic rhinosinusitis with nasal polyps; ESS = endoscopic sinus surgery; ONS = Office for National Statistics; SCS = systemic corticosteroid

^a Population data are based on mid-2023 population estimate for England (ONS) and 2022-based population projection for England (ONS).²⁸

^b Based on Benson et al. 2023.¹⁶

^c Based on Van der Veen et al. 2017.²⁹

^d Base case population considered in this submission was based on EPOS 2020 guidelines,³⁰ ^e EPOS/EUFOREA 2023 guidelines,^{6, f} and an advisory board³¹ and HCP consultancy¹² conducted by Sanofi.

1.2.1.4 Clinical burden

1.2.1.4.1 Symptomatic burden

People with uncontrolled CRSwNP experience substantial symptomatic burden and have high levels of morbidity.^{23,32} One study compared 36-item Short-Form Health Survey (SF-36) results for 445 people with CRSwNP (in whom the mean duration of symptoms was 12.8 years) with those of the age-adjusted population norm.⁵ People with CRSwNP had worse general health, bodily pain and physical functioning (all $p < 0.0001$ and all exceeded the minimum clinically important difference [MCID]) than the age-adjusted population norm.⁵

The 22-item Sino-Nasal Outcome Test (SNOT-22) is a patient-reported outcome (PRO) measure designed to assess symptomatic burden in people with CRS.⁷ Baseline SNOT-22 data from SINUS-24 and SINUS-52 show that loss of sense of smell/taste is the most burdensome symptom experienced by people with CRSwNP (Section 2.6.3), followed by nasal blockage, post-nasal discharge, thick nasal discharge and poor sleep quality.⁷ Sinonasal obstruction/congestion can greatly impact the physical and emotional functioning of people with uncontrolled CRSwNP, particularly through impaired sleep which increases fatigue and reduces daytime productivity.^{26,33,34}

Some severe cases of CRSwNP are associated with orbital and intracranial complications.^{12,19} For example, polyps that cause orbital compression may lead to ocular symptoms (such as diplopia [double vision] and ophthalmoplegia [paralysis or weakness of eye muscles]), while the presence of sinonasal mucocoeles (mucus-filled cysts) can cause further obstruction of the sinuses.^{1,12}

1.2.1.4.2 Comorbidities associated with type 2 inflammation

People with CRSwNP are frequently diagnosed with comorbidities associated with type 2 inflammation, which include comorbid refractory persistent asthma, inhalant allergy and NSAID-ERD.^{9,16,32,35-38}

The association between CRSwNP and asthma is well-established. One systematic review reported baseline data from 5 clinical trials (representing 1,748 participants), showing that comorbid asthma occurred in 62.3% of people with CRSwNP (range: 56.0% to 71.0%).³⁹ Additional support includes a multicentre cross-sectional study of 869 people by the Global Allergy and Asthma European Network (GALEN) which documented comorbid asthma in 49.6% of people with CRSwNP, and a UK-based survey study (N=1,470) which documented comorbid asthma in 46.9% of people with CRSwNP.^{23,38} When viewed from the opposite perspective, registry data from the Severe Asthma Network Italy (SANI) have recorded CRSwNP in 40.6% of people with severe asthma.⁴⁰

The estimated prevalence of inhalant allergy among people with CRSwNP in the UK is significantly higher than the prevalence among matched normal controls (31.0% vs. 13%; respectively, $p < 0.001$).³⁸ Common allergens reported in the UK study included house dust mites and grass pollen.³⁸

NSAID-ERD is defined as the presence of CRSwNP with asthma and NSAID sensitivity; NSAID-ERD is a progressive condition with increased prevalence among people over 40 years of age.^{27,37,41} A study in the UK documented aspirin sensitivity in almost 10% of people with CRSwNP (62/651 people; mean age of 56 years).³⁸

The presence of comorbidity correlates with increased severity of CRSwNP symptoms and increased need for revision ESS.^{9,42} In particular, the severity of CRSwNP has been correlated with the presence of comorbid asthma ($p < 0.0001$), inhalant allergy ($p = 0.0017$) and aspirin sensitivity ($p < 0.0001$).⁴² In a study of 724 people with CRSwNP, when compared with people without comorbid asthma, those with comorbid asthma had higher mean Lund-Mackay- (LMK-) Computed Tomography (CT) scores (indicating greater opacification ('clouding') of sinuses), higher mean SNOT-22 scores and higher mean total symptom scores (all $p < 0.001$).³⁵ Comorbid asthma is also more common among people with CRSwNP

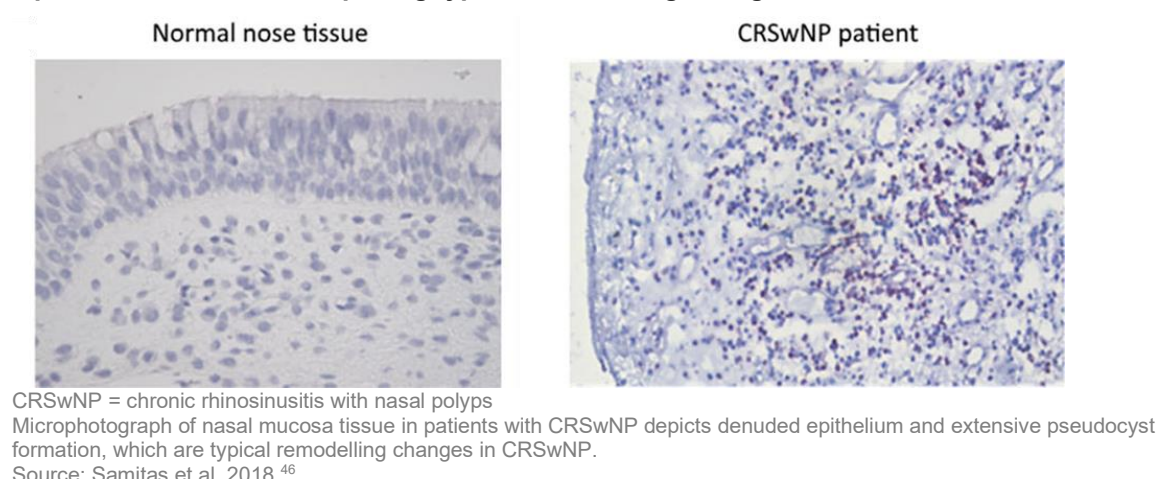
who have experienced loss of sense of smell (indicative of severity) compared with those in whom sense of smell is maintained ($p < 0.0001$).⁴³

1.2.1.4.3 *Recurrence and the clinical burden of revision surgery*

Several types of ESS exist for the treatment of people with CRSwNP including polypectomy, 'functional' ethmoidectomy (conserves the mucosa) and radical ethmoidectomy (removes some or all of the mucosa).⁴⁴ Functional ESS (FESS) refers to surgeries aiming to restore the normal physiology of the sinuses, such as ethmoidectomy.^{1,44} Based on the criteria described in Section 1.2.2.1.2, people with uncontrolled CRSwNP may be offered ESS with the intention of removing nasal polyps and improving aeration of the occluded paranasal sinuses, along with opening up the ethmoid and sphenoid sinuses and improving drainage from the maxillary antrum (i.e. spheno-ethmoidectomy with middle meatal antrostomy).^{10,12,19} ESS can alleviate sinonasal symptoms and improve the delivery of INCS; however the 5-year revision rate for sinonasal surgery has been estimated at ~15% and increases among people who had one or more previous surgeries (20.2% vs. 9.8% in patients with and without prior sinonasal surgery, respectively).⁸ The clinical benefits of surgery are not only temporary but may also be unsatisfactory for the patient. For example, there is no assurance that a person's sense of smell will return following multiple surgeries.¹² During consultation between Sanofi and UK clinical experts, it was estimated that 75% to 80% of people with CRSwNP do not achieve satisfactory improvement in their sense of smell following ESS, and the likelihood of gaining an improved sense of smell further diminishes following a second and third sinonasal surgery.^{12,45} In CRSwNP, loss of smell may be caused by the degeneration of olfactory neurones and shedding of the olfactory epithelium due to type 2 inflammation, which explains this decreasing likelihood of smell improvement with increasing numbers of surgeries as surgery does not address inflammation.⁴⁵

People with CRSwNP who require revision surgery must be re-referred by their GP to a rhinology clinic. Revision sinonasal surgeries are rarely prioritised in the NHS (with the exception of severe cases, such as those involving bone erosion), and a duration of 2 to 3 years may elapse between recurrence and revision surgery.¹² During this delay to surgery, ongoing type 2 inflammation promotes upper airway remodelling in the nose and sinonasal cavities (Figure 4), causing compression of the olfactory nerves and reducing the likelihood that a person will ever regain their sense of smell.¹² Patients on the waiting list for revision surgery are also exposed to the cumulative toxicity of both SCS and high dose INCS (Section 1.2.2.2.1).¹²

Figure 4. Representative microphotographs of nasal mucosal tissue from a healthy control and a patient with CRSwNP depicting typical remodelling changes



The burden of invasive surgical procedures for people with uncontrolled CRSwNP involves a period of recovery for the patient (approximately 14 days in the UK), in addition to carrying a risk of post-operative complications.^{10,12} For patients requiring revision surgery (Section 1.2.2.2.2), the risk of complications increases with each subsequent surgery.^{8,16} Additionally, some patients may receive SCS in the postoperative setting, which amplifies the cumulative SCS burden.³⁰

The risk of recurrence following surgery increases among people with type 2 comorbidities indicative of a severe type 2 inflammation burden, such as asthma or NSAID-ERD.^{9,12,16,35,36} A retrospective UK-based study using ten years of data from the HES database (April 2010 to March 2020) analysed the rates of revision ESS among people with CRSwNP with or without comorbidities (Table 5).⁹ Multiple surgeries were required by ~20% and ~35% of people with CRSwNP and comorbid asthma or CRSwNP and comorbid NSAID-ERD, respectively, compared to ~10% for people with CRSwNP and no comorbidity.⁹ The study also identified a shorter median time to first revision surgery for people with CRSwNP and comorbid asthma (7 years) or NSAID-ERD (5 years) vs. people with CRSwNP and no comorbidity (9 years; both $p < 0.001$).⁹ Over the 10-year study period, the median number of non-surgical events (i.e., any encounter with an ENT or respiratory specialist) ranged from 6.0 for people with no comorbidity up to 14.9 for people with comorbid NSAID-ERD.⁹ This high number of non-surgical events in people with CRSwNP and comorbid NSAID-ERD is indicative of the transient clinical benefit of surgical intervention and the disease burden incurred between revision surgeries.⁹ People with CRSwNP and comorbid NSAID-ERD or CRSwNP and comorbid asthma represent a population with uncontrolled disease, who may be at the highest risk of surgical failure.^{9,12,16,35,36}

Table 5. Burden of sinonasal surgery in adults with CRSwNP by type 2 comorbidity^a

Comorbidity	Patients, N	Patients with ≥2 surgeries, N (%)	Patients with ≥3 surgeries, N (%)	Patients with ≥4 surgeries, N (%)	Median time to first revision surgery (years)	Mean number of non-surgical events, N
None	64,461	6,649 (10.3)	1,384 (2.2)	488 (0.8)	9	6.0
Asthma	32,050	6,285 (19.6)	1,787 (5.6)	679 (2.1)	7	9.1
NSAID-ERD	4,544	1,594 (35.1)	660 (14.5)	277 (6.1)	5	14.9

CRSwNP = chronic rhinosinusitis with nasal polyps; HES = Hospital Episode Statistics; NSAID-ERD = non-steroidal anti-inflammatory drug exacerbated respiratory disease

^a Data are from the UK HES database and represent surgery and non-surgical events over a period of 10 years (April 2020 to March 2020)

1.2.1.5 Humanistic burden

The impairment in HRQoL experienced by people with CRS (CRSwNP or CRSsNP) is comparable to that associated with other serious chronic diseases.⁴⁷ When assessed using SF-36, mean scores for physical functioning in patients with CRS (CRSwNP or CRSsNP; 87.3) have been found to be similar to those for patients with chronic conditions such as migraine (82.4) and epilepsy (78.9).⁴⁷ The persistent symptoms of CRSwNP have a substantial adverse impact on patients' HRQoL, affecting their sleep quality, mood and activities of daily living.⁵⁻⁷

Analysis of data collected by GALEN show that compared with age-matched population norms, people with CRSwNP have significantly lower SF-36 scores in the domains of mental health, emotional functioning, social functioning and vitality (all $p < 0.0001$).⁵ Further worsening of SF-36 scores is noted for patients with CRSwNP and comorbid asthma or NSAID-ERD.⁵

For people with uncontrolled CRSwNP, symptoms reported to have the greatest impact on HRQoL are sinonasal congestion and/or obstruction, loss of sense of smell and sleep impairment.^{4,6,7} The impact of CRSwNP on patients mental health is also evident, as patients are at greater risk of neuropsychiatric conditions (such as anxiety and depression) compared with the general population ($p < 0.0005$).³²

During patient interviews in the UK (see [Appendix S](#) for the full Patient Insights Workshops Report), several patients with uncontrolled CRSwNP mentioned that sinonasal congestion/obstruction associated with nasal discharge had a substantial negative impact on their daily life.²⁶ Patients reported embarrassment and anxiety in work and social settings due to the constant need to blow their nose and changes in their voice caused by these symptoms.²⁶ This anxiety leads some patients to avoid social situations and public speaking, with two patients explaining:²⁶

- *'I lost confidence in social situations. I started to avoid some social situations because I felt like I sounded strange when I spoke.'*
- *'There were times when I was asked to speak in a meeting or a conference and I declined because I couldn't speak in front of everybody [as a result of her CRSwNP] and especially strangers, I couldn't have done it.'*

Loss of smell associated with the presence of nasal polyps is an often underappreciated symptom that increases with disease severity and adversely influences daily life in many ways.^{7,26,48} Most people with CRSwNP find that loss of smell negatively impacts their mental health and their ability to perform and/or enjoy multiple daily activities.⁴⁸ Living with CRSwNP may also mean people experience an impaired ability to enjoy food due to impaired olfaction and taste, experience decreased appetite and poorer well-being, suffer from anxiety and depression, and have reduced awareness of personal hygiene.^{2,12,26,48} People with CRSwNP can also face danger through an inability to smell rancid food, smoke or fire.^{1,48}

Sleep disorder due to the inability to breathe through the nose along with post nasal drip is also a driver of reduced HRQoL in people with nasal polyposis and may be twice as likely (odds ratio [OR] 2.25; 95% confidence interval [CI]: 1.54, 3.29) to occur in people with CRSwNP compared with healthy controls.^{49,50} Based on interviews with UK patients with uncontrolled CRSwNP, some patients experience panic attacks due to not being able to breathe through their nose while falling asleep, they were:²⁶

- *'I was almost having panic attacks at night because of drifting off to sleep and instinctively trying to breathe through my nose and remembering that I couldn't.'*
- *'Sometimes when you're just drifting off to sleep. I try and breathe through my nose. And you can't. And then I just would go into panic mode.'*

During consultation with clinical experts in the UK, it was mentioned that CRSwNP does not only impact the patients' sleep but may also disturb their partner's sleep due to snoring and snorting.¹² Interviews of patients in the UK confirmed this detrimental effect on partners; a patient said *'my wife and I have not been in the same bedroom for a good number of years now because of the snoring.'*²⁶

Surgical removal of nasal polyps can improve HRQoL for people with uncontrolled CRSwNP, as measured by SNOT-22 and European Quality of Life Scale-5 dimension (EQ-5D) scores.⁵¹ However, this improvement in HRQoL generally lasts only up to 6 months based on interviews with people with CRSwNP in the UK.²⁶ Studies investigating HRQoL among patients who require revision surgery are sparse, however one US-based study found that

mean EQ-5D VAS scores decreased with increasing number of sinus surgeries (mean EQ-5D VAS scores for patients with 1 prior surgery, ≥ 1 surgery and ≥ 2 surgeries were 68.6, 66.4 and 60.8, respectively).^{51,52} Data collected in a study by GALEN support this observation, with lower SF-36 scores among people with CRSwNP and a history of sinus surgery compared to people with CRSwNP and no history of sinus surgery.⁵

Notably, the impact of CRSwNP on patients' HRQoL may be underestimated. As CRSwNP is a chronic condition, people with CRSwNP typically adapt to their disease and underestimate the severity of their symptoms.¹² For instance, the underestimation of the negative impact that loss of smell/taste has on patients' HRQoL was captured by a quote from interviews with UK patients with uncontrolled CRSwNP: *'The hardest thing is the no smell and no taste. You adjust to it, and you live with it, but that's the thing I miss most, smelling and tasting food.'*²⁶ Patient interviews also demonstrated that symptoms are continuous, which potentially magnifies the underestimation of the HRQoL impact; a patient said about CRSwNP *'can be a bit depressing because it's relentless. There's no escape from it. It gets you down, combine that with tiredness and it does get a bit depressing after a while.'*²⁶ The poor reliability of nasal polyp score (NPS; [Appendix M](#)) as a method of assessing patient outcome is illustrated by cases of CRS with multiple polyps; while a person with a high NPS may adjust to impaired breathing (i.e., breathing through their mouth rather than their nose), they can remain distressed by their loss of sense of smell.¹²

1.2.1.6 Economic burden

CRSwNP is associated with productivity loss due to absenteeism and presenteeism, as well as substantial healthcare resource utilisation (HCRU) largely attributable to outpatient care.^{1,9,51,53} A high proportion of people with CRSwNP are of working age, therefore indirect costs make a greater contribution to the overall economic burden of CRSwNP compared with direct costs.^{1,53} The substantial burden of reduced work productivity in CRSwNP was reflected in patient interviews in the UK, during which patients reported difficulties following a normal working schedule.²⁶ Some patients had to reduce their working hours and some had to completely stop working.²⁶

In a Dutch cross-sectional analysis of productivity cost questionnaire (iPCQ) responses from 115 people with CRSwNP, total indirect costs incurred by people with CRSwNP amounted to €5,659.30 per patient per year (PPPY; cost year: 2014).⁵³ People with CRSwNP reported a mean of 10.6 (standard deviation [SD]: 44.4) missed days of work per year, and about one third (34.9%) of people reported reduced effectiveness when at work.⁵³ Mean absenteeism and presenteeism costs represented €1,441.20 and €1,447.30 PPPY, respectively.⁵³

Additionally, reduced productivity related to unpaid work represented a mean of 23.7 (SD: 77.1) days per year and was associated with substantial productivity loss costs, amounting to €2,770.80 PPPY.⁵³ Annual days of absence and indirect costs are presented for patients with paid work (n=83) and those without paid work (n=32) in [Table 6](#).

Table 6. Mean annual days of absence and productivity losses with related indirect costs per patient with CRSwNP (cost year: 2014)⁵³

Expenditure	With paid work (N=83)		W/o paid work (N=32)		Total (N=115)	
	N° of days (SD)	Costs, € (SD)	N° of days (SD)	Costs, € (SD)	N° of days (SD)	Costs, € (SD)
Work absence	10.6 (44.4)	1,996.8 (7,212.9)	NA	NA	NA	1,441.2 (6,183.1)
Work productivity loss	30.4 (65.9)	2,005.3 (5,892.2)	NA	NA	NA	1,447.3 (5,078.1)
Unpaid work productivity loss	15.9 (66.0)	1,877.8 (11,555.0)	43.9 (98.7)	5,087.2 ^a (21,718.7)	23.7 (77.1)	2,770.8 (15,046.4)
Total	56.8 (124.9)	5,879.9 (18,155.2)	43.9 (98.7)	5,078.2^a (21,718.7)	23.7 (77.1)	5,659.3 (19,117.6)

CRSwNP = chronic rhinosinusitis with nasal polyps; NA = not applicable; SD = standard deviation; w/o = without

^a These costs are presented as in the publication but there seems to be a typo, as the total cost should be the sum of the other costs in the column, and so should be similar to the unpaid work productivity loss cost.

Source: Lourijssen 2020.⁵³

Direct medical costs are driven by outpatient and inpatient costs, along with costs of surgeries.^{9,53} Treatment with SCS is associated with additional HCRU and direct medical costs, including costs related to the incidence of SCS-related adverse outcomes, especially in people with ≥4 SCS prescriptions within one year.¹³ There is a strong case for SCS stewardship among people with uncontrolled CRSwNP, and especially in those with comorbid asthma who may be prescribed SCS for management of both conditions.¹² Screening for adverse effects of prolonged use of SCS may include bone density scans and cataract screening, as well as blood lipid and cholesterol tests.¹² Similarly, invasive surgical procedures for the removal of nasal polyps are associated with additional direct costs,^{9,51} as well as indirect costs due to the post-surgery period of recovery, which necessitates time away from work.¹⁰

A retrospective study assessed HCRU among 33,107 adults with CRSwNP in the UK, between 1 January 2007 and 30 June 2019, using medical and prescription record data from the CPRD – Aurum database with HES linkage.¹⁶ People with CRSwNP were followed for a mean duration of 5.3 years.¹⁶ Data for the first 90 days of follow-up post-surgery showed a greater use of SCS, INCS and antibiotics for people who had required multiple surgeries during the study.¹⁶ Furthermore, there was no decline in the number of primary care visits following multiple surgeries ([Table 7](#)), suggesting that patients continued to experience inadequate symptom control even following repeated surgical intervention.¹⁶ Inpatient and

outpatient hospital visits accounted for an overall increase in HCRU among people with multiple surgeries ([Table 7](#)).¹⁶

Table 7. HCRU and treatment of people with CRSwNP in the UK^a during the first 90 days following sinonasal surgery (including the day of surgery)¹⁶

Variable	≥1 surgery ^b N=7,793	≥2 surgeries ^c N=722
Treatment (primary care physician prescribed), n (%)		
INCS spray or drops	3,376 (43.3)	366 (50.7)
SCS	488 (6.3)	106 (14.7)
Antibiotics	1,656 (21.3)	197 (27.3)
HCRU, mean number of visits (SD)		
Primary care	3.1 (3.1)	3.5 (3.4)
Inpatient	1.1 (0.6)	1.2 (1.7)
Outpatient	1.5 (1.6)	1.8 (2.0)
All	5.6 (4.0)	6.4 (5.1)

CPRD = Clinical Practice Research Datalink; CRSwNP = chronic rhinosinusitis with nasal polyps; HCRU = healthcare resource utilisation; HES = Hospital Episode Statistics; INCS = inhaled corticosteroid; SCS = systemic corticosteroids; SD = standard deviation

a Data are from a retrospective analysis of medical and prescribing records in the UK (CPRD and HES). People with CRSwNP were followed from the index date (date of first CRSwNP diagnosis) for a period of at least 180 days up to 30 June 2019. The number of surgeries received during this follow-up period is tabulated above (≥1 or ≥2).

b Data are for the first 90 days following the first surgical intervention

c Data are for the first 90 days following the second surgical intervention

Source: Benson et al., 2023¹⁶

In a separate retrospective analysis of HES data, 101,054 people with CRSwNP underwent sinus surgery between 2010 and 2020 in England, including 38,051 revision surgeries in 14,528 people.⁹ Excluding sinus surgery, people had an average of 7.0 and 0.4 CRSwNP-related events over this period in the outpatient and inpatient settings, respectively ([Table 8](#)).⁹ These events corresponded to accrued CRSwNP-related costs of £86.3 million (outpatient: £56.8 million; inpatient: £29.5 million).⁹ The average cost of sinus surgery was £1,725.66 per patient, which amounted to an overall surgical burden of £174 million over 10 years, including £66.7 million attributable to revision surgeries.⁹ Thus, surgery is the main driver of direct medical costs among people with CRSwNP who undergo sinus surgery.⁹

Table 8. CRSwNP-related HCRU and costs in people with CRSwNP who underwent sinus surgery between 2010 and 2020 in England (N=101,054)⁹

Event type	Average number of events per patient (95% CI)	Average total costs of events per patient (95% CI)
All	7.4 (7.26, 7.54)	£853.61 (851.41, 855.81)
Outpatient	7.0 (6.91, 7.09)	£561.72 (557.38, 566.05)
Inpatient	0.4 (0.39, 0.41)	£291.89 (290.96, 292.82)
Sinus surgery	1.2 (NR)	£1,725.66 (1,723.41, 1,727.91)

CI = confidence interval; CRSwNP = chronic rhinosinusitis with nasal polyps; HCRU = healthcare resource utilisation; NR = not reported

Source: Hopkins 2022.⁹

1.2.2 Clinical pathway of care

1.2.2.1 *Current treatment options in the UK*

Guidance on the diagnosis and management of CRS in England is based on recommendations published by the European Rhinologic Society (published as the EPOS, 2020).⁵⁴ Supportive recommendations are provided by the British Rhinological Society (BRS) and European Forum for Research and Education in Allergy and Airway Disease (EUFOREA).^{1,6,10,55} As detailed below, these recommendations include use of an INCS at each step of the treatment pathway, while only short-term use of SCS is recommended for the alleviation of acute exacerbations (i.e., worsening of symptoms back to baseline severity) in people who do not respond to an INCS, with the aim of reducing nasal polyp size and providing rapid relief.^{1,10} ESS may be recommended for people with uncontrolled CRSwNP, with the goal of alleviating sinonasal symptoms and improving the delivery of INCS.¹⁰ Following surgery, people are advised to continue use of an INCS with saline rinses in order to maintain the clinical benefits of ESS.¹⁰ Short courses of SCS may be used for acute exacerbations both before and after ESS.¹ When waiting for revision surgery, patients commonly receive SCS in clinical practice,¹² despite a strong recommendation from the European Academy of Allergy & Clinical Immunology (EAACI) against the use of SCS in people with CRSwNP in the preoperative setting.⁵⁶

1.2.2.1.1 *Definition of sinonasal surgeries in EPOS and EUFOREA*

EPOS 2020 guidelines define FESS as ESS aiming to restore the normal physiology of sinuses, while full FESS is defined as ESS with complete sinus opening, anterior/posterior ethmoidectomy, middle meatal antrostomies, sphenoidotomy and frontal opening.¹ Extended and radical ESS have a similar definition to full ESS, but extended ESS may involve areas beyond the sinuses and radical ESS includes significant removal of mucosa.¹ Updated EPOS/EUFOREA 2024 guidelines state that there is no consensus on the extent of ESS, except for the recommendation against polypectomy alone without a complete ESS.¹⁰

1.2.2.1.2 *EPOS and EUFOREA recommendations*

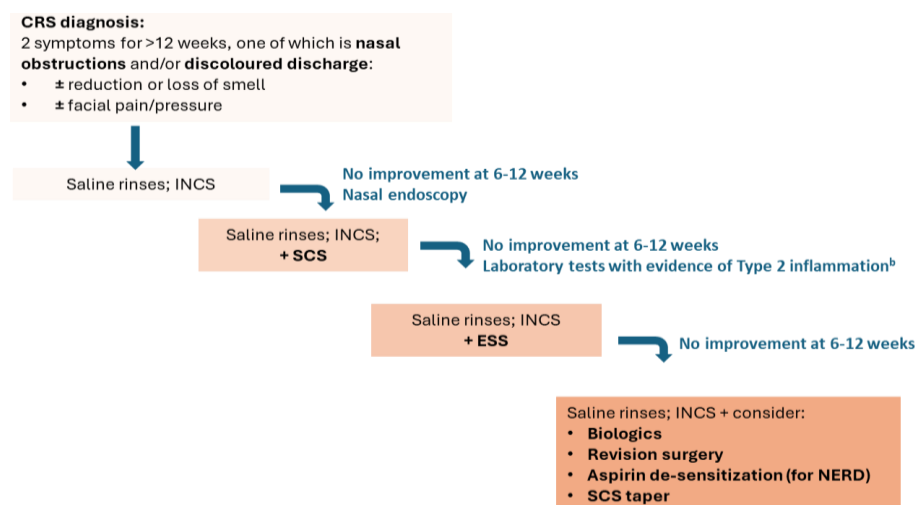
According to EPOS 2020 guidelines, people who are diagnosed with uncontrolled CRSwNP who do not show clinical improvement after 6 to 12 weeks of appropriate medical treatment may be offered primary ESS, unless surgery/anaesthesia are contraindicated ([Figure 5](#)).¹ Updated guidance (2024) from EPOS and EUFOREA also now state that people with CRSwNP are eligible for primary ESS if:¹⁰

- They have severe CRSwNP symptoms despite nasal rinses, INCS and 1 to 2 course(s) of OCS in the last 12 months

- They have comorbidities that might favour surgery
- The patient is willing/able to undergo surgery

For people with no improvement at 6 to 12 weeks following appropriate medical treatment and ESS, and who have evidence of type 2 inflammation, EPOS recommend either aspirin de-sensitisation (for people with comorbid NSAID-ERD only), revision ESS or a treatment with a biologic ([Figure 5](#)).¹ EPOS highlight that the time between revision ESS decreases with increasing numbers of revision ESS.³⁰

Figure 5. EPOS 2020 recommendations on the diagnosis and treatment of CRSwNP^{a,1}



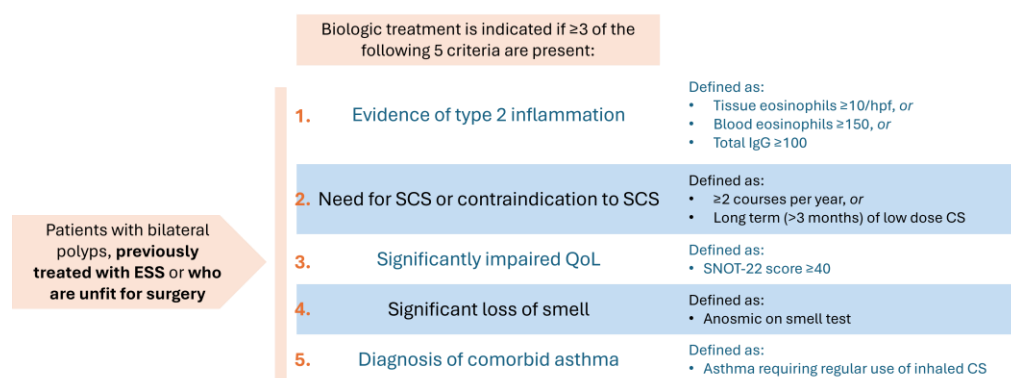
CRS = chronic rhinosinusitis; CRSwNP = chronic rhinosinusitis with nasal polyps; CT= computed tomography; ENT = ear, nose and throat; EPOS = European Position; ESS = endoscopic sinonasal surgery; INCS = intranasal corticosteroid; NERD = NSAID-exacerbated respiratory disease; NSAID = non-steroidal anti-inflammatory drug; SCS = systemic corticosteroid. Updated 2024 EPOS and EUFOREA guidance now states that people with CRSwNP are eligible for primary ESS if 1) they have severe symptoms despite nasal rinses and INCS and 1 to 2 course(s) of SCS in the last 12 months; 2) they have comorbidities that might favour surgery; or 3) the person is willing/able to undergo surgery¹⁰

^a Please note that a simplified version of the EPOS recommended treatment pathway focused on the diagnosis and treatment of CRSwNP and type 2 inflammation has been presented. ^b Evidence of type 2 inflammation includes elevated IgE and eosinophilia on laboratory test results. Sources: Current clinical guidance in Fokkens et al., 2020¹ and Hellings et al., 2024¹⁰

1.2.2.1.3 EPOS and EUFOREA recommendations for biologic therapy

Criteria for determining patient eligibility for biologic therapy are available in updated EPOS and EUFOREA guidance.^{6,10} Biologic therapy is offered to people with CRSwNP who have received primary ESS (or who are ineligible for surgery) and meet at least 3 of 5 criteria ([Figure 6](#)).^{6,10}

Figure 6. EPOS/EUFOREA criteria for the use of biologic therapy in the treatment of people with CRSwNP^{6,10}



CRSwNP = chronic rhinosinusitis with nasal polyps; CS = corticosteroid; EPOS = European Position Paper on Rhinosinusitis and Nasal Polyps; ESS = endoscopic sinonasal surgery; EUFOREA = European Forum for Research and Education in Allergy and Airway Diseases; hpf = high-power field; IgG = immunoglobulin G; QoL = quality of life; SCS = systemic corticosteroids; SNOT-22 = 22-item Sinonasal Outcomes Test

Source: Generated based on current clinical guidance in Fokkens et al., 2023³⁶ and Hellings et al., 2024¹⁰

1.2.2.1.4 **BRS recommendations for biologic therapy**

BRS experts have provided similar recommendations to that of EPOS and EUFOREA for selecting people with CRSwNP for biologic therapy.⁵⁵ The consensus among 16 clinical experts is for biologics to be considered for people with CRSwNP who have an LMK ≥ 8 , with SNOT-22 ≥ 21 (or VAS ≥ 4) and a score of ≥ 5 points according to their need for SCS, number of prior surgeries and comorbidities ([Table 9](#)).⁵⁵

Table 9. BRS criteria for the use of biologic therapy in the treatment of people with CRSwNP⁵⁵

Factor	Points	Requirement for eligibility
LMK	Score ≥ 8	Both required
SNOT-22	Score ≥ 21 (or VAS ≥ 4)	
Need for SCS (up to 2 points)		≥ 5 points are required in addition to the criteria for SNOT-22 and LMK scores
1 course in the last 12 months	1	
≥ 2 courses in the last 12 months	2	
Use of SCS is contraindicated	2	
Previous sinus surgeries for CRSwNP (up to 3 points)		
1 surgery	1	
2 surgeries	2	
≥ 3 surgeries	3	
Patients is unfit for surgery	3	

Factor	Points	Requirement for eligibility
Comorbidities		
• Asthma	1	
• NERD	1 (+1 for asthma)	

BRS = British Rhinological Society; CRSwNP = chronic rhinosinusitis with nasal polyps; LMK = Lund-Mackay Score; NERD = NSAID-exacerbated respiratory disease; NSAID = non-steroidal anti-inflammatory drug; SCS = systemic corticosteroids; SNOT-22 = 22-item Sinonasal Outcomes Test; VAS = visual analogue scale

^a patient with CRSwNP is considered eligible for treatment with a biologic if they have an LMS ≥ 8 , with a SNOT-22 score ≥ 21 (or VAS ≥ 4) and a score of ≥ 5 points made up according to their need for SCS, history of surgery and presence of comorbid conditions (asthma and/or NERD)

Source: Hopkins et al., 2021⁵⁵

1.2.2.2 **Limitations of current treatment options**

CRSwNP is characterised by a long disease duration and resistance to therapy.² As described in Section 1.2.2.1, the standard of care (hereafter described as ‘established clinical management’ or ECM) for people with uncontrolled CRSwNP includes INCS with saline rinses, SCS for exacerbations and, for patients whose disease remains uncontrolled (defined as per EPOS 2020 guidelines; Section 1.2.1.2), surgery.^{1,10} Despite being part of ECM, SCS and surgery provide only limited clinical benefit to some people with uncontrolled CRSwNP, and can be associated with high morbidity.¹²

In people with comorbid NSAID-ERD, treatment may also include aspirin de-sensitisation.^{1,10} However, only a few centres offer this treatment in the UK, so it is not considered part of the ECM for the purpose of this submission. Aspirin desensitisation is also associated with a limited efficacy and poor safety profile in comparison to biologics.⁵⁷ Based on a systematic literature review (SLR) with network meta-analysis (NMA) including 29 RCTs in patients with CRSwNP (N=3,461), aspirin desensitisation was associated with an increased incidence of adverse events and lower clinical benefit compared with biologics, including dupilumab.⁵⁷

1.2.2.2.1 **Limitations of SCS**

Therapy with SCS reduces type 2 inflammation by suppressing the immune system but is limited by its inability to only target the type 2 pathways specifically, which underlies the pathogenesis of CRSwNP.¹¹ It is not possible therefore to provide a sustained response, and the clinical benefits of SCS diminish over time.¹⁰

Extensive (cumulative courses >300 mg within one year) use of SCS in people with CRSwNP is also associated with an increased risk of adverse events, including but not limited to bruising, osteoporosis, diabetes, hypertension, myocardial infarction (if used at high doses over a long period), sleep and mood disturbances, cataracts and glaucoma.^{10,12,56,58} Despite this, clinicians may prescribe longer courses of SCS, as reported during patient interviews in the UK (*‘Well, for a long time I would get three months of steroids and then I would stop for a month or two and then I’d get another three months’*), reflecting a

lack of alternative options.^{10,26} Clinicians estimate that following surgery, ~10% of people with uncontrolled CRSwNP develop reliance on SCS as a maintenance therapy.¹² A UK study with a minimum follow-up of 2 years found use of SCS in people with asthma and/or chronic obstructive pulmonary disorder (COPD) increased the risk of osteoporosis (diagnosis or fracture), pneumonia, heart failure, cardio- or cerebro-vascular disease and cataracts.⁵⁹ Notably, comorbid asthma in people with CRSwNP may increase the risk of adverse events associated with SCS (Table 10).¹³

Table 10. Risk of SCS-related adverse events in people with CRSwNP with and without comorbid asthma

SCS-related adverse event	IRR (95% CI) vs. controls	
	People with comorbid asthma using SCS (n=12,441)	People without comorbid asthma using SCS (n=25,299)
Any	1.16 (1.04, 1.30) ^a	1.07 (1.01, 1.12) ^a
Myocardial infarction	3.89 (1.22, 12.4) ^a	0.85 (0.60, 1.20)
Hypertension	1.27 (1.02, 1.58) ^a	1.07 (0.97, 1.17)
Pneumonia	3.32 (2.00, 5.52) ^a	1.29 (0.97, 1.70)

CI = confidence interval; IRR = incidence rate ratio; SCS = systemic corticosteroids

Controls were patients with nasal polyps who were not treating with SCS. There were 1,225 and 5,806 patients in the control groups for 'with comorbid asthma' and without comorbid asthma', respectively.

^a The increased risk relative to the control group was significant (p<0.05)

Source: Davis 2022¹³

1.2.2.2.2 Limitations of Surgery

Surgical intervention for uncontrolled CRSwNP provides partial and temporary relief of some sinonasal symptoms, however the underlying driver of disease (type 2 inflammation) remains, with the potential for polyps to recur.^{8,10} Based on patient interviews conducted in the UK, symptoms return quickly following sinonasal surgery; one patient said regarding their symptoms post-surgery: 'So, within two months it was just full polyps everywhere.'²⁶

Furthermore, surgery may not be appropriate for all people with CRSwNP and is contraindicated in those with severe uncontrolled asthma due to the risks associated with anaesthesia.¹⁰ Although people with CRSwNP without previous surgery are outside of the patient population considered in this submission, those with CRSwNP and comorbid severe uncontrolled asthma may be able to benefit from dupilumab within the asthma indication.⁶⁰

Invasive surgical procedures for uncontrolled CRSwNP also carry a risk of complications.^{10,14} Minor complications, occurring in up to ~21% of patients, include perioperative bleeding, post-operative infection and synechiae in the nose.¹⁵ Severe complications occur in up to 1.5% of patients and include cerebral spinal fluid leaks, haemorrhage, orbital complications (which may include blindness in most severe cases) and intracranial complications.^{15,30}

For patients requiring revision surgery, the risk of complications increases with each subsequent surgery.^{8,16} It has been found that, before undergoing ESS, patients are most concerned about the risk of revision surgery and wait time for surgery.³⁰ Based on interviews

with UK patients with uncontrolled CRSwNP, surgery was a very negative experience for some patients (*'My body went into shock over it. I mean, the pain was horrific. It was just the most horrific experience'*).²⁶ Thus, some patients are reluctant to undergo revision surgery; for instance a patient said *'It is not something I would relish, the thought of having an operation again to be honest with you. If anything, I'd rather not have surgery again, to be honest with you.'*²⁶ As described in Section [1.2.2.2.2](#), revision surgeries may not address some of the CRSwNP symptoms (e.g., smell) and offer only temporary symptomatic benefit and limited improvement in patient HRQoL.⁵ One patient currently treated with dupilumab for CRSwNP through the Compassionate Use Scheme in the UK said that, prior to initiating dupilumab, he *'suffered constant inflammation, congestion, pressure headaches, migraines, and the loss of smell and taste'* despite six surgeries over the course of ten years.⁶¹

1.2.2.3 Proposed positioning of dupilumab

Dupilumab targets the underlying type 2 inflammation driving the pathophysiology of CRSwNP.^{17,18} Specifically, type 2 inflammation is targeted by dupilumab through selective inhibition of IL-4 and IL-13 signalling, which is a central and key driver of type 2 inflammation.^{17,18} The clinical relevance of type 2 inflammation in people with CRSwNP, particularly in people who require revision surgery, was illustrated in a retrospective study of 33,107 patients in the UK CPRD Aurum database (January 2007 to June 2019), in which investigators documented increasing levels of blood eosinophils (biomarker for type 2 inflammation) in patients requiring multiple rounds of revision surgery for nasal polyps.¹⁶

While dupilumab and other biologics have received regulatory approval for the treatment of people with uncontrolled CRSwNP in the UK, none are available to patients through the NHS. Of the other biologics, mepolizumab and omalizumab also target the type 2 inflammatory pathways but at different points further downstream compared to dupilumab.^{17,18,62-64} Mepolizumab targets IL-5 which, although it may contribute to the increase in blood eosinophils (biomarker for type 2 inflammation), plays a minor role in the type 2 inflammation response relative to that of IL-4/IL-13.⁶² Omalizumab targets IgE,⁶³ which is produced only in response to upstream IL-4/IL-13 signalling ([Figure 2](#)).⁶⁴ In contrast, dupilumab targets IL-4 and IL-13 which play several major driving roles in type 2 inflammation ([Table 11](#)).^{17,18,64} Accordingly, treatment with dupilumab has a comprehensive effect, suppressing type 2 inflammation and causing significant reductions in multiple type 2 inflammatory biomarkers, including IgE and eotaxin-3 (both in the blood and nasal secretions).⁶⁴

Table 11. Role of type 2 inflammatory cytokines and immunoglobulins in CRSwNP

Component	Known role(s)
IL-4/IL-13 (targeted by dupilumab)	• Induce the production of IL-5 and eotaxin, resulting in trafficking of eosinophils to the site of inflammation • Increase the expression of periostatin, promoting nasal polyp formation • Stimulate goblet cell mucus production (IL-13) • Promote IgE class switching of B cells, leading to IgE production • Inhibition of olfactory neurons
IL-5	• Stimulates eosinophil production and recruitment
IgE	• Promotes further production of cytokines

CRSwNP = chronic rhinosinusitis with nasal polyps; IgE = immunoglobulin E; IL = interleukin
Source: Bachert 2024,⁶⁴ Dupilumab SmPC.^{17,18}

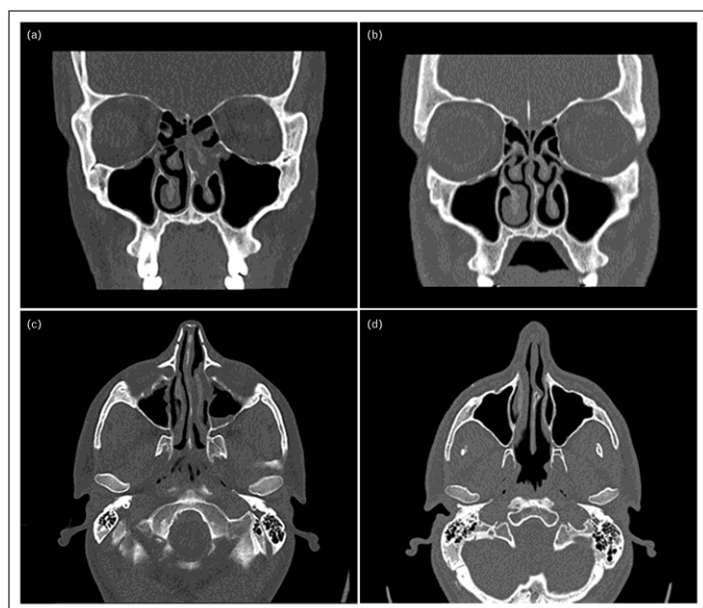
Among people with uncontrolled CRSwNP and a history of surgery, the HRQoL benefit gained from subsequent revision surgery is limited.^{5,51,52} However, post-hoc analyses of pivotal trials show SNOT-22 scores among people with uncontrolled CRSwNP and a history of surgery can be improved if they receive treatment with dupilumab (dupilumab vs. placebo, OR 9.66 [95% CI: 4.62, 20.20]; $p < 0.0001$) (Section [2.6.3](#)).⁶⁵ The benefit of dupilumab in the treatment of people with uncontrolled CRSwNP is also evident based on CT scan imaging ([Figure 7](#)).⁶⁶ Based on a real-world questionnaire study in Austria, this benefit of dupilumab results in patients' preference for treatment with dupilumab.⁶⁷ Among 75 patients with CRSwNP and a history of both surgery (≥ 1) and dupilumab treatment (≥ 3 months), 91.5% of patients reported their preference for dupilumab treatment over revision surgery.⁶⁷ Similarly, a patient currently treated with dupilumab for CRSwNP through the Compassionate Use Scheme in the UK, reported a preference for dupilumab over the treatments previously received:

*'Within three days of my first dose, I could breathe more clearly than I had in over a decade, and by the end of the first week, all symptoms vanished. Four years later, I remain symptom-free, my sense of taste and smell fully restored. [...] Dupixent has truly been life-changing, succeeding where everything else had failed.'*⁶¹

The HCP managing the patient's care said about the patient:

*'He is now virtually symptom free, with normal sense of smell and a changed person. It is one of the most complete responses I have seen to any treatment in CRS patients.'*⁶¹

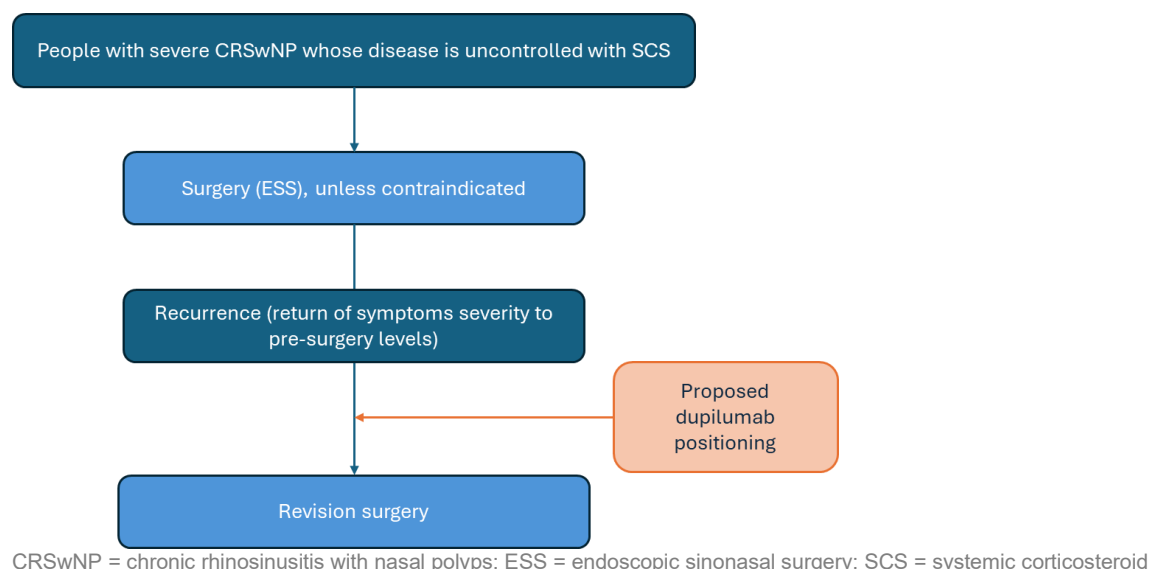
Figure 7. Coronal and axial CT scan performed before (a, c) and after (b, d) 16 weeks of dupilumab treatment in a patient with CRSwNP⁶⁶



CRSwNP = chronic rhinosinusitis with nasal polyp; CT = computed tomography
Source: Poto et al. 2024.⁶⁶

The proposed positioning of dupilumab in the treatment of people with uncontrolled CRSwNP is depicted in [Figure 8](#). In line with pivotal studies, it is anticipated that dupilumab will be used in combination with INCS in people who have received one or more prior sinonasal surgeries, with the goal of reducing type 2 inflammation, improving sinonasal symptoms and HRQoL, and reducing the risk of revision surgery and need for rescue SCS.⁶⁸ As described in Section 1.3, current ECM for patients following one sinonasal surgery consists of INCS (combined with saline rinses) and SCS, with the goal of decreasing the requirement for revision surgeries.¹ Therefore the most appropriate comparator for dupilumab as an add-on therapy to INCS, based on current clinical practice guidelines, is ECM consisting of SCS and revision surgery.

Figure 8 Proposed positioning of dupilumab for the treatment of uncontrolled CRSwNP in England



1.3 *Equality considerations*

It is expected that introduction of dupilumab in ECM will reduce existing inequalities in the care of patients with CRSwNP, as described below.

Although biologics targeting type 2 inflammation have regulatory approval in the UK for CRSwNP (including dupilumab), none are currently reimbursed.^{17,18,62,63} People with uncontrolled CRSwNP are therefore at a significant disadvantage compared to people with other forms of chronic type 2 inflammatory conditions, such as asthma and atopic dermatitis (AD), for whom targeted biologic therapies are already reimbursed.^{17,18,60,69} A NICE recommendation for dupilumab in uncontrolled CRSwNP could positively impact this inequality.

Consultation with physicians in the UK indicates that people with uncontrolled CRSwNP are likely to remain on a waiting list for ESS for a duration of 6 months up to 3 years depending on where they live, and ~50% of these people are waiting for revision surgery.¹² Based on the evidence presented in this submission, adding dupilumab to ECM (i.e., INCS) is expected to reduce the number of people with uncontrolled CRSwNP who require revision ESS.¹² Thus, the addition of dupilumab to ECM has the potential to alleviate CRSwNP burden on the NHS and reduce wait times for ESS, while the number of patients on waiting lists for treatment in England is currently increasing.^{12,70} The benefits of including dupilumab as part of ECM for patients with uncontrolled CRSwNP have been demonstrated in Scotland (NHS Tayside) where, in response to long wait times for elective surgery (>9 months), use of

dupilumab among ~30 patients with severe asthma and CRSwNP led to a 50% decrease in the rate of nasal polyp recurrence within 12 months of ESS.¹²

2 Clinical effectiveness

An SLR identified two high-quality clinical trials for dupilumab in the relevant patient population as defined by the NICE scope (SINUS-24 and SINUS-52)

- SINUS-24 and SINUS-52 are phase 3, placebo-controlled, double-blind, randomised, parallel group, multicentre international trials, evaluating the efficacy and safety of dupilumab 300 mg added to standard of care in adult patients with severe CRSwNP versus placebo group.
- In both trials, the co-primary endpoints were the change in bilateral endoscopic NPS; range 0 to 8) and nasal congestion/obstruction (NC) score (range 0 to 3) from baseline to Week 24.
- Individual results from both trials and results from the prespecified pooled analysis are presented in this submission and have informed the economic analysis.

SINUS-24 and SINUS-52 have robustly demonstrated the efficacy of dupilumab in uncontrolled CRSwNP

- In both trials, dupilumab resulted in statistically significant and clinically meaningful improvements in the co-primary endpoints of NPS and NC score at Week 24 compared to placebo. Improvements were observed as early as the first post-baseline assessment and continuously improved through Week 24. In SINUS-52, these results were maintained through Week 52 in patients treated with dupilumab once every 2 weeks (Q2W).
- In both trials, dupilumab resulted in statistically significant and clinically meaningful improvements in each hierarchically tested secondary endpoint at Week 24, compared to placebo. In SINUS-52, these results were maintained through Week 52.
- Quality of life, as measured by the SNOT-22, was significantly better with dupilumab compared to placebo.
- CRSwNP symptoms, as measured by the total symptom score (TSS), University of Pennsylvania Smell Identification Test (UPSIT) and loss of smell (LoS), were significantly improved with dupilumab compared to placebo.
- Analysis of pooled data from SINUS-24 and SINUS-52 showed that the proportion of patients who required SCS or sinonasal surgery during the treatment period was significantly lower for those receiving dupilumab vs. placebo (9.6% vs. 33.9%, respectively, $p < 0.0001$).

The safety profile of dupilumab for the treatment of CRSwNP is acceptable and consistent with existing safety data in patients with AD, asthma, COPD and prurigo nodularis (PN)

- Dupilumab has an established and robust safety profile, validated by an extensive clinical development programme involving 15,834 participants and further supported by real-world safety data across multiple indications, with no new safety signals identified in patients with CRSwNP. To date over 1 million patients have been treated with dupilumab for licenced indications worldwide.
- Dupilumab demonstrated a favourable benefit-risk and tolerability profile in CRSwNP in the SINUS-24 and SINUS-52 trials.
- Dupilumab has the potential to generate a significant step-change in the effective treatment of uncontrolled CRSwNP in England, providing meaningful benefits to a burdened patient population with limited treatment options.

2.1 Identification and selection of relevant studies

An SLR was conducted with a cut-off date of 01 October 2024 to identify all relevant RCTs reporting on the clinical efficacy and safety of dupilumab and other relevant treatments in adults with uncontrolled CRSwNP.

A total of 16,856 publications were identified in the database searches, and following removal of duplicates, 15,359 publications underwent title and abstract screening. Overall, 465 publications were selected for full-text screening, along with 6 publications identified through grey literature searches, and 141 publications were included in the SLR. These 141 publications reported data from 39 unique RCTs. Among the RCTs identified, 19 investigated biologics (including dupilumab, omalizumab, mepolizumab, benralizumab, reslizumab and CM310), four investigated surgery and 16 investigated other interventions (including corticosteroids [CSs], leukotriene receptor antagonists [LTRA] and implants comprising CSs). The two RCTs which investigated dupilumab, LIBERTY NP SINUS-24 (i.e., SINUS-24) and LIBERTY NP SINUS-52 (i.e., SINUS-52), are described in detail below.

Full details of the SLR methodology, study selection process, inclusion and exclusion criteria and results are presented in [Appendix D.1](#).

2.2 *List of relevant clinical effectiveness evidence*

The relevant clinical effectiveness evidence for dupilumab in CRSwNP was generated from the SINUS-24 and SINUS-52 trials which are summarised in [Table 12](#). The two trials had similar designs, except for the study duration and the number of dupilumab treatment arms:⁶⁸

- The trial duration was 24 weeks for SINUS-24 and 52 weeks for SINUS-52.
- SINUS-24 included one dupilumab treatment arm (Q2W), while SINUS-52 included two dupilumab treatment arms with a different dosing to SINUS-24 in one of the arms (Arm A: Q2W; Arm B: Q2W to Week 24, then once every four weeks [Q4W] to Week 52).

Both studies were multinational, multicentre, randomised, double-blind, placebo-controlled, parallel group phase 3 trials evaluating the efficacy and safety of dupilumab 300 mg in adult patients with severe CRSwNP receiving standard of care (defined as 100 µg mometasone furoate nasal spray [MFNS] in each nostril twice daily).⁶⁸

Table 12. Overview of SINUS-24 and SINUS-52 trials^{68,71,72}

Study characteristics	SINUS-24 (NCT02912468)	SINUS-52 (NCT02898454)
Study design	Multinational, multicentre, randomised, double-blind, placebo-controlled, parallel group phase 3 trials	
Population	Patients with bilateral sinonasal polyposis that persisted despite prior treatment with SCS within the past 2 years; and/or had a medical contraindication/ intolerance to SCS; and/or had prior sinonasal surgery for nasal polyps, and had: • An endoscopic bilateral NPS ≥5 with a minimum score of 2 in each nasal cavity	

Study characteristics	SINUS-24 (NCT02912468)	SINUS-52 (NCT02898454)
	Ongoing symptoms of nasal congestion or obstruction, and either decreased/loss of smell or rhinorrhoea	
Interventions	Dupilumab 300 mg SC Q2W All patients received concomitant MFNS (100 µg in each nostril twice daily)	- Arm A: dupilumab 300 mg SC Q2W to Week 52 - Arm B: dupilumab 300 mg SC Q2W to Week 24, then Q4W to Week 52 All patients received concomitant MFNS (100 µg in each nostril twice daily)
Comparator	Placebo Q2W	
Indicate if study supports application for marketing authorisation	Yes	
Indicate if study used in the economic model	Yes	
Rationale if study not used in model	Not applicable	
Reported outcomes specified in the decision problem (in hierarchical order)	Clinician-assessed efficacy outcomes NPS - Lund-Mackay - UPSIT - PNIF Patient-reported efficacy outcomes - NC score - Decreased/loss of smell Patient-reported HRQoL outcomes SNOT-22 score - EQ-5D VAS Safety assessments TEAEs - SAEs	
All other reported outcomes	Clinician-assessed efficacy outcomes - FEV₁ Patient-reported efficacy outcomes - TSS - ACQ-6 - Overall rhinosinusitis VAS - Rhinorrhoea severity Safety assessments - PK/PD	

ACQ-6 = 6-item Asthma Control Questionnaire; EQ-5D = European Quality of Life Scale-5 dimension scale; FEV₁ = forced expiratory volume in 1 second; HRQoL = health-related quality of life; MFNS = mometasone furoate nasal spray; NC = nasal congestion; NPS = nasal polyp score; PD = pharmacodynamics; PK = pharmacokinetics; PNIF = peak nasal inspiratory flow; Q2W = once every two weeks; Q4W = once every four weeks; SAE = serious adverse event; SC = subcutaneous; SCS = systemic corticosteroids; SNOT-22 = 22-item Sinonasal Outcomes Test; TEAE = treatment-emergent adverse event; TSS = total symptom score; UPSIT = University of Pennsylvania Smell Identification Test; VAS = visual analogue scale. Sources: Bachert 2019;⁶⁸ Sanofi. Data on File, Clinical Study Report SINUS-24;⁷¹ Sanofi. Data on File, Clinical Study Report SINUS-52.⁷²

Several post-hoc analyses of data from SINUS-24 and SINUS-52 have been conducted. The post-hoc analyses, which further inform the outcomes within the decision problem of this submission, are presented in [Table 13](#) with their objectives.

Table 13. Overview of SINUS-24 and SINUS-52 post-hoc analyses

Publication	Objectives
Bachert et al. 2024¹¹	Assessing dupilumab efficacy according to different definitions of type 2 inflammatory signatures
Bachert et al. 2024⁷³	Evaluating the achievement of mild-to-no-symptom months and symptom-free months with dupilumab vs. placebo for four key symptoms in the SINUS trials
Bachert et al. 2022⁷⁴	Investigating the effect of dupilumab on the proportions of patients with improved, stable or worsened NPS and NC over time in the SINUS trials
Bachert et al. 2020⁷⁵	Evaluating the effect of dupilumab on reported respiratory infection rates in patients in SINUS- 52
Busse et al. 2023⁷⁶	Assessing the effect of dupilumab on CRSwNP and asthma outcomes in patients with coexisting asthma stratified by baseline asthma characteristics
Busse et al. 2022⁷⁷	Assessing the effect of dupilumab on the SNOT-22 sleep and function domain scores
Chuang et al. 2022⁷⁸	Assessing the effect of dupilumab on patient-reported sinonasal symptoms and objective measures using responder thresholds for clinically meaningful within-patient improvement
Desrosiers et al. 2021⁷⁹	Investigating whether dupilumab was superior to ECM in reducing the need for SCS use or sinonasal surgery
Fujieda et al. 2022⁸⁰	Determining whether eosinophilic status in CRSwNP, classified using the JESREC algorithm, was a predictor of dupilumab efficacy
Gevaert et al. 2023⁸¹	Assessing the early onset and durable long-term effects of dupilumab on patient-reported symptoms of NC, LoS and rhinorrhoea
Gurnell et al. 2024⁸²	Investigating SCS use and asthma outcomes among patients with comorbid asthma
Hellings et al. 2022⁸³	Investigating the onset of action, magnitude and time course of treatment effects of dupilumab across disease and HRQoL measures in patients with and without prior sinonasal surgery, and comorbid asthma, NSAID-ERD and allergic rhinitis
Hopkins et al. 2024⁷	Identifying the SNOT-22 items most important to patients in the SINUS trials, determining dupilumab effects on the severity of these items, and determining the changes in objective disease measures for patients with and without improvement in these items
Hopkins et al. 2021⁸⁴	Assessing the efficacy of dupilumab in patients in the SINUS trials by history of prior sinus surgery (by number of surgeries [≥ 1 , 1, 2 or ≥ 3 prior surgeries] and time since last surgery [< 3 , 3 to < 5 , 5 to < 10 or ≥ 10 years since most recent])
Laidlaw et al. 2021³⁵	Evaluating the effect of dupilumab on a range of airway function and HRQoL outcome measures in patients with comorbid asthma in the SINUS trials
Lane et al. 2022⁸⁵	Assessing dupilumab effect on anosmia in patients with baseline smell impairment
Lee et al. 2023⁸⁶	Investigating the relationship between sinus disease severity based on LMK-CT score and olfactory impairment at baseline and following treatment with dupilumab in patients in the SINUS trials
Lee et al. 2022⁶⁵	Evaluating dupilumab effects on disease-specific HRQoL and general health status measures

Publication	Objectives
Mullol et al. 2022 ⁴³	Assessing the effects of dupilumab on olfactory outcomes

CRSwNP = chronic rhinosinusitis with nasal polyps; ECM = established clinical management; ERD = exacerbated respiratory disease; HRQoL = health-related quality of life; JESREC = Japanese Epidemiological Survey of Refractory Eosinophilic Rhinosinusitis; LMK-CT = Lund-Mackay computed tomography; LoS = loss-of-smell; NC = nasal congestion/obstruction; NSAID = non-steroidal anti-inflammatory drug; SCS = systemic corticosteroid; SNOT-22 = 22-item Sino-Nasal Outcome Test. Sources: Bachert 2024;¹¹ Bachert 2024;⁷³ Bachert 2022;⁷⁴ Bachert 2020;⁷⁵ Busse 2023;⁷⁶ Busse 2022;⁷⁷ Chuang 2022;⁷⁸ Desrosiers 2021;⁷⁹ Fujieda 2022;⁸⁰ Gevaert 2023;⁸¹ Gurnell 2024;⁸² Hellings 2022;⁸³ Hopkins 2024;⁷ Hopkins 2021;⁸⁴ Laidlaw 2021;³⁵ Lane 2022;⁸⁵ Lee 2023;⁸⁶ Lee 2022;⁶⁵ Mullol 2022.⁴³

Additionally, the AROMA registry study, which was a prospective, observational, multicentre, open-label, single arm, real-world study, provides data on the use of dupilumab in clinical practice including efficacy and safety data relative to the outcomes within the decision problem of this submission.⁸⁷ The AROMA registry study is summarised in [Table 14](#).

Table 14. Overview of AROMA registry study

Study design	Global, prospective, observational, multicentre, open-label, single-arm, real-world study
Objectives	Primary objectives - Longitudinally characterising the long-term effectiveness of dupilumab through assessment of patient-reported symptoms and HRQoL related to CRSwNP and other type 2 comorbidities - Characterising patients who receive dupilumab for CRSwNP in a real-world setting in terms of medical history, demographic, disease characteristics and type 2 comorbidities Secondary objectives - Characterising real-world utilisation of dupilumab in patients with CRSwNP - Collecting global assessment of disease severity and treatment satisfaction - Collecting long-term safety data for dupilumab in patients with CRSwNP Exploratory objectives - Assessing INCS/SCS treatment patterns in patients with CRSwNP - Assessing the use of controller medications in patients with comorbid asthma - Collecting information on surgery for CRSwNP in patients treated with dupilumab and recurrence of CRSwNP in these patients
Population	Adult patients (aged ≥18 years) newly initiating dupilumab for CRSwNP according to country-specific prescribing information, as part of their routine care following prescription by their physician
Treatment	Dupilumab prescribed as per usual local clinical practice (patients may receive other medicines and treatments for CRSwNP and for any comorbidities as per local standards of care)
Endpoints	Primary endpoints - Descriptive summary of symptoms and HRQoL and their change over time (including several efficacy outcomes also evaluated in the SINUS-24 and SINUS-52 trials: NC score, Lund-Mackay, decreased/loss of smell, SNOT-22 score, TSS, UPSIT, PNIF, ACQ-6 and FEV₁) - Descriptive summary of patients and disease characteristics for CRSwNP and type 2 comorbidities Secondary endpoints - Descriptive summaries of CRSwNP treatment patterns (dupilumab and other treatments, including most commonly used treatments, dosage, adherence, interruption, place and frequency of administration)

	• Reasons for initiation of new CRSwNP treatment(s), concomitant therapies, treatment durations and discontinuation and/or switching • Global assessment of disease severity and treatment satisfaction (patient and physician) • Descriptive summary of AEs Exploratory endpoints • Descriptive summaries of INCS/SCS use in CRSwNP patients pre- and post-use of dupilumab • Descriptive summaries of controller medication use in patients with comorbid asthma • Descriptive summary of history of surgeries and recurrence rate of nasal polyposis post-dupilumab initiation

ACQ-6 = 6-item Asthma Control Questionnaire; AE = adverse event; CRSwNP = chronic rhinosinusitis with nasal polyps; FEV1 = forced expiratory volume in 1 second; INCS = intranasal corticosteroid; NC = nasal congestion/obstruction; PNIF = peak nasal inspiratory flow; SCS = systemic corticosteroid; SNOT-22 = 22-item Sinonasal Outcomes Test; TSS = total symptom score; UPSIT = University of Pennsylvania Smell Identification Test.

Source: Regeneron Pharmaceuticals data on file, AROMA Registry Study Protocol.⁸⁷

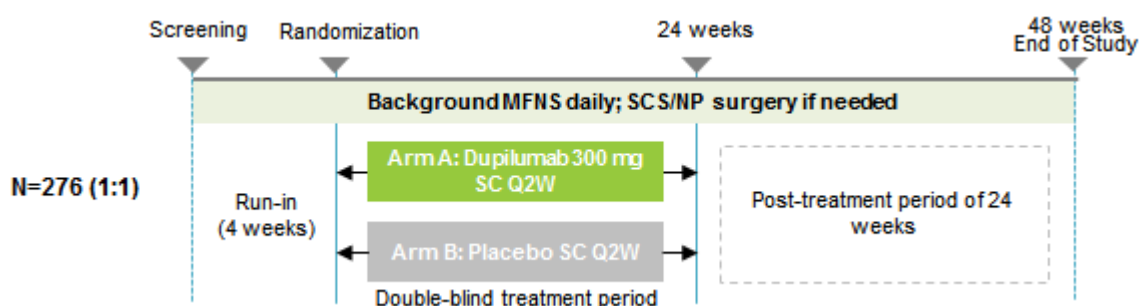
2.3 Summary of methodology of the relevant clinical effectiveness evidence

2.3.1 Trial Design

SINUS-24 and SINUS-52 were both multinational, multicentre, randomised, double-blind, placebo-controlled, parallel group phase 3 trials evaluating the efficacy and safety of dupilumab 300 mg added to standard of care in adult patients with severe CRSwNP.⁶⁸

The SINUS-24 study included a 4-week run-in period (± 3 days), a 24-week treatment period (± 3 days) and a 24-week post-treatment follow-up period (± 3 days; no dupilumab/placebo received).⁶⁸ Patients were randomised (1:1) to receive dupilumab or placebo until Week 24; all patients also received standard of care treatment with MFNS (100 μ g in each nostril twice daily) until Week 24 (Figure 9).⁶⁸

Figure 9. SINUS-24 study design⁷¹



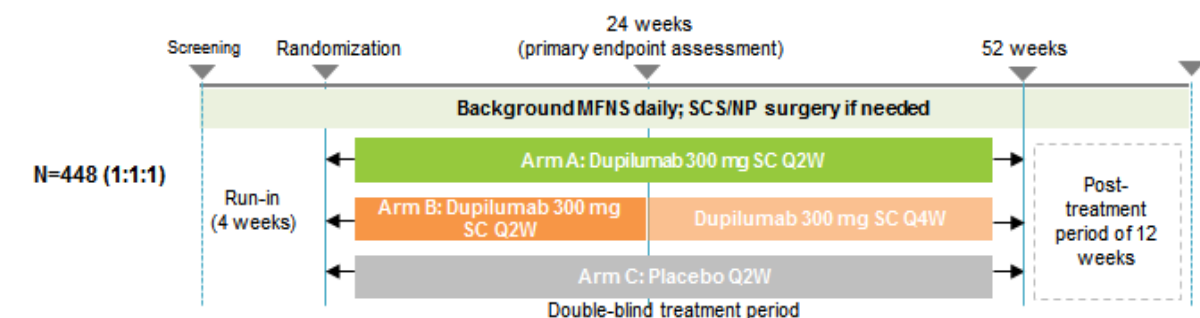
MFNS = mometasone furoate nasal spray; NP = nasal polyp; Q2W = once every 2 weeks; SC = subcutaneous; SCS = systemic corticosteroids.

Source: Sanofi data on file, Clinical Study Report SINUS 24.⁷¹

The SINUS-52 study included a 4-week run-in period (± 3 days), a 52-week treatment period (± 3 days) and a 12-week post-treatment period (± 3 days).⁶⁸ Patients were randomised

(1:1:1) to receive dupilumab Q2W until Week 52 (Arm A), dupilumab Q2W (Arm B) until Week 24 followed by dupilumab Q4W until Week 52 (Arm B), or placebo until Week 52 (Arm C); all patients also received standard of care treatment with MFNS (100 µg in each nostril twice daily) until Week 52 ([Figure 10](#)).⁶⁸

Figure 10. SINUS-52 study design⁷²



MFNS = mometasone furoate nasal spray; NP = nasal polyp; Q2W = once every 2 weeks; Q4W = once every 4 weeks; SC = subcutaneous; SCS = systemic corticosteroids
Source: Sanofi. Data on File, Clinical Study Report SINUS-52.⁷²

The study completion dates for SINUS-24 and SINUS-52 were 5 July 2018 and 29 August 2018, respectively.⁶⁸

The study protocols for SINUS-24 and SINUS-52 included a prespecified pooled analysis (Section [2.4.2.3](#)).

2.3.2 Patient eligibility

Eligible patients enrolled in SINUS-24 and SINUS-52 comprised adults with bilateral sinonasal polyposis and symptoms of CRS despite INCS therapy and who had received SCS in the preceding two years (or had a medical contraindication or intolerance to SCS) or previous surgery for nasal polyps.⁶⁸ Key inclusion and exclusion criteria for SINUS-24 and SINUS-52 are presented in [Table 15](#).

Table 15. Inclusion and exclusion criteria for SINUS-24 and SINUS-52^{68,71,72}

Inclusion criteria
- Patients with bilateral sinonasal polyposis that persisted despite prior treatment with SCS within the past 2 years; and/or had a medical contraindication/intolerance to SCS; and/or had prior sinonasal surgery for nasal polyps, and had: - An endoscopic bilateral NPS ≥ 5 at Visit 1 (maximum score of 8) with a minimum score of 2 in each nasal cavity - Ongoing symptoms (for at least 8 weeks before Visit 1)* of nasal congestion or obstruction (moderate or severe: score 2 or 3 at Visit 1 and a weekly average severity of >1 at Visit 2), and either loss of smell (partial or total) or rhinorrhoea (anterior or posterior)
Exclusion criteria
- Aged <18 years - Had taken:

Inclusion criteria
- o Biologic therapy/systemic immunosuppressant to treat inflammatory disease or autoimmune disease (e.g., rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus or multiple sclerosis) ≤ 2 months before Visit 1 or 5 half-lives, whichever is longer - o Any experimental monoclonal antibody within 5 half-lives before Visit 1 or ≤ 6 months if the half-life is unknown - o Anti-IgE therapy (e.g., omalizumab) ≤ 130 days prior to Visit 1 • Patients who are receiving leukotriene antagonists/modifiers at Visit 1, unless they were on continuous treatment for ≥ 30 days prior to Visit 1 • Initiated allergen immunotherapy ≤ 3 months prior to Visit 1 or planned to begin therapy or change dosing during the run-in period or the randomised treatment period • Underwent any intranasal and/or sinonasal surgery (including polypectomy) ≤ 6 months prior to Visit 1 • Had a sinonasal or sinonasal surgery changing the lateral wall structure of the nose making the evaluation of NPS impossible • Had conditions/concomitant diseases making them non-evaluable at Visit 1 or for the primary efficacy endpoint, such as antrochoanal nasal polyps, acute rhinosinusitis, upper respiratory infection, allergic granulomatous angiitis/eosinophilic granulomatosis with polyangiitis, granulomatosis with polyangiitis, cystic fibrosis, fungal rhinosinusitis, Young syndrome, Kartagener syndrome or dyskinetic cilia syndrome • Had nasal cavity malignant tumour or benign tumours at screening • Had FEV₁ $\leq 50\%$ of predicted normal at screening • Prior participation to another dupilumab study

* ≥ 8 weeks before screening followed by 4 weeks prior to randomisation (total 12 weeks of symptoms).

FEV₁ = forced expiratory volume in 1 second; IgE = immunoglobulin E; NPS = nasal polyp score; SCS = systemic corticosteroids.

Sources: Bachert 2019;⁶⁸ Sanofi. Data on File, Clinical Study Report SINUS-24;⁷¹ Sanofi. Data on File, Clinical Study Report SINUS-52.⁷²

2.3.3 Settings and locations

SINUS-24 was conducted at 79 centres in 13 countries (Bulgaria, Republic Czech, France, Germany, Hungary, Italy, Netherlands, Poland, Romania, Ukraine, Russia, the UK and the US).⁷¹ Of these 79 centres, 67 randomised at least one participant.⁷¹ Six sites were located in the UK which included a randomised total of 19 patients; two of these 19 patients withdrew prematurely from the study.

SINUS-52 was conducted at 119 centres in 14 countries (including Argentina, Australia, Belgium, Canada, Chile, Israel, Mexico, Portugal, Russia, Spain, Sweden, Turkey, Japan and the US).⁷² Of these 119 centres, 117 randomised at least one participant.⁷²

2.3.4 Trial drugs and concomitant medications

Patients in the SINUS-24 and SINUS-52 studies were randomised 1:1 to receive either dupilumab or placebo, with randomisation stratified by history of asthma, history of NSAID-ERD, for nasal polyps and country.^{68,71,72}

In SINUS-24, patients were randomised (1:1) to receive 300 mg of dupilumab subcutaneously (SC) Q2W or placebo Q2W until Week 24,⁶⁸ while in SINUS-52, patients were randomised (1:1:1) to receive the following treatment regimens:⁶⁸

- Dupilumab 300 mg SC Q2W until Week 52 (Arm A)
- Dupilumab 300 mg SC Q2W until Week 24, then SC Q4W until Week 52 (Arm B)
- Placebo Q2W until Week 52 (Arm C)

In both SINUS-24 and SINUS-52, all patients were receiving standard of care which consisted of 2 self-administered actuations of MFNS (50 µg/actuation) in each nostril twice daily (400 µg per day total) from the beginning of the run-in period and throughout the study.^{68,71,72} If patients were unable to tolerate the MFNS dose, or its use was prohibited due to a specific regulatory requirement, patients could reduce the dose to 2 actuations of MFNS in each nostril once daily (200 µg per day total).⁶⁸

The following treatments were permitted as rescue therapies throughout both studies:^{71,72}

- Nasal lavage with saline and/or systemic antibiotics (≤2 weeks in case of acute infection)
- Short course SCS (≤2 weeks prednisone or prednisolone)
- Sinonasal surgery for nasal polyps

Other permitted concomitant therapies included short term antibiotics (<2 weeks), short and long-acting beta agonists, long-acting muscarinic antagonists, methylxanthines, INCS and systemic antihistamines, as well as leukotriene antagonists/modifiers and allergen immunotherapy if started prior to screening.^{71,72}

2.3.5 Outcomes

The co-primary endpoints in SINUS-24 and SINUS-52 were the change in bilateral endoscopic NPS (range 0 to 8) and NC score (range 0 to 3) from baseline at Week 24.⁶⁸ In Japan, the change in sinus opacification (LMK-CT score) was included as a third co-primary outcome, whereas it was a key secondary outcome in the other trial countries.⁶⁸ Two of the key secondary endpoints in both trials, which assessed HRQoL and one of the most burdensome symptoms in patients with CRSwNP, were changes from baseline at Week 24 in SNOT-22 score and in daily symptoms of decreased/loss of smell, respectively.⁶⁸

Additionally, two key secondary endpoints (proportion of patients requiring rescue treatment with SCS or sinonasal surgery and change from baseline in lung function in patients with

comorbid asthma) were multiplicity adjusted and included as part of the statistical hierarchy using pooled data from SINUS-24 and SINUS-52.⁶⁸

Primary and key secondary efficacy endpoints evaluated in SINUS-24 and SINUS-52 are presented in [Table 16](#). Further details on the efficacy endpoints are presented in [Appendix M](#).

Table 16. Primary and secondary endpoints in SINUS-24 and SINUS 52^{*68,71,72}

Type	Endpoint	Time period
Endpoints included in hierarchical testing (in order of testing)		
Co-primary endpoints	Change from baseline in NPS as assessed by nasal endoscopy	Baseline to Week 24
	Change from baseline in NC score based on patient evaluation	
Key secondary endpoints	Change from baseline in sinus opacification as assessed by CT scans using the Lund-Mackay scoring system**	Baseline to Week 24
	Change from baseline in TSS	
	Change from baseline in smell test (UPSIT)	
	Change from baseline in daily symptoms of decreased/loss of smell	
	Change from baseline in SNOT-22 scores	
	Change from baseline in NPS as assessed by nasal endoscopy	Baseline to Week 52 (SINUS-52)
	Change from baseline in NC score based on patient evaluation	
	Change from baseline in SNOT-22 scores	
	Pooled analysis only: Proportion of patients requiring rescue treatment (SCS or sinonasal surgery) and time-to-event for rescue treatment†	Baseline to Week 24 (SINUS-24 and SINUS-52 Arm B) or Week 52 (SINUS-52 Arms A and C)
	Pooled analysis only: Change from baseline in FEV ₁ in patients with asthma†	Baseline to Week 24

Type	Endpoint	Time period
Endpoints not included in hierarchical testing		
Other secondary endpoints	Change from baseline and time course profiles in NPS, NC score, Lund-Mackay score, TSS, UPSIT, daily loss of smell and SNOT-22 score	Baseline to Week 48 (SINUS-24) or Week 52 (SINUS-52)
	Proportion of responders per NPS criteria (improvement ≥ 1 point or ≥ 2 points)	Baseline to Week 24
	Change from baseline in: VAS for overall rhinosinusitis VAS for EQ-5D Severity of rhinorrhoea (anterior/posterior nasal discharge) daily symptom score assessed by the patient	Baseline to Week 24 (SINUS-24), or Week 24 and Week 52 (SINUS-52)
	Change from baseline in PNIF	Baseline to Week 24
	Change from baseline in ACQ-6 total score in patients with asthma	Baseline to Week 24 (SINUS-24), or Week 24 and Week 52 (SINUS-52)

ACQ-6 = 6-item Asthma Control Questionnaire; CT = computed tomography; EQ-5D = European Quality of Life Scale-5 dimension scale; FEV1 = forced expiratory volume in 1 second; NC = nasal congestion; NP = nasal polyp; NPS = nasal polyp score; PNIF = peak nasal inspiratory flow SCS = systemic corticosteroids; SNOT-22 = 22-item Sinonasal Outcomes Test; TSS = total symptom score; UPSIT = University of Pennsylvania Smell Identification Test; VAS = visual analogue scale
Note: Blue and orange shadings represent endpoints unique to SINUS-52 and to SINUS-24/SINUS-52 pooled analysis, respectively.

* In SINUS-52, comparisons at Week 24 were conducted for pooled Arms A and B vs. placebo, and comparisons at Week 52 were conducted for Arm A vs. placebo.

** This endpoint was assessed as a co-primary endpoint for study participants in Japan.

† Two prespecified analyses (proportion of patients requiring rescue with SCS or sinonasal surgery and FEV1 at Week 24) were included in the statistical hierarchy using pooled data from SINUS-24 and SINUS-52.

Sources: Bachert 2019;⁶⁸ Sanofi. Data on File, Clinical Study Report SINUS-24;⁷¹ Sanofi. Data on File, Clinical Study Report SINUS-52.⁷²

2.3.6 Baseline characteristics

A total of 276 patients were randomised in the SINUS-24 study (n=143 in dupilumab arm; n=133 in placebo arm) and 448 patients in the SINUS-52 study (n=150 in Arm A [dupilumab Q2W]; n=145 in Arm B [dupilumab Q2W to Q4W]; n=153 in placebo arm).⁶⁸

In SINUS-24, 263 patients completed study treatment during the randomised 24-week treatment period; 12 (4.3%) patients discontinued treatment prior to Week 24 and 13 (4.7%) patients had discontinued from the study at Week 48.⁶⁸ One patient randomised to dupilumab 300 mg Q2W was not treated.⁶⁸ The majority of patients completed the 24-week treatment period (placebo: n=130 [97.7%]; dupilumab: n=141 [98.6%]), as well as the entire study period including post-treatment follow up (placebo: n=124 [93.2%]; dupilumab: n=138 [96.5%]).⁶⁸

In SINUS-52, 419 patients completed the first 24 weeks of study treatment (dupilumab: n=285 [96.6%]; placebo: n=133 [86.9%]); 29 patients (6.5%) among the full study population discontinued treatment during the 24-week period.⁶⁸ Only 49 patients (10.9%) discontinued study treatment prior to Week 52, with the majority of patients completing study assessments over the 52-week period (Arm A: n=146 [97.3%]; Arm B: n=142 [97.9%]; placebo arm: n=140 [91.5%]).⁶⁸

In both SINUS-24 and SINUS-52, baseline and demographic factors were balanced between treatment arms and were consistent with a population with severe CRSwNP, based on the ubiquity of chronic rhinosinusitis symptoms, bilateral obstructive polyps and extensive sinus involvement ([Table 17](#)).⁶⁸

The mean patient age was 52 years (range: 42, 61) and the majority of the patients were male (60%).⁷¹ The studies met their prespecified enrolment goal of 50% patients with comorbid asthma and/or NSAID-ERD and 50% with prior sinonasal surgery.⁶⁸ History of sinonasal surgery and SCS use was comparable among the treatment groups.⁶⁸ The mean time since first diagnosis of CRSwNP in the overall study population was 11.0 years (SD: 9.45).⁶⁸ Most patients (63%) had previous surgery for nasal polyps with the number of surgeries ranging from 1 to 11.^{68,71,72} In the two years prior to randomisation, 74% of patients received SCS at least once. The mean number of days of SCS use was 14.4 days (range: 1 to 135) in SINUS-24 and 45.5 days (range: 1 to 732) in SINUS-52.^{71,72}

There were 577 (80%) patients with a medical history of ≥ 1 type 2 inflammation-mediated condition, including 428 (59%) patients with a history of asthma.^{68,71,72} The most frequently reported comorbidity other than asthma was allergic rhinitis (SINUS-24: 52.5%; SINUS-52: 60.7%) seasonal or perennial, followed by allergic conjunctivitis (SINUS-24: 10.1%; SINUS-52: 12.1%) and food allergy (SINUS-24: 10.1%; SINUS-52: 8.9%) which were comparable between treatment groups.^{71,72}

In the population with comorbid asthma:^{71,72}

- In SINUS-24:
 - o The mean time since asthma diagnosis was 15.5 years (range: 0.1 to 65.5) and the mean baseline percent predicted forced expiratory volume in 1 second (FEV₁) was 85.3% (range: 49.0 to 191.0)
 - o Most patients (88.8%) were on asthma medication in the prior year, with most (76.7%) using both ICS and long-acting beta agonists
 - o At baseline, asthma was uncontrolled in some patients as reflected by median 6-item Asthma Control Questionnaire (ACQ-6) score of 1.67
- In SINUS-52:
 - o The mean time since asthma diagnosis was 17.7 years (range: 0.2 to 74.6) and the mean baseline percent predicted FEV₁ was 83.4% (range: 52 to 188.3)

- o Most patients (92.1%) with asthma were on asthma medication in the prior year, with most (72.0%) using both INCS and long-acting beta agonists
- o At baseline, asthma was uncontrolled in some patients as reflected by median ACQ-6 score of 1.50

Table 17. Baseline characteristics of participants in SINUS-24 and SINUS-52 (ITT population)^{68,71,72}

	SINUS-24		SINUS-52		
	Dupilumab Q2W	Placebo	Dupilumab Q2W	Dupilumab Q2W to QW4	Placebo
N	143	133	150	145	153
Male, n (%)	88 (62)	70 (53)	97 (65)	87 (60)	95 (62)
Age, mean (SD)	50.2 (13.6)	50.8 (13.2)	51.9 (11.9)	52.3 (12.9)	51.7 (12.7)
Race, n (%)					
Caucasian/White	138 (96.5)	126 (94.7)	124 (82.7)	120 (82.8)	128 (83.7)
Black/African decent	2 (1.4)	7 (5.3)	2 (1.3)	2 (1.4)	3 (2.0)
Asian/Oriental	1 (0.7)	0	17 (11.3)	19 (13.1)	18 (11.8)
American Indian/Alaska Native	1 (0.7)	0	7 (4.7)	2 (1.4)	3 (2.0)
Native Hawaiian/Other Pacific Islander	0	0	0	1 (0.7)	0
Multiple	0	0	0	1 (0.7)	1 (0.7)
Unknown	1 (0.7)	0	0	0	0
Ethnicity					
Hispanic or Latino	5 (3.5)	1 (0.8)	50 (33.3)	42 (29.2)	40 (26.1)
Not Hispanic or Latino	138 (96.5)	130 (99.2)	100 (66.7)	102 (70.8)	113 (73.9)
Territory					
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)
BMI (kg/m ²), mean (SD)	27.49 (5.11)	28.36 (5.76)	27.96 (5.51)	27.96 (5.51)	27.91 (5.50)
Time since first diagnosis of nasal polyps (years), mean (SD)	11.42 (9.69)	10.77 (8.57)	11.28 (10.28)	10.67 (9.12)	10.88 (9.40)
Previous surgeries for nasal polyps, n (%)					
≥1 previous surgery	99 (69)	99 (74)	88 (59)	85 (59)	88 (58)
≥3 previous surgeries	33 (23)	29 (22)	22 (15)	9 (6)	18 (12)
Time since most recent surgery for nasal polyps (years), mean (SD)	5.93 (5.57)	5.54 (5.07)	7.54 (7.02)	8.41 (6.83)	8.77 (7.15)
SCS use in the past 2 years, n (%)	92 (64.3)	87 (65.4)	121 (81)	116 (80)	122 (80)
Bilateral endoscopic NPS* (scale 0-8), mean (SD)	5.64 (1.23)	5.86 (1.31)	6.07 (1.22)	6.29 (1.20)	5.96 (1.21)

	SINUS-24		SINUS-52		
	Dupilumab Q2W	Placebo	Dupilumab Q2W	Dupilumab Q2W to QW4	Placebo
NC score* (scale 0-3), mean (SD)	2.26 (0.57)	2.45 (0.55)	2.48 (0.62)	2.44 (0.59)	2.38 (0.54)
SNOT-22 total score* (scale 0-110), mean (SD)	48.00 (20.16)	50.87 (20.22)	50.16 (19.72)	51.89 (21.05)	53.48 (21.85)
Smell test (UPSIT) score** (scale 0-40), mean (SD)	14.68 (8.66)	14.44 (8.31)	13.46 (8.20)	13.60 (7.57)	13.78 (8.31)
LoS score* (scale 0-3), mean (SD)	2.70 (0.57)	2.73 (0.51)	2.81 (0.46)	2.73 (0.59)	2.72 (0.52)
LMK-CT total score* (scale 0-24), mean (SD)	18.55 (4.55)	19.55 (4.26)	18.42 (3.61)	17.81 (3.89)	17.65 (3.76)
Rhinosinusitis disease severity* (VAS 0-10cm), mean (SD)	7.42 (2.01)	7.96 (2.06)	8.24 (1.77)	7.78 (2.20)	7.98 (2.22)
Baseline PNIF** (L/min), mean (SD)	98.59 (56.70)	83.52 (56.30)	80.96 (50.15)	84.86 (59.98)	87.47 (56.14)
Baseline blood eosinophils (x10 ⁹ cells/L), mean (SD)	0.44 (0.35)	0.44 (0.31)	0.45 (0.39)	0.40 (0.30)	0.45 (0.36)
Baseline total IgE (IU/mL), mean (SD)	202.06 (282.37)	222.55 (269.11)	210.82 (256.78)	282.28 (463.72)	227.80 (267.13)
Baseline eotaxin-3 (pg/mL), mean (SD)	74.94 (63.36)	67.36 (73.53)	70.61 (45.16)	83.36 (164.07)	90.84 (111.25)
Any comorbid type 2 medical history including asthma and NSAID-ERD, n (%)	109 (76)	99 (74)	122 (81)	120 (83)	127 (83)
Comorbid asthma, n (%)	82 (57)	79 (59)	85 (57)	91 (63)	91 (59)
Comorbid NSAID-ERD, n (%)	46 (32)	38 (29)	35 (23)	41 (28)	44 (29)
Any comorbid type 2 medical history excluding asthma and NSAID-ERD, n (%)	81 (57)	75 (56)	96 (64)	99 (68)	98 (64)
Age of asthma onset in patients with comorbid asthma (years)	38.28 (13.96)	33.42 (15.42)	35.54 (15.57)	33.57 (18.18)	33.29 (16.14)

ERD = exacerbated respiratory disease; IQR = interquartile range; ITT = intention-to-treat; LMK-CT = Lund-Mackay computed tomography; LoS = loss-of-smell; NC = nasal congestion/obstruction; NPS = nasal polyp score; NSAID = non-steroidal anti-inflammatory drug; PNIF = peak nasal inspiratory flow; Q2W = every 2 weeks; Q4W = every 4 weeks; SD = standard deviation; SNOT-22 = 22-item Sino-Nasal Outcome Test; UPSIT = University of Pennsylvania Smell Identification Test; VAS = visual analogue scale

*Higher scores indicate greater disease severity.

** Higher scores indicate lower disease severity.

Source: Bachert 2019;⁶⁸ Sanofi. Data on File, Clinical Study Report SINUS-24;⁷¹ Sanofi. Data on File, Clinical Study Report SINUS-52.³

2.4 *Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence*

2.4.1 Study population

In the SINUS-24 study, 276 patients were randomised 1:1 to the two treatment groups (dupilumab Q2W: 143; placebo: 133).⁶⁸ All 276 randomised patients were included in the intention-to-treat (ITT) population (used for all primary and secondary efficacy endpoints) and 275 randomised patients (dupilumab Q2W: 143; placebo: 132) were included in the safety population (defined as all patients randomly assigned to study intervention who received at least one dose of study drug).^{68,71}

In the SINUS-52 study, 448 patients were randomised 1:1 to the two treatment groups (dupilumab Q2W: 150; dupilumab Q2W to Q4W: 145; placebo: 153).⁶⁸ All 448 randomised patients were included in the ITT population (used for all primary and secondary efficacy endpoints) and 447 randomised patients (dupilumab Q2W: 149; dupilumab Q2W to Q4W: 148; placebo: 150) were included in the safety population (defined as all patients randomly assigned to study intervention who received at least one dose of study drug).^{68,72}

2.4.2 Statistical analyses

2.4.2.1 *Main efficacy analyses*

Statistical analyses undertaken in the main efficacy analyses of SINUS-24 and SINUS-52 studies summarised in Table 18.

Table 18. Summary of statistical analyses in SINUS-24 and SINUS-52^{68,71,72}

Trial name (number)	SINUS-24 (NCT02912468)	SINUS-52 (NCT02898454)
Multiplicity adjustment	A pre-specified hierarchical multiplicity procedure was used to control the overall type-I error rate for testing the co-primary and key secondary endpoints, with an overall $\alpha = 0.05$. Primary and key secondary endpoints were tested in comparison with placebo following the statistical hierarchy presented in Figure 11 with a two-sided α of 0.05.	
Statistical analysis	Comparison at Week 24 was conducted for Arm A vs. placebo. Efficacy analyses were conducted in the ITT population (all patients who underwent randomisation) according to the treatment assigned (whether the patient received a dose of the treatment assigned or not). Each of the co-primary efficacy endpoints (and key secondary endpoints) were multiplicity-adjusted and analysed using a hybrid method of the WOCF and MI methods. Data collected after treatment discontinuation were included in the analysis. The imputed completed data were analysed by fitting an ANCOVA model with the baseline value of the corresponding co-primary endpoint, treatment group, asthma/NSAID-ERD status, prior surgery history and regions as covariates. Statistical inference obtained from all imputed data was combined using Rubin's rule.	Comparisons at Week 24 were conducted for pooled Arms A and B vs. placebo, and comparisons at Week 52 were conducted for Arm A vs. placebo. Efficacy analyses were conducted in the ITT population (all patients who underwent randomisation) according to the treatment assigned (whether the patient received a dose of the treatment assigned or not). Each of the co-primary efficacy endpoints (and key secondary endpoints) were multiplicity-adjusted and analysed using a hybrid method of the WOCF and MI methods. Data collected after treatment discontinuation were included in the analysis. The imputed completed data were analysed by fitting an ANCOVA model with the baseline value of the corresponding co-primary endpoint, treatment group, asthma/NSAID-ERD status, prior surgery history and regions as covariates. Statistical inference obtained from all imputed data was combined using Rubin's rule.
Sample size, power calculation	Based on results from the phase 2 study (ACT12340), ⁸⁸ it was estimated that using a two-tailed test with an α of 0.05, approximately 120 patients per treatment arm were necessary to give 98% power to detect an effect size of 0.588 in NPS and 95% power to detect an effect size of 0.534 in NC at Week 24 in the dupilumab arm. The combined power for both co-primary endpoints would be 93% (assuming no negative correlation between the endpoints).	Based on results from the phase 2 study (ACT12340), ⁸⁸ it was estimated that the pooling of Arm A and Arm B with approximately 240 patients (120 patients per treatment arm) would give 99% power to detect an effect size of 0.588 in NPS and 0.534 in NC at Week 24 in the dupilumab arm. The combined power for both co-primary endpoints would be 98% (assuming no negative correlation between the endpoints).
Baseline values	• Efficacy parameters: defined as the last available value up to randomisation but prior to the first dose of study drug, unless otherwise specified • Safety parameters: defined as the last available value prior to the first dose of study drug • Other parameters: generally defined as the last available value prior to the first dose of study drug if the patient received a dose of the study drug, or the last available value up to randomisation if the patient did not receive a dose of the study drug	
Data management, patient withdrawals	Temporary discontinuation of study treatment was allowed for AEs treatment/resolution, and mandatory for infections/infestations and pre-specified laboratory abnormalities. Study treatment had to be permanently discontinued, if >2 doses were missed. Patients could permanently discontinue study treatment at their own request or request by their legal representative, the investigator or the sponsor for safety/well-being reasons, or in case of surgery for CRSwNP, code-break request, protocol deviation, pregnancy or specific TEAEs.	

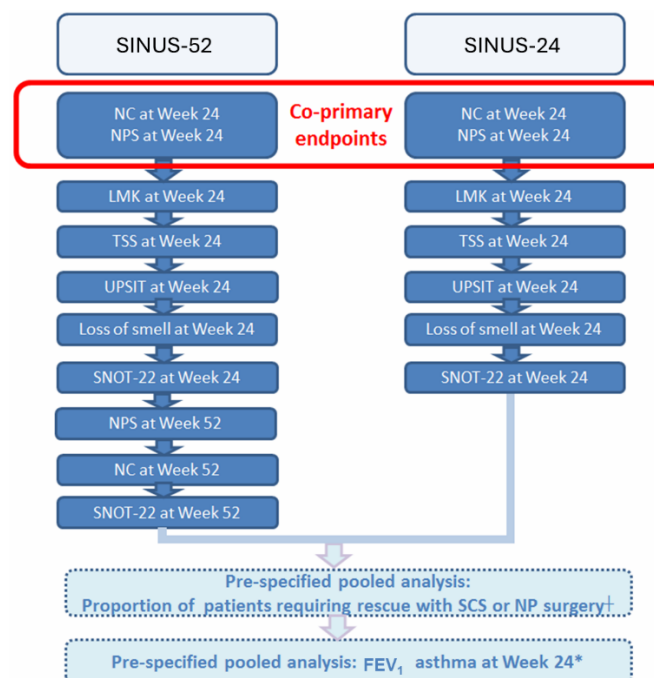
Trial name (number)	SINUS-24 (NCT02912468)	SINUS-52 (NCT02898454)
	Patients who discontinued treatment were continued to be evaluated for both efficacy and safety.	

AE = adverse event; ANCOVA = analysis of covariance; CRSwNP = chronic rhinosinusitis with nasal polyps; ERD = exacerbated respiratory disease; ITT = intention-to-treat; MI = multiple imputation; NC = nasal congestion/obstruction; NPS = nasal polyp score; NSAID = non-steroidal anti-inflammatory drug; TEAE = treatment-emergent adverse event; WOCF = worst-observation carried forward

Sources: Bachert 2019;⁶⁸ Sanofi. Data on File, Clinical Study Report SINUS-24;⁷¹ Sanofi. Data on File, Clinical Study Report SINUS-52.⁷²

As mentioned in [Table 18](#) above, co-primary end key secondary endpoints were multiplicity adjusted and tested the statistical hierarchy presented in [Figure 11](#).

Figure 11. Hierarchical statistical testing order for co-primary and key secondary outcomes in SINUS-24 and SINUS-52^{71,72}



FEV1 = forced expiratory volume in 1 second; LMK = Lund-Mackay score; NC = nasal congestion/obstruction score; NP = nasal polyp; NPS = nasal polyp score; SCS = systemic corticosteroids; SNOT-22 = 22-item Sino-nasal Outcome Test; TSS = total symptom score; UPSIT = University of Pennsylvania Smell Identification Test.

† The pooled analysis for this endpoint will be tested in the hierarchy only when, in both SINUS-24 and SINUS-52 hierarchies, all endpoints before this one reach statistical significance with $p \leq 0.05$.

* The pooled analysis for this endpoint will be tested in the hierarchy only when the previous endpoint (the pooled analysis for the proportion of patients requiring rescue treatment of SCS or surgery for NP) achieves statistical significance in this hierarchical testing procedure.

2.4.2.2 Sensitivity and subgroup efficacy analyses

Supportive and sensitivity analyses (e.g., mixed-effect model with repeated measures [MMRM], pattern mixture model with copy increment from placebo, tipping point analysis, as-observed analysis, MMRM approach for NC as binary response data) were conducted on the co-primary outcomes.^{71,72} For all sensitivity analyses (except for the ‘as-observed’ analysis), data collected post-surgery or post-SCS were set to ‘missing’ for patients who underwent surgery for nasal polyps or received SCS for any reason.⁶⁸ Note that the ‘as-observed’ analysis included data post-SCS for any reason and/or treatment discontinuation but excluded data post-surgery for nasal polyps.^{71,72}

Pre-specified subgroup analyses of the co-primary outcomes were conducted by age, gender, region, territory, race, ethnicity, baseline weight, baseline body mass index (BMI), prior surgery for nasal polyps, asthma comorbidity and/or NSAID-ERD, and SCS use in the

prior two years.^{71,72} An analysis of covariance (ANCOVA) model incorporating subgroup-by-treatment interactions was built to test the interaction between treatment and subgroup factor.^{71,72}

2.4.2.3 *Pre-specified pooled analyses*

Two prespecified pooled analyses of SINUS-24 and SINUS-52 data (proportion of patients requiring rescue treatment [SCS or sinonasal surgery] and FEV₁ at Week 24) were included in the statistical hierarchy ([Figure 11](#)):⁶⁸

- For FEV₁, data from all dupilumab arms and placebo arms at Week 24 were pooled.
- For the proportion of patients requiring rescue treatment, data from SINUS-24 were pooled at Week 24, and data from SINUS-52 were pooled at Week 52 for dupilumab Arm A and the placebo arm, and at Week 24 for dupilumab Arm B.

The change from baseline in FEV₁ was analysed using the same hybrid method of worst observation carried forward (WOCF) and multiple imputation (MI) methods as for the co-primary and key secondary outcomes, followed by an ANCOVA model, with an additional covariate of the study indicator in the ANCOVA model.⁶⁸

The proportion of patients requiring rescue treatment was analysed using the Cox proportional hazards model and the Kaplan Meier method.⁶⁸ The Cox model used the event as the dependent variable and the study indicator, treatment group, asthma or NSAID-ERD strata, previous surgery strata and study region as covariates.⁶⁸

2.4.2.4 *Post-hoc analyses*

Methods of post-hoc analyses of the SINUS-24 and SINUS-52 trials are summarised in [Table 19](#).

Table 19. Methods of SINUS-24 and SINUS-52 post-hoc analyses

Reference	Objective/Methods
Bachert et al. 2024¹¹	• Objective: assessing dupilumab efficacy according to different definitions of type 2 inflammatory signatures in patients in the SINUS trials • Pooled SINUS-24 and SINUS-52 (dupilumab Q2W) ITT populations (N=724; subgroups: patients enrolled from Japan/Asia, patients without coexisting asthma, patients with low eosinophil count [<150 cells/μL], and patients with low IgE levels [<30 IU/μL]) • Six definitions of type 2 inflammation: - o Eosinophils ≥ 150 cells/μL or IgE ≥ 100 IU/mL with a coexisting Type 2 condition - o Eosinophils ≥ 150 cells/μL or IgE ≥ 100 IU/mL

Reference	Objective/Methods
	- o Eosinophils ≥ 150 cells/μL - o Eosinophils ≥ 250 cells/μL or IgE ≥ 100 IU/mL - o Coexisting asthma or eosinophils ≥ 300 cells/μL - o Presence of a coexisting type 2 condition • Outcomes of interest: NPS, NC, LoS, SNOT-22, LMK-CT, UPSIT
Bachert et al. 2024⁷³	• Objective: evaluating the achievement of mild-to-no-symptom months and symptom-free months with dupilumab vs. placebo for 4 key symptoms in the SINUS trials • Pooled SINUS-24 and SINUS-52 (dupilumab Q2W) ITT populations (N=724) • Outcomes of interest: NC, LoS, anterior rhinorrhoea, posterior rhinorrhoea • Mild-to-no-symptom month was defined as a 28-day period with only mild (score of 1) or no symptoms (score of 0) for each of the 4 symptoms (no score >1 on any day) • Symptom-free month was defined as a 28-day period with no symptoms (score of 0) for each of the 4 symptoms (no score >0 on any day)
Bachert et al. 2022⁷⁴	• Objective: investigating the effect of dupilumab on the proportion of patients with improved, stable or worsened NPS and NC over time in the SINUS trials • Pooled SINUS-24 and SINUS-52 (dupilumab Q2W) ITT populations (N=724) • Outcomes of interest: NPS, NC
Bachert et al. 2020⁷⁵	• Objective: evaluating the effect of dupilumab on reported respiratory infection rates in patients in SINUS- 52 • SINUS-52 safety population (N=447) • Outcomes of interest: annualised rates of specific treatment-emergent infections
Busse et al. 2023⁷⁶	• Objective: assessing the effect of dupilumab on CRSwNP and asthma outcomes in patients in the SINUS trials with coexisting asthma stratified by baseline asthma characteristics • Pooled SINUS-24 and SINUS-52 (dupilumab Q2W) ITT populations (N=724) • Patients were stratified into 5 groups based on asthma characteristics: - o Blood eosinophil levels ≥ 150 cells/μL (type 2 inflammatory asthma) - o ≥ 300 cells/μL (type 2 inflammatory asthma) - o ACQ-5 score <1.5 (controlled asthma) - o ≥ 1.5 (uncontrolled asthma) - o FEV₁ $<80\%$ predicted (reduced lung function) • Outcomes of interest: NPS, NC, LoS, SNOT-22, LMK-CT, UPSIT, ACQ-5, FEV₁
Busse et al. 2022⁷⁷	• Objective: assessing the effect of dupilumab on the SNOT-22 sleep and function (fatigue, productivity and concentration) domain scores in SINUS-24 and SINUS-52 • SINUS-24 and SINUS-52 (dupilumab Q2W) ITT populations (N=579) • Outcomes of interest: SNOT-22 sleep and function domains
Chuang et al. 2022⁷⁸	• Objective: assessing the effect of dupilumab vs. placebo on patient-reported sinonasal symptoms and objective measures in SINUS-24 and SINUS-52 using responder thresholds for clinically meaningful within-patient improvement for NC, LoS, TSS, NPS, UPSIT, and LMK-CT scores • Pooled SINUS-24 and SINUS-52 (dupilumab Q2W) ITT populations (N=724)

Reference	Objective/Methods
	- Outcomes of interest: NPS, NC, LoS, TSS, LMK-CT, UPSIT - Clinically meaningful within-patient change from baseline threshold definitions: - NC: ≥ 1.0 point - LoS: ≥ 1.0 point - TSS: ≥ 3.0 points - UPSIT: ≥ 8.0 points - NPS: ≥ 1.0 point - LMK-CT: ≥ 5.0 points
Desrosiers et al. 2021⁷⁹	- Objective: investigating whether dupilumab was superior to ECM in reducing the need for SCS use or sinonasal surgery, after SCS use in SINUS-24 and SINUS-52 and ALSO in subgroups of patients with or without prior SCS use or sinonasal surgery - Pooled SINUS-24 and SINUS-52 (dupilumab Q2W) ITT populations (N=724) - Outcomes of interest: patients with SCS use or sinonasal surgery, number and duration of SCS courses, annualised SCS dose
Fujieda et al. 2022⁸⁰	- Objective: determining whether eosinophilic status in CRSwNP, classified using the JESREC algorithm, was a predictor of dupilumab efficacy compared with placebo in SINUS-52 - SINUS-52 ITT population (N=438) - ECRS was defined as JESREC score ≥ 11: - Mild: not both blood eosinophils $>5\%$ + ethmoid $>$ maxillary (CT shadow), and no asthma and NSAID-ERD - Moderate: not both blood eosinophils $>5\%$ + ethmoid $>$ maxillary (CT shadow) + asthma and/or NSAID-ERD; or blood eosinophils $>5\%$ + ethmoid $>$ maxillary (CT shadow), and no asthma and NSAID-ERD - Severe: blood eosinophils $>5\%$ + ethmoid $>$ maxillary (CT shadow) + asthma and/or NSAID-ERD - Outcomes of interest: NPS, NC, SNOT-22, LMK-CT, UPSIT, TSS, CRSwNP VAS
Gevaert et al. 2023⁸¹	- Objective: assessing the early onset and durable long-term effects of dupilumab on patient-reported symptoms of NC, LoS and rhinorrhoea in SINUS-24 and SINUS-52 - Pooled SINUS-24 and SINUS-52 (dupilumab Q2W) ITT populations (N=724) - Outcomes of interest: proportion of patients achieving no or mild symptoms for NC, LoS and rhinorrhoea
Gurnell et al. 2024⁸²	- Objective: investigating SCS use and asthma outcomes among patients with comorbid asthma in the SINUS trials - Pooled SINUS-24 and SINUS-52 (dupilumab Q2W) populations with comorbid asthma (N=337)
Hellings et al. 2022⁸³	- Objective: investigating the onset of action, magnitude and time course of treatment effects of dupilumab across disease and HRQoL measures in patients with and without prior sinonasal surgery, and comorbid asthma, NSAID-ERD and allergic rhinitis, in the SINUS trials - Pooled SINUS-24 and SINUS-52 (dupilumab Q2W) ITT populations (N=724) - Outcomes of interest: NPS, NC, LoS, SNOT-22, LMK-CT, UPSIT, TSS, PNIF

Reference	Objective/Methods
Hopkins et al. 2024⁷	- Objectives: identifying the SNOT-22 items most important to patients in the SINUS trials, determining dupilumab effects on the severity of these items, and determining the changes in objective disease measures for patients with and without improvement in these items - For assessment of the change in SNOT-22 item severity over time, scores were grouped as 'mild' (score 0 or 1), 'moderate' (score 2 or 3) or 'severe' (score 4 or 5); 'improvement' was defined as ≥ 1 severity group point and 'no improvement' as no change, or worsening of ≥ 1 severity group point - Pooled SINUS-24 and SINUS-52 (dupilumab Q2W) ITT populations with SNOT-22 data (N=712) - Outcomes of interest: SNOT-22, NPS, LMK-CT
Hopkins et al. 2021⁸⁴	- Objective: assessing the efficacy of dupilumab in patients in the SINUS trials by history of prior sinus surgery (by number of surgeries [≥ 1, 1, 2 or ≥ 3 prior surgeries] and time since last surgery [< 3, 3 to < 5, 5 to < 10 or ≥ 10 years since most recent]) - Pooled SINUS-24 and SINUS-52 (dupilumab Q2W) ITT populations (N=724) - Outcomes of interest: NPS, NC, LoS, SNOT-22, LMK-CT, UPSIT, patients with SCS use or sinonasal surgery
Laidlaw et al. 2021³⁵	- Objective: evaluating the effect of dupilumab on a range of airway function and HRQoL outcome measures in patients with comorbid asthma in the SINUS trials - Pooled SINUS-24 and SINUS-52 (dupilumab Q2W) ITT populations (N=724) - Outcomes of interest: NPS, NC, PNIF, SNOT-22, LMK-CT, FEV₁, ACQ-6, rhinosinusitis VAS, EQ-5D VAS
Lane et al. 2022⁸⁵	- Objective: assessing dupilumab effect on anosmia in patients with baseline smell impairment in SINUS-24 and SINUS-52 - Pooled SINUS-24 and SINUS-52 (dupilumab Q2W) populations of patients with baseline smell impairment (N=282)
Lee et al. 2023⁸⁶	- Objective: investigating the relationship between sinus disease severity based on LMK-CT score and olfactory impairment at baseline and following treatment with dupilumab in patients in the SINUS trials - Pooled SINUS-24 and SINUS-52 (dupilumab Q2W) ITT populations (N=724)
Lee et al. 2022⁶⁵	- Objective: evaluating dupilumab effects on disease-specific HRQoL and general health status measures in patients from the SINUS trials, including difficult-to-treat subgroups - Pooled SINUS-24 and SINUS-52 (dupilumab Q2W) ITT populations (N=724) - Outcomes of interest: SNOT-22 (total and domain scores, items), EQ-5D

Reference	Objective/Methods
Mulloi et al. 2022 ⁴³	- Objective: assessing the effects of dupilumab on olfactory outcomes in patients in the SINUS trials - Pooled SINUS-24 and SINUS-52 (dupilumab Q2W) ITT populations (N=724) - Outcomes of interest: LoS, UPSIT, SNOT-22 'decreased sense of smell/taste' item, anosmia

ACQ-5 = 5-item Asthma Control Questionnaire; CI = confidence interval; CRSwNP = chronic rhinosinusitis with nasal polyps; ECM = established clinical management; ECRS = eosinophilic chronic rhinosinusitis; EQ = EuroQoL; ERD = exacerbated respiratory disease; HR = hazard ratio; HRQoL = health-related quality of life; IgE = immunoglobulin E; ITT = intention-to-treat; JESREC = Japanese Epidemiological Survey of Refractory Eosinophilic Rhinosinusitis; LMK-CT = Lund-Mackay computed tomography; LoS = loss-of-smell; LS = least square; NC = nasal congestion/obstruction; NP = nasal polyp; NPS = nasal polyp score; NSAID = non-steroidal anti-inflammatory drug; PNIF = peak nasal inspiratory flow; PRO = patient-reported outcome; Q2W = every 2 weeks; RR = relative risk; SCS = systemic corticosteroid; SNOT-22 = 22-item Sino-Nasal Outcome Test; UPSIT = University of Pennsylvania Smell Identification Test; VAS = visual analogue scale
Sources: Bachert 2024;¹¹ Busse 2023;⁷⁶ Busse 2022;⁷⁷ Chuang;⁷⁸ Bachert 2024;¹¹ Bachert 2024;⁷³ Bachert 2022;⁷⁴ Bachert 2020;⁷⁵ Busse 2023;⁷⁶ Busse 2022;⁷⁷ Chuang 2022;⁷⁸ Desrosiers 2021;⁷⁹ Fujieda 2022;⁸⁰ Gevaert 2023;⁸¹ Gurnell 2024;⁸² Hellings 2022;⁸³ Hopkins 2024;⁷ Hopkins 2021;⁸⁴ Laidlaw 2021;³⁵ Lane 2022;⁸⁵ Lee 2023;⁸⁶ Lee 2022;⁶⁵ Mulloi 2022.⁴³

2.5 Critical appraisal of the relevant clinical effectiveness evidence

Where available, the primary source of clinical effectiveness evidence was study results published in a peer-reviewed journal; clinical study reports (CSRs) were used as additional data sources as needed. The quality of the SINUS-24 and SINUS-52 trials, which are high-quality studies (double-blinded RCTs with generally balanced patient demographics and characteristics) that are pertinent to the decision problem, was assessed using the Cochrane Risk of Bias Assessment Tool 2.0,⁸⁹ in line with recommendations from NICE and good practice guidelines. Overall, the risk of bias was considered low for both trials (Table 20). A detailed quality assessment of all the included RCTs is provided in Appendix D.

Table 20. Quality assessment results for SINUS-24 and SINUS-52^{68,71,72}

Type of bias	Risk of bias judgement	
	SINUS-24 (NCT02912468)	SINUS-52 (NCT02898454)
Random sequence generation (selection bias)	Low	Low
Allocation concealment (selection bias)	Low	Low
Blinding of participants and personnel (performance bias)	Low	Low
Blinding of outcome (detection bias)	Low	Low
Incomplete outcome data (attrition bias)	Low	Low
Selective outcome reporting (reporting bias)	Low	Low
Other sources of bias (other bias)	Low	Low

2.6 Clinical effectiveness results of the relevant studies

Results from the pooled analysis of SINUS-24 and SINUS-52 (including the prespecified pooled analysis for three of the key secondary endpoints) and from selected post-hoc

analyses of the trials are presented in this section. Individual trial results for SINUS-24 and SINUS-52 are presented in [Appendix N](#).

The co-primary endpoints were successfully met in both SINUS-24 and SINUS-52, and in the pooled ITT population.^{68,90} Dupilumab demonstrated statistically significant and clinically meaningful improvements in NPS and NC score between baseline and Week 24 compared to placebo.^{68,90}

Please note the thresholds for meaningful changes in scores for objective and patient-reported treatment outcomes are not well defined in CRswNP.^{71,72} Based on a post-hoc pooled analysis of SINUS-24 and SINUS-52 data which used an anchor-based method, the thresholds for clinically meaningful within-patient change were estimated to be 1 point for NC, 1 point for NPS, 5 points for LMK-CT, 3 points for TSS, 8 points for UPSIT and 1 point for LoS.⁹¹ For SNOT-22 total and ACQ-6 scores, the validated MCID defined by the developer is 8.9 points for the SNOT-22 total score and 0.5 points for ACQ-6.⁷¹ The definition of 'clinically meaningful' improvements in efficacy in this section, along with the relevant values for each outcome, are presented in [Appendix M](#).

2.6.1 Pooled analysis of SINUS-24 and SINUS-52 primary and key secondary endpoints

SINUS-24 and SINUS-52 primary and key secondary endpoints were successfully met in the pooled ITT population; results are summarised in [Table 21](#).⁹⁰

Patients treated with dupilumab demonstrated statistically significant and clinically meaningful improvements in the co-primary endpoints of NPS and NC score at Week 24 compared with the placebo arm ([Figure 12](#), [Figure 13](#), [Table 21](#)), including:⁹⁰

- Change in NPS from baseline to Week 24: least square (LS) mean difference: -1.91 (95% confidence interval [CI]: -2.14, -1.68), $p < 0.0001$.
- Change in patient-reported NC score from baseline to Week 24: LS mean difference: -0.88 (95% CI: -1.00, -0.76), $p < 0.0001$.

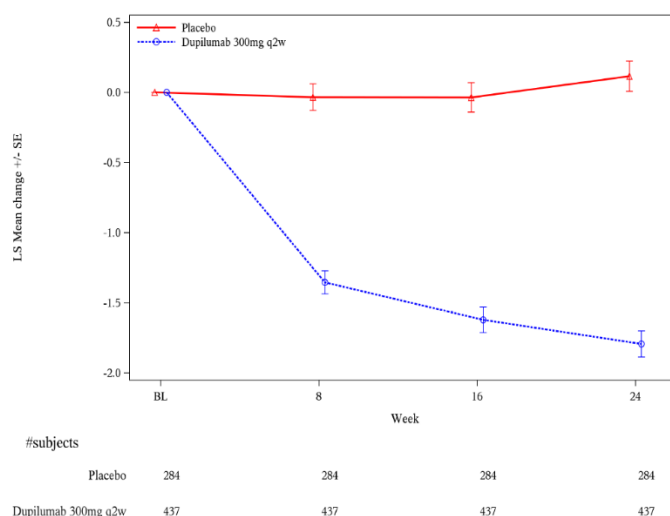
Table 21. Summary of primary and key secondary endpoint results in SINUS-24 and SINUS-52 pooled ITT population⁹⁰

Endpoint	Placebo (N=286)		Dupilumab Q2W (N=438)		
	Mean (SD)	LS mean change from baseline (SE)	Mean (SD)	LS mean change from baseline (SE)	LS mean difference vs. placebo (95% CI; P value)
Primary endpoints at Week 24					
Bilateral NPS	6.02 (1.31)	0.12 (0.11)	4.23 (1.95)	-1.79 (0.09)	-1.91 (-2.14, -1.68; p<0.0001)
NC score	1.96 (0.81)	-0.42 (0.06)	1.11 (0.86)	-1.30 (0.05)	-0.88 (-1.00, -0.76; p<0.0001)
Key secondary endpoints at Week 24					
LMK-CT score	18.31 (4.20)	-0.16 (0.26)	12.21 (4.30)	-6.27 (0.22)	-6.12 (-6.67, -5.57; p<0.0001)
TSS	6.05 (1.99)	-1.08 (0.14)	3.57 (2.30)	-3.59 (0.12)	-2.52 (-2.82, -2.21; p<0.0001)
UPSIT score	13.90 (8.27)	-0.03 (0.55)	24.38 (9.32)	10.54 (0.48)	10.57 (9.40, 11.74; p<0.0001)
LoS score	2.50 (0.78)	-0.26 (0.06)	1.48 (1.01)	-1.30 (0.05)	-1.04 (-1.17, -0.91; p<0.0001)
SNOT-22 score	41.38 (23.14)	-10.36 (1.24)	22.17 (17.77)	-29.22 (1.09)	-18.86 (-21.52, -16.20; p<0.0001)

CI = confidence interval; ITT = intention-to-treat; LMK-CT = Lund-Mackay computed tomography; LoS = loss-of-smell; NC = nasal congestion/obstruction; NPS = nasal polyp score; SD = standard deviation; SE = standard error; SNOT-22 = 22-item Sino-Nasal Outcome Test; TSS = total symptom score; UPSIT = University of Pennsylvania Smell Identification Test
Sources: Sanofi. Data on File, Summary of Clinical Efficacy.⁹⁰

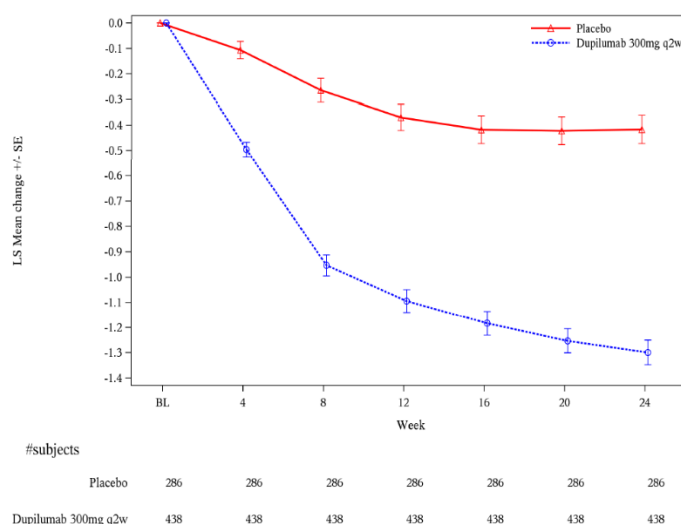
Compared with placebo, patients in the dupilumab arm had significantly greater improvement in NPS and NC score; improvements were observed as early as the first post-baseline assessment (Week 8 for NPS and Week 4 for NC score), improving continuously through Week 24 ([Figure 12](#), [Figure 13](#)).⁹⁰

Figure 12. LS mean change from baseline in bilateral NPS up to Week 24 in the pooled ITT population (a co-primary endpoint)⁹⁰



BL = baseline; ITT = intention-to-treat; LS = least squares; NPS = nasal polyp score; Q2W = once every 2 weeks; SE = standard error. Source: Sanofi. Data on File, Summary of Clinical Efficacy.⁹⁰

Figure 13. LS mean change from baseline in NC up to Week 24 in the pooled ITT population (a co-primary endpoint)⁹⁰



BL = baseline; ITT = intention-to-treat; LS = least squares; NC = nasal congestion/obstruction score; Q2W = once every 2 weeks; SE = standard error. Source: Sanofi. Data on File, Summary of Clinical Efficacy.⁹⁰

At Week 24, patients treated with dupilumab showed statistically significant and clinically meaningful improvements in each hierarchically tested secondary endpoint compared with patients in the placebo arm who showed no or minimal improvement ([Table 21](#)).⁹⁰ The onset of symptom improvement in patients treated with dupilumab was rapid (by Week 2 for UPSIT, Week 4 for TSS and self-reported LoS and Week 4 for SNOT-22) and continuous, with improvement reported through Week 24; no improvement was observed in the placebo arm at Week 24 (except for SNOT-22, for which a minimal improvement was observed from Week 8).^{68,90}

Results for key secondary endpoints evaluated at Week 52 in SINUS-52, including bilateral NPS, NC score and SNOT-22 score, are presented in [Appendix N](#).

2.6.2 Prespecified pooled analysis of SINUS-24 and SINUS-52

The key secondary outcomes in the prespecified pooled analysis of SINUS-24 and SINUS-52 were successfully met.⁶⁸ Dupilumab resulted in a 76% lower proportion of patients who required SCS or sinonasal surgery (73.9% lower for SCS and 82.6% for sinonasal surgery, individually; [Table 23](#)) during the treatment period and demonstrated statistically significant and clinically meaningful improvements in FEV₁ and ACQ-6 in patients with comorbid asthma between baseline and Week 24, compared to placebo.⁶⁸

Pre-planned pooled analyses of data from SINUS-24 and SINUS-52 were conducted for three outcomes:⁶⁸

- The proportion of patients requiring rescue treatment (SCS or sinonasal surgery for nasal polyps)
- The change from baseline at Week 24 in FEV₁ in the subset of patients with comorbid asthma
- The change from baseline at Week 24 in ACQ-6 score in the subset of patients with comorbid asthma

Data used in the pre-planned pooled analyses are summarised in [Table 22](#).

Table 22. Summary of data used in the prespecified pooled analysis of SINUS-24 and SINUS-52

Endpoint	Data pooled
Prespecified pooled analysis	
Patients requiring SCS or sinonasal surgery	Entire treatment period of patients on dupilumab 300 mg Q2W (n=438): - SINUS-24: dupilumab arm up to Week 24 - SINUS-52: Arm A up to Week 52 and Arm B up to Week 24 Entire treatment period of patients on placebo (n=286): - SINUS-24: up to Week 24 - SINUS-52: up to Week 52
Prespecified pooled analysis in patients with comorbid asthma at Week 24	
FEV₁	All patients with comorbid asthma on dupilumab Q2W up to Week 24 (n=258) All patients with comorbid asthma on placebo up to Week 24 (n=170)
ACQ-6	

ACQ-6 = 6-item Asthma Control Questionnaire; FEV₁ = forced expiratory volume in 1 second; Q2W = once every 2 weeks; SCS = systemic corticosteroid
Source: Bachert 2019.⁶⁸

In the pre-specified pooled analysis, the proportion of patients who required SCS or sinonasal surgery during the treatment period was 76% lower with dupilumab (42 patients) compared with placebo (97 patients; hazard ratio [HR]: 0.243; 95% CI: 0.169, 0.351; $p < 0.0001$; [Figure 14](#), [Table 23](#)); specifically:⁶⁸

- The proportion of patients who required SCS decreased by 73.9% with dupilumab vs. placebo (HR: 0.26; 95% CI: 0.18, 0.38; $p < 0.0001$).
- The proportion of patients who required surgery decreased by 82.6% with dupilumab vs. placebo (HR: 0.17; 95% CI: 0.07, 0.46; $p = 0.0005$).

The difference in the proportion of patients who required SCS or sinonasal surgery was evident by Week 8 and continued to become greater in magnitude throughout the treatment period (up to Week 24 for SINUS-24 and Arm B of SINUS-52, and up to Week 52 for Arm A of SINUS-52).⁶⁸ Overall, 9.6% of patients receiving dupilumab and 33.9% of patients receiving placebo required rescue treatment over the treatment period.⁶⁸

Figure 14. Time to first use of SCS or sinonasal surgery (pooled SINUS-24 and SINUS-52 ITT population)⁶⁸

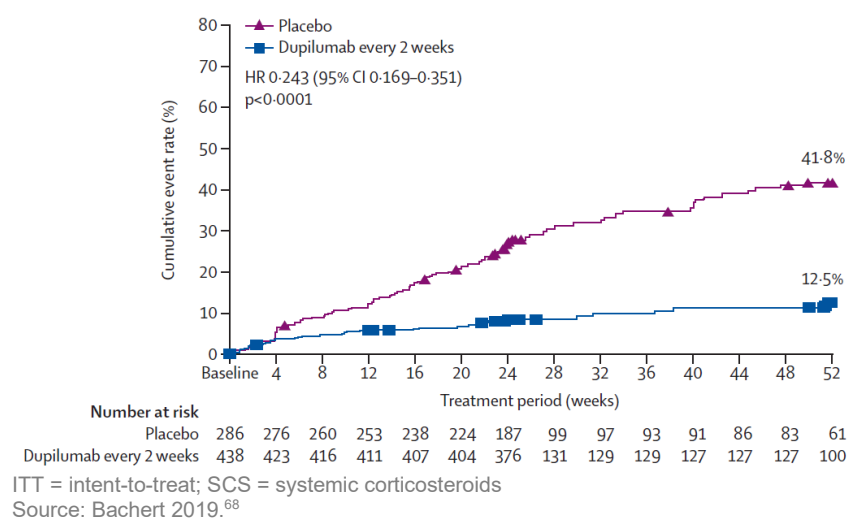


Table 23. Number of patients requiring SCS or sinonasal surgery (pooled SINUS-24 and SINUS-52 ITT population)⁶⁸

Endpoint	Pooled placebo (N=286)	Pooled dupilumab Q2W (N=438)	HR vs. placebo (95% CI; P value)
Prespecified pooled analysis			
Patients requiring SCS or sinonasal surgery, n (%)	97 (33.9)	42 (9.6)	0.243 (0.169, 0.351; p<0.0001)
Patients requiring SCS, n (%)	88 (30.8)	41 (9.4)	0.261 (0.179, 0.379)
Patients requiring sinonasal surgery, n (%)	22 (7.7)	5 (1.1)	0.174 (0.066, 0.462)

CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat; Q2W = every 2 weeks; SCS = systemic corticosteroid.
Source: Bachert 2019.⁶⁸

Among patients with comorbid asthma in the SINUS-24 and SINUS-52 pooled population (n=258 on dupilumab Q2W, n=170 on placebo), patients receiving dupilumab had statistically significant and clinically meaningful improvements in FEV₁ and ACQ-6 compared with placebo at Week 24 (Table 24):⁶⁸

- Change in FEV₁ from baseline to Week 24: LS mean difference for dupilumab vs. placebo: 0.21 (95% CI: 0.13, 0.29), p<0.0001)
- Change in ACQ-6 score from baseline to Week 24: LS mean difference vs. placebo: -0.82 (95% CI: -0.98, -0.67), p<0.0001

Meaningful improvement was observed as early as Week 4 (first post-baseline assessment), with continued improvement through Week 24.⁶⁸

Table 24. Prespecified efficacy endpoints in the pooled SINUS-24 and SINUS-52 population with comorbid asthma⁶⁸

Endpoint	Pooled placebo with comorbid asthma (n=170)		Pooled dupilumab Q2W with comorbid asthma (n=258)		
	Mean (SD)	LS mean change from baseline (SE)	Mean (SD)	LS mean change from baseline (SE)	LS Mean difference vs. placebo (95% CI; p-value)
Prespecified pooled analysis in patients with comorbid asthma at Week 24					
FEV₁ (L)	2.57 (0.80)	-0.07 (0.04)	2.76 (0.91)	0.14 (0.03)	0.21 (0.13, 0.29; p<0.0001)
ACQ-6	1.52 (1.11)	-0.02 (0.07)	0.70 (0.82)	-0.84 (0.06)	-0.82 (-0.98, -0.67; p<0.0001)

ACQ-6 = six-item Asthma Control Questionnaire; CI = confidence interval; FEV₁ = forced expiratory volume in 1s; LS = least squares; Q2W = every 2 weeks; SD = standard deviation; SE = standard error.

Source: Bachert 2019.⁶⁸

2.6.3 Post-hoc analyses of SINUS-24 and SINUS-52

Results of post-hoc analyses of the SINUS-24 and SINUS-52 trials are summarised in [Table 25](#).

Post-hoc analyses of the SINUS-24 and SINUS-52 trials demonstrated the efficacy of dupilumab across various CRSwNP outcomes, including reduction of SCS use and sinonasal surgery, improvements in objective disease measures and improvements in patient-reported symptoms and disease-specific HRQoL.^{7,11,35,43,65,73,74,76-81,83-86} Improvements with dupilumab were observed across various subgroups of patients including patients with type 2 inflammatory signature, comorbid asthma, comorbid NSAID-ERD, eosinophilic CRSwNP, smell impairment or history of sinus surgery.^{7,11,35,43,65,73,76-85}

The treatment effects with dupilumab, which had a rapid onset and were maintained through Week 52, resulted in statistically significant, clinically meaningful improvements in patient-reported symptom outcomes and objective measures:^{74,78,81,83}

- In terms of **olfactory outcomes**, dupilumab produced rapid (as early as Day 3 for LoS) and sustained improvements regardless of prior sinonasal surgery, SCS use or comorbid asthma and/or NSAID-ERD.⁴³
- Dupilumab reduced **anosmia** in patients with smell impairment, and 11.5% of patients even achieved **normosmia**.⁸⁵
- In a patient population with smell impairment and almost complete sinus opacification, dupilumab significantly reduced **sinus opacification**, a reduction which was correlated with improvements in the **sense of smell**.⁸⁶

- Dupilumab reduced the need for **SCS use** by 73.9% and **sinonasal surgeries** by 82.6% in patients with CRSwNP even in those with a history of SCS use and/or sinonasal surgery.⁷⁹
- **Loss of smell/taste** and **nasal obstruction-related symptoms** were of high importance to patients in the SINUS trials, and dupilumab demonstrated significant improvement in these symptoms.⁷
- Dupilumab increased the number of patients able to achieve mild or no symptoms of nasal congestion, LoS or rhinorrhoea over a month, with 50% of patients who reported a **symptom-free month** and 38.3% who reported a mild-to-no symptom month after 52 weeks of treatment with dupilumab.⁷³
- In terms of HRQoL, patients in the SINUS trials had worse HRQoL compared with the general population, and dupilumab significantly improved **general health status** and all components of **disease-specific HRQoL** including sleep, sense of smell and fatigue.^{65,77}
- Dupilumab reduced the incidence of **infections**, specifically the adverse event (AE) categories 'infections and infestations' and 'upper respiratory infections.'⁷⁵

Most patients in the SINUS trials (64.3-95.3% of the pooled population depending on the definition used) displayed type 2 inflammatory signature, and dupilumab was effective across type 2 inflammatory signatures definitions.¹¹ Most patients in the SINUS trials (63.4% of the pooled population) had a history of sinus surgery, and dupilumab was effective regardless of the number of prior surgeries and time since last surgery.⁸⁴ Similarly, most patients in the SINUS trials (83.3% of the pooled population) displayed eosinophilic disease, and dupilumab was effective regardless of eosinophilic status.⁸⁰ In patients with comorbid asthma who represented almost 60% of the SINUS trials pooled population and had more severe CRSwNP disease compared with those without comorbid asthma:^{35,76,82}

- Dupilumab significantly improved upper and lower airway outcomes irrespective of relevant baseline asthma characteristics and comorbid NSAID-ERD
- Dupilumab significantly improved asthma outcomes and reduced SCS use irrespective of asthma exacerbations history and prior SCS use
- Dupilumab significantly improved HRQoL outcomes.

Table 25. Results of SINUS-24 and SINUS-52 post-hoc analyses

Ref	Results
Bachert et al. 2024¹¹	• Most patients (64.3-95.3% depending on the definitions used) displayed type 2 inflammatory signature at baseline • Significantly greater improvements with dupilumab vs. placebo for all outcomes at Week 24 and Week 52 across the six definitions of type 2 inflammatory signature • Similar time course for the improvements with dupilumab across the six definitions of type 2 inflammatory signature • Higher odds of achieving a clinically meaningful response with dupilumab vs. placebo for all outcomes across the six definitions of type 2 inflammatory signature; at Week 24 ORs (dupilumab vs. placebo) ranged from: - o NPS: 11.4 to 14.9 - o NC: 6.5 to 9.6 - o SNOT-22: 4.3 to 5.3 - o LoS: 12.2 to 17.8 - o UPSIT: 21.1 to 34.7
Bachert et al. 2024⁷³	• Few patients had a mild-to-no-symptom month (MSM) or symptom-free month (SFM) just before baseline for the 4 key symptoms (NC, LoS, anterior rhinorrhoea, posterior rhinorrhoea) in both the dupilumab and placebo groups: - o NC: MSM (dupilumab: 0.5%; placebo: 0%); SFM (dupilumab: 0%; placebo: 0%) - o LoS: MSM (dupilumab: 1.4%; placebo: 0.7%); SFM (dupilumab: 0.5%; placebo: 0.7%) - o Anterior rhinorrhoea: MSM (dupilumab: 4.8%; placebo: 3.8%); SFM (dupilumab: 0.7%; placebo: 0.3%) - o 5.6Posterior rhinorrhoea: MSM (dupilumab: 9.2%; placebo: 0%); SFM (dupilumab: 3.7%; placebo: 2.8%) • Dupilumab resulted in significantly higher odds of achieving MSM vs. placebo for all 4 symptoms at Week 24 (31.0% vs. 4.4% of patients; OR 12.9; 95%CI: 6.4, 25.8; p<0.0001) • Dupilumab resulted in significantly higher odds of achieving SFM vs. placebo for ≥1 of the 4 symptoms at Week 24 (35.4% vs. 10.8%; OR 4.9; 95%CI: 3.1, 7.8; p<0.0001) and Week 52 (50.0 % vs. 9.2%; OR 9.1; 95% CI: 4.6, 17.9; p<0.0001) • Statistically significantly higher proportions of patients on dupilumab vs. placebo achieved MSM for ≥1 of the 4 symptoms at Week 24 (71.8% vs. 37.5%; p<0.0001) and Week 52 (78.1% vs. 34.5%; p<0.0001) • Statistically significantly higher proportions of patients on dupilumab vs. placebo achieved MSM and SFM for each symptom individually (all p<0.0001) • At Week 52, 38.3% of patients on dupilumab achieved MSM for all 4 symptoms and 50.0% achieved SFM for ≥1 of the 4 symptoms

Ref	Results
	Dupilumab resulted in higher proportions of patients achieving MSM and SFM vs. placebo at Weeks 24 and 52 regardless of prior SCS use and history of sinonasal surgery
Bachert et al. 2022⁷⁴	- Dupilumab resulted in significantly higher odds of demonstrating improvements (change from baseline >0) in NPS and NC vs. placebo from as early as the first post-baseline assessment (Week 4 for NC, Week 8 for NPS) and up to Week 24 (all p<0.0001): - NPS (OR; 95% CI): Week 8 (4.8; 3.4, 6.7), Week 16 (6.6; 4.6, 9.3), Week 24 (7.4; 5.2, 10.5) - NC (OR; 95% CI): Week 4 (3.7; 2.7, 5.2), Week 8 (3.5; 2.5, 5.0), Week 12 (4.0; 2.8, 5.7) Week 24 (5.1; 3.5, 7.3) - In SINUS-52, significantly higher odds of demonstrating improvements in NPS (OR 10.6; 95% CI: 6.0, 18.7) and NC (OR 6.4; 95% CI: 3.5, 11.5) with dupilumab vs. placebo were maintained through Week 52 - Higher proportions of patients on dupilumab vs. placebo showed clinically meaningful change (change from baseline >1) in NPS and NC from as early as the first post-baseline assessment (Week 4 for NC, Week 8 for NPS) and up to Week 24: - NPS: Week 8 (59.5% vs. 23.8%), Week 24 (66.9% vs. 16.5%) - NC: Week 4 (19.5% vs. 2.8%), Week 24 (65.6% vs. 24.5%) - In SINUS-52, higher proportions of patients on dupilumab vs. placebo showing clinically meaningful change in NPS (72.3% vs. 16.2%) and NC (67.6% vs. 22.9%) were maintained through Week 52
Bachert et al. 2020⁷⁵	- Dupilumab resulted in significantly lower annualised rates of specific treatment-emergent infections per 100 PY vs. placebo at the patient level (patients with ≥1 infection [nP] /100 PY) and the event level (events [nE] /100 PY) over the 64-week safety evaluation period: - Infections and infestations (MedRA System Organ Class): 75.01 vs. 115.79 nP/100 PY (RR 0.65; 95% CI: 0.51, 0.84; p=0.0008); 183.00 vs. 276.97 nE/100 PY (RR 0.66; 95% CI: 0.59, 0.74; p<0.0001) - Upper respiratory infections: 45.78 vs. 80.87 nP/100 PY (RR 0.57; 95% CI: 0.43, 0.76; p<0.0001); 59.52 vs. 87.01 nE/100 PY (RR 0.68; 95% CI: 0.56, 0.84; p=0.0003) - Upper respiratory tract infections (MedRA High Level Term): 41.44 vs. 73.52 (RR 0.57; 95% CI: 0.43, 0.76; p=0.0001); 53.68 vs. 80.76 (RR 0.66; 95% CI: 0.54, 0.83; p=0.0002)
Busse et al. 2023⁷⁶	59.1% of the pooled SINUS population reported comorbid asthma, with 50.9% of these patients reporting uncontrolled asthma - Patients receiving dupilumab demonstrated significant improvements in NPS, NC, LoS and SNOT-22 vs. placebo at Week 24 and Week 52, regardless of asthma characteristics (all p<0.0001) - Dupilumab demonstrated clinically important improvements in SNOT-22 total score (all p<0.001) in:

Ref	Results
	- o 76.1% of patients with baseline eosinophils $\geq 150/\mu\text{L}$ - o 77.3% of patients with baseline eosinophils $\geq 300/\mu\text{L}$ - o 78.7% of patients with controlled asthma - o 77.4% of patients with uncontrolled asthma - o 72.0% of patients with reduced lung function • Patients receiving dupilumab demonstrated significant improvements in FEV₁ at Week 24 and Week 52 regardless of asthma characteristics (all $p < 0.001$, except for Week 52 in patients with uncontrolled asthma for which $p > 0.05$) • Patients receiving dupilumab demonstrated significant improvements in ACQ-5 at Week 24 and Week 52 regardless of asthma characteristics (all $p < 0.001$) • Dupilumab demonstrated clinically important improvements in ACQ-5 score (all $p < 0.001$) in: - o 53.0% of patients with baseline eosinophils $\geq 150/\mu\text{L}$ - o 53.4% of patients with baseline eosinophils $\geq 300/\mu\text{L}$ - o 35.2% of patients with controlled asthma - o 74.2% of patients with uncontrolled asthma • 61.7% of patients with reduced lung function • Dupilumab improved all CRSwNP and asthma outcomes at Week 24 regardless of asthma characteristics and presence of comorbid NSAID-ERD
Busse et al. 2022⁷⁷	• Baseline mean SNOT-22 sleep and function domain scores ranged from 2.00 to 2.50 • Dupilumab improved SNOT-22 sleep domain scores vs. placebo at Week 24 in SINUS-24 (LS mean difference: -0.97; 95% CI: -1.24, -0.71; $p < 0.0001$) • Dupilumab improved SNOT-22 sleep domain scores vs. placebo at Week 52 in SINUS-52 (LS mean difference: -0.93; 95% CI: -1.18, -0.68; $p < 0.0001$) • Dupilumab improved SNOT-22 function domain scores vs. placebo at Week 24 in SINUS-24 (LS mean difference: -0.86; 95% CI: -1.11, -0.61; $p < 0.0001$) • Dupilumab improved SNOT-22 function domain scores vs. placebo at Week 52 in SINUS-52 (LS mean difference: -0.76; 95% CI: -1.01, -0.51; $p < 0.0001$) • Improvements in SNOT-22 sleep and function domain score were observed from Week 8 (both $p < 0.0001$) • Dupilumab significantly improved SNOT-22 sleep and function domains vs. placebo regardless of comorbid asthma or NSAID-ERD, SCS use in the past 2 years, allergic rhinitis or history of prior sinonasal surgery

Ref	Results
Chuang et al. 2022⁷⁸	- Statistically significantly higher proportions of patients showed clinically meaningful change from baseline for patient-reported symptoms for dupilumab vs placebo at Weeks 24 and 52; at Week 24: - NC: 64% vs. 24% (OR 6.4; 95% CI: 4.5, 9.1; p<0.0001) - LoS: 63% vs. 14% (OR 12.1; 95% CI 8.0, 18.5; p<0.0001) - TSS: 62% vs. 15% (OR 10.4; 95% CI 6.9, 15.5; p<0.0001) - Statistically significantly higher proportions of patients showed clinically meaningful change from baseline for objective measures at Weeks 24 and 52; at Week 24: - UPSIT: 54% vs. 6% (OR 20.7; 95% CI 11.8, 36.0; p<0.0001) - NPS: 63% vs. 14% (OR 11.6; 95% CI 7.7, 17.4; p<0.0001) - LMK-CT : 59% vs. 3% (OR 56.8; 95% CI 26.3, 122.4; p<0.0001)
Desrosiers et al. 2021⁷⁹	- Dupilumab resulted in a 82.6% reduction in the number of patients requiring sinonasal surgery vs. placebo over the treatment period (1.1% vs. 7.7%; HR 0.174; 95% CI: 0.066, 0.462; p=0.0005) - Dupilumab demonstrated a reduction in the rate of sinonasal surgery regardless of history of sinonasal surgery or of SCS use within the past 2 years - Dupilumab resulted in a 73.9% reduction in the number of patients requiring SCS use vs. placebo over the treatment period (9.4% vs. 30.8%; HR 0.261; 95% CI: 0.179, 0.379; p=0<0001) - Dupilumab resulted in a 75.3% reduction in the number of SCS courses required vs. placebo over the treatment period (0.21 vs. 0.84; RR 0.247; 95% CI: 0.167, 0.365; p=0<0001) - The main reason for requiring SCSs was for relieving NP symptoms in both groups (dupilumab: 36.6%; placebo: 68.2%) - Dupilumab demonstrated a reduction in SCS use regardless of history of sinonasal surgery or of SCS use within the past 2 years - Based on sensitivity analyses with data post-SCS use (excluding post-sinonasal surgery data) in the studies were consistent and demonstrated the superiority of dupilumab vs. ECM (all p<0.0001)
Fujieda et al. 2022⁸⁰	- At baseline, 83.3% of patients (n=365) had an ECRS phenotype (mild: n=61; moderate: n=144; severe n=160) - Dupilumab demonstrated significant improvements in each ECRS subgroup (including non-ECRS) from baseline in NPS, NC and LMK-CT scores at Weeks 24 and 52, consistent with the overall SINUS-52 population - At Week 24, changes from baseline with dupilumab Q2W were all statistically significantly greater vs. placebo for NPS, NC and LMK-CT scores across all ECRS subgroups (all p<0.001)

Ref	Results
	- Improvements in NPS, NC and LMK-CT with dupilumab were maintained or increased through Week 52 irrespective of ECRS status - There was no association between treatment effect and ECRS status, except for LMK-CT at Week 24, where there was a greater effect of dupilumab in the moderate/severe ECRS subgroup compared with the non/mild ECRS subgroup ($p=0.0275$) - Dupilumab demonstrated similar improvements in each ECRS subgroup for change from baseline in UPSIT, SNOT-22, TSS and CRSwNP VAS scores at Weeks 24 and 52 - For all secondary efficacy endpoints (except SNOT-22 at Week 52 in the non-ECRS subgroup), dupilumab demonstrated significantly greater improvements at Weeks 24 and 52 vs. placebo ($p\leq 0.0271$) across ECRS subgroups - Dupilumab was well tolerated over 52 weeks across JESREC subgroups, with a safety profile similar to the one observed in the overall SINUS-52 population
Gevaert et al. 2023⁸¹	- Significantly greater proportions of patients achieved no or mild symptoms (scores ≤ 1) with dupilumab vs. placebo for NC, LoS and rhinorrhoea by Week 2, as well as at Week 24 and Week 52; at Week 52, patients were: ~7 times more likely to achieve no or mild NC symptoms with dupilumab vs. placebo: OR 6.9 (95% CI: 3.7, 12.6; $p<0.0001$) >17 times more likely to have no or mild LoS symptoms: OR 17.4 (95% CI: 6.9, 43.8; $p<0.0001$) ~6 times more likely to have no or mild rhinorrhoea symptoms: OR 5.9 (95% CI: 3.0, 11.9; $p<0.0001$) - Results at Weeks 24 and 52 in the subgroups of patients with comorbid asthma or prior sinonasal surgery were consistent with those of the overall pooled population, with significantly more patients in each subgroup achieving no or mild symptoms vs. placebo; at Week 52, patients with comorbid asthma were: ~13 times more likely to achieve no or mild NC symptoms with dupilumab vs. placebo: OR 13.3 (95% CI: 5.5, 32.2; $p<0.0001$) >140 times more likely to have no or mild LoS symptoms: OR 141.8 (95% CI: 11.8, 1,709.4; $p<0.0001$) ~11 times more likely to have no or mild rhinorrhoea symptoms: OR 10.7 (95% CI: 3.8, 29.7; $p<0.0001$)
Gurnell et al. 2024⁸²	- At baseline, 74.7% of patients in the placebo arm and 69.5% of patients in the dupilumab arm had a history of asthma exacerbation - A lower proportion of patients on dupilumab required SCSs during treatment vs. those on placebo regardless of asthma exacerbation history and prior SCS use - At Week 24, dupilumab demonstrated significant improvements from baseline in ACQ-6, FEV₁ and percent predicted FEV₁ vs. placebo regardless of asthma exacerbations history and prior SCS use ($p\leq 0.0016$ for all outcomes)
Hellings et al. 2022⁸³	Dupilumab showed significant improvement across all daily outcomes within 4 days of treatment initiation (all $p<0.05$ vs. placebo):

Ref	Results
	- o NC: by day 2 - o LoS: by day 3 - o TSS: by day 2 - o PNIF: by day 4 • Patients on dupilumab demonstrated significant improvements vs. placebo from the first postbaseline assessments: - o UPSIT: Week 2 (LS mean difference 5.53; 95% CI: 4.38, 6.69; p<0.0001) - o NPS: Week 4 in SINUS-52 (-1.15; 95% CI: -1.40, -0.91; p<0.0001), Week 8 in SINUS-24 (-1.42; 95% CI: -1.75, -1.10; p<0.0001) - o SNOT-22: Week 8 (-14.8; 95% CI: -17.4, -12.2; p<0.0001) • Onset of action, magnitude and maintenance of dupilumab treatment effect were similar in patients with prior sinonasal surgery, or comorbid asthma, NSAID-ERD or allergic rhinitis
Hopkins et al. 2024⁷	• SNOT-22 items ranked as most important by patients at baseline: - o Decreased sense of smell/taste (87.4%) - o Nasal blockage (82.4%) - o Post-nasal discharge (39.5%) - o Thick nasal discharge (37.1%) - o Wake up at night (25.7%) • Dupilumab resulted in symptom improvements in a higher proportion of patients vs. placebo in all the five most important SNOT-22 items at Week 24 and Week 52: - o Decreased sense of smell/taste (Week 24: 76.7% vs. 30.4%; Week 52: 73.3% vs. 21.6%) - o Nasal blockage (Week 24: 79.5% vs. 44.4%; Week 52: 76.0% vs. 29.4%) - o Post-nasal discharge (Week 24: 67.4% vs. 38.8%; Week 52: 66.7% vs. 30.1%) - o Thick nasal discharge (Week 24: 71.9% vs. 40.2%; Week 52: 73.3% vs. 28.8%) - o Wake up at night (Week 24: 56.6% vs. 36.7%; Week 52: 54.7% vs. 21.6%) • Dupilumab resulted in decreased odds of reporting severe symptoms for all the five most important SNOT-22 items vs. placebo at Week 24 and Week 52 (all p<0.0001): - o Decreased sense of smell/taste (Week 24: OR 0.09; Week 52: OR 0.11)

Ref	Results
	- o Nasal blockage (Week 24: OR 0.19; Week 52: OR 0.12) - o Post-nasal discharge (Week 24: OR 0.36; Week 52: OR 0.20) - o Thick nasal discharge (Week 24: OR 0.20; Week 52: OR 0.15) - o Wake up at night (Week 24: OR 0.33; Week 52: OR 0.24) • Dupilumab resulted in significant improvements in NPS and LMK-CT score in patients with and without improvement in the five most important SNOT-22 items ($p < 0.0001$) at Week 24 and Week 52
Hopkins et al. 2021⁸⁴	• At baseline, 63.4% of patients in the SINUS trials had ≥ 1 prior sinus surgery, with a mean number of 1.96 (SD: 1.56) prior surgeries and a median time of 5.3 years since last surgery • Dupilumab demonstrated significantly greater improvements at Weeks 24 vs. placebo, regardless of number of prior surgeries and time since last surgery for all outcomes assessed (NPS, NC, LMK-CT, UPSIT, LoS, SNOT-22) • Statistically significantly higher proportions of patients on dupilumab vs. placebo showed clinically meaningful change from baseline in NPS (≥ 1), NC (≥ 1) and SNOT-22 (≥ 8.9) at Week 24 regardless of number of prior surgeries and time since last surgery • Dupilumab reduced the proportion of patients who required rescue treatment (SCS and/or sinus surgery) vs. placebo at Week 24 regardless of the number of prior sinus surgeries and the time since last surgery (significantly except for the subgroups of patients with two prior sinus surgeries and those who had surgery ≥ 10 years prior): - o Number of surgeries (HR; 95% CI): 0 (0.338; 0.178, 0.640), ≥ 1 (0.220; 0.130, 0.372), 1 (0.187; 0.090, 0.387), 2 (0.325; 0.099, 1.060), ≥ 3 (0.246; 0.086, 0.698) - o Time since last surgery (HR; 95% CI): < 3 years (0.178; 0.069, 0.463), 3 to < 5 years (0.078; 0.016, 0.383), 5 to < 10 years (0.124; 0.041, 0.380) ≥ 10 years (0.590; 0.212, 1.641) • Dupilumab demonstrated numerically lower rates of TEAEs up to Week 24 vs. placebo, regardless of prior sinus surgery
Laidlaw et al. 2021³⁵	• At baseline, 59.1% ($n=428$) of patients had a history of comorbid asthma; these patients had more severe disease, with increased sinus opacification and symptom burden, worse HRQoL and more often a history of sinonasal surgery compared with those without a history of comorbid asthma • Dupilumab significantly improved upper airway outcomes vs. placebo at Week 24 regardless of comorbid asthma; in those with comorbid asthma (LS mean differences [95% CI]; all $p < 0.001$): - o Endoscopic NPS: -2.04 (-2.35, -1.74) - o NC: -1.04 (-1.19, -0.89) - o LMK-CT: -6.43 (-7.15, -5.72)

Ref	Results
	- o PNIF: 46.15 L/min (37.82, 54.47) • Dupilumab significantly improved lower airway outcomes vs. placebo at Week 24 in patients with comorbid asthma (LS mean differences [95% CI]; all $p < 0.001$): - o FEV₁: 0.21 L (0.13, 0.29) - o ACQ-6: -0.82 (-0.98, -0.67) • Dupilumab significantly improved HRQoL outcomes vs. placebo at Week 24 in patients with comorbid asthma (LS mean differences [95% CI]; all $p < 0.001$): - o SNOT-22: -21.42 (-24.97, -17.87) - o Rhinosinusitis VAS: -3.40 (-3.90, -2.90) - o EQ-5D VAS: 8.24 (5.03, 11.45) • Incidence of TEAEs was similar regardless of comorbid asthma with a lower proportion of patients with comorbid asthma who reported asthma as a TEAE on dupilumab vs. placebo (2.2% vs. 12.0%)
Lane et al. 2022⁸⁵	• At baseline, most patients had anosmia (dupilumab: 81.6%; placebo: 77.4%) • At Week 52, the proportion of patients with anosmia decreased with dupilumab (29.2%) but not placebo (76.8%) • At Week 52, 11.5% of patients reported normosmia with dupilumab vs. none with placebo • At Week 52, greater mean changes from baseline in NPS, NC and SNOT-22 were observed in patients reporting normosmia vs. those reporting anosmia with dupilumab
Lee et al. 2023⁸⁶	• At baseline, the mean total LMK-CT score demonstrated almost complete sinus opacification (18.26 and 18.53 in the dupilumab and placebo groups, respectively) and 95.0% of patients reported impaired smell, with highest sinus opacification in patients with the most severe loss of smell • Based on baseline data, sinus opacification measured by LMK-CT total score showed correlation with loss of smell measured by LoS, SNOT-22 smell/taste item and UPSIT, with sinus opacification increasing with loss of smell severity (all $p < 0.0001$) • Change from baseline in LMK-CT total score with dupilumab showed weak correlation with changes from baseline in measures of smell (LoS, SNOT-22 smell/taste item and UPSIT) at Weeks 24 and 52 • A statistically significantly higher proportion of patients on dupilumab vs. placebo achieved clinically meaningful change in LMK-CT total score (≥ 5 points) at Weeks 24 and 52: - o Week 24: 59.4% vs. 3.1% (OR 56.8; 95% CI: 26.3, 122.4; $p < 0.0001$)

Ref	Results
	o Week 52: 63.3% vs. 2.0% (OR 67.5; 95% CI: 21.4, 212.6; p<0.0001)
Lee et al. 2022⁶⁵	• Patients in the SINUS trials had poor disease-specific HRQoL (SNOT-22 mean [SD] total score: 50.94 [20.66]) and general health status (EQ-VAS mean [SD] score: 65.4 [20.4]) below general population norms • Significantly greater reductions in SNOT-22 total scores observed with dupilumab at Week 24 and Week 52 vs. placebo regardless of comorbid asthma or NSAID-ERD, or history of prior sinonasal surgery with (all p<0.0001) • Dupilumab improved all SNOT-22 domain scores vs. placebo at Week 24 with the greatest improvement observed in the nasal domain (LS mean difference: -1.16; 95% CI: -1.31, -1.02) • Dupilumab significantly improved all SNOT-22 items vs. placebo regardless of comorbid asthma or NSAID-ERD, or history of prior sinonasal surgery with (all p<0.05) • A significantly higher proportion of patients achieved a clinically meaningful improvement in SNOT-22 total scores vs. placebo at Week 24 and Week 52, with greater improvements observed in difficult-to-treat patients • Dupilumab resulted in significant improvements in EQ-VAS scores vs. placebo at Week 24 and Week 52 regardless of comorbid asthma or NSAID-ERD, or history of prior sinonasal surgery with (all p<0.05) • At Week 24 and Week 52, patients on dupilumab achieved EQ-VAS scores within the general population norms, while patients in the placebo group still had EQ-VAS scores below the norms (except for patients without asthma) • Significantly more patients achieved a clinically meaningful improvement in EQ-VAS scores with dupilumab vs. placebo at Week 24 (46.8% vs. 25.9%; OR 2.58; p<0.0001) and Week 52 (50.0% vs. 18.3%; OR 4.30; p<0.0001), with greater improvements observed in difficult-to-treat patients
Mullol et al. 2022⁴³	• Dupilumab resulted in significant differences in LoS, UPSIT and 'decreased sense of smell/taste' with a rapid onset: - o LoS: by day 3 - o UPSIT: at Week 2 - o SNOT-22 item 'decreased sense of smell/taste': at Week 8 • Improvements in LoS, UPSIT and SNOT-22 'decreased sense of smell/taste' scores were continuous and significantly greater vs. placebo (LS mean differences [95% CI]): - o LoS: -1.04 (-1.17, -0.91; p<0.0001) at Week 24, -1.10 (-1.31, -0.89; p<0.0001) - o UPSIT: 10.57 (9.40, 11.74; p<0.0001) at Week 24, 10.30 (8.5, 12.10; p<0.0001) at Week 52 - o SNOT-22 'decreased sense of smell/taste': -1.97 (-2.19, -1.75; p<0.0001) at Week 24, -2.23 (-2.57, -1.88; p<0.0001) at Week 52

Ref	Results
	- The proportion of anosmic patients declined with dupilumab from 78% at baseline to 45% at week 2 and 28% at week 24 (both $p < 0.0001$), while there was no change with placebo - Dupilumab effects on olfactory outcomes were observed regardless of gender, age, CRSwNP duration, prior surgery, recent SCS use, comorbid asthma or NSAID-ERD, disease severity, blood eosinophil count or serum IgE levels

ACQ-5 = 5-item Asthma Control Questionnaire; CI = confidence interval; CRSwNP = chronic rhinosinusitis with nasal polyps; ECM = established clinical management; ECRS = eosinophilic chronic rhinosinusitis; EQ = EuroQol; ERD = exacerbated respiratory disease; HR = hazard ratio; HRQoL = health-related quality of life; IgE = immunoglobulin E; ITT = intention-to-treat; JESREC = Japanese Epidemiological Survey of Refractory Eosinophilic Rhinosinusitis; LMK-CT = Lund-Mackay computed tomography; LoS = loss-of-smell; LS = least square; NC = nasal congestion/obstruction; NP = nasal polyp; NPS = nasal polyp score; NSAID = non-steroidal anti-inflammatory drug; OR = odds ratio; PNIF = peak nasal inspiratory flow PRO = patient-reported outcome; Q2W = every 2 weeks; RR = relative risk; SCS = systemic corticosteroid; SNOT-22 = 22-item Sino-Nasal Outcome Test; UPSIT = University of Pennsylvania Smell Identification Test; VAS = visual analogue scale

Sources: Bachert 2024;¹¹ Bachert 2024;⁷³ Bachert 2022;⁷⁴ Bachert 2020;⁷⁵ Busse 2023;⁷⁶ Busse 2022;⁷⁷ Chuang 2022;⁷⁸ Desrosiers 2021;⁷⁹ Fujieda 2022;⁸⁰ Gevaert 2023;⁸¹ Gurnell 2024;⁸² Hellings 2022;⁸³ Hopkins 2024;⁷ Hopkins 2021;⁸⁴ Laidlaw 2021;³⁵ Lane 2022;⁸⁵ Lee 2023;⁸⁶ Lee 2022;⁶⁵ Mullol 2022.⁴³

2.7 Subsequent treatments used in the relevant studies

Beyond ECM no treatments were used after dupilumab in the SINUS trials.

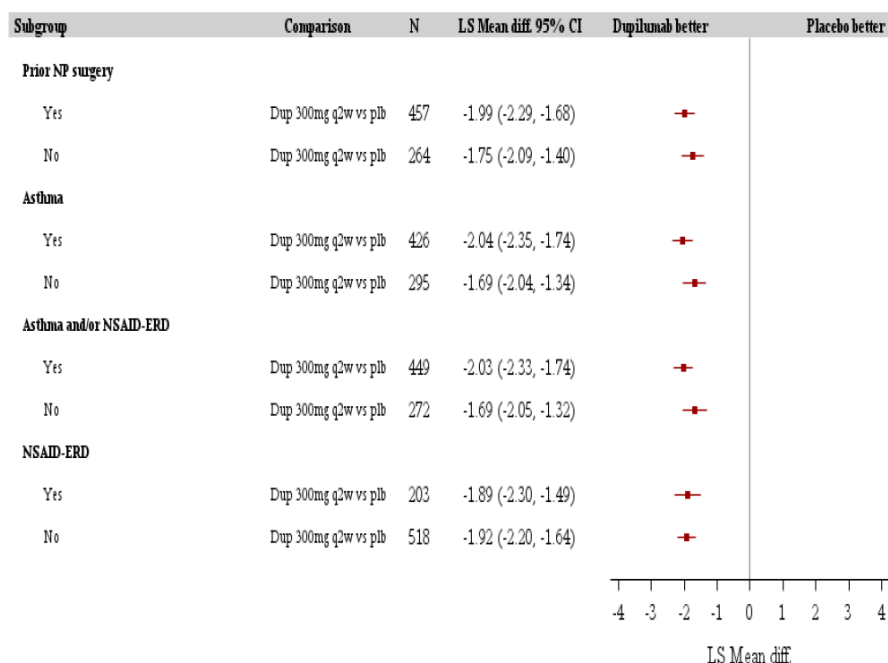
2.8 Subgroup analyses

Pre-specified subgroup analyses of the co-primary outcomes were conducted by age, gender, region, territory, race, ethnicity, baseline weight, BMI, prior surgery for nasal polyps, asthma comorbidity and/or NSAID-ERD, and SCS use in the prior two years.^{71,72}

Based on these subgroup analyses in the SINUS-24 and SINUS-52 pooled ITT population, results for the primary and key secondary endpoints were consistent in patients with comorbid asthma, NSAID-ERD or history of surgery for nasal polyps.⁹⁰ Results from the subgroup analyses in the individual SINUS-24 and SINUS-52 trial populations are presented in [Appendix E](#).

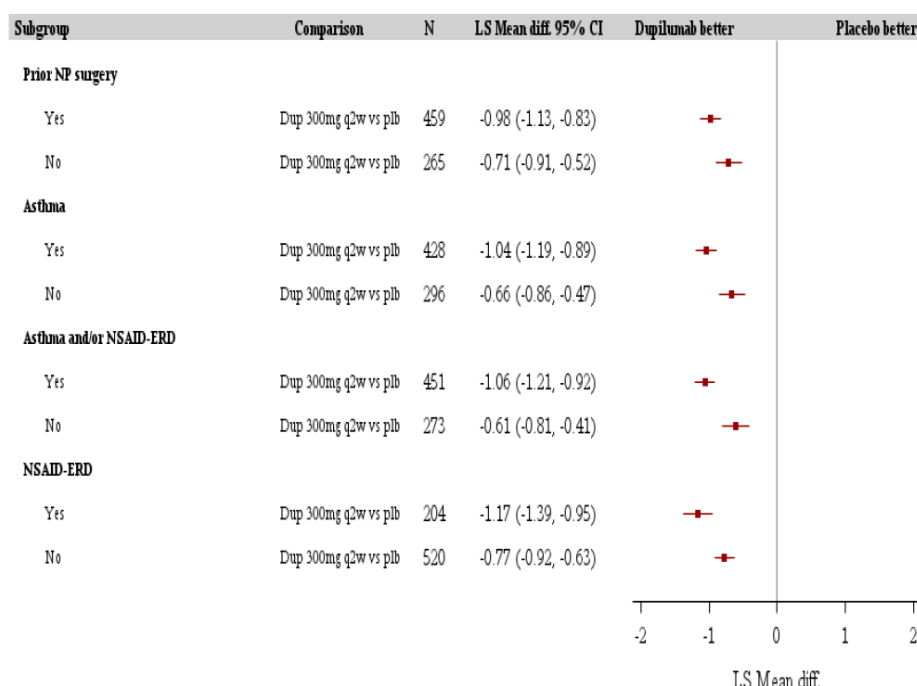
Results of the subgroup analyses conducted for the co-primary endpoints are presented in [Figure 15](#) and [Figure 16](#).

Figure 15. LS mean change from baseline in bilateral NPS at Week 24 in the pooled ITT population by disease characteristic subgroup⁹⁰



CI = confidence interval; ITT = intention-to-treat; LS = least squares; NP = nasal polyp; NPS = nasal polyp score; NSAID-ERD = nonsteroidal anti-inflammatory drug-exacerbated respiratory disease; Q2W = once every 2 weeks.
Source: Sanofi. Data on File, Summary of Clinical Efficacy.⁹⁰

Figure 16. LS mean change from baseline in NC at Week 24 in the pooled ITT population by disease characteristic subgroup⁹⁰



CI = confidence interval; ITT = intention-to-treat; LS = least squares; NC = nasal congestion/obstruction score; NP = nasal polyp; NSAID-ERD = nonsteroidal anti-inflammatory drug-exacerbated respiratory disease; Q2W = once every 2 weeks. Source: Sanofi. Data on File, Summary of Clinical Efficacy.⁹⁰

2.9 AROMA registry study

2.9.1 Methodology

AROMA was a study designed to characterise patients who receive dupilumab for CRSwNP in a real-world setting and the long-term effectiveness of dupilumab in these patients.⁸⁷

AROMA was a global, prospective, observational, multicentre, open-label, single-arm, real-world registry study assessing the safety and effectiveness of dupilumab by evaluating objective measures and PROs in adult patients with CRSwNP.⁸⁷

AROMA included a screening period (1 day to 12 weeks long) followed by an assessment period (≤36 months long) which started from completion of the baseline visit and corresponded to the initiation of treatment with dupilumab.⁸⁷ Patients who discontinued from the study before the end of study visit at Month 36 were asked to complete an early termination visit.⁸⁷ The timing of visits and the allowed missed visits and unscheduled visits were intended to reflect real-world clinical practice, while allowing adequate analysis and interpretation of the data collected.⁸⁷

Eligible patients enrolled into AROMA comprised adults who initiated dupilumab for CRSwNP according to country-specific prescribing information as part of their routine care, following prescription by their physician.⁸⁷ Key inclusion and exclusion criteria for AROMA are presented in [Table 26](#).

Table 26. Inclusion and exclusion criteria for AROMA

Inclusion criteria
• ≥18 years of age at dupilumab initiation • Newly initiating dupilumab for the treatment of CRSwNP according to country-specific prescribing information • Willing and able to comply with clinic visits and study-related procedures
Exclusion criteria
• <18 years of age at dupilumab initiation • Contraindication to dupilumab according to country-specific prescribing information • Previous treatment with dupilumab for any condition • Any condition that may interfere with the patient's ability to participate in the study as per the investigator's opinion (e.g., short life expectancy, substance abuse, severe cognitive impairment, other medical/social/ personal conditions and circumstances) • Participation in an ongoing interventional or observational study that might influence AROMA's registry study assessment as per the treating physician's opinion

CRSwNP = chronic rhinosinusitis with nasal polyps

Source: Regeneron Pharmaceuticals data on file, AROMA Registry Study Protocol.⁸⁷

Table 27. AROMA registry site locations

Country	Number of sites
Canada	5
US	48
Japan	7
Germany	8
Italy	10
Netherlands	4

US = United States

Source: Regeneron Pharmaceuticals data on file, AROMA Registry Study Protocol.⁸⁷

There were no protocol requirements regarding treatment with dupilumab or other agents during the study.⁸⁷ Patients were allowed to receive drugs as necessary for the treatment of CRSwNP and/or comorbid conditions.⁸⁷ Treatments other than dupilumab administered during the study (screening and/or assessment periods), including medications started before, during and after treatment with dupilumab, were considered concomitant medications or procedures.⁸⁷ Temporary or permanent discontinuation of dupilumab and/or any other treatment were permitted based on physician's decision.⁸⁷ Patients could stay enrolled in the study irrespective of their CRSwNP treatment(s).⁸⁷

The co-primary endpoints in AROMA were the descriptive summary of symptoms/HRQoL and their change over time, and the descriptive summary of patients and disease characteristics for CRSwNP and type 2 comorbidities.⁸⁷ Several efficacy outcomes evaluated in AROMA had also been evaluated in the SINUS-24 and SINUS-52 trials including NC score, LMK-CT, decreased/loss of smell, SNOT-22, TSS, UPSIT, PNIF, ACQ-6 and FEV₁.⁸⁷ Among these outcomes, LMK-CT, PNIF and FEV₁ were not required per the protocol and were assessed at the treating physician's discretion.⁸⁷ The time frames for assessing the outcomes were as follows:⁸⁷

- LMK-CT, SNOT-22, PNIF and FEV₁ were assessed every three months up to Month 24 and then every six months from Months 24 to 36
- NC score, decreased/loss of smell and TSS were assessed every three months up to Month 6 and then every six months from Months 6 to 36
- UPSIT and ACQ-6 were assessed every six months throughout the study period.

The sample size was selected empirically as no statistical analysis was conducted.⁸⁷ Considering an estimated study discontinuation rate of approximately 15% to 20% per year, a sample size of approximately 1,000 patients was decided.⁸⁷ Patients who prematurely withdrew from the study could be replaced, if needed, to ensure an adequate number of evaluable patients.⁸⁷ The population definitions used in AROMA are presented in [Table 28](#); the registry evaluation analysis set (REAS) population was used for all analyses.⁸⁷

Table 28. Study populations in AROMA

Population	Definition
Registry analysis set (RAS)	All eligible patients who consented to participate in the study
Registry safety analysis set (RSAF)	All eligible patients who consented to participate in the study and have received ≥1 dose of dupilumab
Registry evaluation analysis set (REAS)	Patients in the RSAF population with ≥1 post-baseline effectiveness or safety assessment

RAS = registry analysis set; REAS = registry evaluation analysis set; RSAF = registry safety analysis set
Source: Regeneron Pharmaceuticals data on file, AROMA Registry Study Protocol.⁸⁷

2.9.2 Baseline characteristics

A total of 691 patients were enrolled in AROMA, with 676 (97.8%) patients who stayed in the study for over 6 months, 664 (96.1%) for over 12 months and 639 (92.5%) for over 24 months.⁹² The mean patient age was 51.3 years (range: 18, 87) and the majority of the patients were male (55.7%).⁹² Approximately one fifth of the patients (19.1%) had at least one surgery for nasal polyps in the year prior to baseline, with a median time since most

recent surgery of 153.5 days (range: 1, 362).⁹² In the two years prior to randomisation, 65.8% of patients received SCS.⁹² At baseline, over two thirds of patients (69.2%) had comorbid asthma and 23.2% of patients had comorbid NSAID-ERD (Table 29).⁹²

Table 29. Baseline characteristics of participants in AROMA (RAS population)

Characteristic	Total (N=691)
Male, n (%)	385 (55.7)
Age	
Mean (SD)	51.3 (13.33)
Median (range)	53.0 (18 – 87)
18 – 39 years, n (%)	148 (21.4)
40 – 64 years, n (%)	432 (62.5)
≥65 years, n (%)	111 (16.1)
Race, n (%)	
Caucasian/White	480 (69.5)
Black/African American	66 (9.6)
Asian	67 (9.7)
American Indian/Alaska Native	3 (0.4)
Multiple	24 (3.5)
Not reported	30 (4.3)
Unknown	13 (1.9)
Missing	8 (1.2)
Ethnicity	
Not Hispanic or Latino	572 (82.8)
Hispanic or Latino	47 (6.8)
Not reported	72 (10.4)
BMI (kg/m ²)	
Mean (SD)	27.89 (5.96)
Median (range)	26.80 (9.1 – 67.3)
Missing, n (%)	201 (29.1)
≥1 surgery for nasal polyps in the past 12 months, n (%)	132 (19.1)
Time since most recent surgery for nasal polyps (days)	
Mean (SD)	164.3 (107.51)
Median (range)	153.5 (1 – 362)
SCS use in the past 24 months, n (%)	455 (65.8)
Prior antibiotic use, n (%)	281 (40.7)
SNOT-22 total score* (scale 0-110)	
Mean (SD)	45.9 (21.37)
Median (range)	46.0 (0 – 97)
Missing, n (%)	139 (20.1)
Comorbid asthma, n (%)	478 (69.2)
ACQ-6* (scale 0-6) in patients with comorbid asthma, n (%)	
<1	144 (30.1)
1 to <1.5	70 (14.6)
≥1.5	141 (29.5)
Comorbid NSAID-ERD, n (%)	160 (23.2)

ACQ-6 = 6-item Asthma Control Questionnaire; ERD = exacerbated respiratory disease; NSAID = non-steroidal anti-inflammatory drug; SCS = oral corticosteroid; RAS = registry analysis set; SD = standard deviation; SNOT-22 = 22-item Sino-Nasal Outcome Test

*Higher scores indicate greater disease severity.

Source: Regeneron Pharmaceuticals data on file, AROMA Registry Study Raw Data.⁹²

2.9.3 Effectiveness and safety results

In AROMA, patients demonstrated clinically meaningful improvements in SNOT-22 score at 6 months, with a mean change from baseline of –25.0 points (SD: 21.13).⁹² Improvements were maintained at 12 months and 24 months, with mean changes from baseline of –27.3 points (SD: 22.61) and –18.0 points (SD: 16.63), respectively ([Table 30](#)).⁹²

A total of 7 (1.0%) patients required sinonasal surgery in the first six months of the study.⁹² No patients required sinonasal surgery over the period from six months to 24 months.⁹² A total of 72 (10.4%) patients required treatment with SCS in the first six months of the study.⁹² Among these patients who required SCS in the first six months, the need for SCS decreased thereafter ([Table 30](#)).⁹²

- 47 (6.8%) patients required SCS both in the first six months and between 6 and 12 months.
- 27 (3.9%) patients required SCS both in the first six months, between 6 and 12 months, and between 12 and 24 months.

Table 30. Summary of results for SNOT-22, proportion of patients requiring sinonasal surgery and proportion of patients requiring SCS in AROMA (RAS population)

Endpoint	6 months		12 months		24 months	
	Mean (SD)	Mean CFB (SD)	Mean (SD)	Mean CFB (SD)	Mean (SD)	Mean CFB (SD)
SNOT-22 score	19.7 (15.60)	–25.0 (21.13)	17.1 (14.27)	–27.3 (22.61)	19.8 (19.20)	–18.0 (16.63)
	Number (%)		Number (%)		Number (%)	
Patients requiring surgery	7 (1.0)		0		0	
Patients requiring SCS	72 (10.4)		47 (6.8)*		27 (3.9)*	

CFB = change from baseline; RAS = registry analysis set; SCS = systemic corticosteroids; SD = standard deviation; SNOT-22 = 22-item Sino-Nasal Outcome Test

*The proportion of patients requiring SCS at 12 months is presented as the proportion of patients who required SCS in both the first six months and between 6 and 12 months; similarly, the proportion of patients requiring SCS at 24 months is presented as the proportion of patients who required SCS in both the first six months, between 6 and 12 months, and between 12 and 24 months.

Source: Regeneron Pharmaceuticals data on file, AROMA Registry Study Raw Data.⁹²

A summary of treatment-emergent adverse events (TEAEs) by primary system organ class and including the most common preferred terms (≥1%) within the AROMA Registry Analysis Set (RAS) population is presented in [Table 31](#). During the first 12 months, the incidence of any TEAE (23.3%) was low.⁹² The primary system organ classes most commonly affected were ‘infections and infestations’ (8.5%), ‘musculoskeletal and connective tissue disorders’ (4.9%) and ‘general disorders and administration site conditions’ (3.9%).⁹² Over 24 months,

the incidence of any TEAE during both the first 12 months and between 12 and 24 months was very low (2.6%).⁹²

Table 31. TEAEs by primary system organ class and most common preferred terms (≥1%) in AROMA (RAS population)

TEAE, n (%)	12 months	24 months*
Any TEAE	161 (23.3)	18 (2.6)
Infections and infestations	59 (8.5)	12 (1.7)
COVID-19	14 (2.0)	1 (0.1)
Upper respiratory tract infection	7 (1.0)	1 (0.1)
Musculoskeletal and connective tissue disorders	34 (4.9)	1 (0.1)
Arthralgia	22 (3.2)	0
General disorders and administration site conditions	27 (3.9)	0
Injection site reaction	9 (1.3)	0
Skin and subcutaneous tissue disorders	22 (3.2)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	20 (2.9)	2 (0.3)
Eye disorders	15 (2.2)	0
Nervous system disorders	14 (2.0)	1 (0.1)
Headache	7 (1.0)	0
Gastrointestinal disorders	10 (1.4)	1 (0.1)
Cardiac disorders	8 (1.2)	0
Ear and labyrinth disorders	5 (0.7)	0
Injury, poisoning and procedural complications	4 (0.6)	1 (0.1)
Investigations	4 (0.6)	0
Neoplasms benign, malignant and unspecified (incl. cysts/polyps)	3 (0.4)	0
Renal and urinary disorders	3 (0.4)	1 (0.1)
Blood and lymphatic system disorders	2 (0.3)	0
Hepatobiliary disorders	2 (0.3)	0
Reproductive system and breast disorders	2 (0.3)	0
Endocrine disorders	1 (0.1)	0
Psychiatric disorders	1 (0.1)	0

COVID-19 = Coronavirus disease 2019; RAS = registry analysis set; TEAE = treatment-emergent adverse event.

*The proportion of patients reporting TEAEs at 24 months is presented as the proportion of patients who reported a TEAE in both the first 12 months and between 12 and 24 months.

Source: Regeneron Pharmaceuticals data on file, AROMA Registry Study Raw Data.⁹²

2.10 *Meta-analysis*

Pooled efficacy results from SINUS-24 and SINUS-52 are presented in Section [2.6.3](#) and Section [2.6.2](#). The SLR did not identify any additional relevant phase 3 studies assessing the efficacy of dupilumab in patients with CRSwNP. Therefore, no additional meta-analyses were conducted. The economic analysis is based on a within-trial comparison with ECM.

2.11 *Indirect and mixed treatment comparisons*

There are currently no NICE-recommended targeted systemic treatments for patients with previously treated uncontrolled CRSwNP. As none of the comparators identified in the clinical SLR for the treatment of patients with previously treated uncontrolled CRSwNP are recommended in England, no indirect or mixed-treatment comparisons with other systemic therapies were conducted.

2.12 *Adverse reactions*

The safety profile of dupilumab has been established in an extensive clinical development programme involving 15,834 participants (as of 28 March 2024) included in the safety population and 12,250 exposed to dupilumab of various ages and in multiple indications (AD, allergic bronchopulmonary aspergillosis, allergy, asthma, bullous pemphigoid, chronic pruritus of unknown origin, COPD, eosinophilic gastritis, eosinophilic oesophagitis, PN, rhinosinusitis, ulcerative colitis and urticaria).⁹³ The cumulative exposure to dupilumab parenteral formulations is estimated to be 1.9 million patient years⁹³ and to date, over 1 million patients have been treated with dupilumab for licenced indications worldwide.⁹⁴ Favourable long-term safety and tolerability of dupilumab have been demonstrated based on five-year safety data, contributing to a well-characterised benefit-risk profile.^{17,18} Furthermore, according to the latest Periodic Benefit-Risk Evaluation Report based on the evaluation of the cumulative safety data, the benefit-risk balance of dupilumab across all indications remains positive in the currently approved conditions of use.⁹³

2.12.1 Pooled safety analysis of SINUS-24 and SINUS-52

A pooled safety evaluation was conducted using data up to Week 24 from the safety populations of SINUS-24 and SINUS-52 populations.⁶⁸ Safety results from the individual SINUS-24 and SINUS-52 trials are presented in [Appendix F](#). A total of 722 randomised patients from both studies were exposed to either dupilumab 300 mg Q2W (n=440) or placebo (n=282) and included in the pooled safety analysis set.⁶⁸ Most patients in the

dupilumab and placebo groups completed 24 weeks of treatment (96.6% and 90.8%, respectively) and both groups had a median duration of treatment of 168 days.⁹⁵

During the 24-week treatment period, patients treated with dupilumab vs. placebo had a lower incidence of any TEAE (69.3% vs 73.8%), severe TEAE (3.9% vs 6.4%), serious TEAE (3.4% vs 5.7%) and TEAE leading to permanent discontinuation (2.5% vs 5.3%) (Table 32).⁶⁸ No injection site reactions resulted in treatment discontinuation and all injection site reactions in the dupilumab group were classified as resolving or resolved despite treatment continuation.⁹⁵

Table 32. Summary of TEAEs in pooled safety population from SINUS-24 and SINUS-52⁶⁸

TEAE, n (%)	Placebo (N=282)	Dupilumab Q2W (N=440)	Risk difference, % (95% CI) dupilumab vs. placebo
Any	208 (74)	305 (69)	-6.48 (-13.04, 0.08)
Any serious	16 (6)	15 (3)	-2.80 (-6.30, 0.70)
Leading to permanent treatment discontinuation	15 (5)	11 (3)	-2.66 (-6.01, 0.69)
Leading to death	0	0	0

CI = confidence interval; Q2W = once every 2 weeks; TEAE = treatment-emergent adverse event.
Source: Bachert 2019.⁶⁸

A summary of common TEAEs (incidence of $\geq 5\%$ in either treatment group) within the pooled safety population is presented in Table 33. The safety endpoint of worsening nasal polyps or asthma from baseline was over four times more likely in patients in the placebo arm compared with the dupilumab arm (11.7% vs. 2.7% and 7.1% vs. 1.6%, respectively).⁶⁸

Table 33. Common TEAEs ($\geq 5\%$ in any treatment group) in pooled safety population from SINUS-24 and SINUS-52⁶⁸

TEAE, n (%)	Placebo (N=282)	Dupilumab Q2W (N=440)
Asthma*	20 (7.1)	7 (1.6)
Epistaxis	20 (7.1)	25 (5.7)
Headache	24 (8.5)	32 (7.3)
Injection-site erythema	22 (7.8)	28 (6.4)
Nasal polyps**	33 (11.7)	12 (2.7)
Nasopharyngitis	41 (14.5)	55 (12.5)

Q2W = once every 2 weeks; SCS = systemic corticosteroid; TEAE = treatment-emergent adverse event

* 'Asthma' refers to a worsening of asthma from baseline.

** 'Nasal polyps' refers to a worsening of nasal polyps resulting in sinonasal surgery or SCS treatment.

Source: Bachert 2019.⁶⁸

Overall, serious TEAEs were more common in the placebo group (5.7%) vs. the dupilumab group (3.4%) (Table 32).⁶⁸ No serious TEAE in either group had an incidence rate $\geq 1\%$. The

most frequently reported serious TEAE was worsening of nasal polyps, occurring in 1 patient (0.2%) in the dupilumab group and 2 patients (0.7%) in the placebo group. Most other serious TEAEs were single occurrences in either dupilumab or placebo groups.⁹⁵

The rate of treatment discontinuation as a result of TEAEs was lower in patients treated with dupilumab (2.5%) compared with patients on placebo (5.3%) ([Table 32](#)).⁶⁸ The most frequently reported TEAE leading to permanent treatment discontinuation in both groups was worsening of nasal polyps (0.5% in the dupilumab group and 1.8% in the placebo group). The remaining TEAEs resulting in discontinuation of treatment were individual occurrences.⁹⁵

No deaths were reported in the 24-week treatment period of the safety pool.⁹⁵ Outside the treatment period of the safety pool, there were two deaths in the CRSwNP programme which were considered unrelated to the study drug.⁶⁸

2.13 *Ongoing studies*

[Table 34](#) presents the list of ongoing Sanofi-sponsored studies with dupilumab in CRSwNP with expected results available before the fourth quarter (Q4) of 2025.

Table 34. Summary of ongoing Sanofi-sponsored studies of dupilumab in CRSwNP with expected results available before Q4 2025

Study name	Objectives/Endpoints	Study design and population	Location	Treatments	Study dates
EVEREST	Primary endpoint: UPSIT and NPS at Week 24	Head-to-head study of dupilumab vs. omalizumab in patients with severe CRSwNP and comorbid asthma (N=320)	Belgium, Canada, Czechia, Denmark, Finland, France, Germany, Hungary, Italy, Mexico, Poland, Portugal, Romania, Spain, Sweden, UK, US	- Dupilumab - Omalizumab	- Study start: September 2021 - Primary completion: October 2024 - Study end: January 2025 - Results availability: Q1 2025
INVENT	Evaluate the comparative real-world efficacy of different biologics	Regional and national registries in patients with severe uncontrolled CRSwNP after 6 months of treatment (N~1,500)	Several academic centres in Europe	- Dupilumab - Mepolizumab - Omalizumab - Tezepelumab	- Study start: January 2025 - Results availability: Q3 2025 (cross-sectional results)
AROMA	Longitudinally characterise the long-term effectiveness of dupilumab (beyond 52 weeks) through assessment of patient-reported symptoms and HRQoL related to CRSwNP, and characterise patients who receive dupilumab for CRSwNP in a RW setting	Non-interventional, open-label observational study with an 84-day screening period and a 3-year observational period in adult patients prescribed dupilumab for CRSwNP (N=717)	Canada, Germany, Italy, Japan, Netherlands, US	Dupilumab	- Study start: August 2021 - Study end: January 2027 - Results availability: February/March 2025 (1st data cut-off)
ProGNOSE	Characterise patients who receive dupilumab for CRSwNP in a RW setting	RW evidence study with descriptive summary of relevant data, including patterns of use and long-term effectiveness over 2 years (N=180)	Germany	Dupilumab	- Study start: November 2021 - Study end: October 2025 - Results availability: May 2024 (presented at EAACI congress 2024)

Study name	Objectives/Endpoints	Study design and population	Location	Treatments	Study dates
OPALE	Describe the utilisation patterns of dupilumab, including patient characteristics, disease characteristics, prior treatments for severe CRSwNP and treatment prescription modalities	RW evidence single-arm study with descriptive summary of relevant data, including patterns of use and long-term effectiveness over 2 years (N=150)	France	Dupilumab	- Study start: October 2023 - Study end: Q1 2025 - Results availability: Q4 2025 – Q1 2026
OM-1	Evaluate the RW effectiveness of dupilumab in patients with severe CRSwNP	Retrospective observational study looking at the RW effectiveness of dupilumab, 12-month pre-/post-treatment initiation in patients with severe CRSwNP (N=1,016)	US	Dupilumab	- Study start: June 2019 - Study end: June 2022 - Results availability: (unpublished as of October 2024)

CRSwNP = chronic rhinosinusitis with nasal polyps; EAACI = European Academy of Allergy & Clinical Immunology; HRQoL = health-related quality of life; NPS = nasal polyp score; Q1 = first quarter; Q3 = third quarter; RW = real-world; UK = United Kingdom; UPSIT = University of Pennsylvania Smell Identification Test; US = United States
Sources: ClinicalTrials.gov; Sanofi data on file, CRSwNP Evidence Generation: List of Active Studies.⁹⁶

2.14 Interpretation of clinical effectiveness and safety evidence

The challenges in achieving optimal CRSwNP disease control for many patients are driven by the lack of NICE-recommended systemic treatments for patients with uncontrolled CRSwNP experiencing recurrence after sinonasal surgery, and, beyond dupilumab, the absence of systemic treatments targeting type 2 inflammation via the IL-4/IL-13 signalling pathway.

In patients with uncontrolled CRSwNP and a history of sinonasal surgery, treatment options include SCS therapy and revision surgery, which are associated with limited clinically meaningful benefit and AEs/complications.^{1,10,14,55,59} Given that the majority of patients do not experience sufficient treatment efficacy from subsequent revision surgeries, there is a significant clinical unmet need for alternative therapies. Patients and clinicians require alternative, efficacious and well-tolerated treatment solutions to address type 2 inflammation, reduce the burden of LoS and sinonasal congestion/obstruction, and improve HRQoL, with specific focus on sleep and mental health.^{7,12}

Data used to support the efficacy and safety of dupilumab in CRSwNP for this submission were taken directly from the randomised, double blind, Phase 3 SINUS-24 and SINUS-52 trials which represent the most robust available evidence to address the decision problem. SINUS-24 and SINUS-52 had similar study designs but differed in the timing of some of their secondary endpoints and locations.^{68,71,72} Safety results and efficacy results for two of the key secondary efficacy endpoints (proportion of patients requiring rescue treatment [SCS or sinonasal surgery] and FEV₁ at Week 24) from SINUS-24 and SINUS-52 were pooled as part of a prespecified protocol to increase the statistical power of these efficacy and safety analyses.⁶⁸

Results from both the pooled analysis and individual pivotal phase 3 studies demonstrated the efficacy and tolerability of dupilumab vs. placebo in improving the symptoms of CRSwNP.⁶⁸ Statistical significance was achieved for the co-primary endpoints in both individual studies, as measured by change in NPS and change in patient-reported NC from baseline to Week 24.⁶⁸ Furthermore, the proportion of patients with improvement in both NPS (defined as a decrease from baseline ≥ 1 point) and NC (defined as a decrease from baseline ≥ 0.5 points) was higher with dupilumab vs. placebo at Week 24 ($p < 0.0001$ in both studies).⁶⁸

Key secondary endpoints were also met across both studies.⁶⁸ In SINUS-24 and SINUS-52, patients treated with dupilumab showed statistically significant and clinically meaningful

improvements in each hierarchically tested secondary endpoint compared with patients in the placebo arm, who showed no or minimal improvement.⁶⁸ Treatment with dupilumab significantly improved symptoms compared with placebo, as measured by the LMK-CT score, TSS, UPSIT score and LoS score from baseline to Week 24 in both studies, and NPS and NC score from baseline to Week 52 in SINUS-52.⁶⁸ In addition, dupilumab provided significantly greater improvement in HRQoL compared with placebo, as measured by the SNOT-22 score from baseline to Week 24 in both studies and Week 52 in SINUS-52, in a trial population which had worse HRQoL compared with the general population at baseline.^{65,68}

Similarly, key secondary endpoints that were assessed in the prespecified pooled analyses were met.⁶⁸ The proportion of patients who required SCS or sinonasal surgery during the treatment period was 76% lower with dupilumab compared with placebo (HR: 0.243; $p < 0.0001$).⁶⁸ Patients with comorbid asthma receiving dupilumab had statistically significant and clinically meaningful improvements in FEV₁ and ACQ-6 compared with placebo.⁶⁸

In SINUS-24 and SINUS-52, the onset of symptom improvement in patients treated with dupilumab was rapid (by Week 2 for UPSIT, Week 4 for TSS and self-reported LoS and as early as Week 4 for SNOT-22) and continuous, with improvement reported through Week 24.⁶⁸ Furthermore, in SINUS-52, patients receiving dupilumab continued to experience improvement in clinical outcomes and symptoms through Week 52, beyond what was observed at Week 24.⁶⁸ Therefore, it is likely that in the longer term, the efficacy benefits of dupilumab in CRSwNP will continue beyond Week 52. Real-world data in patients treated with dupilumab for CRSwNP from the AROMA registry study supports this hypothesis, with improvements in SNOT-22 score maintained over 24 months.⁹²

Treatment with dupilumab was well tolerated in patients with CRSwNP in the SINUS-24 and SINUS-52 studies.⁶⁸ In the pooled safety analysis, 69.3% of patients on dupilumab vs. 73.8% on placebo experienced at least one TEAE, of which the majority were mild or moderate in intensity.⁶⁸ Only 2.5% of patients in the dupilumab group discontinued treatment due to TEAEs compared to 5.3% of patients in the placebo group and no new safety signals were identified.⁶⁸ Data from SINUS-24 and SINUS-52 are generally consistent with existing safety data in patients with asthma, AD, COPD and PN. Therefore, it can be concluded that dupilumab has favourable long-term safety and tolerability and is associated with mostly mild or moderate TEAEs, a low rate of treatment discontinuation and a low rate of serious TEAEs.⁶⁸

A combined total of 724 patients (n=440 received dupilumab) were randomised in SINUS-24 and SINUS-52.⁶⁸ This number of participants was considered sufficient to demonstrate the benefit of dupilumab in patients with CRSwNP given the existing safety database in patients with AD, asthma, COPD and PN ; the SINUS-24 and SINUS-52 studies were accepted by the European Medicines Agency (EMA) and Medicines and Healthcare products Regulatory Agency (MHRA) as sufficient evidence for approval of dupilumab in patients with CRSwNP. Overall, the efficacy and safety of dupilumab in CRSwNP has been demonstrated in SINUS-24 and SINUS-52 and is further supported by clinical trial outcomes in several other approved indications.

Subgroup analyses have demonstrated that dupilumab is efficacious regardless of comorbid conditions (asthma, NSAID-ERD) or history of sinonasal surgery.⁶⁸ In addition, post-hoc analyses have demonstrated the efficacy of dupilumab across various CRSwNP outcomes, including reduction of SCS use and sinonasal surgery, improvements in objective disease measures and improvements in patient-reported symptoms and disease-specific HRQoL.^{7,11,35,43,65,73,74,76-81,83-86} Improvements with dupilumab were observed across various subgroups of patients including patients with type 2 inflammatory signature, comorbid asthma, comorbid NSAID-ERD, eosinophilic CRSwNP, smell impairment and history of sinus surgery.^{7,11,35,43,65,73,76-85} Dupilumab significantly improved general health status and all components of disease-specific HRQoL including sleep and mental health.^{7,12,65,77}

In conclusion, dupilumab provides sustained, clinically meaningful and statistically significant improvements in CRSwNP signs and symptoms, as well as HRQoL, while having a manageable safety profile.¹¹ Dupilumab has an acceptable risk-benefit profile in patients with CRSwNP who are uncontrolled on SCS therapy after sinonasal surgery.¹¹ Dupilumab can represent a significant step change in the treatment trajectory of patients with uncontrolled CRSwNP, providing clinically and humanistically meaningful benefits to a burdened patient population with limited available treatment options.

3 Economic analysis

Model Overview

- A cost-effectiveness analysis was conducted to evaluate dupilumab plus ECM in comparison to ECM alone, for the treatment of adults with uncontrolled CRSwNP for whom therapy with SCS and/or surgery do not provide adequate disease control. from the perspective of the English NHS.
- Following a systematic review of the literature, a cost-utility model structure was chosen consisting of a 1-year decision tree followed by a Markov model with an annual cycle duration. The decision tree, directly modelling the trial period, addresses short-term treatment decisions and initial response to treatment. The Markov component addresses long-term treatment response, potential need for nasal polyp surgery, the post-operative period and the possibility of revision surgery.
 - *Population:* Adults with uncontrolled disease following one (or more) surgeries. This reflects a subgroup of the full licensed indication for dupilumab in CRSwNP, as described in the scope and decision problem.
 - *Trial model inputs:* The pre-specified pooled SINUS-24 & -52 phase 3 trials provides the most robust clinical efficacy and safety data for dupilumab.
 - *Real world evidence:* Where appropriate other sources of evidence to inform discontinuation, HCRU and the societal perspective are included.
- Utility data were derived using a published mapping algorithm from the SNOT-22 data collected directly during the SINUS-24 and SINUS-52 trials. These values were tested in extensive sensitivity analyses using the observed EQ-5D data.
- Resource utilisation and unit costs were based on published data^{13,97} and NHS Reference Costs 2022/2023.⁹⁸ Estimated unit costs for SCS and antibiotics were based on the drug price from the eMIT National Database, and daily dosage derived from 2016 UK Commissioning Guide for CRS.^{99,100}
- A combined efficacy response criterion was included at Week 24 in the model to determine the proportion of patients continuing treatment with dupilumab plus ECM. This was developed in consultation with clinicians and defined as:
 - Change from baseline in SNOT-22 ≥ 8.9 and NPS ≥ 1 .
 - Efficacy response was derived from analysis of pooled SINUS-24 & -52 data.
 - The rate of sustained response at Week 52 was modelled using data from Week 24 responders in SINUS-52.

Results of the cost effectiveness modelling

- The base case generated a probabilistic incremental cost-effectiveness ratio (ICER) of £24,491 per quality-adjusted life-year (QALY) gained (Deterministic: £24,383).
- Base case results were driven by utility values for the controlled and uncontrolled health states and the proportion of responders (dupilumab and ECM) at Week 52.
- Choice of utility was examined in sensitivity analyses, (Mapped vs. Regression or observed change from baseline) and was found to be the biggest driver in sensitivity analysis.
- Scenario analysis for alternative populations indicated modest differences in cost-effectiveness between the modelled subgroups.

Conclusions

- Dupilumab is a clinically- and cost-effective use of NHS resources in adults with uncontrolled CRSwNP for whom therapy with SCS and/or surgery do not provide adequate disease control.
- Adding dupilumab to ECM is a cost-effective approach to addressing significant unmet need and burden among people with CRSwNP, alleviating symptoms and lowering the requirement for revision surgeries.
- Dupilumab has the potential to relieve pressure on the healthcare system through a reduction in in-patient wait times, the need for sinus surgery and primary care visits.

3.1 *Published cost-effectiveness studies*

An SLR was conducted to identify published economic evaluations and cost-effectiveness studies of treatments for people with uncontrolled CRSwNP ([Appendix G](#)). The SLR was conducted on the 6 June 2019 and limited to articles published after 1 January 1999. An update to this SLR was performed on 4 September 2024, limiting to articles published after 1 March 2019. No geographical or language restrictions were applied in the searches.

In the original SLR (June 2019), a total of 868 unique records were identified from electronic database sources and were eligible for screening, including 660 unique records via Embase, 151 via MEDLINE and 57 records via the Cochrane Library. Internet searches, performed between 25 and 26 June 2019, yielded a total of 53 abstracts deemed relevant and eligible for detailed screening, whilst hand searching the bibliographies of 3 SLRs and 6 economic evaluations of treatments identified an additional 49 unique and relevant references. Therefore, a total of 970 articles were screened.

In the updated SLR (September 2024), an additional 1,049 unique records were identified from electronic database sources and were eligible for screening, including 935 unique records via Embase, 54 via MEDLINE, 59 via the Cochrane library, and one via the International Network of Agencies for Health Technology Assessment (INHATA). Internet searches, conducted between 15 August and 25 September 2024, yielded 17 unique abstracts considered eligible for detailed screening. Hand searching the bibliographies of 8 SLRs and one HTA submission identified 12 unique and relevant references. Therefore, a total of 1,078 articles were screened. The combined total of unique reports for screening from the original and updated SLR was 2,048.

Considering the original and updated SLR, exclusion of reports based on title/abstract screening resulted in a total of 95 unique reports for systematic review ([Appendix G](#)), six of which were not selected for data extraction. In total, there were 19 economic evaluations of

treatment strategies, 60 reports of cost and resource use (56 unique references and 4 secondary references) and 16 were utility studies.

Of the 19 economic evaluations identified ([Table 35](#)), most provided economic analyses from the United States (n=7) and Canada (n=5). In addition, three studies were conducted in Italy, two in Colombia, and one in Sweden. For the one remaining study, the country was not reported. Of the included studies, 9 included an assessment of one or more biologics, nine included an assessment of ESS or other forms of surgery and one compared routine histologic screening compared with no routine histologic screening. Five articles reported on disease severity,¹⁰¹⁻¹⁰⁵ only 3 of which specified the tool(s) used to assess severity.¹⁰¹⁻¹⁰³ Most studies employed either a healthcare payer perspective (e.g., national health system payer), followed by government and third-party payer perspectives. One study was performed from a societal perspective.

Table 35 Summary list of published cost-effectiveness studies

Author	Year	Study design	Country	Title
Alvarez	2023	CUA	Colombia	Cost–utility analysis of dupilumab compared with endoscopic sinus surgery in patients with chronic rhinosinusitis with nasal polyps. Evaluation in Colombia, a developing country.
Berggren	2003	Cost minimisation analysis	Sweden	Cost effectiveness of nasal budesonide versus surgical treatment for nasal polyps.
CADTH	2023	CUA	Canada	CADTH Reimbursement Review - Mepolizumab (Nucala). February 2023
De Corso	2022	CUA	Italy	Cost–Utility Analysis of Dupilumab for the Treatment of Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) in Italy.
Kumar	2020	CEA	Canada	Cost-effectiveness of Endoscopic Polypectomy in Clinic compared to Endoscopic Sinus Surgery: A modelling study.
La Mantia	2024	Cost-per-responder and cost-per-percentage of improvement analyses	Italy	Multidimensional Impact of Dupilumab on Chronic Rhinosinusitis with Nasal Polyps: A Complete Health Technology Assessment of Clinical, Economic, and Non-Clinical Domains.
Parasher	2022	CEA	US	Economic Evaluation of Dupilumab Versus Endoscopic Sinus Surgery for the Treatment of Chronic Rhinosinusitis With Nasal Polyps.
Rudmik	2016	CUA	Canada	Endoscopic polypectomy in the clinic: A pilot cost-effectiveness analysis.
Scangas	2018	CUA	US	The value of frontal sinusotomy for chronic rhinosinusitis with nasal polyps—A cost utility analysis.
Scangas	2017	CUA	US	Cost utility analysis of endoscopic sinus surgery for chronic rhinosinusitis with and without nasal polyposis.
Scangas	2017	CUA	US	The impact of asthma on the cost effectiveness of surgery for chronic rhinosinusitis with nasal polyps.
Scangas	2021	CUA	US	Cost Utility Analysis of Dupilumab Versus Endoscopic Sinus Surgery for Chronic Rhinosinusitis With Nasal Polyps.

Author	Year	Study design	Country	Title
Trimarchi	2022	Time-driven activity-based costing analysis	Italy	Determination of costs for the CRSwNP pathway. A time-driven activity-based costing experiment.
Upegui	2023	Cost per responder analysis	Colombia	EE403 Economic Analysis of Dupilumab Use in Patients With Chronic Rhinosinusitis With Nasal Polyps in Colombia.
Velez	2018	CUA	US	Cost-effectiveness of eds-flu in sinus surgery candidates who have chronic rhinosinusitis with nasal polyps.
Velez	2019	CEA (work productivity loss as an outcome)	NR	Lifetime Work Productivity Gains Among Patients with Chronic Rhinosinusitis with Nasal polyps (CRSwNP) Treated with EDS-FLU.
Wong	2015	CEA (life-year as the outcome)	Canada	The usefulness of routine histopathology of bilateral nasal polyps - A systematic review, meta-analysis, and cost evaluation.
Yong	2023	CEA	Canada	Cost-effectiveness analysis of biologics for the treatment of chronic rhinosinusitis with nasal polyps in Canada.
Yong	2021	CEA and CUA	US	Cost-effectiveness analysis comparing dupilumab and aspirin desensitization therapy for chronic rhinosinusitis with nasal polyposis in aspirin-exacerbated respiratory disease.

CADTH = Canada's Drug and Health Technology Agency; CEA = cost-effectiveness analysis; CRSwNP = chronic rhinosinusitis with nasal polyps; CUA = cost-utility analysis; EDS-FLU = exhalation delivery system with fluticasone; UK = United Kingdom; US = United States

Models used in the 19 economic evaluations identified through SLR ([Table 35](#) and [Appendix G](#)) were either decision trees, Markov structures, or a combination of both. In alignment with the economic evaluations identified, and with previous NICE appraisals of biologics for other type 2 inflammatory conditions, we have chosen a decision tree followed by a Markov model structure for this submission. This model structure is the most appropriate option to capture the benefits of dupilumab as an add-on to ECM for the treatment of adults with uncontrolled CRSwNP for whom therapy with SCS and/or surgery do not provide adequate disease control.

It is important for the economic model to fully capture the costs and health outcomes associated with the life-long management of people uncontrolled CRSwNP. The model chosen for this submission is based on that published by De Corso et al., 2022, which was developed by Sanofi to evaluate the cost-effectiveness of dupilumab as a treatment for people with uncontrolled CRSwNP.¹⁰⁴ For the purposes of this submission, modifications to some model inputs have been made in order for the model to reflect the specific patient population for which dupilumab reimbursement is sought. Refinement of the model has also been achieved through the inclusion of utilities values which we consider to be more appropriate compared with those used in the model published by De Corso et al., 2022.¹⁰⁴

3.1.1 Key considerations for the CEM

People with CRSwNP require lifelong treatment due to the persistent, relapsing nature of the condition. Therefore, the economic model captures both short- and long-term costs and outcomes associated with the management of CRSwNP.

Costs and burden of disease associated with CRSwNP:

- *Definition of Control:* The EUFOREA/EPOS guideline defines controlled CRSwNP as minimal or no symptoms (e.g., nasal obstruction, nasal discharge, facial pain/pressure, loss of smell) that do not significantly impact daily activities or quality of life, and where no urgent surgical intervention is required.^{1,6}
- *Assessment of Control:* Main criteria include patient-reported symptom scores (e.g., SNOT-22), endoscopic evaluation of nasal polyp size, and imaging assessments such as CT-scans (though the latter may not be feasible in routine practice). See Section 1.2.1.2 for a definition of efficacy response criteria.
- *Challenges to Maintain Long-term Control:* Variability in patient response, treatment adherence, and the chronic, relapse-prone nature of CRSwNP make long-term management complex. Patients who fail to maintain control risk symptom worsening, additional treatments, and possible surgical intervention.
- *Healthcare Resource Use:* Because CRSwNP requires ongoing medical management (e.g., intranasal corticosteroids, oral steroids, or biologics), the cumulative costs over a patient's lifetime can be substantial. Frequent specialist visits, diagnostic tests, and potential comorbidity treatments (e.g., for asthma) further add to the economic burden.

Costs and burden of surgery:

- *ESS:* Sinus surgery is often indicated for uncontrolled or refractory CRSwNP. While it can offer symptomatic relief, recurrence of nasal polyps is common, limiting long-term effectiveness.¹⁶
- *Risks and Costs:* ESS involves significant procedural and post-operative expenses, including pre-operative assessment, anaesthesia, potential complications (e.g., bleeding, infection, anaesthesia-related complications), and future revision surgeries.⁹⁷
- *Burden on the NHS:* Long wait times (up to three years in some regions of England) reflect both the high demand for sinus surgery and systemic resource constraints, highlighting the need for effective non-surgical treatments.³¹

In the UK, dupilumab is indicated as add-on maintenance treatment for adults with severe CRSwNP or for whom therapy with SCS and/or surgery do not provide adequate disease control.¹⁷ To fully capture the burden of uncontrolled CRSwNP as well as the clinical benefits of dupilumab in this population, the model structure considers the key relationships summarised in [Table 36](#).

Table 36. Key considerations of the cost-effectiveness model for dupilumab as a treatment for people with CRSwNP

Parameters	Rationale
Long-term control	As disease management (HCRU) and utilities depend on CRSwNP control, a lifetime model needs to capture response and recurrence of disease (measured as a combination of NPS and SNOT-22 [see Section 1.2.1.2 for efficacy response criteria]) to reflect the progression of CRSwNP over time, any impact of disease recurrence and the need for rescue therapy.
Number of previous surgeries	Sinus surgery is a key factor in the economic burden of CRSwNP. Evidence exists to show that prior surgery (cumulative number) is associated with the probability and frequency of future surgery.
Treatment effect is limited to trial duration of 52 weeks	The SINUS-24 trial duration was 24 weeks, and the SINUS-52 trial duration was 52 weeks. Therefore, from the clinical trial data it is not clear whether the benefits of dupilumab can be maintained beyond 52 weeks. However, the AROMA study has provided real world evidence of continued benefit (Section 2.9.3). The model needs to be flexible to allow testing of different assumptions around the long-term benefit of dupilumab and allow for incorporating long-term efficacy outcomes.
Use of external data to model long-term progression of CRSwNP	Modelling disease progression for CRSwNP cannot solely rely on the 52-week trial data. The model needs to incorporate appropriate external data to estimate outcomes beyond the trial follow-up period.
Use of real-world evidence to inform surgery rate, discontinuation and compliance rates and HCRU	Data to reflect real-world UK patients that are not available from the clinical trials must be incorporated in the model. The time horizon of the studies is not long enough to collect sufficient discontinuation, compliance data and surgery rate. For example, surgery rate from the AROMA study is used (Section 2.9.3). HCRU is a key driver of the burden on the NHS; however, as UK HCRU data were not collected in the clinical trials, these data must be sourced externally.
Generalisability of external data to SINUS-24 and SINUS-52 populations	The SINUS-24 and SINUS-52 trial populations include patients with severe CRSwNP. When incorporating external data, the generalisability to the SINUS-24 and SINUS-52 trial populations must be considered.

CRSwNP = chronic rhinosinusitis with nasal polyps; HCRU = healthcare resource utilisation; NHS = National Health Service; NPS = nasal polyp score; SNOT-22 = Sinonasal Outcome Test-22

Based on the considerations listed above and the rationale provided in [Table 36](#) we have developed a cohort Markov model structure with a decision tree component representing the first year (trial period), which accurately captures key aspects of the disease and treatment practices while reflecting the key trial endpoints and treatment effect of dupilumab. Our approach was endorsed at an advisory board held by Sanofi in June 2024 ([Appendix R](#)),³¹ followed by consultancy meetings led in November 2024 with nine British clinicians (4 English) with expertise in CRSwNP and one health economist ([Appendix R](#)).¹²

3.1.2 Patient population

Dupilumab is licensed in the UK for adults with severe CRSwNP for whom therapy with SCS and/or surgery do not provide adequate disease control.^{17,18} After consulting with clinicians and people with CRSwNP, it is clear that the optimal place in therapy for dupilumab is after treatment failure with current standard of care ([Appendix R](#)).¹² This includes surgery, which for some people can be a good and lasting option ([Appendix R](#)).¹² However, people with more aggressive disease can experience rapid recurrence and for these patients, revision surgery(ies) does not provide long term satisfactory outcomes.^{8,31} Therefore the base case population focuses on people with uncontrolled disease following one (or more) surgeries. This is a subgroup of the licensed indication.^{17,18} We do recognise that not all people with CRSwNP are eligible for surgery and that patients with comorbid type-2 conditions usually have worse symptoms and could benefit from biologics.¹⁰ Therefore, in addition to the base case population we also provide two scenarios in line with the scope, which consider people with any prior type-2 medical history:

- Patients with type 2 medical history
- Patient with prior surgery AND any prior type-2 medical history

Patient characteristics in the model were based on those of the pooled SINUS-24 and SINUS-52 trials.⁶⁸

3.1.3 Cost-effectiveness model structure

The CEM was developed in Microsoft Excel® using a cohort Markov model structure with a decision tree component representing the first year (trial period).

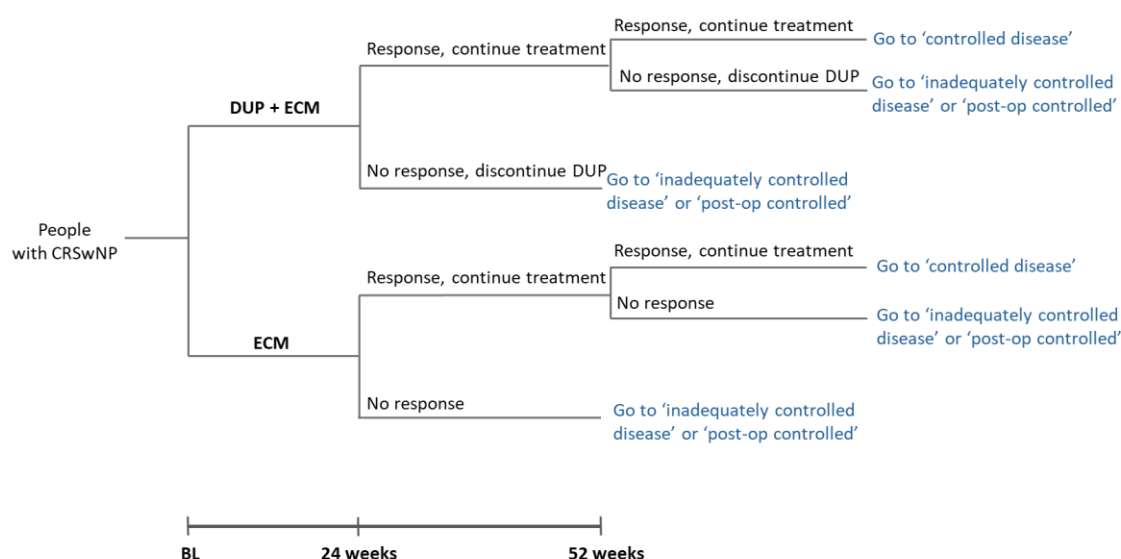
The model structure begins with a 1-year decision tree followed by a Markov model with an annual cycle duration. The decision tree, which directly models the trial period, addresses short-term treatment decisions and initial response to treatment, while the Markov component addresses long-term treatment response, potential need for NP surgery (including revision surgery) and the post-operative period. A similar structure (i.e., a short-

term decision tree and Markov model for long time effect) has been used to model the cost effectiveness of dupilumab in the treatment of atopic dermatitis^{69,106}, prurigo nodularis¹⁰⁷ asthma⁶⁰ and CRSwNP¹⁰⁸, and for the use of biologics in the treatment of psoriasis.¹⁰⁹

In the decision tree (Figure 17) people with inadequately controlled CRSwNP can be treated with either dupilumab plus established clinical management (DUP + ECM) or ECM alone. Treatment response is determined at two different assessment points:

- First assessment (Week 24):
 - o Responders remain in the decision tree until the second assessment (Week 52).
 - o Dupilumab non-responders discontinue dupilumab and enter the Markov model in either the inadequately controlled disease health state, or, if they receive surgery, the post-operative controlled health state.
 - o ECM non-responders can enter the Markov model in either the inadequately controlled disease health state or the post-operative controlled health state.
 - o One-off costs and utilities associated with surgery are applied when people first arrive in the post-operative controlled health state.
- Second assessment (Week 52):
 - o Responders enter the controlled health state of the Markov model.
 - o Dupilumab non-responders discontinue dupilumab and enter the inadequately controlled or post-operative controlled health state of the Markov Model.
 - o ECM non-responders can enter the Markov model in either the inadequately controlled disease health state, or the post-operative controlled health state.

Figure 17. Decision tree structure



CRSwNP = chronic rhinosinusitis with nasal polyps; DUP = dupilumab; ECM = established clinical management; post-op = post-operative; BL = Base Line

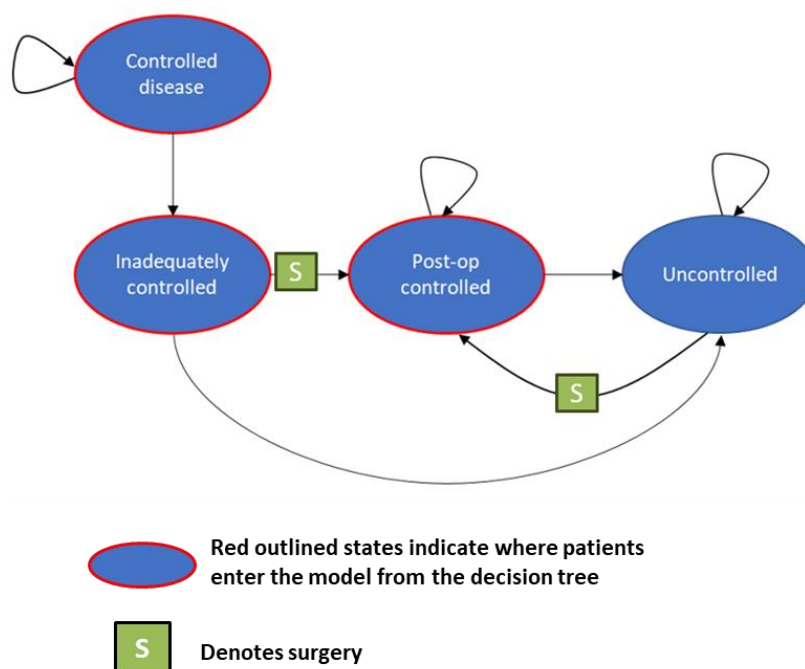
In the Markov model ([Figure 18](#)), people remain in the controlled disease health state until discontinuation for reasons such as loss of response, AEs or patient/physician preference. After discontinuation, people enter the inadequately controlled disease health state – a temporary state in which people can stay for only 1 year. This health state is included to model the gradual loss of quality of life before returning to the fully uncontrolled health state where baseline utility is applied. Utilities for the inadequately controlled disease health state are based on Week 52 utility weights from people in the placebo arms of the SINUS trials who did not respond at Weeks 24 and 52.

Following 1 year in the inadequately controlled health state, people can either:

- Move to the uncontrolled health state (where baseline utility is applied).
- Receive surgery and move to the post-operative controlled health state, where they remain until the disease becomes uncontrolled again. The model permits multiple surgeries.

People who are ineligible for surgery transition to the uncontrolled health state and stay there for the remaining time horizon. All health states may transition to the death health state.

Figure 18. Markov model structure



Post-op = post-operative

The base case analysis takes the UK NHS perspective. A societal perspective is also provided in sensitivity analysis to account for productivity loss and out of pocket expenses. The base-case analysis uses a lifetime horizon (49 years), starting with treatment initiation.

Alternative shorter time horizons (i.e., 5 years, 10 years and 20 years) are explored in scenario analyses.

The cost-year for the analysis was 2024. Costs quoted for other cost-years are inflated to 2024 costs using annual inflation rates from Unit Costs of Health and Social Care 2023 from the Personal Social Services Research Unit (PSSRU) and Consumer Price Inflation (CPI) annual rates from Office for National Statistics.^{110,111}

In the base-case analysis, costs and outcomes are discounted at the same rate according to the reference case: 3.5% for both costs and outcomes. Alternative discounting rates of 3% and 5% were explored in the sensitivity analyses.

Half cycle correction is applied in the Markov portion of the model.

3.1.4 Intervention technology and comparators

The model is designed to compare the use of dupilumab plus ECM, with ECM alone in England. ECM treatments in England include nasal irrigation with saline solution, INCS and SCS.¹ The model did not evaluate the cost impact of INCS because the SINUS-24 and SINUS-52 clinical trials were not designed to show a difference in INCS use between the 2 treatment arms and so costs were assumed to be the same in both arms. This is likely to be a conservative approach.⁶⁸

Short courses of SCSs or antibiotics can also be considered to manage moderate-to-severe CRSwNP, according to guidance published by EUFOREA and EPOS (Section [1.2.2.1](#)).^{1,10} The same guidelines describe surgical intervention (endoscope sinonasal surgery, ESS) for the treatment of people with CRSwNP whose disease is uncontrolled by ECM, with revision ESS recommended for people with recurrent disease (Section [1.2.2.1](#)).¹⁰

Although ESS is a key element in the treatment pathway^{1,10} and is considered in the modelling as an event which drives patients between health states, it is not considered as the main comparator in its own right, but rather as a component of ECM. Note that the majority of people treated with dupilumab in the SINUS-24 and SINUS-52 clinical trials had received at least 1 surgery prior to enrolment (92% and 74%, respectively).⁶⁸ As outlined in Section [1.2.2.3](#), dupilumab is positioned for use following 1 surgery and ESS is considered a subsequent treatment for a proportion of patients. SCS and antibiotic use were considered in the calculations of ECM treatment for all patients.

Other biologics with regulatory approval for the treatment of patients with CRSwNP (omalizumab and mepolizumab) are not currently reimbursed in the UK and so are not valid

comparators or components of ECM. These have not been included as comparators in the model.^{62,63} A third biologic, benralizumab has been evaluated in clinical trials for CRSwNP but is currently not approved for use in the UK and therefore also not included in the model.¹¹²

3.2 Clinical parameters and variables

3.2.1 Baseline characteristics

Baseline characteristics in the model (patient age, percentage male, utility weight, NPS and SNOT-22 score) were populated with inputs according to the population of interest. In the base case this is people with *inadequately controlled CRSwNP AND at least one prior surgery* derived from the pooled analysis of SINUS-24 and SINUS-52 trials.⁶⁸ The sex and mean age of the population were used to estimate all-cause mortality. Baseline utility weight and change from baseline are used to estimate the health-state utility weights ([Appendix O](#), [Appendix P](#)).

The baseline characteristics for the subgroup of people with at least 1 prior surgery (the base case) are presented in [Table 37](#).

Table 37. Baseline characteristics of the modelled population (Pooled SINUS-24 & SINUS-52)

Characteristic	Placebo	Dupilumab	Overall
N	187	272	459
Male, n (%)	103 (55.1)	165 (60.7)	268 (58.4)
Age, years (SD)	50.97 (13.16)	51.66 (12.23)	51.38 (12.61)
Race, n (%)			
Caucasian/White	170 (90.9)	239 (87.9)	409 (89.1)
Black/African decent	4 (2.1)	3 (1.1)	7 (1.5)
Asian/Oriental	12 (6.4)	25 (9.2)	37(8.1)
American Indian/Alaska Native	1 (0.5)	4 (1.5)	5 (1.1)
Native Hawaiian/Other Pacific Islander	0	0	0
Multiple	0	1 (0.4)	1 (0.2)
Unknown	0	0	0
Territory, n (%)			
North America	27 (14.4)	53 (19.5)	80 (17.4)
European Union	82 (43.9)	100 (36.8)	182 (39.7)
Rest of the World	78 (41.7)	119 (43.8)	197 (42.9)
BMI (kg/m ²), mean (SD)	27.70 (5.46)	27.54 (5.20)	27.60 (5.30)
Time since first diagnosis of nasal polyps (years), mean (SD)	13.75 (9.16)	14.51 (9.93)	14.20 (9.62)
Previous surgeries for nasal polyps, n (%)			
1 previous surgery	101 (54.0)	153 (56.3)	254 (55.3)
2 previous surgeries	39 (20.9)	55 (20.2)	94 (20.5)
≥3 previous surgeries	47 (25.1)	64 (23.5)	111 (24.2)

Characteristic	Placebo	Dupilumab	Overall
Time since most recent nasal polyp surgery (years), mean (SD)	7.06 (6.33)	7.22 (6.52)	7.16 (6.44)
SCS use in the past 2 years, n (%)	118 (63.1)	174 (64.0)	292 (63.6)
Bilateral endoscopic NPS* (scale 0-8), mean (SD)	5.74 (1.27)	5.94 (1.26)	5.86 (1.26)
NC score* (scale 0-3), mean (SD)	2.47 (0.53)	2.42 (0.59)	2.44 (0.56)
SNOT-22 total score* (scale 0-110), mean (SD)	53.47 (19.92)	50.35 (20.32)	51.63 (20.19)
Smell test (UPSIT) score** (scale 0-40), mean (SD)	13.01 (7.46)	12.65 (7.57)	12.80 (7.52)
LoS score* (scale 0-3), mean (SD)	2.77 (0.48)	2.80 (0.55)	2.79 (0.52)
LMK-CT total score* (scale 0-24), mean (SD)	19.16 (4.10)	19.01 (3.89)	19.07 (3.97)
Rhinosinusitis disease severity* (VAS 0-10 cm), mean (SD)	8.10 (2.00)	7.92 (2.00)	8.00 (2.00)
Baseline NPIF** (L/min), mean (SD)	87.68 (55.43)	90.44 (58.74)	89.32 (57.37)
Baseline blood eosinophils (x10 ⁹ cells/L), mean (SD)	0.46 (0.39)	0.47 (0.39)	0.47 (0.36)
Baseline total IgE (IU/mL), mean (SD)	202.29 (241.54)	236.13 (369.79)	222.31 (323.75)
Any comorbid type 2 medical history including asthma and NSAID-ERD, n (%)	154 (82.4)	232 (85.3)	386 (84.1)
Comorbid asthma, n (%)	121 (64.7)	183 (67.3)	304 (66.2)
Comorbid NSAID-ERD, n (%)	65 (34.8)	94 (34.6)	159 (34.6)
Any comorbid type 2 medical history excluding asthma and NSAID-ERD, n (%)	117 (62.6)	177 (65.1)	294 (64.1)
Age at asthma onset in patients with comorbid asthma, years (SD)	32.91 (14.88)	34.68 (15.53)	33.98 (15.28)

ERD = exacerbated respiratory disease; IQR = interquartile range; ITT = intention-to-treat; LMK-CT = Lund-Mackay computed tomography; LoS = loss-of-smell; NC = nasal congestion/obstruction; NPIF = nasal peak inspiratory flow; NPS = nasal polyp score; NSAID = non-steroidal anti-inflammatory drug; SD = standard deviation; SNOT-22 = 22-item Sino-Nasal Outcome Test; UPSIT = University of Pennsylvania Smell Identification Test; VAS = visual analogue scale.

*Higher scores indicate greater disease severity.

** Higher scores indicate lower disease severity.

3.2.2 Clinical parameters and variables

Clinical parameters included in the model are listed below (and are described in detail in the following subsections):

- Efficacy response criteria and rates from the SINUS-24/52 trials
- Long-term response rate (post SINUS-24/52 trials): Probability of discontinuation including loss of response each year from year 2 onwards
- Clinical data inputs & transition probabilities for the post-operative controlled, inadequately controlled and uncontrolled health states, including:

- o Surgery rate to move from inadequately controlled and uncontrolled to post-operative controlled
 - o Loss of response rate (after surgery) to move from post-operative controlled to uncontrolled
- Annual discontinuation rates
- Mortality increase for people with comorbid asthma

3.2.2.1 Efficacy response criteria and rates

Efficacy response criteria define which patients continue treatment with dupilumab plus ECM. In the model, the base-case response criterion is defined as improvement (reduction) from baseline ≥ 8.9 in SNOT-22 and improvement from baseline ≥ 1 point in NPS. For SNOT-22, the MCID to detect the meaningful change by a patient has been defined as ≥ 8.9 points and used as an anchor to determine the clinically meaningful score change for NPS as ≥ 1 point.^{91,113}

This combined efficacy response criterion was tested with clinicians at an Advisory Board held on 26 June 2024³¹ and consultancy meetings on 13 November 2024 ([Appendix R](#)).¹² Clinicians told us that SNOT-22 is highly applicable and routinely used as a patient-reported outcome measure alongside their preferred objective measurement assessment of NPS to provide a meaningful response to treatment. They emphasised this combined approach resonates with clinical practice.

Assessment of nasal polyp size alone using the objective NPS measure does not necessarily provide an all-round indicator of response because loss of smell has a significant impact on patients. Similarly, SNOT-22 improvement alone which is a subjective measure, does not necessarily encompass all the elements necessary to assess disease control. Taken together the combined efficacy response criteria were deemed to be a suitable efficacy response measure by the clinicians we have spoken to. Furthermore, they supported the response criteria at the level of an improvement in SNOT-22 and NPS where a change was greater than the minimally clinically important difference in each measure (≥ 8.9 in SNOT-22 and improvement from baseline ≥ 1 for NPS).

Week-24 efficacy response: The response data available for people with inadequately controlled CRSwNP **AND** at least one prior surgery at Week 24 were derived from pooled analyses of SINUS-24 and SINUS-52 trials.

Week-52 efficacy response: Rate of sustained response at Week 52 was modelled using data from Week 24 responders in the SINUS-52 trial. The results for the ITT and base case

population according to the response criteria of SNOT 22 Total score and NPS (1-point improvement) are provided in [Table 38](#).

Table 38. Comparison of response for the ITT population and base case population with inadequately controlled CRSwNP AND ≥1 NP surgery according to the response criteria of SNOT 22 total score and NPS (1-point improvement)

	Pooled ITT population		Base case population	
	Placebo	Dupilumab 300 mg Q2W	Placebo	Dupilumab 300 mg Q2W
Overall response at Week 24				
	N = 286	N = 438	N=187	N=272
Responders				
Non-responders				
OR vs placebo (95% CI) ^a				
P value vs placebo ^b	<0.0001		<0.0001	
Overall population: Response at Week 52				
	N = 153	N = 150	N=88	N=88
Responders				
Non-responders				
OR vs placebo (95% CI) ^a				
P value vs placebo ^b	<0.0001		<0.0001	
Subpopulation: Responders at Week 24 - Response at Week 52				
	N = 11	N = 77	N=5	N=46
Responders				
Non-responders				
OR, 95% CI vs placebo ^a	NE (NE, NE)		NE (NE, NE)	
P-value vs placebo ^b	<0.0001		<0.0001	

CI = confidence interval; ITT = intent-to-treat; NE = not estimable; OR = odds ratio; Q2W = every 2 weeks

^a OR: odds ratio, derived from Mantel-Haenszel estimator.

^b CMH test was performed on the association between the responder status and treatment group (dupilumab vs placebo), stratified by asthma/NSAID-ERD status, prior surgery history, and region.

Source: Sanofi data on file, 2019

Response data inputs used in the model for the base-case (See [Table 38](#) above) and subgroups with comorbid asthma are presented in [Table 39](#) below.

Table 39. Response data inputs used in the economic model.

Response criteria and timepoint	Base case: people with inadequately controlled CRSwNP AND ≥1 NP surgery		Scenario analysis: people with any prior type 2 medical history		Scenario analysis: people with prior sinus surgery AND any prior type 2 medical history	
	DUP + ECM	ECM	DUP + ECM	ECM	DUP + ECM	ECM
Proportion achieving SNOT-22 change from BL ≥8.9 and NPS change from BL ≥1						
Week 24, %						
Week 52, %						

BL = baseline; CRSwNP = chronic rhinosinusitis with nasal polyps; DUP = dupilumab; ECM = established clinical management; NP = nasal polyp; NPS = nasal polyp score; SNOT-22 = Sinonasal Outcomes Test-22.

3.2.2.2 *Probability of moving to the inadequately controlled disease health state from Year 2 onwards.*

After Week 52, people in the controlled disease health state can move to the inadequately controlled disease health state for reasons such as loss of response, AEs or patient/physician preference. People treated with dupilumab plus ECM who discontinue dupilumab enter the inadequately controlled disease health state (where they continue to receive ECM).

In SINUS-52, [REDACTED] of people who were classified as dupilumab plus ECM responders at Week 24, continued to have a sustained response by the end of Week 52. In comparison, only [REDACTED] % of ECM responders had a sustained response by the end of Week 52. (Sanofi data on file, 2019a) Based on this, 28-week probabilities of sustained response by treatment arm were estimated for the subgroup population, and were converted to annual probabilities for moving from the controlled disease to the inadequately controlled disease health state. The annual probability of moving from the controlled disease to the inadequately controlled disease health state is therefore [REDACTED] % for people receiving dupilumab plus ECM, and [REDACTED] % for those receiving ECM alone. The transition probabilities presented in [Table 40](#) are summarised in [Figure 19](#).

Table 40. Transition probabilities for patients in the controlled disease health state

Annual transition probabilities, %	Data Input	Source
DUP+ECM people moving to the inadequately controlled health state, %	[REDACTED]	SINUS-24/52 (Sanofi data on file, 2019a)
DUP+ECM people remaining in the controlled health state for 1 year, %	[REDACTED]	
ECM people moving to the inadequately controlled health state, %	[REDACTED]	
ECM people remaining in the controlled health state for 1 year, %	[REDACTED]	

DUP = dupilumab; ECM = established clinical management

Sources: Sanofi data on file 2019a

The annualised discontinuation rate from Month 12 to Month 24 in the AROMA study was 2.2% (11/492 patients). This is tested in sensitivity analysis for year 2 and onwards in the model.

3.2.2.3 *Transition probabilities for people in the inadequately controlled disease health state.*

In the decision tree portion of the model which reflects the clinical trial, ████████ of dupilumab patients and ████████ of patients in the ECM arm receive surgery up to week 24. From week 24 to 52, ████████ and ████████ respectively receive surgery.

The inadequately controlled health state in the Markov model is a temporary state. People can stay in this health state for 1 cycle only and then either move to the uncontrolled health state or, if they receive surgery, to the post-operative controlled health state.

In the base case, the percentage of people who are ineligible for surgery was based on data from the pooled analyses of SINUS-24/52 (23.7%; Sanofi data on file, 2019a) In the Markov model people ineligible for surgery move to the uncontrolled health state and remain in that state until death. Among the 76.3% of people who are eligible for surgery, 15.1% (11.5% of all patients in the health state) receive surgery in the following year and transition to the post-operative controlled health state every year.¹⁶ The remaining 64.8% of surgery-eligible patients (total of 88.5%) move to the uncontrolled health state [Figure 19]).

No age limit for surgery was applied, although the model offers the option to increase the ineligibility to surgery with age (linear or polynomial increase). This is tested in sensitivity analysis. If age is a factor in decision making, we have assumed that ineligibility due to age is accounted for in the overall ineligible for surgery rate. Base case clinical data inputs for the inadequately controlled disease state are summarised in [Table 41](#) and in [Figure 19](#).

Table 41. Clinical data and transition probabilities for people in the inadequately controlled disease health state

Parameter	Data Input	Source
People who are ineligible for surgery, %	23.7	Pooled analyses of SINUS-24 and SINUS-52 (Sanofi, data on file, 2019a)
Maximum age eligible for surgery, years	No age limit applied in the base case	Assumption
Annual transition probabilities, %		
Eligible people moving to the post-operative surgery health state, %	11.5	Benson 2023
Eligible people moving to the uncontrolled health state, %	64.8	Calculated

Sources: Benson 2023;¹⁶ Sanofi, data on file 2019a

3.2.2.4 *Transition probabilities for the post-operative controlled health state*

People who have received NP surgery (either from the inadequately controlled health state or the uncontrolled health state) remain in the post-operative controlled health state until they become uncontrolled again. People becoming uncontrolled again move to the uncontrolled health state.

The rate of losing control after this NP surgery was derived from on Benson et al. 2023 (For people in the base case: mean time to third surgery for patients having had >2 surgeries during the follow-up period – adjusted to reflect average wait time for surgery in England). These inputs were also confirmed by English clinicians' expertise (consultancy report).¹² The base-case transition probability inputs for the post-operative controlled health state are provided in [Table 42](#) and [Figure 19](#).

Table 42. Transition probabilities for people in the post-operative controlled disease health state

Annual transition probability	Data Input	Source
People moving to the uncontrolled health state, %	42.8	Benson et al., 2023, HCP consultancy report
People remaining in the post-operative controlled health state for 1 year, %	57.2	Calculated

HCP = healthcare professional

Sources: HCP consultation report;¹² Benson 2023¹⁶

3.2.2.5 *Transition probabilities for the uncontrolled health state*

People in the uncontrolled health state remain in this health state until they receive revision NP surgery. People who receive revision surgery move to the post-operative controlled health state.

The revision surgery rate was derived from Benson et al 2023 (rate of surgery amongst surgery-eligible patients in the CPRD/HES databases in England) and was also confirmed by English clinicians' expertise (consultancy report).¹² The base-case transition probability inputs for the uncontrolled health state are provided in [Table 43](#) and [Figure 19](#).

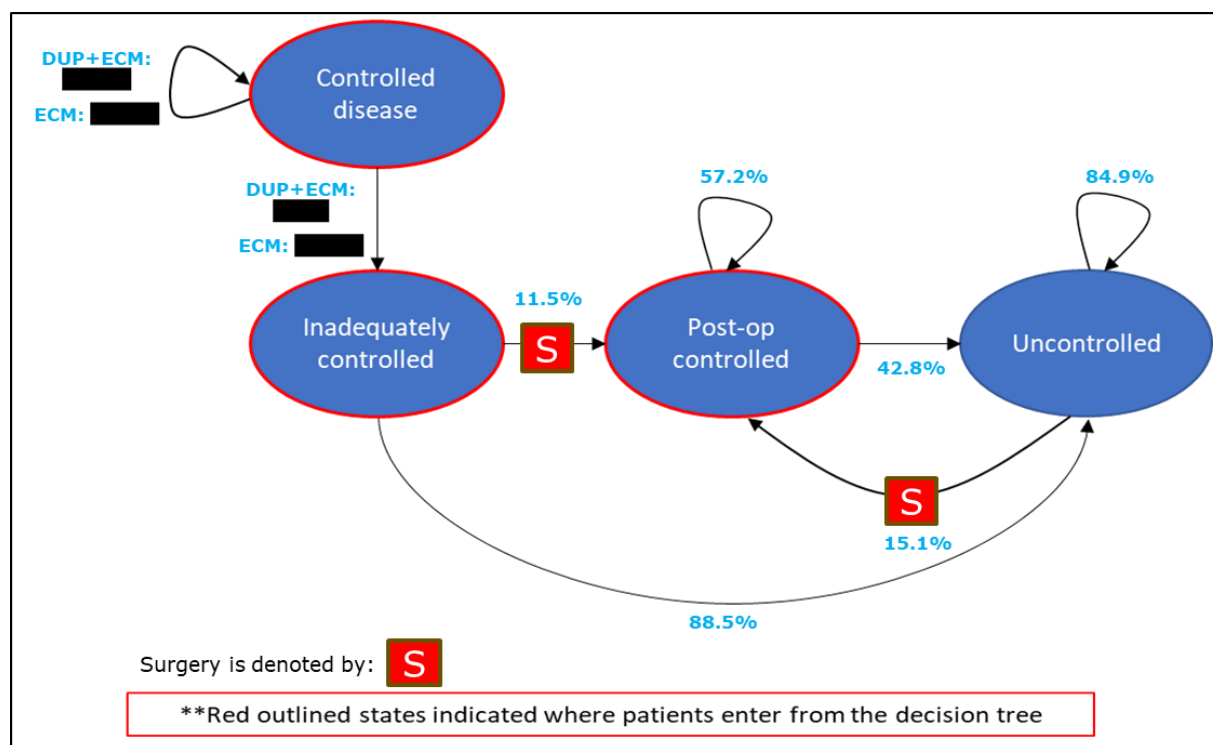
Table 43. Transition probabilities for people in the uncontrolled disease health state

Annual transition probability	Data Input	Source
People moving to post-operative controlled health state, %	15.1	Benson 2023
Eligible people remaining in the uncontrolled health state for 1 year, %	84.9	Calculated

Sources: Sanofi, data on file ; HCP consultation report;¹² Benson 2023¹⁶

The transition probabilities presented in [Table 40](#), [Table 41](#), [Table 42](#), and [Table 43](#) are summarised in [Figure 19](#).

Figure 19. Transition probabilities in the Markov model



DUP = dupilumab; ECM = established clinical management; post-op = post-operative; S = surgery

3.2.2.6 Mortality

In itself, CRSwNP is not expected to increase mortality and so in the base case, only all-cause mortality by age and sex was included for patients with no asthma comorbidity. UK life tables were used to populate the all-cause mortality.¹¹⁴ Conversely there is an increased risk of mortality with severe asthma and so a relative risk of increased mortality due to comorbid asthma is applied in the base case. The relative risk used is 1.36 which was taken from a meta-analysis of asthma studies that examined the relationship between asthma and all-cause mortality. This is tested in sensitivity analysis.¹¹⁵

3.3 Measurement and valuation of health effects

3.3.1 Published health-related quality-of-life studies

An SLR with a cut-off date of 6 June 2019 was conducted and limited to reports published after 1 January 1999. This SLR was updated on 4 September 2024 to capture additional reports published since 1 March 2019 (Section [3.1](#)) and included studies reporting health utility values and HRQoL measures in patients with severe CRSwNP ([Appendix H](#)). Of the 95 studies included following full text screening, 11 were utility studies, 5 were economic

evaluations with utility estimates and one was a cost and resource use study also reporting utilities. The 16 reports included 10 prospective studies (US, n=5; Canada, n=1; US and Canada, n=1; Colombia, n=1; UK, n=1; country not reported, n=1), 1 cross-sectional interview study (US), 1 cross-sectional questionnaire-based study (Finland), 3 publications of clinical trial data, and 1 vignette study (Brazil) ([Table 44](#)).

The instrument most commonly employed (in 7/16 studies reporting utility estimates) was the SF-6D Health Survey (SF-6D). Other instruments were the EQ-5D (5 studies), the SF-15D (1 study), SNOT-22 (2 studies) and time trade-off (TTO) (1 study).

Utility estimates are linked to distinct interventions in the 16 utility studies, with 2 reporting utility values for dupilumab.^{104,116}

Table 44. Utilities studies in patients with severe CRSwNP identified by SLR (N=16)

Author	Year	Study design	Country	Title
Alvarez	2023	Prospective	Colombia	Cost-utility analysis of dupilumab compared with endoscopic sinus surgery in patients with chronic rhinosinusitis with nasal polyps. Evaluation in Colombia, a developing country
DeCorso	2022	RCT	Multinational	Effectiveness of Dupilumab in the Treatment of Patients with Severe Uncontrolled CRSwNP: A “Real-Life” Observational Study in the First Year of Treatment
Falavigna	2024	Vignette	Brazil	Assessing Time Trade-Off Utilities in Health States of Chronic Rhinosinusitis with Nasal Polyps: A Pilot Study in Brazil https://www.ispor.org/docs/default-source/intl2024/ispor24falavignapcr195poster138171-pdf.pdf?sfvrsn=15d46515_0
Ference	2015	Cross-sectional interviews	US	Measurement and comparison of health utility assessments in chronic rhinosinusitis.
Kumar	2020	Prospective	Canada	Cost-effectiveness of Endoscopic Polypectomy in Clinic compared to Endoscopic Sinus Surgery: A modelling study
Luk	2015	Observational, prospective cohort	US and Canada	Health utility outcomes in patients undergoing medical management for chronic rhinosinusitis: a prospective multi-institutional study.
Rudmik	2014	Prospective longitudinal	NR	Long-term utility outcomes in patients undergoing endoscopic sinus surgery.
Scangas	2018	Prospective	US	The value of frontal sinusotomy for chronic rhinosinusitis with nasal polyps-A cost utility analysis.
Scangas	2017a	Prospective	US	The impact of asthma on the cost effectiveness of surgery for chronic rhinosinusitis with nasal polyps.
Smith	2019	Prospective observational	US	Long-term Outcomes of Endoscopic Sinus Surgery in the management of Adult Chronic Rhinosinusitis
Soler	2011	Prospective observational	US	Health state utility values in patients undergoing endoscopic sinus surgery.
Soler	2020	RCT (NAVIGATE I, NAVIGATE II)	Multinational	Exhalation delivery system with fluticasone improves quality of life and health status: pooled analysis of phase 3 trials NAVIGATE I and II

Author	Year	Study design	Country	Title
Tashman	2024	Prospective observational cohort	US	Five-year EuroQol 5-Dimension Outcomes After Endoscopic Sinus Surgery
Velez	2018b	RCT	NR	EDS-FLU improves quality of life and health status: Pooled analysis of phase 3 trials navigate I and II.
Wahid	2020	Prospective case-control	England, UK	The socioeconomic cost of chronic rhinosinusitis study
Ylitalo-Heikkilä (2018)	2018	Cross-sectional questionnaire-based	Finland	Different rhinologic diseases cause a similar multidimensional decrease in generic health-related quality of life.

CRSwNP = chronic rhinosinusitis with nasal polyps; EDS-FLU = exhalation delivery system with fluticasone; NR = not reported; RCT = randomised controlled trial; SLR = systematic literature review

3.3.2 Health-related quality-of-life data collected during the clinical trials

The impact of dupilumab on HRQoL was captured in the SINUS-24 and SINUS-52 trials using the SNOT-22 disease specific instrument (Section 3.3.3.2) and the EQ-5D generic measure (Section 3.3.3.5). The SLR carried out for the purposes of this evaluation did not identify a more appropriate source reporting data on the impact of dupilumab on HRQoL in patients with severe CRSwNP (Section 3.3.1; Appendix H).

SNOT-22. The HRQoL impact with a focus on rhinological symptoms was assessed in both trials using the 22-item SNOT-22 outcomes measure, with data collected at baseline and during follow-up:

- In SINUS-24 at Weeks 0 (baseline), 8, 16, 24, 36, 48
- In SINUS-52 at Weeks 0 (baseline), 4, 8, 16, 24, 40, 52

EQ-5D. In both SINUS-24 and SINUS-52, HRQoL was evaluated using EQ-5D-5L at baseline and during follow-up:

- In SINUS-24 at Weeks 0, 16, 24
- In SINUS-52 at Weeks 0, 4, 8, 16, 24, 40, 52

Results for all PRO measures are reported in Section 2.6.

In the model, the impact of treatment on patient HRQoL is accounted for by the following:

- Health state utilities (Section 3.3.3.1)
- Disutilities associated with surgery (Section 3.3.3.8)
- Disutilities associated with adverse events are not included to avoid double counting (Section 3.3.3.10)

3.3.3 Health-related quality-of-life data used in the cost-effectiveness analysis

3.3.3.1 Description of the health state utilities

The utilities used in the model are chosen to reflect the health states in the Decision tree and in the Markov portion of the model. An explanation is provided in [Table 45](#).

Table 45. Description of the health state utilities and assumptions for utility estimation used in the economic model

Health state	Description of utility (SNOT-22 mapped to EQ-5D)
Decision tree	
Week 0 - 12	Baseline utility weight from the studies (Pooled analysis of SINUS-24 and SINUS-52) indicating uncontrolled disease on established clinical management and the need for intervention.
Week 13-24	Utility weight at Week 24 by treatment arm from the pooled analysis of SINUS-24 and SINUS-52. Applied for the full 13- to 24-week period to reflect the rapid benefits seen in the studies for disease control. (Section 2.6.1)
Responder definition	Patients are classified as responders and non-responders in the model at Week 24 and Week 52. In the base case the responder definition is a combination of change from baseline in SNOT-22 of ≥ 8.9 points and in the NPS score of ≥ 1 point (Section 3.2.2.1).
Week 25 to 52 responders	Average of responder utility weight at Week 24 and Week 52 by treatment arm (pooled analysis) in order not to overestimate utility by applying Week 52 utility for the whole period.
Week 25 to 52 non-responders	Average of non-responder utility weight at Week 24 and Week 52 by treatment arm in order not to overestimate utility by applying Week 52 utility for the whole period.
Markov model	
Controlled disease	All responder utility weight at Week 52: Pooled analysis of the SINUS-24 and SINUS-52 studies.
Inadequately controlled disease	Utility weight at Week 52 from patients on ECM (pooled from SINUS-24 and SINUS-52), who did not respond at Week 24 and Week 52. This is higher than uncontrolled disease to reflect the benefit of receiving optimised care but recognising that for many patients in this population established clinical management is not adequate.
Post-operative controlled health state	Estimated based on patients' utility weight prior to the surgery, utility gain from surgery, and short-term disutility associated with surgery. A utility gain from surgery of 0.051 from Soler 2011 is applied to appropriate inadequately controlled and uncontrolled disease health states. This is tested in sensitivity analysis using Remenschneider 2015.
Uncontrolled disease	Assumed to be the baseline utility (or utility of inadequately controlled HS if lower). Ultimately for patients who lose any disease control quality of life will be significantly impaired and a return to baseline is expected.

ECM = established clinical management; EQ-5D = EuroQoL 5-Dimensions; HS = health state; NPS = nasal polyp score; SNOT-22 = Sinonasal Outcomes Test-22

Sources: Remenschneider 2015;¹¹⁷ Soler 2011¹¹⁸

Utility weights are used in the model to calculate QALYs to reflect the incremental benefit of treatment with dupilumab. Two options are included in the model for estimating utility weights:

- For the base case we have used the published mapping algorithm by Crump et al. to estimate utility weights from the SNOT-22 disease specific instrument.¹¹⁹
- We have provided alternative utilities weights estimated using a mixed model regression based on all EQ-5D utility values collected in the SINUS trials in sensitivity analysis. In accordance with the requirements of the reference case the EQ-5D-5L utility scores collected during the study were mapped to EQ-5D-3L utility scores using the UK crosswalk tariff developed by Hernández Alava and are tested in sensitivity analysis using the Van Hout cross walk ([Appendix P](#)).¹²⁰
- Directly observed change from baseline in EQ-5D

The choice to use the SNOT-22 derived utility weights in the base case is discussed below in Sections [3.3.3.2](#) to [3.3.3.3](#) and in [Appendix O](#). The regression analysis based on EQ-5D utility values is described in Sections [3.3.3.5](#) to [3.3.3.6](#) and in [Appendix P](#).

3.3.3.2 Base case: Derivation of utility weights from SNOT-22

CRSwNP is a disease which primarily affects olfactory function with wide ranging and significant impact on quality of life. Patients report that loss of smell (anosmia) and sleep disturbance both due to nasal obstruction are the most troubling symptoms.

EQ-5D-5L was collected during the SINUS studies and whilst it does show differences in severity of disease across the duration of the studies, the high utility values observed suggest that it may not fully capture the burden of disease and differentiate well between levels of response. For example, the utility score derived for patients in the controlled health state (responders) as they enter the MARKOV model at 52 weeks is 0.917 (pooled SINUS 24 and 52 data. Regression ‘Model 1’; 3L cross walked to 5L using Hernandez Alva; Section [3.3.3.5](#)). This is much higher than the utility experienced by people of equivalent age in the UK general population (0.834 population norm for persons aged 53 years old)¹²¹ and so lacks face validity. Testimony from patients at a round table held by SINUS UK in January 2025 ([Appendix S](#)), highlighted that CRSwNP causes issues with breathing, speaking, hearing, socialising and overall confidence. Poor sleep caused by breathing difficulties leads to fatigue, reduced productivity, work problems and relationship stresses. They said that at its worst, CRSwNP leaves them in a “*desperate state*” and feeling like they “*can’t carry on*” living like that. The EQ-5D utility observed in the studies used to describe uncontrolled disease in the model is assumed to be pooled study baseline (0.782). For example, this is equivalent to utilities reported in well-controlled diabetes¹²² or stable coronary disease¹²³ and is not commensurate with the real world lived experience described by patients with CRSwNP.

EQ-5D HUV is a generic instrument which does not include items specifically related to anosmia and sleep, the key domains of HRQoL impact for patients, and this may be why scores from the dupilumab studies are higher than might be expected.

However, at baseline the EQ-5D VAS score from the pooled SINUS-24 and SINUS-52 studies is very much lower (Mean (SD) baseline EQ-VAS = 65.4 (20.4)) than population norm, which is 82.0 (Section [2.6.3](#)).⁶⁵ This score at baseline is lower than those of other chronic conditions including rheumatoid arthritis, type-2 diabetes, and asthma (Global Initiative for Asthma steps 1–3 and 4–5).¹²⁴ The preference-based measure of utility using the EQ-5D HUV is not the same as the VAS but it is noteworthy that there is more correspondence between population norm utility and the VAS score for this age group (0.857 vs. 82.0) than in the baseline values for patients in the dupilumab studies (0.782 vs. 65.4). Other studies have shown that although the VAS is not used to measure HUV, it may possibly reflect a broader underlying construct of general health compared to the EQ-5D HUV in CRS and other conditions, since it likely reflects dimensions of health (such as sleep disturbance) that are not included in the calculation of EQ-5D HUV.¹²⁵ The comparison of the VAS score and the HUV at baseline may indicate poor performance of the EQ-5D HUV in this context.

Analysis of the correlation between disease specific measures and EQ-5D from the pooled SINUS data at baseline and change from baseline also suggests that EQ-5D does not perform well. The Spearman correlation coefficients for the relationship between Decreased/loss of sense of smell score, UPSIT smell test score, Nasal polyposis score, Nasal congestion/obstruction score and Lund-Mackay score at baseline and change to week 24 are provided in [Table 46](#) below.

Table 46. Exploration of the relationship between EQ-5D-5L utilities and efficacy data

Score	Spearman correlation coefficient	P value
Relationship between baseline EQ-5D-5L utilities (Hernandez 2020 crosswalk method, UK tariffs) and baseline efficacy		
Decreased/loss of sense of smell score	-0.06	0.143
UPSIT smell test score	0.13	<0.001
Nasal polyposis score	-0.07	0.055
Nasal congestion/ obstruction score	-0.13	<0.001
Lund-Mackay score	-0.04	0.241
Relationship between change from baseline in EQ-5D-5L utilities (Van Hout Crosswalk 2012, UK tariffs) at Week 24 and change from baseline in efficacy at Week 24		
Decreased/loss of sense of smell score	-0.23	<0.001
UPSIT smell test score	0.21	<0.001
Nasal polyposis score	-0.19	<0.001
Nasal congestion /obstruction score	-0.26	<0.001

Score	Spearman correlation coefficient	P value
Lund-Mackay score	-0.18	<0.001

EQ-5D-5L = EuroQol -5 Dimensions 5-Levels; UPSIT = University of Pennsylvania Smell Identification Test

All the correlation coefficients are between 0.3 and -0.3 indicating poor correlation for these objective and subjective measures.

Overall, the observations above suggest that EQ-5D HUV is unlikely to fully capture the burden of CRSwNP or sufficiently describe changes to that burden and so may not be reflective of either the disease impact on patients or the potential benefit of treatments.

The 22-item Sinonasal Outcome Test (SNOT-22) is the most widely used and generally preferred CRS-specific patient reported measure to record quality of life. This assesses 22 symptoms with 6 levels of severity from 0 (no problem) to 5 (maximum problem). The SNOT-22 reflects CRS-specific impairment that patients feel across multiple domains, which include nasal symptoms, sensory deprivation, sleep quality/disturbance, craniofacial discomfort, emotional disturbance, and functional impairment.

Analysis of the SNOT-22 data from the SINUS clinical trials suggests that dupilumab treatment was associated with significant improvements in all SNOT-22 items vs. placebo, with the two domains most important to patients (decreased sense of smell/taste and nasal symptoms/blockage) showing the greatest improvement (Section 2.6.2) for the SNOT-22 data for the base case population).¹²⁵ It is therefore reasonable to consider that the disease specific SNOT-22 instrument is a more appropriate measure of quality-of-life impact on patients than EQ-5D, and we consider that mapping between the two instruments provides suitable utility values for use within the economic model.

The mapping to derive utilities from SNOT-22 is summarised below in Section 3.3.3.3 and in detail in [Appendix O](#). The results for the application of the Crump mapping algorithm 'Crump Models 1 - 3' to the SINUS data are shown in [Table 48](#) for the base case population and responder definition (patients with prior surgery and responder definition of SNOT-22 change from baseline [cfb] ≥ 8.9 AND NPS cfb ≥ 1). All of the results for 'Models 2 and 3' are provided in [Appendix O](#) including the population scenarios.

3.3.3.3 Mapping SNOT-22 to EQ-5D

A systematic review conducted by the Health Economics Research Centre (HERC) identified mapping algorithms in various disease areas (including but not limited to chronic rhinosinusitis) between 2013 and January 2023.¹²⁶ The database identified Crump et al., 2017¹¹⁹ as the only relevant publication in the target population. We carried out a targeted

review to supplement the research conducted by Dakin et al. 2023,¹²⁷ with the aim of capturing any additional relevant published information since January 2023 ([Appendix Q](#)).

The targeted review included any publications with chronic rhinosinusitis and was not restricted by intervention. Health related quality of life outcomes were included in the search strategy. Additionally, economic studies in the target population were also reviewed to ensure a wide search of published literature. The targeted review was carried out in PubMed and all results were restricted by date of publication between January 01, 2023 to January 17, 2025 ([Appendix Q](#)).

A total of 351 unique HRQoL publications, and 19 economic studies were identified. The titles and abstracts were screened to identify mapping algorithms or models for mapping SNOT-22 on the EQ5D scale. No further studies beyond Crump et al. 2017¹¹⁹ were identified in the HERC database of mapping studies¹²⁸ were found.

A detailed discussion of the mapping using the results from Crump et al., 2017¹¹⁹ carried out for the purposes of this submission is provided in [Appendix O](#).

Crump presents three regression models developed using SNOT-22 and EQ-5D-3L data collected in 2012 from adult CRS patients in Vancouver entered into the Vancouver Coastal Health Authority registry. Patients enrolled in the registry were awaiting bilateral endoscopic surgery and so are likely to be representative of the population considered in this submission. A side-by-side comparison of baseline characteristics between the Crump cohort and the SINUS studies is provided in [Appendix O](#) as are the model regression coefficients along with their p-values. 'Model 1' includes only the SNOT-22 global score as a covariate whereas 'Models 2 and 3' include all 22 of the items from SNOT-22 (weighted equally). In addition, 'Model 3' includes Age and Gender.

The analysis included the pooled data from the two Phase 3 studies SINUS-24 and SINUS-52, encompassing visits where both SNOT-22 and EQ-5D-5L were assessed. After excluding missing data, the final dataset for mapping consisted of 3,011 observations.

- Notably, missing data occurred only when all items of the SNOT-22 or all dimensions of the EQ-5D-5L were absent, and no imputation was performed when scoring SNOT-22 total or EQ-5D-5L utility using tariffs.
- The distribution of SNOT-22 and EQ-5D-5L measures was highly similar between the two studies, and their relationship remained stable over time. As a result, data from both studies and all visits were pooled for analysis.

3.3.3.3.1 SNOT-22 total score according to response

The baseline and change from baseline SNOT-22 data from the pooled SINUS 24 and 52 studies used in the base case for the mapping to EQ-5D are provided in [Table 47](#) below. For responders to dupilumab at 12 months, the reduction in SNOT-22 was -40.273. This is line with a retrospective, observational, real-world study published amongst 47 patients treated with dupilumab at a single centre in France between December 2021 and July 2023.¹²⁹ In this study, SNOT-22 scores decreased by a similar amount from 52.4±24.3 to 12.7±10.5 at 12 months ($p<0.001$).¹²⁹

Table 47. SNOT-22 total score and change from baseline for the base case population according to response based on SNOT-22 total score and NPS (1-point improvement) (pooled)

CHANGE FROM BASELINE TO WEEK 24				
	Sub-population Responders at Week 24		Subpopulation: Non-responders at Week 24	
	Placebo (N=20)	Dupilumab 300 mg Q2W (N=154)	Placebo (N=167)	Dupilumab 300 mg Q2W (N=118)
Baseline				
Number	20	154	166	112
Mean (SD)	47.350 (11.641)	54.195 (19.862)	54.205 (20.598)	45.063 (19.823)
Week 24				
Number	20	154	157	104
Mean (SD)	22.800 (16.536)	17.545 (14.368)	45.586 (21.088)	27.538 (18.271)
Change from baseline				
Number	20	154	157	104
Mean (SD)	-24.550 (9.859)	-36.649 (19.608)	-8.070 (19.108)	-17.394 (19.910)
LS Mean (SE) a	-28.886 (0.523)	-36.712 (0.247)	-7.047 (1.809)	-21.721 (2.088)
LS Mean Diff vs. placebo (95% CI)		-7.826 (-8.843, -6.809)		-14.673 (-19.025, -10.321)
P value vs. placebo		<.0001		<.0001
CHANGE FROM BASELINE TO WEEK 52				
	Sub-population Responders at Week 52		Subpopulation: Non-responders at Week 52	
	Placebo (N=2)	Dupilumab 300 mg Q2W (N=44)	Placebo (N=86)	Dupilumab 300 mg Q2W (N=44)
Baseline				
Number	2	44	86	41
Mean (SD)	47.000 (11.314)	54.068 (20.146)	55.558 (21.377)	45.488 (18.013)
Week 52				
Number	2	44	80	39
Mean (SD)	20.500 (17.678)	13.795 (15.740)	48.088 (21.246)	27.897 (20.897)
Change from baseline				
Number	2	44	80	39
Mean (SD)	-26.500 (6.364)	-40.273 (19.776)	-7.275 (18.340)	-18.205 (17.864)
LS Mean (SE) a	-32.997 (10.263)	-42.375 (2.531)	-5.730 (2.274)	-21.132 (2.985)
LS Mean Diff vs. placebo (95% CI)		-9.378 (-31.296, 12.541)		-15.403 (-22.134, -8.671)

CHANGE FROM BASELINE TO WEEK 24				
	Sub-population Responders at Week 24		Subpopulation: Non-responders at Week 24	
	Placebo (N=20)	Dupilumab 300 mg Q2W (N=154)	Placebo (N=167)	Dupilumab 300 mg Q2W (N=118)
P value vs. placebo		0.3732		<.0001

CI = confidence interval; LS = least-squares; NPS = nasal polyp score; Q2W = every 2 weeks; SD = standard deviation; SE = standard error; SNOT-22 = Sinonasal Outcomes Test-22

3.3.3.4 Results from mapping SNOT-22 to EQ-5D-3L

The results for the application of the Crump mapping algorithm 'Crump Models 1 - 3' to the SINUS data are shown in [Table 48](#) for the base case population and responder definition. (Patients with prior surgery and responder definition of SNOT-22 cfb ≥ 8.9 AND NPS cfb ≥ 1). These utility values are varied in probabilistic sensitivity analysis by applying the standard errors associated with the change from baseline for the SNOT-22 scores and a normal distribution in the mapping calculations. All of the results for 'Models 2 and 3' are provided in [Appendix Q](#) including the population scenarios.

Table 48. Base case population and responder definition: Mapped SNOT-22 to EQ-5D-3L health state utilities ('Crump Models 1 - 3')

Health state	'Crump Model 1' (Base case)		'Crump Model 2'		'Crump Model 3'	
	ECM	DUP + ECM	ECM	DUP + ECM	ECM	DUP + ECM
Decision tree utilities						
Week 0–12	0.524	0.524	0.648	0.648	0.651	0.651
Week 13–24	0.727	0.596	0.765	0.692	0.769	0.695
Week 25–52 responders	0.793	0.734	0.811	0.796	0.813	0.805
Week 25–52 non-responders	0.673	0.587	0.721	0.694	0.726	0.698
Markov model utilities						
	'Crump Model 1' (Base case)		'Crump Model 2'		'Crump Model 3'	
Controlled disease	0.809		0.825		0.826	
Inadequately controlled disease	0.594		0.706		0.711	
Uncontrolled disease	0.524		0.648		0.651	
Utility gain from surgery (Soler et al. 2011)	0.051		0.051		0.051	
Post-operative controlled disease* - patients from DUP+ECM No response HS	0.724		0.772		0.777	
Post-operative controlled disease* - patients from ECM No response HS	0.638		0.745		0.749	
Post-operative controlled disease* - patients from Inadequately controlled HS	0.645		0.757		0.762	
Post-operative controlled disease* - patients from Uncontrolled HS	0.575		0.699		0.702	

DUP = dupilumab; ECM = established clinical management; EQ-5D-3L = EuroQoL 5-Dimension 3-Level; HS = health state; SD = standard deviation; SNOT-22 Sinonasal Outcomes Test-22

*In the post-operative controlled health state, utility gain from surgery of 0.051 (from Soler et al. 2011) is applied to the utility weight of the origin health state or response arm of the patient (no response DUP+ECM, no response ECM, inadequately controlled and uncontrolled disease health states).

Source: Soler et al. 2011¹¹⁸

‘Crump models 2 & 3’ provide higher estimates for utility values than ‘Crump model 1’. However, inspection of the coefficients for models ‘2 and 3’ suggests that including the individual level terms in the models may not be an optimal approach. This because some of the individual level items have positive coefficients. (See Table 2, [Appendix O](#) for a full list of the regression coefficients).

Consider the case where the worst value possible (“Problem as bad as it can be”) is recorded for the SNOT22 items with a positive coefficient, and 0 (“No problem at all”) for the other items. In this case a utility value larger than 1.0 is predicted (We have estimated this at 1.2144).

In the extreme case a patient with the characteristics above would have a utility score higher than the patient provided as an example in the published paper (No problem at all for the 22 items: utility=0.8390).

We contacted the authors of the study to discuss the scenario above but did not receive an answer.

This may explain the higher values estimated for ‘Crump models 2 and 3’. Therefore, we have chosen ‘Crump Model 1’ for our base case which uses the SNOT-22 total score and avoids the issue of the individual positive regression coefficients above. We also conducted a post-hoc analysis to measure the level of correlation between the SNOT-22-derived utilities and the EQ-5D-5L utilities from SINUS clinical trials at baseline and Week 24.

The Spearman correlation coefficients were higher for ‘Model 1’ which gave us more confidence in our selection of it for the base case analysis ([Appendix O](#)). The utilities derived from the other models were also tested in sensitivity analysis (see Section [3.10.3](#)).

3.3.3.5 *EQ-5D from the studies. Utility Weight Estimation Based on a Regression Model*

The mapped EQ-5D data derived from the disease specific SNOT-22 instrument, is the more appropriate utility source for use in this evaluation for the reasons discussed above.

However, we also provide the EQ-5D data collected in the clinical trials for comparison in sensitivity analysis. Linear regression analysis was performed to estimate utility weights for use in the model using EQ-5D-5L data from the studies converted to EQ-5D-3L, using the UK crosswalk tariffs. This is summarised below. More detail is provided in [Appendix P](#) along with details for the alternative subgroups tested in scenario analysis.

Utility scores up to Week 52 were incorporated, utilising all the observed data points. Linear mixed models were fitted to the EQ-5D utility score as the response variable using a forward selection process, controlling for age, gender, and baseline EQ-5D utility score for each trial with the following variables as predictors:

- Total SNOT-22 score
- Total NPS score
- Interaction between total SNOT-22 score and total NPS score
- Treatment (DUP Q2W-Q2W, DUP Q2W-Q4W, or BSC)

Four models were considered. A summary of the models and the fit statistics is provided in [Table 49](#) for the Hernandez Alva cross-walked EQ-5D data. Further detail is presented in [Appendix P](#) including the alternative Van Hout cross walked EQ-5D data.

Table 49. Summary of the regression models including information criterion statistics (Hernandez Alva cross walk)

	Model 1	Model 2	Model 3	Model 4
Covariates included in the models				
Female gender	✓	✓	✓	✓
Age	✓	✓	✓	✓
Baseline EQ-5D score	✓	✓	✓	✓
SNOT-22 total score	✓	✓	✓	✓
NPS total score	x	✓	✓	✓
Interaction between SNOT-22 and total NPS total score	x	x	✓	✓
Treatment	x	x	x	✓
Selection criteria				
AIC	-3131.9	-3056.2	-3039.9	-3026.5
AICC	-3131.8	-3056.2	-3039.9	-3026.5
BIC	-3122.8	-3047.2	-3030.8	-3017.4

AIC = Akaike's information criterion; AICC = Akaike Information Criterion corrected; BIC = Bayesian information criterion; EQ-5D = EuroQoL 5-Dimension; NPS = Nasal Polyps Score; SNOT-22 = Sinonasal Outcomes Test-22

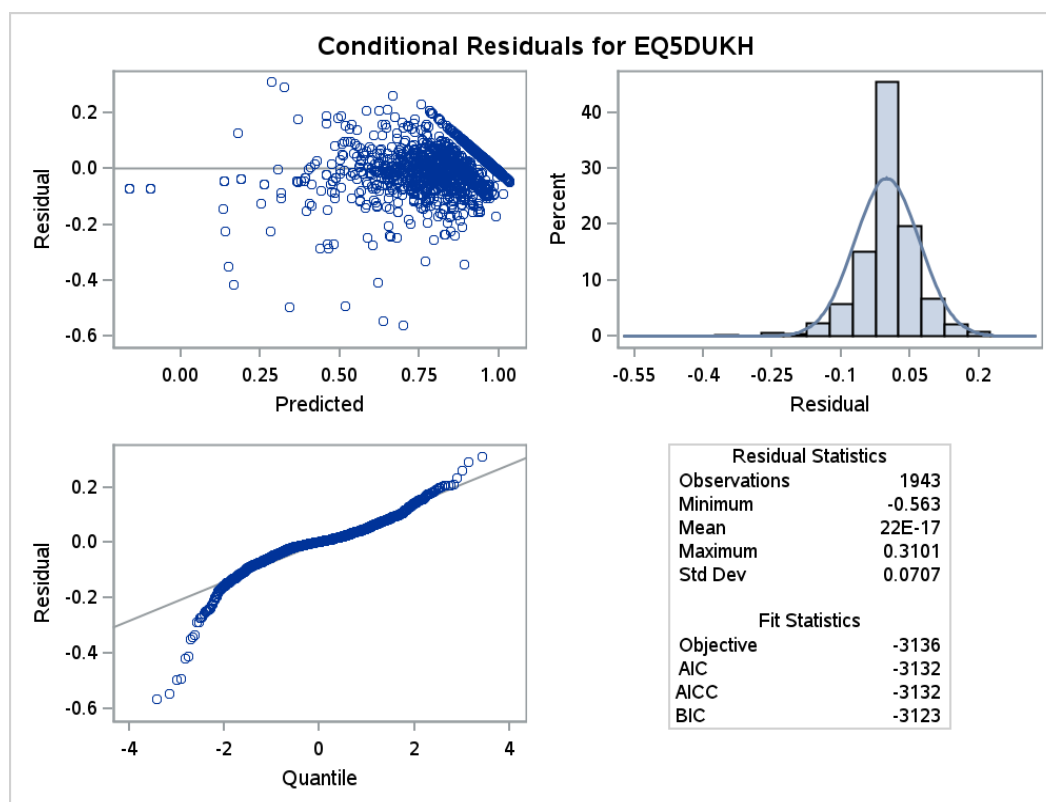
Significant variables were kept in the regression for the final model used, and goodness-of-fit was assessed using diagnostic plots, Akaike's information criterion (AIC), and the Bayesian information criterion (BIC) statistics. Based on the AIC and BIC, the best-fit model included SNOT-22 total score only, adjusted for age, gender, and baseline utility weight. This and all of the other regression outputs are available in the economic model for sensitivity analysis. [Table 50](#) presents the parameter estimates and [Figure 20](#) shows the conditional residuals from the linear regression model for 'Model 1'. (The covariance Matrix for 'Model 1' is shown in [Appendix P](#)).

Table 50. 'Model 1' covariates (Hernandez Alva crosswalk)

Effect	Estimate	Standard Error	Pr > t	Lower	Upper
Intercept	0.7074	0.02759	<.0001	0.6533	0.7616
SEX (F)	-0.00195	0.008753	0.8235	-0.01914	0.01523
SEX (M)					
AGE	-0.00116	0.000330	0.0005	-0.00181	-0.00051
EQUKHBL	0.3894	0.02305	<.0001	0.3442	0.4347
SNTOTAL	-0.00360	0.000171	<.0001	-0.00394	-0.00326

EQUKHBL: EQ-5D at baseline; SNTOTAL: Post baseline total 22-item sinonasal outcome test score

Figure 20. Mixed model diagnostics



AIC = Akaike's information criterion; AICC = AICc: Akaike's information criterion (the lower-case 'c' indicates that the value has been calculated from the AIC test, corrected for small sample sizes); BIC = Bayesian information criterion

The model discussed above uses the EQ-5D data from the Hernandez Alva crosswalk to estimate the EQ-5D-3L utilities for use in the model. Utility values estimated using the other regression models with both Hernández Alva and the alternative Van Hout crosswalk tariffs, are presented in [Appendix P](#) and available in the model for the purposes of sensitivity analysis. The utility values used in the economic model for the best fit regression ('Model 1') are presented below in [Table 51](#), using the base case responder definition of SNOT-22 cfb ≥ 8.9 AND NPS cfb ≥ 1 in the base case population.

Table 51. Utility measurements associated with each CRSwNP state used in sensitivity analysis for patients with one or more prior surgery (Hernandez Alva crosswalk: 'Model 1')

Health state	Model 1	
	DUP + ECM	ECM
Decision tree utility		
Week 0–12	0.782	0.782
Week 13–24	0.874	0.799
Week 25–52 responders	0.908	0.877
Week 25–52 non-responders	0.843	0.789
Markov model utility		
Controlled disease	0.917	
Inadequately controlled disease	0.786	
Post-operative controlled disease* - patients from DUP+ECM No response HS	0.894	
Post-operative controlled disease* - patients from ECM No response HS	0.840	
Post-operative controlled disease* - patients from Inadequately controlled HS	0.837	
Post-operative controlled disease* - patients from Uncontrolled HS	0.833	
Uncontrolled disease	0.782	

DUP = dupilumab; ECM: established clinical management; EQ-5D-3L = EuroQoL 5-Dimension 3-Level; HS = health state; SD = standard deviation; SNOT-22 Sinonasal outcomes Test-22

*In the post-operative controlled health state, utility gain from surgery of 0.051 (from Soler et al. 2011) is applied to the utility weight of the origin health state or response arm of the patient (no response DUP+ECM, no response ECM, inadequately controlled and uncontrolled disease health states).

Source: Soler et al. 2011¹¹⁸

3.3.3.6 EQ-5D from the studies. Utility Weights based on observed change from base line

The directly observed EQ-5D data is also available for sensitivity analysis in the model expressed as observed change from baseline. The utility data used in the model for the base case population and scenario populations are shown below in [Table 52](#).

Table 52. Utility measurements associated with each CRSwNP state used in sensitivity analysis for patients with one or more prior surgery (observed utility)

Health state	Population					
	Base case (Uncontrolled patients with 1 or more prior surgeries)		Patients with prior type 2 medical history including asthma/NSAID-ERD		Patients with prior surgery and with prior type 2 medical history including asthma/NSAID-ERD	
	DUP + ECM	ECM	DUP + ECM	ECM	DUP + ECM	ECM
Decision tree utility						
Week 0–12	0.782	0.782	0.773	0.773	0.780	0.780
Week 13–24	0.883	0.827	0.874	0.815	0.874	0.816
Week 25–52 responders	0.915	0.888	0.903	0.892	0.907	0.869
Week 25–52 non-responders	0.845	0.814	0.841	0.805	0.848	0.813
Markov model utility						
Controlled disease	0.925		0.900		0.909	
Inadequately controlled disease	0.803		0.798		0.812	
Uncontrolled disease	0.782		0.773		0.780	

Health state	Population					
	Base case (Uncontrolled patients with 1 or more prior surgeries)		Patients with prior type 2 medical history including asthma/NSAID-ERD		Patients with prior surgery and with prior type 2 medical history including asthma/NSAID-ERD	
	DUP + ECM	ECM	DUP + ECM	ECM	DUP + ECM	ECM
Utility gain from surgery (Soler et al. 2011)	0.051		0.051		0.051	
Post-op controlled disease* - patients from DUP+ECM No response HS	0.896		0.892		0.899	
Post-op controlled disease* - patients from ECM No response HS	0.865		0.856		0.864	
Post-op controlled disease* - patients from Inadequately controlled HS	0.854		0.849		0.863	
Post-op controlled disease* - patients from Uncontrolled HS	0.833		0.824		0.831	

DUP = dupilumab; ECM: established clinical management; EQ-5D-3L = EuroQoL 5-Dimension 3-Level; HS = health state; SD = standard deviation; SNOT-22 Sinonasal outcomes Test-22

*In the post-operative controlled health state, utility gain from surgery of 0.051 (from Soler et al. 2011) is applied to the utility weight of the origin health state or response arm of the patient (no response DUP+ECM, no response ECM, inadequately controlled and uncontrolled disease health states).

Source: Soler et al. 2011¹¹⁸

3.3.3.7 *Utility adjustments according to age*

As patients age in the model, adjustments are made using the multiplicative or additive method. In the multiplicative method, general population utility weights from Ara and Brazier (2011) are used to estimate the relative decline over time.¹²¹ In the additive method, a linear trendline to the Ara and Brazier (2011) data is fit to estimate how much utility is lost with each year of age gained. In the base-case analysis, utility weights are adjusted over time using the multiplicative method.

3.3.3.8 *Disutility associated with surgery*

In the immediate postoperative period following endoscopic sinus surgery for CRSwNP, patients typically experience a temporary decline in health-related quality of life due to several factors.^{12,26} Nasal congestion, drainage, and pain are common, and some individuals may require nasal packing that exacerbates discomfort. These symptoms often interfere with sleep, daily activities, and social interactions, leading to a short-term reduction in overall well-being. However, this period of reduced quality of life is generally limited to the first one to three weeks after surgery and tends to improve as healing progresses and nasal function is restored.

Direct evidence from the clinical studies is not available to support this and so we have used published data from Scangas et al. (2017) applied a short-term postoperative disutility of 0.15 over a two-week period in their cost-utility analysis of endoscopic sinus surgery for chronic rhinosinusitis (with and without nasal polyposis).¹³⁰ This value reflects the temporary decrease in patients' health-related quality of life due to postoperative pain, congestion, and

general recovery. This level of disutility is consistent with prior cost-effectiveness research in chronic rhinosinusitis, which frequently applies short-term disutilities ranging from -0.10 to -0.20 for one to three weeks post-surgery.¹³⁰ By incorporating this commonly accepted short-term decrement, the economic model captures both the immediate morbidity of the surgery and the longer-term utility gains (via the post-operative controlled HS utility). It is assumed that acute disutility associated with sinus surgery lasts for 2 weeks, while no chronic impact (i.e., longer than 2 weeks) of surgery on utility is included.

3.3.3.9 *Health-related quality of life in the post-operative controlled health state*

In the longer term, utility gain from surgery is expected whilst in the post-operative health state. Once again evidence from the SINUS studies is not available and so we have identified two alternative sources. In the base case, utility gain from surgery of 0.051 taken from Soler et al. 2011 is applied to the inadequately controlled and uncontrolled disease health states from which surgery patients originated.¹¹⁸ An alternative value based on EQ-5D was taken from Remenschneider et al. 2015 estimated to be 0.08; this was tested in sensitivity analysis.¹¹⁷ Of the two sources, Soler was considered the most appropriate because it is estimated using SF-6, which is deemed more appropriate to capture the burden of disease for conditions such as CRSwNP.

3.3.3.10 *Disutility associated with adverse reactions*

The list of adverse events (AEs) considered in the model was derived from Bachert et al. (2019) which is the published pooled analysis for the SINUS studies.⁶⁸ Events occurring with a rate more than 5% were chosen. Annual incidences were estimated from pooled analyses of SINUS-24 and SINUS-52 (Sanofi data on file, 2019a), based on the number of treatment-emergent AEs (TEAEs) per 100 patient-years during the entire treatment-emergent AE period. These events are costed in the model (Section 3.4.6) but while each AE could in principle have an associated disutility and duration, we do not apply any separate disutility for these TEAEs in our base-case analysis. This decision reflects both the limited and predominantly mild nature of the TEAEs observed in the dupilumab studies and the assumption that any minor impact on quality of life is already captured by the EQ-5D utility measurements in each health state. Consequently, no additional disutility is modelled for TEAEs in either treatment arm.

3.4 Cost and healthcare resource use identification, measurement and valuation

Resource utilisation rates and unit costs most appropriate to this submission were identified through a systematic review of the literature to identify published and unpublished studies, an advisory board conducted in June 2024 and several consultancy meetings conducted in November 2024 to validate British clinicians' perceptions on HCRU among people with severe CRSwNP.

3.4.1 Resource identification, measurement and valuation studies.

An SLR with a cut-off date of 6 June 2019 was conducted and limited to reports published after 1 January 1999. This SLR was updated on 4 September 2024 to capture additional reports published since 1 March 2019 (Section 3.1). Studies included those with cost and resource use data related to the management of people with severe CRSwNP ([Appendix I](#)). Of the 95 unique reports included in the SLR, 55 were unique studies of costs and resource use ([Appendix I](#)). Among the 55 unique studies, 33 reported resource use, 31 reported direct costs, 11 reported indirect costs, and 1 reported productivity. Most studies were conducted in the US (n=31), with other study countries including Spain (n=5), England (n=4), China (n=3), Finland (n=3), France (n=2), US and Canada (n=2), Canada (n=1), the Netherlands (n=1), Japan (n=1), Sweden (n=1). There was one multinational study.

3.4.2 Advisory board and consultancy meetings to evaluate UK clinical perceptions of HCRU

A UK HTA advisory board was held on the 26th of June 2024 with six clinicians and one health economist with a geographical spread across the UK. A further series of consultancies (with some overlap between attendees) focused on England alone which included a panel of four rhinology experts and one respiratory expert were held in November 2024. Several of these experts have published on HCRU for CRSwNP in the English setting.^{9,16} These experts advised on the current UK treatment pathway for patients with severe CRSwNP, and other aspects of the disease and its burden on patients for the purposes of this assessment ([Appendix Q](#)).

The experts were presented with the estimates shown in [Table 53](#) below derived from Davies 2022¹³ to stimulate discussion about the likely levels of HCRU for patients in the controlled and uncontrolled disease health states. In this publication, CRSwNP-related events were collected for 2 separate groups of patients:

- Patients who did not require SCS used in the 12 months prior (assumed to equivalent to the 'controlled' patients in the model)
- Patients who required 1-4 courses of SCS in the 12 months prior (assumed to be equivalent to the uncontrolled patients in the model)

Table 53. Suggested healthcare resource use categories (number of visits per year) amongst controlled and uncontrolled patients derived from Davies et al. 2022

Category	Controlled disease	Uncontrolled disease
GP	0	6
Outpatient consultant	0.8	1.7
Accident and emergency	0.01	0.03
Hospitalisation	0.01	0.02
Imaging and diagnostics	0.8	1.9

GP = General practitioner
Source: Davis et al. 2022¹³

3.4.2.1 GP visits

The experts agreed that patients whose disease is controlled are unlikely to visit the GP for CRSwNP and the number of visits could be set to zero.

For patients who would be regarded as 'uncontrolled' there was less agreement between the advisory board and the subsequent consultancies. The experts consulted during the consultancies agreed that the suggested six GP visits reflect English clinical practice. This is because patients revisit the GP repeatedly while on the surgery waiting list due to recurrent acute exacerbations, repeated infections, stopping and restarting of medications such as INCS and antibiotics, and for management of other symptoms such as loss of sleep. Experts at the advisory board felt that patients would visit the GP more than six times.

3.4.2.2 Outpatient consultant attendance

The advisory board experts agreed that around 1.7 visits per year to see a specialist is reasonable for patients who are uncontrolled. A specialist might see the patients and then put them on a list for surgery, so the advisors felt that two specialist visits is realistic for the modelling.

The experts consulted in the individual consultancies suggested that a patient would have two to three visits to the ENT service before sinus surgery (which characterised the patient as uncontrolled). Typically, at the first ENT appointment, a patient will restart their topical treatments (if necessary). If surgery is still required, the patient is then booked for a CT scan and will be seen back in the clinic after the scan. If the patient is unsure about surgery, they may return for a third appointment through patient-initiated follow-up. If the patient was

originally seen by a general ENT specialist, they may have a further appointment with them before being referred to the rhinology clinic.

The clinicians also advised that patients who are doing well (controlled disease) are often discharged from specialist care and attendance in clinic is generally low for these patients. However, they can return through the patient-initiated follow-up pathway if their disease becomes less well controlled. An estimate of ~1 visit is not unreasonable.

The experts were asked about their expectations for HCRU amongst patients who might be well controlled on a biologic. One of the experts with significant experience of dupilumab commented that a well-controlled patient may only need to see a specialist nurse once a year.

3.4.2.3 *Accident and emergency attendance and hospitalisation*

The experts did not comment on these parameters and did not include them in the patient pathway described. It is also clear from the published literature that these services are not routinely used by CRSwNP patients and very low HCRU is recorded against them.^{9,13}

3.4.3 Healthcare resource use estimates used in the model

With the advice above in mind and estimates taken from the published literature that suggest that HCRU for CRSwNP is generally low for controlled patients we have taken a parsimonious approach and assumed the following limited levels of resource use for the health states in the model (Table 54).

Table 54. Health care resource use implemented in the economic model

Decision Tree Health States							
	DUP+ECM		ECM				
Resource	Response	No Response	Response	No Response			
Primary care visits	0.0	6.0	0.0	6.0			
Outpatient visits	2.0	3.0	1.0	3.0			
Emergency visits	0.0	0.0	0.0	0.0			
Nurse visits	0.0	0.0	0.0	0.0			
Hospitalisation	0.0	0.0	0.0	0.0			
Markov Model Health States							
	Controlled Disease		Inadequately Controlled	Post-Op Controlled		Uncontrolled	
	First Year	Sub. Years		First Year	Sub. Years	First Year	Sub. Years
Primary care visits	0.0	0.0	6.0	0.0	0.0	6.0	6.0
Outpatient visits	1.0	1.0	3.0	0.0	1.0	3.0	3.0
Emergency visits	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Nurse visits	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Hospitalisation	0.0	0.0	0.0	0.0	0.0	0.0	0.0

DUP = dupilumab; ECM = established clinical management

We have assumed that during the first year of treatment with dupilumab two consultant visits are required. One for assessment at Week 24 and another for assessment at Week 52. For patients with poor response in the first year on dupilumab we have added a further consultancy visit. Whilst the advice was that patients controlled on dupilumab may only require one specialist nurse visit thereafter per year we have assumed that instead one consultant attendance is likely to be expected more generally to monitor a biologic new to this therapy area whilst on treatment. We have tested this in sensitivity analysis by replacing with a nurse visit.

We have tested these estimates in sensitivity analysis. Some of the experts at the first advisory board felt that 6 was too low for the number of GP visits so the annual number of primary care visits for uncontrolled patients is varied to 7.64. This is taken from the published estimate from Wahid 2020 which was a prospective case-control study in the East of England in 2013.¹³¹ The study found that the total number of GP visits for the three months recall period was 1.91. We have annualised this figure ($4 \times 1.91 = 7.64$).

In line with the alternative estimate from the advisory board we have tested the number of outpatient visits at 2 per year.

During the year in which a surgery takes place (the first year post operative controlled health state), resource use is treated in a different way in the model and so no HCRU is included in

[Table 54](#) above for this health state. This is to avoid double counting. We have taken this approach because very good recent evidence published by Clarke et al. 2022,⁹⁷ for the total per-person costs to the NHS in England for 1 year in patients receiving surgery for CRSwNP is available. This study included two of our advisors and is discussed in [Section 3.4.5.2](#).

3.4.4 Intervention and comparator costs

3.4.4.1 Drug unit and administration costs

3.4.4.1.1 Dupilumab unit costs

Treatment acquisition costs are calculated based on the package price costs and the drug quantity required according to expected treatment schedules. Treatment schedules are based on the SmPCs for each individual treatment. The dosing of dupilumab is 300 mg given every other week by subcutaneous injection. The annual cost for dupilumab at list price is £16,500 PPPY. According to the confidential simple patient access scheme (approved by NHS England and Improvement and the Patient Access Scheme Liaison Unit in 2021) there is a [REDACTED] discount off the list price of dupilumab corresponding to [REDACTED] PPPY, or [REDACTED] per pack of two 300 mg syringes or pens. In the model, the unit cost per dose is multiplied by the treatment frequency (26 doses required PPPY as per the MHRA licence) to estimate the cycle-specific drug costs. ([Table 55](#)). In the model, different drug-acquisition costs can be entered for the first year alone, the second year alone, and for subsequent years, which enables the model to estimate cost-effectiveness under various patient-access schemes or rebate scenarios.

In the model, dupilumab is assumed to be self-administered following instruction from a nurse. No training is assumed for the administration of ECM. The model also allows users to define the percentage split between self-administration and administration by a nurse for subsequent doses. No nurse administration is assumed in the base case in line with other assessments for dupilumab (TA534, TA751).^{60,69} This is varied to 95% in sensitivity analysis. The unit cost for subcutaneous administration training used in the model is £65.86 taken from the Unit Costs of Health and Social Care 2023 for Hospital-based nurses - Band 6: Cost per working hour with qualification costs; inflated to 2024 ([Table 55](#))

Table 55 Unit costs associated with dupilumab

Items	Drug acquisition net cost (per dose), £	Administration training cost (one off), £
Dupilumab 300 mg	[REDACTED]	65.86

3.4.4.1.2 ECM unit and administration costs

In the model, the cost of ECM treatments was estimated based on the percentage of patients (responders and non-responders) using SCS and/or antibiotics, as well as the average duration of treatment, derived from pooled analyses of SINUS-24 and SINUS-52 trials (Sanofi data on file, 2019a). Usual daily dosage and type of SCS and antibiotics were determined based on the 2016 UK Commissioning Guide for CRS;¹⁰⁰ Estimated unit costs for SCS and antibiotics were estimated based on drug price of prednisolone 5mg and doxycycline 100mg, respectively from the eMIT National Database (Department of Health and Social Care; eMIT National Database;(NHS Electronic Drug Tariff, January 2025)).⁹⁹ There are no administration or administration training costs associated with ECM ([Table 56](#)).

Table 56 Unit costs associated with ECM

Items	Cost per course, £	Daily cost, £
SCS (prednisolone 5mg)	2.77	0.28
Antibiotics (doxycycline 100mg)	3.81	0.18

ECM = established clinical management; SCS = systemic corticosteroids
Source: eMIT database,⁹⁹ ENT UK¹⁰⁰

[Table 57](#) presents the base case treatment acquisition costs for ECM (SCS and antibiotics) according to response. Drug use rates and durations are based on pooled data from the SINUS trials.

Table 57. Base case drug-acquisition costs for SCS and antibiotics according to response

Response	SCS		Antibiotics		Drug costs, £
	Drug use, %	Duration, days	Drug use, %	Duration, days	
Week 0–Week 24					
DUP + ECM responders	0	0	18.9	9.9	0.34
DUP + ECM non-responders	17.9	19.2	27.2	9.3	1.41
ECM responders	0	0	12.9	20.0	0.47
ECM non-responders	45	13.1	31.4	14.9	1.81
Week 25–Week 52					
DUP + ECM responders	0	0	18.2	12.4	0.41
DUP + ECM non-responders	20.5	22.7	20.5	14.5	1.83
ECM responders	0	0	9.1	5.0	0.08
ECM non-responders	28.2	16.2	28.2	14.4	1.99

DUP = dupilumab; ECM = established clinical management; SCS = systemic corticosteroids
Source: eMIT database,⁹⁹ ENT UK¹⁰⁰

3.4.5 Health state unit costs and resource use

3.4.5.1 Cost of ECM according to health state

Table 58 presents base case treatment acquisition costs for ECM (SCS and antibiotics) according to health state. Cost per state is very low due to the low cost of the treatments used and the proportion of steroid and antibiotic use recorded in the studies.

Table 58 Annual drug costs for ECM (SCS and antibiotics) according to model health state

Health state	Annual drug cost, £	Source
Decision tree		
DUP + ECM responders	0.75	Estimated based on drug use in pooled analyses of SINUS-24 and SINUS-52 trials (Sanofi data on file, 2019a) and unit costs presented in Section <u>3.4.4.1</u>
DUP + ECM non-responders	3.25	
ECM responders	0.55	
ECM non-responders	3.81	
Markov model		
Controlled disease	0.40	Assumed to be the average ECM drug costs of DUP + ECM responders and ECM responders
Inadequately controlled	4.17	Assumed to be the same as the ECM drug costs of ECM non-responders
Post-operative controlled	0.40	Assumed to be the average ECM drug costs of DUP + ECM responders and ECM responders
Uncontrolled	4.17	Assumed to be the same as the ECM drug costs of ECM non-responders

DUP = dupilumab; ECM = established clinical management; SCS = systemic corticosteroids
Source: Sanofi data on file, 2019a

3.4.5.2 Surgery costs (first year post operative controlled health state)

Table 54 in Section 3.4.3 provides the estimates for HCRU rates used in the model. We noted that during the year in which a surgery takes place (the first year post operative controlled health state), resource use is treated in a different way from simply multiplying HRCU estimates by an appropriate tariff. An explanation of the treatment of the costs for this health state is provided below.

Costs for the year (cycle) in which the surgery event take place were taken from Clarke 2022.⁹⁷ This was an observational retrospective study examining cost of healthcare of patients receiving CRS surgery and represents a comprehensive assessment of surgery costs. Linked electronic healthcare records from the Clinical Practice Research Data link, Hospital Episode Statistics and the ONS databases were used covering the period 1997–2016. 62685 patients were identified as definitely having CRS and 13,462 received CRS-related surgery and were included in the analysis.

To capture the costs directly associated with the surgery event to align with the annual model cycle length, we have used the reported mean inpatient and outpatient costs for the

quarter in which the surgery took place and included the follow-up costs in the following 3 quarters to estimate the cost for the year containing the surgery. These costs include imaging, biopsy, polypectomy and other elective inpatient costs surgery cost of managing surgery complications. Mean costs for the year including the surgery event and follow up for patients with positive polyps taken from Clarke are presented in [Table 59](#) below.

Table 59. Mean costs for the year including the surgery event for patients with positive polyps⁹⁷

Mean INPATIENT costs per patient-quarter in the QUARTER CONTAINING THE SURGERY by procedure category, split by polyp status					
Day case	Mean cost ppq, £	Elective inpatient	Mean cost ppq, £	Surgical procedure	Mean cost ppq, £
CT/other imaging	0.02	CT/other imaging	0.86	Polypectomy	1,414.69
Minor nose including biopsy	7.85	Minor nose including biospsy	28.44		
Intermediate nose and minor sinus	40.09	Intermediate nose and minor sinus	166.57		
Intermediate Major/ complex/ sinus	152.6	Intermediate Major/ complex/ sinus	474.22		
				Total cost: 2,284.63	
Mean OUTPATIENT costs per patient-quarter in the QUARTER CONTAINING THE SURGERY by procedure category, split by polyp status					
Outpatient	Primary care consultations, £	Primary care Abx	Primary care non=Abx	Total	
62.41	5.59	0.99	7.79	Total cost: 76.78	
Costs per patient-quarter, broken down by healthcare/prescription category, by time period and by polyp status in the 8 QUARTERS FOLLOWING SURGERY					
Inpatient care (DC and EL), £	Outpatient	Primary care consultations, £	Primary care Abx	Primary care non=Abx	Total
20.7	25.6	4.73	0.95	7.63	59.62
				Total cost: 59.62	

Abx = Antibiotics; CT = computed tomography; DC= Day Case; EL = Elective Inpatient; NHS = National Health Service; ppq = per patient per quarter
Source: Clarke 2022⁹⁷

[Table 59](#) above shows mean inpatient costs per patient-quarter in the quarter containing the surgery were £2,284.63. Mean outpatient costs per patient-quarter in the quarter containing the surgery were £76.78 and follow up costs per quarter following surgery were £59.62 for each of the subsequent 8 quarters. On this basis the cost for the year containing surgery is $£2,284.63 + £76.78 + (3 \times £59.62) = £2,540.27$. The aggregate cost for the year reported in the publication is very slightly higher at £2,547. We have been unable to reproduce this cost from the published data and have contacted the authors. It may be the case that the authors used the first 3 quarters directly to estimate the cost for the first year rather than the average value quoted in the published tables. Given the close agreement between these figures we have used the published aggregated value of £2,547 and tested £2,540.27 in sensitivity

analysis. This was inflated to 2024 costs using a combination of inflation indices. The 2016-2023 annual inflation rates were derived from Unit Costs of Health and Social Care 2023¹¹⁰ and for the years 2023-2024 the annual inflation rate based on annual Consumer Price Inflation (CPIH) annual rate, as of September 2024, using the NHS inflation indices providing an estimate of £3,060 per patient per year.^{98,110}

3.4.5.3 Other costs

Unit costs are inflated to 2024 costs based on the inflation rate recorded in the UK Office for National Statistics (ONS). Resource-use costs for the model are shown in [Table 60](#).

Table 60. HCRU unit costs

Resource	Unit Cost, £	Cost used in the model (inflated to 2024 cost year), £	Source
GP visit (10-minute consultation)	49.00	50.42	PSSRU 2023
Specialist visit	168.00	172.87	NHS Schedule of Costs 2022/2023
Nurse visit	64.00	65.86	PSSRU 2023

GP = general practitioner; HCRU = health care resource utilisation; PSSRU = Personal Social Services Research Unit
Sources: PSSRU Unit Costs Manual 2023;¹¹⁰ NHS Cost Collection 2022/2023⁹⁸

3.4.5.4 Resource costs per health state

The resource use estimates from [Table 54](#) above are multiplied by the appropriate cost in [Table 60](#) to derive the health state costs for HCRU. ([Table 61](#))

Table 61 Base case HCRU according to health state

Decision tree		DUP + ECM, response		DUP+ECM, no response		ECM, response		ECM, no response	
Week 0-24		£159.57		£378.99		£79.79		£378.99	
Week 25-52		£186.17		£442.15		£93.08		£442.15	
Markov Model									
DUP + ECM, controlled disease			DUP + ECM, inadequately controlled disease				DUP + ECM, uncontrolled disease		
First year	Subsequent years		First year	Subsequent years		First year	Subsequent years		
£172.87	£172.87		£821.14	£172.87		£821.14	£821.14		
ECM, controlled disease			ECM, inadequately controlled disease				ECM, uncontrolled disease		
First year	Subsequent years		First year	Subsequent years		First year	Subsequent years		
£172.87	£172.87		£821.14	£172.87		£821.14	£821.14		

DUP = dupilumab; ECM = established clinical management; HCRU = health care resource utilisation

3.4.6 Adverse reaction unit costs and resource use

The model calculates an aggregated cost of AE management for each treatment. Since the AEs included in the model are not severe, the unit costs are assumed to be the cost incurred for one GP visit. Costs are sourced from 2022/23 PSSRU based on a 10 minute consultation.¹³²

The list of AEs considered in the model were derived from Bachert et al. (2019).⁶⁸ The annual incidences were estimated based on the number of treatment-emergent AEs per 100 patient-years during the entire treatment-emergent AE period from pooled analyses of SINUS-24 and SINUS-52 (Sanofi data on file, 2019a). [Table 62](#) presents the base-case annual incidence rates per treatment arm, together with corresponding unit costs.

Table 62. Base case data inputs for adverse event costs

TEAE	Annual incidence ^a , %		TEAE unit cost, £	Cost used in the model (inflated to 2024 cost year), £	Source for cost
	DUP + ECM	ECM			
Nasopharyngitis	0.275	0.287	49.00	50.42	One GP visit, Table 60
Headache	0.092	0.181	0	0	Assumed self-treated
Epistaxis	0.106	0.114	0	0	Assumed self-treated
Asthma	0.058	0.173	168.00	172.87	One respiratory consultant visit, Table 60
Injection site reaction	0.395	0.000	273	280.92	One emergency care visit

DUP = dupilumab; ECM = established clinical management; GP = general practitioner; TEAE = treatment-emergent adverse event. ^a Source: Sanofi data on file, 2019a

3.4.7 Miscellaneous unit costs and resource use

3.4.7.1 Asthma

The most common Type-2 comorbidity for people with CRSwNP is asthma (Section [1.2.1.4](#)). Dupilumab has been shown to demonstrate efficacy in several type 2 inflammatory diseases including CRSwNP and asthma by blocking the shared receptor component for IL-4 and IL-13 (Sections [1.2.2.3](#) and [2.8](#)). In this way dupilumab improves upper and lower airway outcome measures in patients with severe CRSwNP and comorbid asthma. Dupilumab is licenced of the treatment of both CRSwNP and asthma and asthma outcomes were also collected in the SINUS CRSwNP studies. For example in the pooled SINUS studies, overall the asthma control questionnaire (ACQ-6) score at week 24 revealed a clinically significant improvement that exceeded the MCID of 0.5 points (LS mean difference vs placebo [95% CI] of -0.82 [-0.98 to -0.67]; nominal $P < .001$).³⁵

In the SINUS-24 and SINUS-52 clinical trials 59.6% and 58.3% respectively of subjects had comorbid asthma at baseline. 24.4% of patients had severe co-morbid asthma in the pooled population defined as GINA step 4-5 at baseline.

At the end of the study period the population of patients with asthma had differential outcomes being distributed between controlled, partially controlled, and uncontrolled asthma according to the asthma control questionnaire (ACQ-6) score administered at week 24 (Table 63). Annual costs have been assigned to these levels of according to Willson et al. 2014, (See Technical appendix, Tables 7 to 9 from the supplementary materials to the publication); assuming that the average resource use of well-controlled (referred to as “controlled” in the source) and partly controlled patients in Willson et al. would be equivalent to the average resource use observed in controlled patients in the model.¹³³

Table 63. Distribution of asthma control at study end* and associated costs from Wilson¹³³

Control level*	DUP+ECM, %	ECM, %	Cost by control status, £
Controlled asthma	76.0	15.4	960
Partially controlled asthma	10.0	19.4	1,795
Uncontrolled asthma	14.0	63.9	2,629

DUP = dupilumab; ECM = established clinical management

*According to asthma control questionnaire (ACQ-6) score at Week 24.

Source: Sanofi data on file, 2019b (pooled trial data from SINUS-24 and SINUS-52).

Given the importance of asthma in this patient population and the differential impact on asthma outcomes between ECM and the dupilumab treated patients we have included asthma related costs in the model. The proportion of patients with severe asthma is multiplied by the distribution of asthma severity level at the end of the study by treatment arm and the cost for each category. These costs are applied at each model cycle.

Real world evidence exists to support the assumption that differential asthma outcomes would be improved in the longer term and persist in the real world. In a prospective follow-up study (January 2021 to May 2022) amongst 166 patients with CRSwNP treated with dupilumab for at least 6 months, changes in ACT scores for those patients with asthma (n = 99) were recorded.¹³⁴ The ACT scores after dupilumab treatment were significantly higher than before dupilumab treatment increasing from 16.923 to >22 (p<0.001). Similarly, in the study by Gal et al., 17% of patients reported completely uncontrolled asthma at baseline compared to 0% at 12 months (p<0.01).¹²⁹

3.4.7.2 Productivity loss

Although not included in the base case, the model incorporates productivity loss inputs (i.e., absenteeism and presenteeism) to estimate indirect costs. In addition, potential out-of-

pocket expenses are estimated. A scenario was also explored to test the impact of including indirect costs associated with absenteeism due to surgery. The scenario assumed that people did not go to work for 10 days after the surgery.⁵³ Table 64 presents the employment parameters and

Table 65 presents the corresponding values that were used for estimation of indirect costs. No statistics on caregiving costs for patients with CRSwNP in England were identified, therefore they have not been considered.

Table 64. Summary of employment inputs

Employment parameter	Input	Source
Value of productivity loss per hour	18.64	ONS 2024. Employee earnings in the UK: 2024: Measures of employee earnings, using data from ASHE, Apr 2025
Percentage employed	75.1	ONS 2024. Table EMP01: Full-time, part-time and temporary workers: People (not seasonally adjusted), Aug-Oct 2024
Daily working hours	4.53	ONS 2024. Table HOUR01: Actual weekly hours of work (not seasonally adjusted), Aug-Oct 2024
Retirement age	67	Department for Work & Pensions, 2024

ASHE = Annual Survey for Hours and Earnings; NA = not applicable; SD = standard deviation
Sources: ONS 2024¹¹¹

Table 65. Summary of productivity losses

Status	Days per year		Source
	Absenteeism	Presenteeism	
Responder	0	0	Assumption
Non-responder	10.55	30.36	Absenteeism: Mean days off work associated with surgery estimated based on NL data (Lourijssen 2020)

NL = Netherlands
Source: Lourijssen 2020⁵³

Productivity loss is only applicable for patients who are below the age of retirement and employed (early retirees are excluded from the calculation). The mean age of retirement was assumed to be 67 and in the absence of data to show that unemployment is higher in patients with CRSwNP we have assumed that the percentage of patients employed is in line with national average rate at 75.1%.

3.4.7.3 *Travel costs*

Travel costs have not been included as these are out of pocket expenses.

3.5 *Severity*

We do not expect the severity modifier to apply to this appraisal.

3.6 *Uncertainty*

Challenges associated with modelling the course of severe CRSwNP and the long-term impact of treatment with dupilumab have the potential to create uncertainty in model outputs. Specifically, uncertainty in the model may result from:

- Issues in capturing the burden of CRSwNP with EQ-5D data
- A lack of consensus on the definition of treatment response in people with severe CRSwNP
- Insufficient published evidence on post-operative disease recurrence and revision surgeries
- Insufficient published evidence on HCRU based on the UK population
- Insufficient published evidence on the long-term impact of SCS overuse in the UK (costs and disutility associated)
- Insufficient published evidence on the impact of comorbid asthma
- The variability of surgery long term outcomes, with differences in the magnitude of response after surgery

There is also uncertainty around the extrapolation of trial data beyond the follow-up period. Dupilumab is the first biologic used to treat moderate-to-severe CRSwNP and so, as is typical for newly approved agents targeting chronic conditions, long-term treatment effect data are limited. Sensitivity and scenario analyses evaluate the uncertainty surrounding the consequent use of external data and assumptions in long-term predictions (Section [3.10](#)).

3.7 *Managed access proposal*

No managed access proposal is included in this submission.

3.8 *Summary of base-case analysis inputs and assumptions*

3.8.1 Summary of base-case analysis inputs

A summary of the inputs used in the base case analysis is provided in [Table 66](#).

Table 66 Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty (distribution)	Reference/corresponding section in this submission
Model characteristics			
Perspective	Healthcare payer (NHS)	Societal costs can be included	NICE reference case (Section 3.1.3)
Patient population	Base case population is people with uncontrolled disease following one (or more) surgeries.	People with prior type 2 medical history including asthma/NSAID-ERD	Taken from the pooled SINUS-24/SINUS-52 populations (Section 3.1.2)
		People with prior surgery and with prior type 2 medical history including asthma/NSAID-ERD	
Time horizon	Lifetime (50 years)	5, 10 & 20 years	NICE reference case
Discount rate, costs and outcomes	3.5%	3% and 5% in OWSA	NICE reference case
Clinical parameters			
Response criteria	(NPS (≥ 1) and SNOT-22 (≥ 8.9)) (reduction from baseline)		Section 3.2.2.1
Response: Week 24 (initial response)	DUP+ECM: [REDACTED]	ECM: [REDACTED]	Pooled analyses of SINUS-24 and SINUS-52 (Section 3.2.2.1)
Response: Week 52 (sustained response)	DUP+ECM: [REDACTED]	ECM: [REDACTED]	
Proportion of patients who have sinus surgery Week 0 - 24	DUP+ECM: [REDACTED]	ECM: [REDACTED]	Pooled analyses of SINUS-24 and SINUS-52 (Section 3.2.2.3)
Proportion of patients who have sinus surgery Week 25 - 52	DUP+ECM: [REDACTED]	ECM: [REDACTED]	
Probability of moving to the inadequately controlled state from controlled disease Years 2 and on	DUP+ECM: [REDACTED]	ECM: [REDACTED]	Pooled analyses of SINUS-24 and SINUS-52 (Section 3.2.2.2)
Patients in the inadequately controlled disease HS	Ineligible for surgery: 23.7%		Pooled analyses of SINUS-24 and SINUS-52 (Section 3.2.2.3)
	Receive surgery 15.1%		Benson 2023 (Section 3.2.2.3)
Post-op controlled HS: transition to uncontrolled HS	42.8%	Beta	Benson 2023, Section 3.2.2.4

Variable	Value			Measurement of uncertainty (distribution)	Reference/corresponding section in this submission
Uncontrolled to post-op HS (receive surgery)	15.1%			Beta	Benson 2023 (Section 3.2.2.3)
Mortality	All patients: Based on UK mortality tables			Not varied	Section 3.2.2.6
	Risk from surgery: 0.0%			Not varied	Section 3.2.2.6
AEs: Nasopharyngitis	DUP+ECM: 0.275	ECM: 0.287		Beta	Pooled analyses of SINUS-24 and SINUS-52 (Section 3.2.2.3)
AEs: Headache	DUP+ECM: 0.092	ECM: 0.181		Beta	
AEs: Epistaxis	DUP+ECM: 0.106	ECM: 0.114		Beta	
AEs: Asthma	DUP+ECM: 0.058	ECM: 0.173		Beta	
AEs: Injection site reaction	DUP+ECM: 0.395	ECM: 0.000		Beta	
Proportion of patients with severe asthma	24.4%			Beta	Section 3.4.7.1
Proportion of patients with controlled asthma at Week 52	DUP + ECM: 76.0%	ECM:16.7%		Beta	Wilson 2014 (Section 3.4.7.1)
Proportion of patients with partially controlled asthma at Week 52	DUP + ECM: 10.0%	ECM: 19.4%		Beta	
Proportion of patients with uncontrolled asthma at Week 52	DUP + ECM: 14.0%	ECM: 63.9%		Beta	
Health effects					
Base case health state utilities Decision tree	Week 0–12	0.524	0.524	• Baseline: Beta • Cfb: Normal (Varied using the SNOT-22 input to the mapping)	Pooled analyses of SINUS-24 and SINUS-52 (Section 3.3.3.4)
	Week 13–24	0.727	0.596		
	Week 25–52 responders	0.793	0.734		
	Week 25–52 non-responders	0.673	0.587		
Base case health state utilities Markov model	Controlled disease	0.809			
	Inadequately controlled disease	0.594			
	Uncontrolled disease	0.524			
	Utility gain from surgery	0.051			

Variable	Value		Measurement of uncertainty (distribution)	Reference/corresponding section in this submission
	Riemenschneider 2015			
	Post-op controlled disease* - patients from DUP+ECM No response HS	0.724		
	Post-op controlled disease* - patients from ECM No response HS	0.638		
	Post-op controlled disease* - patients from Inadequately controlled HS	0.645		
	Post-op controlled disease* - patients from Uncontrolled HS	0.575		
Short term disutility from surgery (14 days)	0.150		Normal	Scangas 2017 (Section 3.3.3.8)
Long term utility gain from surgery (Soler 2011) (1 year)	0.051		Normal	Soler 2011 (Section 3.3.3.9)
Disutilities associated with AEs	0.0		Not varied	Section 3.3.3.10
Cost and healthcare resource use				
Cost of dupilumab, annual cost	[REDACTED]		Not varied	Discount PAS price (Section 3.4.4.1)
Percentage of scheduled doses given to patients	99.2%		Varied in OWSA to 95%	Pooled analyses of SINUS-24 and SINUS-52 (Section 3.3.3.4)
Subcutaneous injection training (Hospital-based nurses - Band 6)	£65.86		Gamma	
Proportion of patients self-administering dupilumab	100%		Varied in OWSA to 95%	
Disease management costs	Various depending on whether disease is controlled vs. uncontrolled		Gamma (SE:10%)	NHS unit costs 2022/2023 (Section 3.4.5)

Variable	Value	Measurement of uncertainty (distribution)	Reference/corresponding section in this submission
Drug acquisition	Various depending on treatment		EMIT prices plus treatment schedules based on SmPCs (Section 3.4.4)
Surgery cost (first year post operative controlled health state)	£3,060		Clarke et al., 2022 (Section 3.4.5)
Unit cost for GP	£50.42		Section 3.4.5.3
Unit cost for specialist visits	£172.87		
Unit cost for emergency room	£288.12		
Unit cost for nurse visits	£65.86		Section 3.4.7.1
Asthma cost: Controlled	£960		
Asthma cost: Uncontrolled	£2,629		
Asthma cost: Partially controlled	£1795		Section 3.4.6
AE cost: Nasopharyngitis	£50		
AE cost: Headache	£0		
AE cost: Epistaxis	£0		
AE cost: Asthma	£208		
AE Injection site reaction	£288		
Productivity loss per hour	£18.64		Section 3.4.7.2
Presenteeism & absenteeism (days/year)	30.36 & 10.55	Gamma	
Retirement age	67	Normal	Section 3.4.3
Number of GP visits: Controlled disease	0	Gamma	
Number of GP visits: uncontrolled disease	6	Gamma	
Number of consultant visits: Controlled disease	1	Gamma	
Number of consultant visits: uncontrolled disease	3	Gamma	

AE = adverse event; BNF = British National Formulary; CRSwNP = chronic rhinosinusitis with nasal polyps; DUP = dupilumab; ECM = established clinical management; GP = general practitioner; HS = health state; NHS = National Health Service; NPS = nasal polyp score; NSAID-ERD = non-steroidal inflammatory drug exacerbated respiratory disease; OWSA = One Way Sensitivity Analysis ; PAS = Patient Access Scheme; SmPC = Summary of Product Characteristics; SNOT-22 = sinonasal outcomes test-22
Sources: Benson 2023¹⁶; Clarke 2022,⁹⁷ Rememschenider 2015¹¹⁷; Scangas 2017¹³⁰; Soler 2011¹¹⁸; Willson 2014¹³³

3.8.2 Assumptions

A summary of the key assumptions made in the economic model, alongside their justifications, is provided in [Table 67](#).

Table 67. Summary of key model assumptions

Assumptions	Justifications	Addressed in scenario analyses?
People receive a first dose of dupilumab in a clinic and receive training on SC administration. People self-administer subsequent doses at home.	Dupilumab has been available for the treatment of atopic dermatitis and asthma for several years. The assumptions for administration are based on standard clinical practice for dupilumab in the real world.	Varied to 5% nurse administration
No AE disutility is included.	Disutility because of AEs is assumed to be accounted for within QoL measures collected during the SINUS trials. Therefore, no additional disutility was included to avoid double-counting.	No
People do not have increased risk of mortality due to CRSwNP	Conservative assumption based on lack of published evidence	No
People with comorbid asthma have increased mortality risk	The increase in all-cause mortality taken from Xu 2017 is applied for asthma participants in the model.	Yes
Costs associated with asthma are included in the base case.	The most common type-2 comorbidity for people with CRSwNP is asthma. Dupilumab has been shown to demonstrate efficacy in asthma. Both CRSwNP and asthma outcomes were improved in the SINUS CRSwNP studies.	Yes. Asthma costs are removed.
Utility benefit from asthma improvement is not included in the base case.	To avoid double counting. QoL improvement is assumed to be captured by SNOT-22 and EQ-5D.	No
Age adjustments are made over time using the multiplicative method.	In the multiplicative method, general population utility weights from Ara and Brazier (2011) are used to estimate the relative decline over time. The additive method is used in sensitivity analysis and a linear trendline to the Ara and Brazier (2011) data is fit to estimate how much utility is lost with each year of age gained.	Yes
Indirect costs such as productivity loss are not included in the base case.	In accordance with the reference case	Yes
Surgery occurs at the start of the annual cycle.	Costs estimated from Clarke 2022 for the year with surgery are used. If, for example, the surgery occurred halfway through the year then cycle costs would need to be adjusted and the following	No

Assumptions	Justifications	Addressed in scenario analyses?
	cycle would contain spill over costs.	
The model does not consider the impact on potential differences in efficacy, costs, or patient QoL from different types of sinonasal surgeries.	The model uses a highly credible recent English source to describe costs in the year containing surgery in the population relevant to this submission. This amounts to a published macro costing.	No
People can have multiple surgeries in the model.	People can move back into the uncontrolled HS and receive additional surgeries. Nearly 50% of patients with CRSwNP undergoing surgery report having received more than one operation, with a mean number of 3.3 procedures per patient (range 2–30) (ENT UK 2016)	No
Post-operative controlled health state	Estimated based on patients' utility weight prior to the surgery, utility gain from surgery, and short-term disutility associated with surgery. A utility gain from surgery of 0.051 from Soler 2011 is applied.	This is tested in sensitivity analysis using Remenschneider 2015.
No age limit for surgery.	Limiting on age alone is discriminatory. If age (frailty or performance status) is a factor in decision making we have assumed that ineligibility due to age is accounted for in the overall ineligible for surgery rate.	No
Percentage of patients eligible for surgery changes over time	As patients age in the model, their eligibility for surgery may decrease. This is tested by linear or polynomial increase.	Yes
Percentage of patients with employment.	In the absence of data we have assumed that the employment rate of patients is equal to the national average at 75%.	No

ACQ-6 = Asthma Control Questionnaire-6; AEs = adverse events; CRSwNP = chronic rhinosinusitis with nasal polyps; EQ-5D = EuroQol 5-dimension; QoL = quality of life; SC = subcutaneous; SNOT-22 = Sinonasal Outcomes Test-22
Sources: Ara and Brazier 2011¹²¹; Clarke 2022⁹⁷; ENT UK 2016¹⁰⁰; Remenschneider 2015¹¹⁷; Soler 2011¹¹⁸; Xu 2017¹³⁵

3.9 **Base-case results**

3.9.1 **Base-case incremental cost-effectiveness analysis results**

The expected positioning of dupilumab for CRSwNP in UK clinical practice is for people with uncontrolled disease following one (or more) surgeries. This reflects the population described in the scope and decision problem. Base case results from the probabilistic and deterministic analysis for are presented in [Table 68](#). Disaggregated results of the model are provided in [Appendix J](#).

Table 68 Base-case deterministic results

Treatments	TOTAL QALYs	TOTAL costs	Incr. QALYs	Incr. costs	ICER
Dupilumab + ECM	██████	██████	██████	██████	£24,383
ECM	██████	██████			

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

At the patient access scheme price, dupilumab plus ECM and ECM alone accumulated costs of ██████ and £██████, and total QALYs of ██████ and ██████ respectively. The ICER was £24,383/QALY which is within the range commonly considered cost-effective for the NHS, as it falls below the conventional NICE willingness-to-pay threshold (WTP) of £30,000 per QALY.

These results demonstrate that dupilumab is an appropriate use of NHS resources. Particularly notable is the scale of QALY gain demonstrating the poor health status of patients at base line and the demonstrated impact that dupilumab can have on their lives.

3.10 Exploring uncertainty

3.10.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) has been conducted to assess the parametric uncertainty associated with the base case model results. All key parameters were assigned probability distributions from which random sampling was done over 1000 simulations. Where uncertainty data were not available for an input, standard errors of 10% of the mean values were assumed. The PSA results are presented in [Table 69](#). The results align with the deterministic results.

Table 69. Summary of the base case PSA results

Treatments	TOTAL QALYs	TOTAL costs	Incr. QALYs	Incr. costs	ICER
Dupilumab + ECM	██████	██████	██████	██████	£24,491
ECM	██████	██████			

ICER = incremental cost-effectiveness ratio; Incr = incremental; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year; ECM Established Clinical Management

In addition, the incremental PSA results and cost-effectiveness acceptability curve (CEAC) are presented in [Figure 21](#) and [Figure 22](#), respectively. At a WTP of £30,000/QALY, the probability of being cost-effective is 99.2%; at £20,000 it is 0.1%.

Figure 21. Scatter plot for incremental cost-effectiveness results (1,000 iterations)

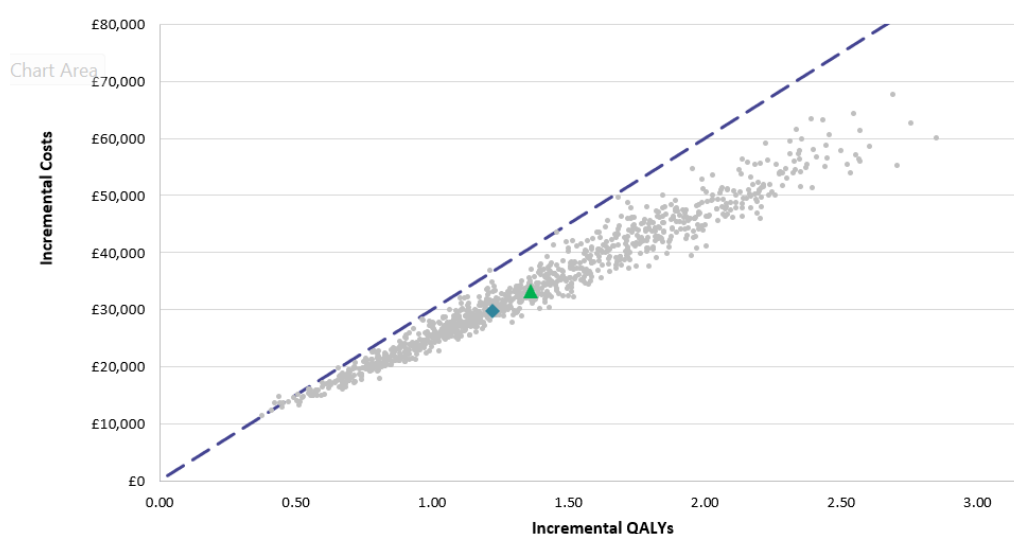
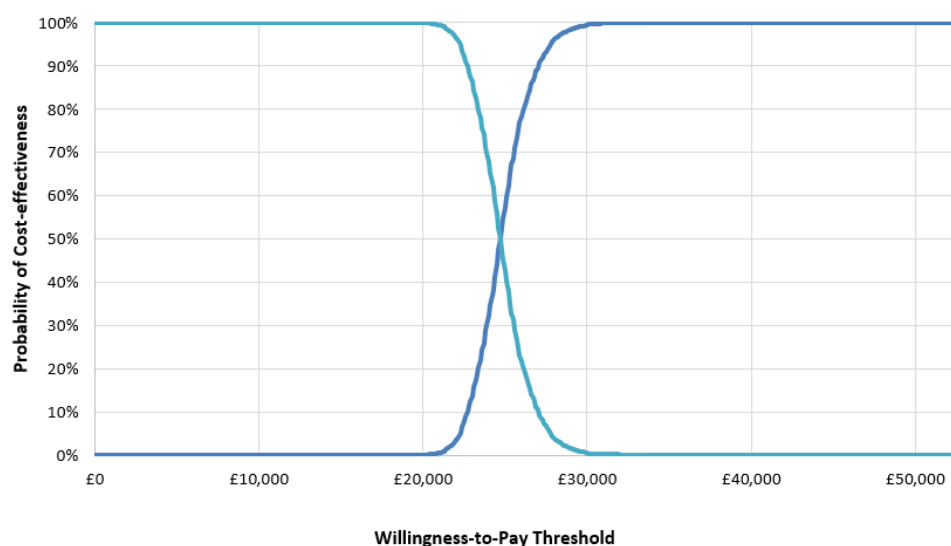


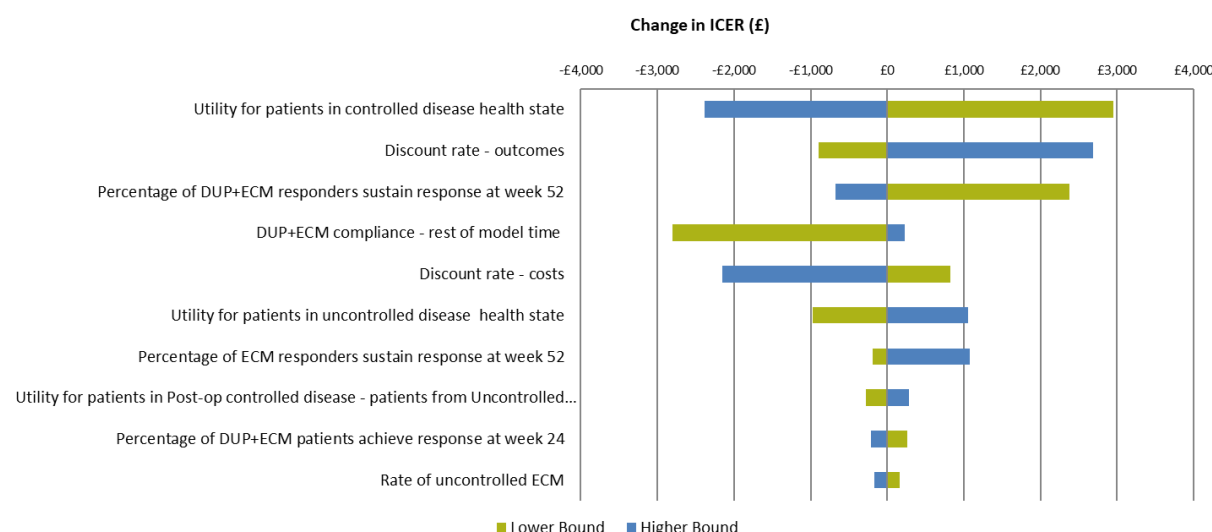
Figure 22. Cost-effectiveness acceptability curve (1,000 iterations)



3.10.2 Deterministic sensitivity analysis

Model inputs used for the base case analysis are varied in a one-way deterministic sensitivity analysis (DSA), changing their values one by one within the ranges provided for dupilumab + ECM vs. ECM only. As shown in the tornado chart ([Figure 23](#)) and [Table 70](#), beyond the impact of the discount rate, the top three drivers of the results are as expected and are the utility for controlled patients and maintenance of treatment response and compliance.

Figure 23. Tornado diagram of ICER (incremental cost per QALY gained) of DUP + ECM vs. ECM



DUP = dupilumab; ECM = established clinical management; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

Table 70. Top 10 drivers of the ICER results

Rank	Parameter	ICER - Lower Bound	ICER - Upper Bound	Difference
Base case ICER (Deterministic)		£24,383		
1	Utility for patients in controlled disease health state	■	■	£5,337
2	Discount rate - outcomes	■	■	£3,575
3	Percentage of DUP+ECM responders sustain response at week 52	■	■	£3,047
4	DUP+ECM compliance - rest of model time	■	■	£3,028
5	Discount rate - costs	■	■	£2,984
6	Utility for patients in uncontrolled disease health state	■	■	£2,020
7	Percentage of ECM responders sustain response at week 52	■	■	£1,274
8	Utility for patients in post-operative controlled disease - patients from Uncontrolled health state	■	■	£568
9	Percentage of DUP+ECM patients achieve response at week 24	■	■	£467
10	Rate of uncontrolled ECM	■	■	£333

DUP = dupilumab; ECM = established clinical management; HS = health state; ICER = incremental cost-effectiveness ratio

3.10.3 Sensitivity and scenario analysis

To test the sensitivity of the cost-effectiveness results due to uncertainty in key parameters and assumptions, various analyses have been explored (Table 71).

Table 71. Sensitivity analysis results – Base case population, PAS price (Probabilistic and deterministic ICERs)

Parameter	Scenario	Incr. QALYs	Incr. costs	ICER*	Rationale
Base case	N/A	■	■	£24,590	N/A
		■	■	£24,383	

Parameter	Scenario	Incr. QALYs	Incr. costs	ICER*	Rationale
Discount, cost	3%			£25,582	Alternative input to the NICE reference case.
				£25,210	
	5%			£22,056	
				£22,226	
Discount, health	3%			£23,568	
				£23,491	
	5%			£27,818	
				£27,066	
Time horizon	5 years			£28,302	
				£28,062	
	10 years			£25,660	
				£25,537	
	20 years			£24,736	
				£24,576	
Utility: Crump models	Crump model 2			£41,022	Alternative to Crump model 1. These regressions include the individual items of the SNOT-22 score
				£40,119	
	Crump model 3			£41,251	
				£40,449	
Utility: regression	Hernandez Model 1			£51,405	Use of EQ-5D with regression from the studies with the Hernandez mapping algorithm (5L to 3L)
				£50,909	
	Hernandez Model 2			£52,955	
				£52,534	
	Hernandez Model 3			£52,167	
				£51,704	
	Hernandez Model 4			£51,136	Use of EQ-5D with regression from the studies with the Van Hout mapping algorithm (5L to 3L)
				£50,422	
	Van Hout (Model 1)			£48,788	
				£48,365	
	Van Hout (Model 2)			£49,281	
				£49,129	
	Van Hout (Model 3)			£49,066	
				£48,586	
	Van Hout (Model 4)			£47,779	
				£47,367	
	Observed change from baseline (Hernandez)			£49,788	Directly observed EQ-5D with each mapping algorithm
				£49,126	
	Observed change from baseline (Van Hout)			£49,719	
				£49,059	
	Utility gain from surgery (Remenschneider, 2015)			£25,262	Alternative source for surgery utility gain
				£24,996	
	Remove short term disutility associated with surgery			£24,633	Test the impact of removing utility decrement
				£24,474	

Parameter	Scenario	Incr. QALYs	Incr. costs	ICER*	Rationale
Utility weight according to Age	Switch from multiplicative to additive	██████	██████	£23,682	Alternative approach to ageing in the model
		██████	██████	£23,733	
Long term discontinuation rate	7.8% from the clinical trials is changed to 2.2% from the AROMA study	██████	██████	£24,247	Alternative real world source for discontinuation
		██████	██████	£23,820	
Long term compliance rate	Rate changed from 99.2% to 95%	██████	██████	£23,438	Reduced compliance for dupilumab patients
		██████	██████	£23,197	
Nurse administration	Nurse administered doses = 5%	██████	██████	£24,774	A very small number of patients may require assistance in injecting
		██████	██████	£24,626	
Asthma related costs	Remove asthma related costs	██████	██████	£25,585	Testing the impact of asthma related costs
		██████	██████	£25,276	
Asthma related mortality	Remove asthma related mortality	██████	██████	£24,829	No direct evidence in the SINUS studies
		██████	██████	£24,748	
Eligibility for surgery	Change from no increase to linear increase	██████	██████	£24,651	Eligibility for surgery may not remain constant over time as patients age
		██████	██████	£24,428	
	Change from no increase to polynomial increase	██████	██████	£24,604	
		██████	██████	£24,395	
HCRU	Non-responder GP appointments increased to 7.64, Consultant appointments decreased to 2.0	██████	██████	£24,951	Alternative suggestions from clinicians at the ad boards
		██████	██████	£24,648	
	1 nurse visit instead of 1 consultant visit for responders	██████	██████	£24,292	
		██████	██████	£24,071	
	Cost of Post op first year (surgery cost) £3,052	██████	██████	£24,640	Sanofi calculation from literature
		██████	██████	£24,387	
Societal perspective	Include indirect costs associated with presenteeism and absenteeism	██████	██████	£18,026	It is important to appreciate that CRSwNP has a profound effect on patients' lives including work
		██████	██████	£17,508	

CFB = change from baseline; CRSwNP = chronic rhinosinusitis with nasal polyps; CW = crosswalk; EQ-5D-5L = EuroQoL 5-Dimensions 5-Level; FEV₁ = forced expiratory volume in 1 second; ICER = incremental cost-effectiveness ratio; Incr = incremental; ITT = intent-to-treat; LS = least squares; N/A= not applicable; NICE = National Institute for Health and Care Excellence; PAS = patient access scheme; RR = risk ratio; RWE = real world evidence; UK = United Kingdom
 *The probabilistic ICER is first followed by the deterministic ICER in each category.

3.11 Subgroups including comorbid asthma and NSAID-ERD

The NICE scope suggests that an important consideration is the impact of asthma, which is a type-2 comorbidity in CRSwNP. We believe that these patients are best described as having the NSAID-ERD.

NSAID-ERD, is characterised by 3 main features:

1. Asthma: This is a chronic inflammatory disease of the airways that causes breathing difficulties
2. Nasal polyps: These are non-cancerous growths in the lining of the nasal passage or sinuses, leading to congestion and sinus issues
3. Aspirin sensitivity: individuals have adverse reactions to aspirin and other NSAIDs, such as ibuprofen and naproxen

In the clinical studies all patients with the asthma comorbidity fell into this category.

It is likely be the case that these patients even without prior surgery, are at higher unmet medical need. The subgroups of interest are therefore: **a)** Patients with prior type 2 medical history including asthma/NSAID-ERD (i.e., no prior surgery) and **b)** Patients with prior surgery and with prior type 2 medical history including asthma/NSAID-ERD. These scenarios are explored in Sections [3.11.1](#) and [3.11.2](#).

3.11.1 Patients with prior type 2 medical history including asthma/NSAID-ERD

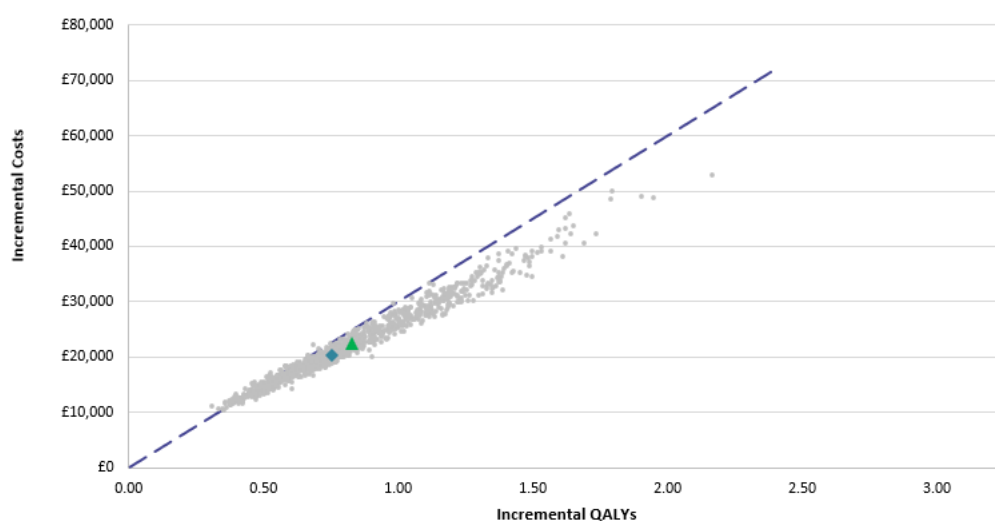
The results for this subgroup are presented in [Table 72](#), [Figure 24](#) and [Figure 25](#).

Table 72. Incremental cost-effectiveness results for the subgroup with prior type 2 medical history including asthma/NSAID-ERD

Treatments	TOTAL QALYs	TOTAL costs	Incr. QALYs	Incr. costs	ICER
Probabilistic analysis					
Dupilumab + ECM	██████████	██████████	██████████	██████████	£27,027
ECM	██████████	██████████			
Deterministic analysis					
Dupilumab + ECM	██████████	██████████	██████████	██████████	£26,983
ECM	██████████	██████████			

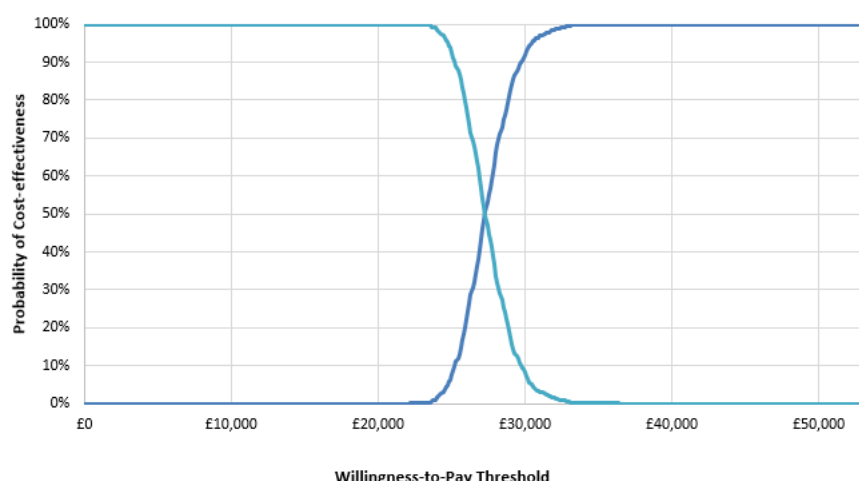
DUP = dupilumab; ECM = established clinical management; ICER = incremental cost-effectiveness ratio; Incr. = incremental; QALY = quality-adjusted life year

Figure 24. Scatter plot for incremental cost-effectiveness for the subgroup with prior type 2 medical history including asthma/NSAID-ERD (1,000 iterations)



NSAID-ERD = Non-steroidal anti-inflammatory drug exacerbated respiratory disease; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure 25. Cost-effectiveness acceptability curve for the subgroup with prior type 2 medical history including asthma/NSAID-ERD (1,000 iterations)



NSAID-ERD = Non-steroidal anti-inflammatory drug exacerbated respiratory disease; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Further sensitivity analyses were carried out for this subgroup, to examine the uncertainty around the key drivers of the ICER. ([Table 73](#)).

Table 73. Sensitivity analysis results (deterministic) – subgroup with prior type 2 medical history including asthma/NSAID-ERD, PAS price

Parameter	Scenario	Incr. QALYs	Incr. costs	ICER*	Rationale
Base case	Subgroup with prior type 2 medical history including asthma/NSAID-ERD	██████	██████	£26,983	N/A
Time horizon	5 years	██████	██████	£31,027	Reference case

Parameter	Scenario	Incr. QALYs	Incr. costs	ICER*	Rationale
	10 years			£28,102	
	20 years			£27,145	
Utility: Crump models	Crump model 2			£50,272	Alternative to Crump model 1. These regressions include the individual items of the SNOT-22 score
	Crump model 3			£50,270	
Utility: regression	Hernandez Model 1			£56,250	Use of EQ-5D with regression from the studies with the Hernandez mapping algorithm (5L to 3L)
	Hernandez Model 2			£57,888	
	Hernandez Model 3			£57,429	
	Hernandez Model 4			£55,904	
	Van Hout (Model 1)			£54,094	Use of EQ-5D with regression from the studies with the Van Hout mapping algorithm (5L to 3L)
	Van Hout (Model 2)			£54,913	
	Van Hout (Model 3)			£54,604	
	Van Hout (Model 4)			£52,979	
	Observed change from baseline (Hernandez)			£57,786	Directly observed EQ-5D with each mapping algorithm
	Observed change from baseline (Van Hout)			£55,125	
Other utility	Utility gain from surgery (Remenschneider, 2015)			£27,832	Alternative source for surgery utility gain
	Remove short term disutility associated with surgery			£27,121	Test the impact of removing utility decrement
Societal perspective	Include indirect costs associated with presenteeism and absenteeism			£19,102	To recognise the wider impact of CRSwNP on societal costs

EQ-5D = EuroQoL 5 Dimensions; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; N/A = not applicable; NSAID-ERD = non-steroidal anti-inflammatory drug exacerbated respiratory disease; PAS = patient access scheme; SNOT-22 = Sinonasal Outcomes Test-22

3.11.2 Patients with prior surgery and with prior type 2 medical history including asthma/NSAID-ERD

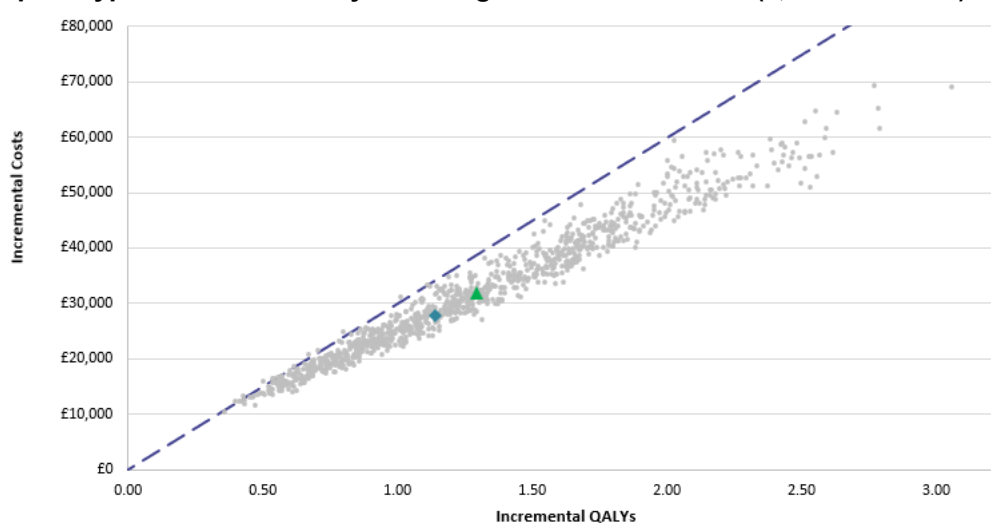
The results for patients with prior surgery and with prior medical history of type 2 inflammation, including NSAID-ERD, are presented in [Table 74](#), [Figure 26](#) and [Figure 27](#).

Table 74. Incremental cost-effectiveness results for the subgroup with prior surgery and with prior type 2 medical history including asthma/NSAID-ERD

Treatments	TOTAL QALYs	TOTAL costs	Incr. QALYs	Incr. costs	ICER
Probabilistic analysis					
Dupilumab + ECM					£24,651
ECM					
Deterministic analysis					
Dupilumab + ECM					£24,504
ECM					

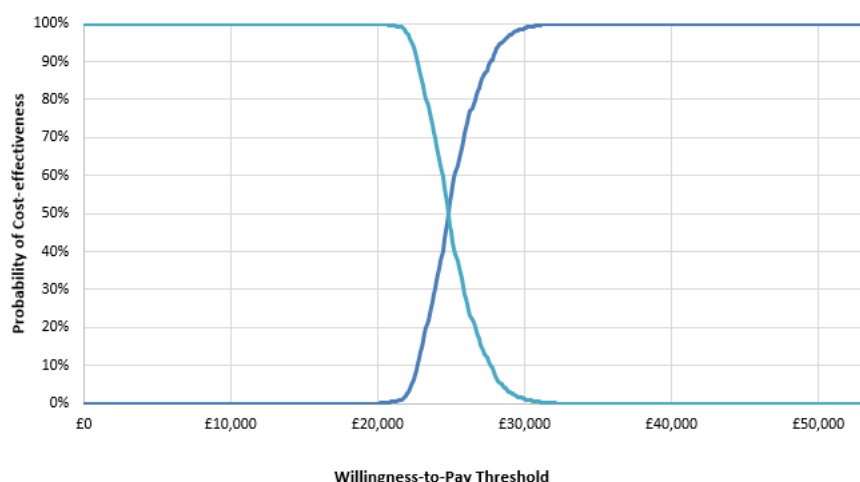
ICER = incremental cost-effectiveness ratio; Incr. = Incremental; NSAID-ERD = Non-steroidal anti-inflammatory drug exacerbated respiratory disease; QALY = quality-adjusted life year

Figure 26. Scatter plot for incremental cost-effectiveness for the subgroup with prior surgery and with prior type 2 medical history including asthma/NSAID-ERD (1,000 iterations)



NSAID-ERD = Non-steroidal anti-inflammatory drug exacerbated respiratory disease; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure 27. Cost-effectiveness acceptability curve for the subgroup with prior surgery and with prior type 2 medical history including asthma/NSAID-ERD (1,000 iterations)



NSAID-ERD = Non-steroidal anti-inflammatory drug exacerbated respiratory disease; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Further sensitivity analyses were carried out for this subgroup, to examine the uncertainty around the key drivers of the ICER (Table 75).

Table 75. Sensitivity analysis results (Deterministic) – Subgroup with prior surgery and with prior type 2 medical history including asthma/NSAID-ERD, PAS price

Parameter	Scenario	Incr. QALYs	Incr. costs	ICER*	Rationale
Base case	Subgroup with prior surgery and with prior type 2 medical history including asthma/NSAID-ERD			£24,504	N/A
Time horizon	5 years			£28,043	Reference case
	10 years			£25,600	
	20 years			£24,684	
Utility: Crump models	Crump model 2			£39,970	Alternative to Crump model 1. These regressions include the individual items of the SNOT-22 score
	Crump model 3			£40,161	
Utility: regression	Hernandez Model 1			£52,028	Use of EQ-5D with regression from the studies with the Hernandez mapping algorithm (5L to 3L)
	Hernandez Model 2			£53,972	
	Hernandez Model 3			£53,107	
	Hernandez Model 4			£51,743	
	Van Hout (Model 1)			£49,625	Use of EQ-5D with regression from the studies with the Van Hout mapping algorithm (5L to 3L)
	Van Hout (Model 2)			£50,510	
	Van Hout (Model 3)			£49,946	
	Van Hout (Model 4)			£48,619	
	Observed change from baseline (Hernandez)			£54,693	Directly observed EQ-5D with each mapping algorithm
	Observed change from baseline (Van Hout)			£52,917	
Other utility	Utility gain from surgery (Remenschneider, 2015)			£25,135	Alternative source for surgery utility gain
	Remove short term disutility associated with surgery			£24,599	Test the impact of removing utility decrement
Societal perspective	Include indirect costs associated with			£17,450	To recognise the wider impact of

Parameter	Scenario	Incr. QALYs	Incr. costs	ICER*	Rationale
	presenteeism and absenteeism				CRSwNP on societal costs

EQ-5D = EuroQoL 5 Dimensions; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; N/A = not applicable; NSAID-ERD = non-steroidal anti-inflammatory drug exacerbated respiratory disease; PAS = patient access scheme; SNOT-22 = Sinonasal Outcomes Test-22

3.12 **Benefits not captured in the QALY calculation**

Holistic impact of dupilumab on symptoms: The model is designed to capture a multitude of benefits, such as quality of life, severity, reductions in surgery, including associated short-term disutility. However, several benefits are likely to remain uncaptured in the QALY. In particular, we discussed the limitations of the EQ-5D instrument in Section [3.3.3.2](#) and showed how the mapping from SNOT-22 is the better choice.

1. **Symptom Relief:** EQ-5D is a generic instrument which does not include items specifically related to anosmia and sleep, the key domains of HRQoL. For example, enhanced sleep quality due to reduced nasal obstruction can have a profound impact on overall health and well-being, which might not be fully represented in the QALY. Our Mapping to SNOT-22 seeks to address this and those data should be considered in the base case.

One of the patient-reported endpoints captured in the SINUS-24 and SINUS-52 trials, in addition to the SNOT-22 outcome, is the E-RS: CRSwNP instrument. SINUS-24 and SINUS-52 showed that dupilumab was associated with greater reductions in E-RS: CRSwNP total score than ECM alone, indicating improvements in the severity of respiratory symptoms in patients receiving dupilumab. However, there is no mapping algorithm available to convert E-RS: CRSwNP scores to EQ-5D. Therefore, this benefit may not have been fully captured by the model in the same way as the SNOT-22 outcomes, which can be mapped to EQ-5D.

2. **Mental Health:** Similarly, the psychological impact of CRSwNP, including anxiety and depression due to chronic discomfort and social embarrassment, might not be adequately reflected in QALY calculations.
3. **Productivity:** Improvements in productivity at work due to better management of symptoms are not captured in the QALY calculation in the base case.
4. **Reduced Healthcare Utilization:** Decreased need for medications, doctor visits, and surgeries can lead to cost savings which are factored into the calculations but more generally the reduced burden on healthcare capacity is not directly captured by QALY. This has been described to us by a senior consultant ENT surgeon who told us:

“Taking revision patients off the waiting list would have a big impact on the wait times for ENT surgery ..., where the wait times are one of the longest across any surgical speciality.” Consultant ENT Surgeon at Guy’s Hospital, London.

3.13 Validation

3.13.1 Validation of cost-effectiveness analysis

A technical model validation was conducted to evaluate the validity of the model programming and sources used to derive input parameters in the model adaptation. The technical validation examines the extent to which mathematical calculations in the model are performed correctly and evaluates their consistency with the model’s specifications. The following steps were performed to ensure the model’s technical validity:

1. Extreme-value testing: Each model parameter was set to extremely low and high values to identify any inconsistencies in model behaviour or unexpected results.
2. Technical review (internal): The model programming was reviewed by a senior modeller who was not part of the project team. The technical review process included using different model settings to ensure that they yielded expected calculations. The validator also checked the links between worksheets to ensure that the correct cells were referenced. In addition, mathematical formulae, and the sequence of calculations for each parameter and the model engine were checked.
3. Technical review (external): Further technical review of the final model was conducted by a third-party agency who provided additional technical expertise. Some minor issues were identified and rectified with very minimal impact on the ICER.
4. Input verification: Values for all parameters were reviewed against source documents, and the inconsistencies were corrected.

Following the validation process, errors identified by the validator were corrected, and the revised model was rechecked by the internal validator.

An additional validation of the model structure and inputs was also performed as part of the advisory board and consultancies held in June and November 2024 with experienced UK clinical experts (including respiratory physicians and experts in respiratory epidemiology and respiratory medicine) and a health economist ([Appendix R](#)).

In addition to the technical validation of the formulae to ensure correctness, the cost-effectiveness model was also subject to external validation, by comparing the model structure and outcomes to published cost-effectiveness models. The most appropriate model comparison is with the model published by De Corso et al. (2022).¹⁰⁴ This is because the structure is similar and the comparison is for Dupilumab as an add-on to BSC vs. BSC, which included: nasal irrigation with saline solution and inhaled corticosteroids; oral corticosteroids and at least one surgery. The authors found incremental costs of € 22,283 and incremental QALs of 1.02 resulting in an ICER of € 21,817 per QALY. The model is from the Italian perspective however these results are close to the outcomes reported for our submission.

3.14 Interpretation and conclusions of economic evidence

Our cost-effectiveness analysis demonstrates that dupilumab represents good value for the NHS as a treatment for patients with uncontrolled CRSwNP who have had one or more surgeries.

At the patient access scheme price, add-on treatment with dupilumab results in higher QALYs (██████) compared with ECM alone but is more expensive (£██████) due to the higher acquisition cost of dupilumab. Dupilumab + ECM generates a probabilistic ICER/QALY of £24,491 which is within the commonly accepted WTP threshold of £30,000/QALY. The base case ICER was most sensitive to the source for utility calculations.

3.14.1 Strengths of the cost-effectiveness analysis

The SINUS-24 and SINUS-52 clinical trials were large robust, duplicate studies which provided strong evidence of a significant treatment effect for dupilumab as add-on to maximal inhaled therapy in patients with inadequately controlled CRSwNP. A key feature of the studies was the close representation of current clinical practice in CRSwNP as defined by various clinical guidelines. To make best use of the clinical data in the economic model, we have used the pooled subgroup data for patients with prior surgery from SINUS 24 and 52 data for our analyses.

Our model was designed based on careful consideration of the existing published models and the clinical characteristics and treatment pathway of patients with inadequately controlled CRSwNP as explained to us by clinical experts. This ensured that key aspects of the disease and English treatment practices are captured.

3.14.2 Limitations of the cost-effectiveness analysis

3.14.2.1 *Treatment effect is limited to trial duration of 52 weeks*

The follow-up period of the SINUS-24 trial extends to 48 weeks, and there was no follow-up period after the 52 weeks of the SINUS-52 trial, therefore whether the benefit of dupilumab can be maintained over the long run is uncertain. However, a phase 4 global registry of dupilumab (AROMA) is currently ongoing, with a follow-up period of 3 years. The model has been developed to assess how those clinical benefits observed within the 52-week trial period can potentially transfer into meaningful economic value over an extended time horizon.

3.14.3 Generalisability to clinical practice in England

The base case population reflects the anticipated place in therapy for dupilumab in England and is driven by the epidemiology for England (Section [1.2.1](#)), the clinical evidence presented (Section [2.6](#)), and English real-world evidence where appropriate (Section [2.9.3](#)). The patient population in the SINUS-24 and SINUS-52 trials included in the economic analysis is generalisable to the patient population expected to be treated with dupilumab in English clinical practice and the study comparator of established clinical management makes a within-trial comparison for the economic assessment the most appropriate analysis.

The cost-effectiveness analysis shows that, in addition to treatment effect, long-term discontinuation rates and surgery rates are model drivers. These factors may significantly vary in local clinical practice, especially considering the extremely long wait time for sinonasal surgery after the pandemic.

The model structure and approaches for the current analysis are designed to not only closely reflect the clinical outcomes observed in the SINUS-24 and SINUS-52 trials, but also provide maximum flexibility to use external data where applicable. This allows the generalisability to clinical practice to be assessed in cases where real world data may differ substantially from the SINUS-24 and SINUS-52 trials. Despite the challenges and limitations of developing a model that addresses the challenges associated with replicating the complex natural history of CRSwNP, the submitted model sufficiently describes the disease to enable the value of dupilumab from both the healthcare and societal perspectives to be assessed, based on the available evidence and data.

3.14.4 Conclusion

The burden of CRSwNP is considerable; medically, socially and economically. For patients whose disease continues to progress, unfortunately the ultimate outcome for patients

inadequately controlled CRSwNP despite systemic steroid or surgery us is to cycle through revision surgeries and overuse of steroids, with impacts on mental health and quality of life. There is no curative treatment for CRSwNP, which is a medical condition led by type-2 inflammation, and not a surgical condition, and none of the biologics developed in this indication are currently reimbursed in the UK. A proportion of severe CRSwNP patients continue to experience debilitating symptoms and poor HRQoL despite maximal available therapy (SCS & surgery which we have characterised as Established Clinical Management). These patients are at high risk of disease recurrence a long-term loss of QoL, as exemplified in the patient quote below:

'At 14, I was diagnosed with one of the most aggressive cases of nasal polyps my doctor had ever seen, leading to six surgeries and a myriad of treatments with steroids and various antibiotics over the course of ten years. Despite these efforts, I suffered constant inflammation, congestion, pressure headaches, migraines, and the loss of smell and taste.'

The sequelae of CRSwNP are driven by underlying chronic inflammation, and type 2 inflammation specifically is associated with a poorer prognosis. Type 2 inflammation (defined by blood EOS ≥ 300 cells/ μ L) can be targeted with dupilumab, and in two phase III studies, SINUS-24 and SINUS-52, dupilumab has been proven to be effective at statistically significant and clinically meaningful improvements in the co-primary endpoints of NPS and NC score at Week 24 compared to placebo. Improvements were observed at week 8 for NPS and week 4 for NC score. In SINUS-52, these results were maintained for a year. Rapid onset of symptom improvement and HRQoL were observed by week 2 for UPSIT, week 4 for TSS, self-reports LoS and SNOT-22. Specifically for SNOT-22 items, the greatest treatment effect relates to improvements in sense of smell/taste and nasal blockage.

There are currently over 1 million patients treated with dupilumab worldwide establishing a strong benefit-risk profile for dupilumab, validated by many clinical trials and further supported by real-world safety data across multiple indications.⁹³ No new safety signals have been identified in patients with CRSwNP. Dupilumab addresses the high unmet need for a targeted, systemic biologic treatment for people with uncontrolled CRSwNP following one (or more) surgeries.

The economic cost of CRSwNP is large, both societally and in terms of medical management (which includes surgery). Our health economic modelling has shown that dupilumab is a cost-effective treatment for uncontrolled CRSwNP with Type 2 inflammation as an add-on to ECM from the NHS perspective. In our base case, we have estimated that

the probabilistic ICER is £24,491 which is below the commonly accepted WTP threshold of £30,000. The ICER results were consistent when tested against a range of key model inputs and assumptions with very few incremental ICERs rising above £30,000/QALY in extreme scenarios.

Dupilumab is the first biologic which has demonstrated significant benefits both in terms of clinical signs and symptoms but also in QoL improvements and is a significant step-change in the effective treatment of uncontrolled CRSwNP with Type 2 inflammation. Dupilumab will provide meaningful benefits to a burdened patient population and has the potential to relieve pressure on the healthcare system through a reduction in in-patient wait times, the need for sinus surgery and burden in primary care.

A patient enrolled in the UK Compassionate Use Scheme told us:

“Within three days of my first dose, I could breathe more clearly than I had in over a decade, and by the end of the first week, all symptoms vanished. Four years later, I remain symptom-free, my sense of taste and smell fully restored, and I no longer need steroids.... Dupixent has truly been life-changing, succeeding where everything else had failed.”

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**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Single technology appraisal

**Dupilumab for treating chronic rhinosinusitis with nasal
polyposis [ID6480]**

Summary of Information for Patients (SIP)

File name	Version	Contains confidential information	Date
ID6480_Dupilumab_SIP_04022025_No CIC	Final	No	04/02/2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the National Health Service (NHS) for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article.

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: Dupilumab

Brand name: DUPIXENT®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Adults with uncontrolled chronic rhinosinusitis with nasal polyps (CRSwNP) following one (or more) surgeries.

Note that dupilumab treatment is not indicated for all people with CRSwNP, only those fulfilling the specific criteria described below.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Dupilumab was authorised as an add-on therapy with intranasal corticosteroids (INCS) for the treatment of adults with severe CRSwNP for whom therapy with systemic corticosteroids (SCS) and/or surgery do not provide adequate disease control by the United Kingdom (UK) regulator, the Medicines and Healthcare products Regulatory Agency (MHRA), on 01 January 2021.(1, 2)

In the UK, dupilumab has also been authorised by the MHRA for the following indications:(1, 2)

Atopic dermatitis (eczema)

Adults and adolescents: Dupixent is indicated for the treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy.

Children 6 months to 11 years of age: Dupixent is indicated for the treatment of severe atopic dermatitis in children 6 months to 11 years old who are candidates for systemic therapy.

Asthma

Adults and adolescents: Dupixent is indicated in adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with Type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled nitric oxide (FeNO), who are inadequately controlled with high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment.

Children 6 to 11 years of age: Dupixent is indicated in children 6 to 11 years old as add-on maintenance treatment for severe asthma with Type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with medium to high dose ICS plus another medicinal product for maintenance treatment.

Prurigo Nodularis (PN)

Dupixent is indicated for the treatment of adults with moderate to severe PN, who are candidates for systemic therapy.

Eosinophilic esophagitis (EoE)

Dupixent is indicated for the treatment of eosinophilic oesophagitis in adults and adolescents 12 years and older, weighing at least 40 kg, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy.

Chronic obstructive pulmonary disease (COPD)

Dupixent is indicated in adults as add-on maintenance treatment for uncontrolled chronic obstructive pulmonary disease (COPD) characterised by raised blood eosinophils on a combination of an inhaled corticosteroid (ICS), a long-acting beta2-agonist (LABA), and a long-acting muscarinic antagonist (LAMA), or on a combination of a LABA and a LAMA if ICS is not appropriate.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Transfers of value between Sanofi UK and the relevant organisations in the UK are outlined in [Table 1](#) below.

Table 1. Disclosure statements

Year	Organisation	Amount (GBP)	Disclosure Statement (including project title)
2022	Sinus UK	5,000.00	Sanofi UK made a financial contribution to support Sinus UK create patient education content. Sanofi had no editorial control or input in the development of content.
2023	Sinus UK	1,456.00	Sanofi has paid a consultancy fee + travel + accommodation for the Sinus UK CEO to attend a patient organisation advisory board on CRSwNP
2024	Sinus UK	16.00	Sanofi has engaged Sinus UK on a zero-fee basis to attend a roundtable on improving patient access to innovative medicines (only travel costs were covered)
2024	Sinus UK	1,805.00	Sanofi has paid a fee for service for Sinus UK to attend their 2024 nasal polyps advisory board
2024	Sinus UK	15,720.00	Sanofi has engaged Sinus UK to arrange 2 roundtables to gather testimonials from participants on living with nasal polyps (partial payment up-front of £7,500 in 2024)
2021	Fifth Sense	2,500.00	Sanofi Genzyme provided financial support to Fifth Sense to help cover meeting costs for its annual conference but had no input in to the agenda or content of the meeting
2022	Fifth Sense	3,000.00	Sanofi UK provided a financial contribution to support Fifth Sense's Volunteer Forum. Sanofi had no input or editorial control in the meeting arrangement or materials used.
2023	Fifth Sense	457.00	Sanofi has approved use of surplus sponsorship from 2021 Fifth Sense conference for use in support of the delivery of their 2023 conference.
2024	Fifth Sense	80.00	Sanofi has engaged Fifth Sense on a zero-fee basis to attend an above-brand roundtable on improving patient access to innovative medicines (only travel costs were covered)

CEO = chief executive officer; CRSwNP = chronic rhinosinusitis with nasal polyps; GBP = British pound sterling; UK = United Kingdom

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

What is CRSwNP?

CRSwNP is a long-term condition affecting the spaces inside the nose and head (sinuses).(3, 4) In people with CRSwNP, the sinuses become inflamed and their lining becomes swollen, forming soft growths inside the nose called nasal polyps.(4, 5) CRSwNP interferes with the way mucus normally drains and may cause troublesome symptoms, including loss of smell and taste, blocked nose (nasal congestion/obstruction), difficulties breathing, runny nose (rhinorrhoea), facial pain/pressure, fatigue, trouble sleeping, infections, hearing issues and mucus running down the throat (post nasal drip).(6-9) These symptoms, especially blocked/runny nose and sleep disturbances, have a significant negative impact on the patients by preventing them from carrying out their daily activities as normal.(9-12)

What causes CRSwNP?

CRSwNP is caused by type 2 inflammation.(4, 6, 13, 14) This inflammation increases immune cells in the sinuses and nasal cavity, leading to tissue damage, excess mucus, and nasal polyp formation.(4, 6) It can also lead to chronic upper airway infections.(4, 6)

How many people are living with CRSwNP in England?

In 2026 (anticipated first full year of patient access to dupilumab for CRSwNP), it is expected that 225,991 adults will be living with CRSwNP in England.(15, 16) Of these, approximately 29,232 will have uncontrolled disease after one (or more) surgeries and are expected to be eligible for treatment with dupilumab.(15, 17)

What is the impact of CRSwNP on a person's quality of life?

The impact of CRSwNP on a person's quality of life is understood to be comparable to that associated with other serious chronic diseases, such as migraine and epilepsy.(18) CRSwNP affects several aspects of people's life, including sleep, mood and daily activities.(10-12) Sinonasal congestion and/or obstruction, loss of smell and taste and difficulties sleeping are the symptoms with the biggest impact on the quality of life of people with severe CRSwNP.(7, 11, 12) The disease also has a negative impact on people's mental health, and people with CRSwNP are at greater risk of conditions such as anxiety and depression.(19)

For example, a study of 445 people with CRSwNP carried out across Europe, found that people with CRSwNP had worse general health, mental health, vitality, and physical, emotional and social functioning compared with the general population of a similar age.(10) Similarly, one patient with CRSwNP interviewed in the UK said that CRSwNP *'can be a bit depressing because it's relentless. There's no escape from it. It gets you down, combine that with tiredness and it does get a bit depressing after a while.'*(9)

CRSwNP also affects the ability to work. A survey in the Netherlands found that people with CRSwNP reported a mean of 10.6 missed days of work per year, and 34.9% of people reported reduced effectiveness when at work.(20)

As CRSwNP is caused by type 2 inflammation, people with CRSwNP often have other existing clinical conditions caused by type 2 inflammation, such as asthma, nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (NSAID-ERD) and inhalant allergy.(15, 19, 21-25) A study with data from five clinical trials (1,748 participants in total) reported that 56.0% to 71.0% of people with CRSwNP have comorbid asthma.(26)

Sanofi interviewed 11 people living with CRSwNP in the UK in 2024 to understand their experience of the condition.(9) Participants reported feelings of anxiety and embarrassment from having a blocked but runny nose, which impact hugely on every aspect of their life.(9) People interviewed explained that the constant need to blow their nose and changes in their voice were causing them to avoid social situations and public speaking.(9) One patient said *'I lost confidence in social situations. I started to avoid some social situations because I felt like I sounded strange when I spoke.'*(9)

These interviews with people with CRSwNP also found that loss of smell and taste had an important negative impact on the people's quality of life: *'The hardest thing is the no smell and no taste. You adjust to it, and you live with it, but that's the thing I miss most, smelling and tasting food.'*(9)

What is the economic cost of CRSwNP to patients and the NHS?

CRSwNP is associated with high indirect costs, causing patients to both take time off work and to be less productive at work, as well as considerable costs to themselves and to the NHS.(4, 20, 23, 27) Surgery is the main driver of medical costs among people with CRSwNP who undergo sinus surgery (see Sections 2c for additional information about treatments).(23) In a study of 101,054 people with CRSwNP who underwent sinus surgery in England, the total cost of sinus surgery from 2010 to 2020 was £174 million, of which £66.7 million was due to revision surgeries.(23)

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

The clinician will initially assess symptoms and history. They will ask if the person experiences persistent nasal blockage (obstruction/congestion), runny nose (rhinorrhoea), facial pain/pressure and/or reduction/loss of smell.(4)

To confirm if a person has CRSwNP, the clinician will ask them to undergo imaging tests, including a nasal endoscopy and/or computed tomography (CT) scan.(4) During an endoscopy, a small camera is passed through the nose to look at the nasal cavity and sinuses.(28) A CT scan provides detailed pictures of the inside of the nose and

sinuses.(29) If endoscopy shows that the person has nasal polyps and/or the CT scan shows changes to the lining of the sinuses/nasal cavity, the clinician may diagnose CRSwNP.(4)

For people with a confirmed CRSwNP diagnosis, dupilumab is only indicated for those fulfilling specific additional criteria as outlined in the licence.(1, 2) The licence states that:(1, 2)

'Dupilumab is licenced in the UK as an add-on therapy with intranasal corticosteroids (INCS) for the treatment of adults with severe CRSwNP for whom therapy with systemic corticosteroids (SCS) and/or surgery do not provide adequate disease control.'

Disease control is defined via a Visual Analogue Scale (VAS), where the severity of symptoms is ranked from 0 (best) to 10 (worst).(4) Partially or uncontrolled CRSwNP corresponds to symptoms of blocked nose, runny nose, facial pain/pressure, reduced smell and sleep disturbance of severity >5, in addition to nasal endoscopy findings and the need for rescue medication (surgery and/or steroid tablets [SCS]).(4)

2c) Current treatment options

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
 - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
 - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Guidance on the management of CRSwNP in England is based on recommendations from the European Rhinologic Society in the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020,(30) and supported by recommendations from the British Rhinological Society (BRS) and European Forum for Research and Education in Allergy and Airway Disease (EUFOREA).(4, 11, 31, 32)

The EPOS 2020 guideline recommendations are presented in Similarly. BRS experts recommend biologics to be considered for people with CRSwNP based on disease severity, impact on quality of life, need for steroids, number of prior surgeries and comorbidities.(31)

Figure 1. The treatment pathway for CRSwNP includes multiple steps and steroid nasal sprays (INCS) are recommended at each one.(32)

- As a first step, patients are generally prescribed saline rinses and steroid nasal spray.(32)

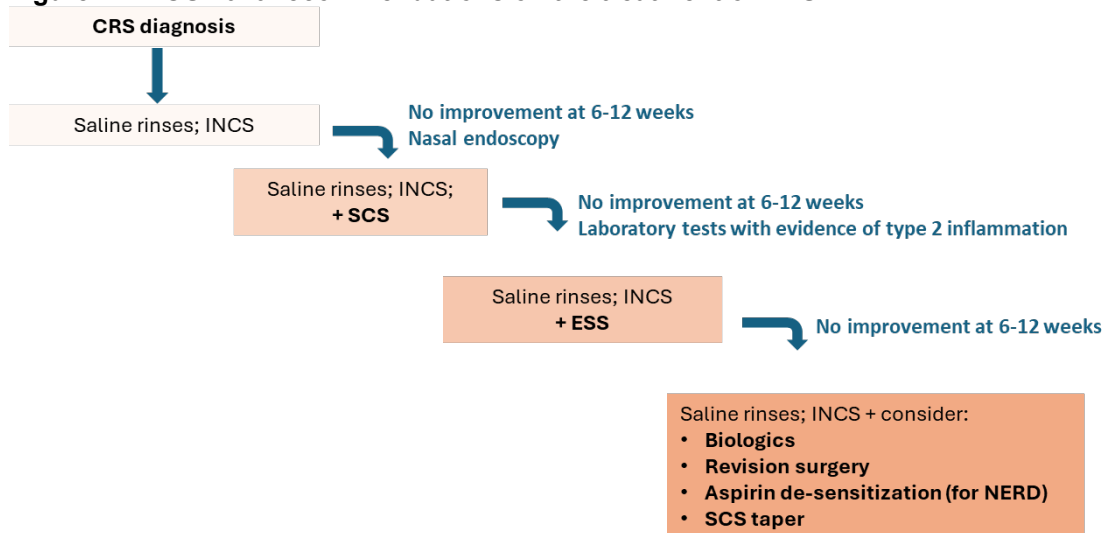
- If symptoms do not improve after 6 to 12 weeks of treatment with saline rinses and steroid nasal spray, short-term treatment (defined as less than 3 weeks) with steroid tablets (SCS) may be considered for relieving acute increase in symptom severity.(32, 33)
- Surgery (endoscopic sinonasal surgery [ESS]) is recommended for people with uncontrolled CRSwNP whose symptoms do not improve after 6 to 12 weeks of treatment with saline rinse and steroid tablets.(4)
- For people with no improvement at 6 to 12 weeks following treatment with saline rinse, steroids and surgery, and who have evidence of type 2 inflammation, EPOS recommend either revision surgery, or a treatment with a biologic (medicine derived from living organisms [e.g., proteins, cells, or tissues]).(4)

Specifically, EPOS and EUFOREA guidance recommend biologic therapy to be offered to people with uncontrolled CRSwNP who have received one surgery (or are ineligible for surgery) and meet at least 3 of the following 5 criteria:(11, 32)

- Evidence of type 2 inflammation
- Need for or contraindication to steroid tablets
- Significantly impaired quality of life
- Significant loss of smell
- Comorbid asthma.

Similarly, BRS experts recommend biologics to be considered for people with CRSwNP based on disease severity, impact on quality of life, need for steroids, number of prior surgeries and comorbidities.(31)

Figure 1. EPOS 2020 recommendations on the treatment of CRSwNP



CRS = chronic rhinosinusitis; CRSwNP = chronic rhinosinusitis with nasal polyps; EPOS = European Position; ESS = endoscopic sinonasal surgery; INCS = intranasal corticosteroid; NERD = NSAID-exacerbated respiratory disease; NSAID = non-steroidal anti-inflammatory drug; SCS = systemic corticosteroid
Sources: Generated based on current clinical guidance in Fokkens et al., 2020(4) and Hellings et al., 2024(32)

However, there are currently no biologic therapies licensed for the treatment of people with CRSwNP in England and available to patients through the NHS.
Currently established treatments for people with uncontrolled CRSwNP include steroid nasal sprays with saline rinses, steroid tablets (for acute increase in symptom severity)

and surgery (for people whose symptoms do not improve despite treatment with saline rinse and steroids).(4, 32)

The established treatments for people with CRSwNP have several limitations, including limited clinical benefit that is temporary.(34) Additionally, there are risks of severe adverse events (AEs) and complications:

- AEs associated with steroid tablets use include osteoporosis (weakened bones), hypertension, pneumonia, heart failure, heart attack, cataracts and glaucoma.(32, 35)
- Complications associated with surgery include bleeding during surgery, post-surgery infection, haemorrhage and orbital/intracranial complications.(34, 36) For people requiring revision surgery, the risk of complications increases with each subsequent surgery.(15, 37)
- Surgery may not be appropriate for all people with CRSwNP and is contraindicated in those with severe uncontrolled asthma due to the risks associated with anaesthesia.(32)

NHS waiting lists for sinonasal surgery (50% of which are revision surgeries) range from 6 months to up to 3 years following specialist referral, and represent another important limitation of surgery.(34) Waiting lists negatively impact people with uncontrolled CRSwNP who, as a result of persistent type 2 inflammation, experience significant and detrimental worsening of their disease and prolonged use of steroid tablets, therefore establishing suboptimal steroids stewardship principles.(34) Steroids stewardship aims to limit the use of steroids to reduce the risk of AEs.(34)

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Sanofi UK interviewed 11 people living with CRSwNP in the UK in 2024 to understand their experience with the disease.(9) All the people interviewed had uncontrolled disease and had undergone at least one surgery for nasal polyps.(9) The interviews reinforced that CRSwNP is a condition characterised by despair for the patient.(9)

People with CRSwNP reported that blocked nose, trouble sleeping and loss of smell and taste hugely impacts every aspect of their life.(9) Patients change their lifestyle and avoid social situations due to the constant need to blow their nose and changes in their voice, which make them embarrassed and anxious.(9) Several people mentioned that their blocked nose would sometimes cause them panic attacks at night.(9) One patient said *'I was almost having panic attacks at night because of drifting off to sleep and instinctively trying to breathe through my nose and remembering that I couldn't.'*(9) Because of sleep

disturbances, people with CRSwNP also feel tired and are unable to continue with their normal daily activities, including work.(9)

People reported that CRSwNP was also a problem for their family:(9)

- *'It doesn't just affect me. It affects my family as well.'*
- *'My wife and I have not been in the same bedroom for a good number of years now because of the snoring.'*

During the interviews, people described CRSwNP as relentless with no durable escape possible;(9) they find that the available treatments (steroids and surgery) only provide benefits for a few months at a time.(9) People with CRSwNP feel stuck in a circle of repeated surgeries and periods of steroid treatment, where little can be done to improve their quality of life.(9) Surgery was a very negative experience for some people and they would like another effective treatment option to be available.(9) People with CRSwNP said:(9)

- *'My body went into shock over it [surgery]. I mean, the pain was horrific. It was just the most horrific experience'.*
- *'I just wish there was an alternative to surgery. If anything, I'd rather not have surgery again, to be honest with you.'*

SECTION 3: The treatment

3a) How does the new treatment work? What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a Summary of Product Characteristics or patient information leaflet, please provide a link to these.

As described in Section 2a, CRSwNP is caused by long-term inflammation known as type 2 inflammation.(4, 6, 13, 14) A study in the UK involving 33,107 people with CRSwNP found that those needing multiple surgeries for nasal polyps had high levels of certain immune cells called eosinophils, which are linked to type 2 inflammation.(15)

Dupilumab

Dupilumab is a special type of medicine called a monoclonal antibody.(1, 2) It works by blocking 2 proteins, interleukin (IL)-4 and IL-13, which are involved in type 2 inflammation.(1, 2) By blocking these proteins, dupilumab reduces type 2 inflammation and prevents damage to the sinuses and nasal cavity.(1, 2)

Dupilumab is a unique treatment for CRSwNP because it specifically targets IL-4 and IL-13, which play a major role in type 2 inflammation.(1, 2) This makes it particularly effective for people with uncontrolled CRSwNP who have not responded well to steroids and/or surgery. Other treatments for people with uncontrolled CRSwNP, such as mepolizumab and omalizumab, target different proteins (IL-5 and immunoglobulin E

[IgE], respectively) that are also involved in type 2 inflammation but play smaller roles compared to IL-4 and IL-13.(38-40)

Safety and Monitoring

One of the advantages of dupilumab is that it can be prescribed without needing routine monitoring beyond what is normally done for people with CRSwNP.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

☒ Yes

☐ No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

It is anticipated that dupilumab will be used as add-on therapy with INCS for the treatment of adults with uncontrolled CRSwNP following one (or more) surgeries.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Dupilumab is intended to be prescribed at all UK specialised centres. These centres currently prescribe dupilumab for conditions like severe asthma and moderate to severe atopic dermatitis (eczema).

The recommended dose of dupilumab for adults with CRSwNP is 300 mg given every other week (once every 2 weeks).(1, 2) Dupilumab can be self-administered or administered by a carer or healthcare professional.(1, 2) It is administered by subcutaneous injection (into the layer of fatty tissue immediately under the skin) in the thigh or abdomen, except for 5 cm around the navel (belly button), using a single-use pre-filled syringe or pen.(1, 2) If the injection is being administered by somebody else, the upper arm can also be used.(1, 2)

Current treatments for people with CRSwNP are nasal sprays (saline rinses, steroids) or tablets (steroids) to be taken daily, so one of the advantages of dupilumab is that it is not given every day but only once every 2 weeks.(1, 2)

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The clinical efficacy and safety of dupilumab for the treatment of CRSwNP has been studied in two phase 3 randomised clinical trials, LIBERTY NP SINUS-24 (i.e., SINUS-24; [NCT02912468](#)) and LIBERTY NP SINUS-52 (i.e., SINUS-52; [NCT02898454](#)).

People enrolled in the SINUS-24 and SINUS-52 trials were adults with severe CRSwNP (signs of nasal polyps on nasal endoscopy that persisted despite prior treatment with SCS in the past 2 years [and/or had a contraindication/intolerance to SCS] and/or prior surgery for nasal polyps), who had:(41)

- Evidence of medium or large size polyps in each nasal cavity on nasal endoscopy
- Ongoing symptoms of blocked nose (nasal congestion/obstruction), and either decreased/loss of smell or runny nose (rhinorrhoea).

SINUS-24 and SINUS-52 primarily looked at how adding dupilumab to background therapy with INCS reduced people's nasal polyps size and nasal blockage over 24 weeks, compared to the nasal polyps size and nasal blockage of people who had been randomly allocated to receive placebo in addition to background therapy.(41)

Both SINUS-24 and SINUS-52 were phase 3, placebo-controlled, double blind, randomised trials.(41) Double blinding means that both the people enrolled in the trial and the healthcare professionals involved do not know which people have been randomised to receive either dupilumab or placebo.(42) The placebo acts as a basis for comparing the effect of the medicine being studied, which is otherwise known as a control.(42)

There were differences between the SINUS-24 and SINUS-52 trials, including study duration (24 weeks in SINUS-24 and 52 weeks in SINUS-52) and the number of dupilumab treatment groups (one group in SINUS-24 and two groups in SINUS-52 with a different dosing to SINUS-24 in one of the groups).(41)

- **SINUS-24(41, 43)** – Completed in July 2018
 - The SINUS-24 trial lasted for 24 weeks.
 - The trial was conducted in 79 sites across 13 countries worldwide, including the UK. SINUS-24 enrolled 19 people from 6 sites in the UK.
 - A total of 276 people with CRSwNP were enrolled and randomised to receive dupilumab (143 people) or placebo (133 people), with continued background therapy with INCS.

- **SINUS-52(41, 43)** – Completed in November 2018
 - The SINUS-52 trial lasted for 52 weeks.
 - The trial was conducted in 119 sites across 14 countries worldwide.
 - A total of 448 people with CRSwNP were enrolled and randomised to receive dupilumab (once every 2 weeks: 150 people; once every 4 weeks: 145 people) or placebo (153 people), with continued background therapy with INCS.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a.

- Are any of the outcomes more important to patients than others and why?
- Are there any limitations to the data which may affect how to interpret the results?

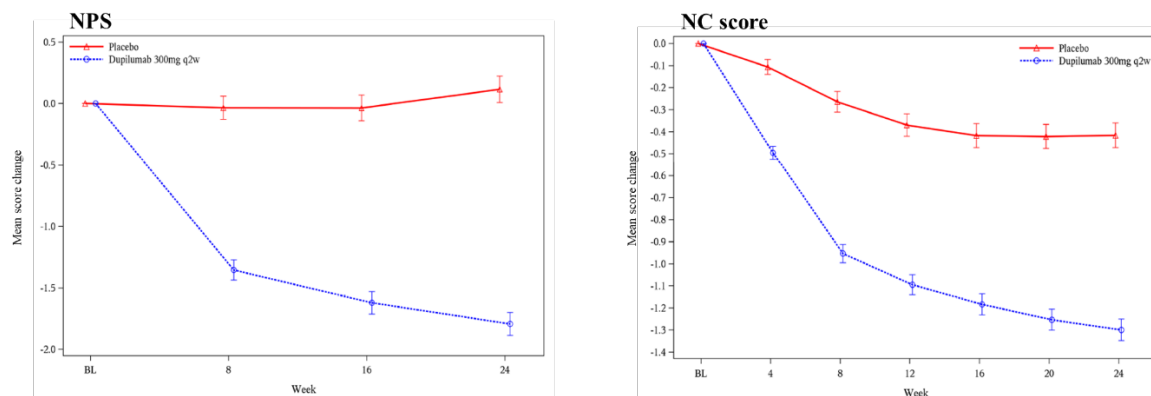
Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

In both the SINUS-24 and SINUS-52 trials, the primary endpoints (the main things that the trials were designed to measure) were nasal polyps size and nasal blockage.(41) Treatment with dupilumab significantly reduced the size of nasal polyps and nasal blockage compared to placebo in the trial participants.(41) These statistically significant improvements were measured in terms of Nasal Polyp Score (NPS) and Nasal Congestion (NC) score,(41) as follows:(43, 44)

- The NPS, which is based on the sum of the right and left nostril scores (total score from 0 to 8, with a score from 0 to 4 per nostril and higher values indicating larger polyps), was determined by physicians from video recordings of nasal endoscopy.
- The NC score was recorded every morning by the participants based on symptom severity over the past 24 hours, from 0 (no symptoms) to 3 (severe symptoms).

In both SINUS-24 and SINUS-52, NPS and NC score rapidly improved starting from 4 weeks and improved continuously throughout 24 weeks ([Figure 2](#)). (41) In SINUS-52, significant improvements in NPS and NC score were maintained at 52 weeks in participants treated with dupilumab once every 2 weeks compared to placebo.(41)

Figure 2. Change from baseline over time in nasal polyp score (NPS) and nasal congestion/obstruction (NC) score in the pooled population of SINUS-24 and SINUS-52



NC = nasal congestion/obstruction; NPS = nasal polyp score; Q2W = once every two weeks
Sources: Sanofi. Data on File, Summary of Clinical Efficacy.(45)

As planned before the start of the trials, data collected in both SINUS-24 and SINUS-52 were combined for the testing of certain endpoints.(41) This was called the “pooled analysis” and people in the dupilumab arms of both trials were combined into one group, and people in the placebo arms of both trials were combined into another group.(41) In this pooled analysis, dupilumab reduced the proportion of participants who required rescue treatment with SCS or sinonasal surgery during the trials by 76% compared to placebo (73.9% for SCS and 82.6% for sinonasal surgery, individually), which was a statistically significant difference.(41)

In people with comorbid asthma, dupilumab led to greater lung function improvements (as measured by forced expiratory volume in 1 second [FEV₁] and Asthma Control Questionnaire 6 [ACQ-6]) compared to placebo at 24 weeks.(41) The FEV₁ is a spirometry test, which measures the volume of air that can be breathed out in the first second of forced exhalation.(43, 44) At 24 weeks, dupilumab improved FEV₁ by 0.21 L compared to placebo.(41) The ACQ-6 is a questionnaire assessing the most common asthma symptoms on a 7-point scale (0 = no impairment to 6 = maximum impairment), with the ACQ-6 score being the mean of the scores for all 6 symptoms.(43, 44) The ACQ-6 was completed weekly by participants.(43, 44) At 24 weeks, dupilumab improved the ACQ-6 score by 0.82 point compared to placebo.(41)

This shows that dupilumab has an impact on nasal polyps, nasal blockage and disease control (reduced need for SCS and/or sinonasal surgery) in people with uncontrolled CRSwNP, as well as lung function in those with uncontrolled CRSwNP and comorbid asthma.(41)

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQoL-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease-specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as patient reported outcomes (PROs).

Please include any patient preference information (PPI) relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Quality of life

In the SINUS-24 and SINUS-52 trials, researchers measured the participants' quality of life using a survey called the 22-item Sinonasal Outcomes Test (SNOT-22).(43, 44) This survey has 22 questions, each scored from 0 (no problem) to 5 (worst problem).(43, 44) The highest possible score is 110, indicating the worst quality of life.(43, 44) To show a meaningful improvement, a treatment needs to reduce the score by at least 8.9 point (the "minimum clinically important difference").(43, 44) In both trials, participants filled out this survey every 2 weeks.(41, 43, 44)

- SINUS-24 trial: dupilumab improved quality of life early (from 8 weeks) and continued to do so up to 24 weeks compared to placebo. At 24 weeks, dupilumab reduced the SNOT-22 total score by 21.12 points compared to placebo.
- SINUS-52 trial: dupilumab also showed early (from 4 weeks) and sustained quality of life benefit at 24 weeks compared to placebo. At 24 weeks, the SNOT-22 total score was 17.36 points lower for dupilumab compared to placebo.(41) These benefits lasted up to 1 year, with a 20.96-point improvement at 1 year.

When combining results from both trials ("pooled analysis"), more people on dupilumab saw a meaningful improvement in their quality of life compared to those on placebo.(46) At 24 weeks, 75.1% of people on dupilumab had an improvement of 8.9 points or more in SNOT-22 total score, compared to 43.4% of people on placebo.(46)

Researchers also used another survey called the EuroQol-5D (EQ-5D) VAS, where participants rated their health from 0 (worst) to 100 (best).(43, 44) A meaningful improvement in the EQ-5D VAS is 8 points or more.(43, 44, 46) At 24 weeks, 46.8% of people on dupilumab saw this improvement compared to 25.9% of people on placebo.(46) While participants had lower health scores compared to the general population at the start of the trials, those on dupilumab reached health scores similar to the general population at 24 weeks.(46)

Sleep

The SNOT-22 survey includes questions about sleep, such as "difficulty falling asleep," "wake up at night," "lack of a good night's sleep," and "wake up tired."(43, 44, 47) During the trials, participants rated their sleep every 2 weeks from 0 (no problem) to 5 (worst problem).(43, 44, 47)

Dupilumab improved sleep early (from 8 weeks) and continued to do so up to 52 weeks compared to placebo.(47) The sleep score improved by 0.97 points at 24 weeks in SINUS-24 compared to placebo and continued to improve through 52 weeks in the SINUS-52 trial (by 0.93 points compared to placebo).(47)

Loss of smell

In both trials, participants rated their sense of smell daily using the Loss of sense of Smell (LoS) scale, from 0 (no symptoms) to 3 (severe symptoms).(43, 44) Based on data from the trials, it was estimated that a meaningful improvement in the LoS is 1 point or more.(48) In both trials, dupilumab led to early (from 4 weeks) and sustained meaningful improvements in the sense of smell at 24 weeks compared to placebo.(41) The LoS score

improved by 1.12 points in SINUS-24 and 0.98 points in SINUS-52 compared to placebo.(41)

Patient preference

In a survey of 75 people with CRSwNP who had undergone at least one surgery and were receiving dupilumab, 91.5% of patients preferred taking dupilumab over having another surgery.(49) Similarly, a patient currently treated with dupilumab for CRSwNP through the Compassionate Use Scheme in the UK, reported a preference for dupilumab over the treatments previously received:(50)

'Within three days of my first dose, I could breathe more clearly than I had in over a decade, and by the end of the first week, all symptoms vanished. Four years later, I remain symptom-free, my sense of taste and smell fully restored. [...] Dupixent has truly been life-changing, succeeding where everything else had failed.'

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Dupilumab is an established treatment for multiple diseases and has been used in England since 2018. Over 1 million people have been treated with dupilumab across multiple licenced indications worldwide.(51)

In SINUS-24 and SINUS-52, dupilumab demonstrated a favourable risk/benefit ratio and tolerability profile in adults with severe CRSwNP (uncontrolled despite prior treatment with SCS and/or prior sinonasal surgery for nasal polyps).(41)

Treatment-emergent adverse events (TEAEs) are safety events recorded in clinical trials that arise during the course of treatment. They may or may not be associated with, or caused by, the treatment (i.e., either dupilumab add-on to background therapy, or placebo add-on to background therapy).

Data from the pooled analysis showed that:(41, 52)

- The proportion of participants with TEAEs was lower with dupilumab (69.3%) compared to placebo (73.8%).
- The most common TEAEs in the dupilumab group were common cold (nasopharyngitis) (12.5%), headache (7.3%) and redness (erythema) at the injection-site (6.4%).
- The most common TEAEs in the placebo group were common cold (nasopharyngitis) (14.5%), worsening of nasal polyps (11.7%) and headache (8.5%).

- Treatment-emergent serious adverse events (SAEs) were reported in 3.9% of participants in the dupilumab group and 6.4% of participants in the placebo group.
- 2.5% of participants receiving dupilumab had to stop treatment due to a TEAE, compared to 5.3% of participants receiving placebo.

As dupilumab is already approved and used for several other conditions (e.g., atopic dermatitis, asthma and chronic rhinosinusitis with nasal polyps), its safety profile is well understood and has been established in several other randomised clinical trials including over 15,000 participants.(53)

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration.

There are currently no therapies targeting type 2 inflammation that are recommended and reimbursed for people with severe CRSwNP in England. Dupilumab has an established safety profile and is the first therapy for uncontrolled CRSwNP that specifically targets IL-4 and IL-13 in the inflammatory pathway, thereby reducing type 2 inflammation and the resulting damage to the sinuses and nasal cavity.(1, 2, 41)

In SINUS-24 and SINUS-52, people treated with dupilumab had reduced nasal polyp size, nasal blockage, loss of smell and need for SCS and/or surgery, less severe symptoms and better quality of life compared to those receiving placebo (see Sections 3d to 3g for additional information about the clinical efficacy and safety outcomes).(41) Dupilumab also demonstrated a favourable safety and tolerability profile, in people with severe CRSwNP and other diseases.(53) In a real-world study of people receiving dupilumab as prescribed by their doctor for the treatment of CRSwNP, the safety and quality of life benefit of dupilumab lasted for 2 years.(54, 55)

The proportion of patients who needed rescue treatment with SCS and/or sinonasal surgery during the SINUS-24 and SINUS-52 trials was reduced with dupilumab, which has the potential to reduce the burden of managing the long-term condition encountered by people with severe CRSwNP in attending multiple appointments for monitoring and for revision surgeries.(34, 41)

Improvements in symptoms and quality of life, especially reduction/loss of smell and sleep, may allow people with uncontrolled CRSwNP to improve their overall wellbeing and to avoid any loss of income due to their disease.(20, 41, 47)

People can self-administer dupilumab (or have a caregiver help with administration) through a simple injection every other week.(1, 2) No additional tests or monitoring beyond those already recommended for people with uncontrolled CRSwNP are required.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

People with CRSwNP may need to travel to their nearest secondary care centre for their first consultation with a specialist to access dupilumab add-on therapy, which may be a challenge for some people (see Section 3i). Dupilumab is self-administered via subcutaneous injection into the thigh or abdomen, except for 5 cm around the navel (belly button), using a single-use pre-filled syringe or pen.(1, 2) Administration via injection may be unpleasant to people who experience a fear of needles or prefer other modes of administration, such as oral pills or inhalation.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Sanofi has submitted a health economic model for evaluation by NICE. The following sections describe how the model was structured and how it attempts to reflect the progression of CRSwNP over time. The goal of the economic modelling is to quantify the differences in outcomes and costs between using dupilumab or established clinical management (ECM). These differences are combined and used by NICE to determine whether dupilumab is cost-effective or not.

How the model reflects the condition

The model starts with a close description of the SINUS-24 and SINUS-52 clinical trials by using a "decision tree", in which people with CRSwNP are allocated to dupilumab plus

ECM or ECM alone. This is a common way of modelling a clinical trial period. At the end of the decision tree, outcomes for the people taking dupilumab are assessed and, if they do not experience a significant improvement of their symptoms (assessed via the NPS [an endoscopic score to measure nasal polyp size] and the SNOT-22 score [a survey to measure quality of life]), their treatment is stopped in the model and they revert back to what they were taking before. This rule is put in place in the model to reflect what may happen in reality to ensure that the NHS does not continue to spend money and resources on treating people who would not benefit.

After the decision tree, people then move to the longer-term part of the model that uses the clinical trial results to predict the difference between what would happen if people were treated with dupilumab plus ECM compared to what would happen if they only received ECM. During this part of the model, the impact of dupilumab treatment on the need for sinonasal surgery is considered as well as how treatment influences disease control and quality of life over time.

Modelling how much a treatment extends life

As people with CRSwNP do not experience an increase in mortality compared to the general population. There is no evidence to suggest that treatment with dupilumab in people with CRSwNP extends life.

Modelling how much a treatment improves quality of life

People with less controlled CRSwNP have worse quality of life. Quality of life was measured during the clinical trials using the SNOT-22 (as described in Section 3f), and SNOT-22 data are used in the model to assess differences in outcomes for people treated with dupilumab + ECM and those treated with ECM only. To do this, the model assigns different quality of life outcomes to each level of disease control (controlled on medication, inadequately controlled, post-operative controlled or uncontrolled disease).

The clinical trials showed that CRSwNP remains controlled for longer whilst taking dupilumab, and so people treated with dupilumab experience better quality of life in the model than people treated with ECM alone. This difference is used to show the benefit of dupilumab over ECM.

Modelling how the costs of treatment differ with dupilumab

The model also compares the cost of treating people with dupilumab plus ECM to ECM alone. It calculates the differences in the cost of the medicines and the cost of NHS services used for the management of CRSwNP, such as general practitioner (GP) appointments or hospital stays.

As would be expected, dupilumab plus ECM is more expensive than ECM alone, as people are receiving two treatments rather than one. However, the cost of CRSwNP on patients and the NHS is substantial (Section 2a), and dupilumab has the potential to reduce these costs by preventing many of the events that occur due to uncontrolled symptoms/disease, revision surgeries and poor quality of life. This is because treatment with dupilumab leads to:

- Reduced symptoms and better quality of life (Section 3f).(41, 47) This could enable people with uncontrolled CRSwNP to avoid any loss of income if they would have

otherwise needed to reduce their working hours or to stop working due to their disease.(9)

- Significantly improved disease control and quality of life, as measured by the NPS and SNOT-22 scores (Section 3e).(41) People with controlled CRSwNP have fewer GP visits, outpatient visits and hospital admissions, and use their rescue medication less (e.g., steroid tablets and surgery). By improving symptoms and reducing nasal polyp size, dupilumab has the potential to reduce the burden of CRSwNP on the NHS, as well as the associated costs.
- Significantly improved lung function in people with uncontrolled CRSwNP and comorbid asthma, which has the potential to reduce the burden of asthma on the NHS, as well as the associated costs.(41)
- Sanofi UK heard from a group of UK clinicians with experience in treating CRSwNP. The clinicians confirmed that dupilumab could reduce the number of times people with uncontrolled CRSwNP have to undergo revision nasal polyp surgery in comparison to the current situation where there is no reimbursed targeted treatment for people with severe CRSwNP in the UK.(34)
- The reduced frequency of revision nasal polyp surgery for people living with uncontrolled CRSwNP that dupilumab treatment represents would reduce the burden for both the person living with CRSwNP (taking time away from work, educational or social activities for pre-surgery appointments, surgery and post-surgery recovery); and also reduce the burden on the healthcare system, freeing up capacity (note that waiting lists are currently up to 3 years) by reducing the number of people requiring nasal polyp surgery.(34)

Dupilumab is self-administered every other week (once every 2 weeks) via a pre-filled syringe or pen, and has a favourable risk/benefit ratio.(1, 2) No tests are required to prescribe dupilumab beyond what is required for routine CRSwNP diagnosis and monitoring.

Uncertainty

Challenges associated with modelling the course of severe CRSwNP and the long-term impact of treatment with dupilumab have the potential to create uncertainty in model outputs. Specifically, these challenges include:

- Insufficient published evidence on post-operative disease recurrence and revision surgeries
- Insufficient published evidence on the utilisation of healthcare resources based on the UK population
- Insufficient published evidence on the long-term impact of steroids overuse in the UK
- The variability of long-term outcomes following surgery.

Additional factors

Some health benefits of dupilumab could not be considered in the health economic model. These additional health benefits of dupilumab include:

- Reducing the pressure on NHS resources during cold weather months by reducing symptoms and the need for revision surgeries in people with CRSwNP, who are especially vulnerable during such time periods
- Reducing the severity of respiratory symptoms in people with CRSwNP
- Reducing the environmental impact of CRSwNP by reducing the number of doctor visits, hospitalisations and revision surgeries that people with CRSwNP need.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see Section 3f)

As the first and only licensed therapy which targets the underlying IL-4/IL-13 signalling pathway that is involved in type 2 inflammation in CRSwNP,(1, 2) dupilumab has demonstrated improvements in clinical outcomes and quality of life compared to INCS alone for people with severe CRSwNP (uncontrolled despite prior treatment with SCS and/or prior sinonasal surgery for nasal polyps).(41)

Other biologics licensed for the treatment of CRSwNP work in a different way to dupilumab and are not currently available to patients through the NHS. The treatments used routinely for people with severe CRSwNP, including steroid nasal sprays, steroid tablets and surgery, are not designed for CRSwNP specifically, are associated with significant safety concerns, and/or provide only temporary and limited clinical benefit.(15, 32, 34, 36, 37, 56)

The pivotal SINUS-24 and SINUS-52 clinical trials have shown that the use of dupilumab as an add-on to background therapy with INCS addresses the current unmet need for a targeted, effective and well-tolerated treatment that can address type 2 inflammation, reduce the burden of loss of smell and sinonasal blockage (congestion/obstruction), and improve quality of life in people with uncontrolled CRSwNP.(41)

Dupilumab provides people with CRSwNP and clinicians with a treatment option that has demonstrated efficacy and a well-established and favourable safety profile.(41) Please see Sections 3d to 3g for additional information about the clinical efficacy and safety outcomes.(41)

3I) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues here

The current lack of licenced, reimbursed, effective and targeted treatments with favourable safety profiles places people with uncontrolled CRSwNP at a significant disadvantage compared to people with other forms of chronic type 2 inflammatory conditions, such as asthma and PN, for whom targeted biologic therapies are already reimbursed.(1, 2, 57, 58) Thus, a NICE recommendation for dupilumab in uncontrolled CRSwNP would have a positive impact on people with uncontrolled CRSwNP.

Additionally, depending on where they live, people with uncontrolled CRSwNP are currently expected to be on a waiting list for nasal polyp surgery for 6 months to up to 3 years, and about half of these people are waiting for revision surgery.(34) Based on the evidence presented here, adding dupilumab to the treatment options for uncontrolled CRSwNP is expected to reduce the number of people who require revision surgery, freeing up capacity and potentially reducing NHS wait times.(34)

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.

Where possible, please provide open-access materials or provide copies that patients can access.

- **SINUS-24:** A Controlled Clinical Study of Dupilumab in Patients With Bilateral Nasal Polyps (SINUS-24). Available at: <https://clinicaltrials.gov/study/NCT02912468>
- **SINUS-52:** Controlled Clinical Study of Dupilumab in Patients With Nasal Polyps (SINUS-52). Available at: <https://clinicaltrials.gov/study/NCT02898454>
- **SINUS-24 and SINUS-52 publication:** Bachert C, Han JK, Desrosiers M, Hellings PW, Amin N, Lee SE, Mullol J, Greos LS, Bosso JV, Laidlaw TM, Cervin AU, Maspero JF, Hopkins C, Olze H, Canonica GW, Paggiaro P, Cho SH, Fokkens WJ, Fujieda S, Zhang M, Lu X, Fan C, Draikiwicz S, Kamat SA, Khan A, Pirozzi G, Patel N, Graham NMH, Ruddy M, Staudinger H, Weinreich D, Stahl N, Yancopoulos GD, Mannent LP. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3

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- Fifth Sense UK: learning zone information sheet #3: chronic rhinosinusitis (CRS) with/without nasal polyps and allergies. Available at: <https://www.fifthsense.org.uk/download/8016/>

Further information on NICE and the role of patients:

- Public Involvement at NICE [Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- NICE's guides and templates for patient involvement in HTAs [Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector \(VCS\) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- EUPATI guidance on patient involvement in NICE: <https://www.eupati.eu/guidance-patient-involvement/>
- EFPIA – Working together with patient groups: <https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf>
- National Health Council Value Initiative. <https://nationalhealthcouncil.org/issue/value/>
- INAHTA: <http://www.inahta.org/>
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Adverse event/Side effect: An unexpected medical problem that arises during treatment with a drug or other therapy. Adverse events may be mild, moderate, or severe.

Clinical trial: A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis or treatment of a disease. Also called clinical study.

EMA (European Medicines Agency): The regulatory body that evaluates, approves and supervises medicines throughout the European Union. Similar to the MHRA for the UK.

Endoscopic sinonasal surgery (ESS): A type of operation used to treat problems in the nose and sinuses. A thin, flexible tube with a camera and light on the end (called an endoscope) is used to see inside the nose and sinuses, so a doctor can remove blockages and fix issues to help people breathe better and reduce sinus problems.

Healthcare resource utilisation (HCRU): Refers to the use of healthcare services, such as treatments, GP visits, outpatient hospital visits, hospitalisations, emergency room admissions etc.

HTA (Health Technology Assessment) bodies: Bodies that make recommendations regarding the financing and reimbursing of new medicines and medical products based on the added value (efficacy, safety, medical resources saving) of a therapy compared to existing ones.

Interleukin: A type of chemical signal produced by white blood cells which regulate the response of the immune system.

Intranasal corticosteroids (INCS): Medications administered as a spray into the nose, which deliver a small dose of steroids directly to the nasal passages. They help to reduce inflammation and swelling.

MHRA (Medicines and Healthcare products Regulatory Agency): The regulatory body that regulates medicines, medical devices and blood components for transfusion in the UK. Similar to the EMA for Europe.

Nasal congestion/obstruction (NC) score: Score measuring the severity of nasal blockage based on a person's own assessment of their daily symptoms of nasal blockage.

Nasal Polyp Score (NPS): Score assessing the severity of nasal polyps given by doctors depending on the size and number of polyps seen in a person's nose during examination.

Pooled analysis: Analysis combining data from several different trials (the data are all "pooled" together).

Primary endpoint: The outcome measured to answer the key question in a clinical trial.

Quality of life: The overall enjoyment of life. Many clinical trials assess it to measure aspects of an individual's sense of wellbeing and ability to carry out activities of daily living.

Recombinant human monoclonal antibody: Identical antibody produced from a single type of immune cells using genetic engineering techniques in a laboratory that can precisely target and neutralize harmful agents in the body and help the immune system fight diseases.

Secondary endpoint: An outcome measured to answer an additional question of interest in a clinical trial.

SNOT-22 (22-item Sinonasal Outcomes Test): Questionnaire used by doctors to measure how much sinus and nasal problems are affecting a person's life.

Systemic corticosteroids (SCS): Medications usually in the form of pills or injections, which work by mimicking hormones that your body naturally produces (steroids) to fight inflammation. They affect the entire body, not just one specific area.

Type 2 inflammation: An overactive immune response in which Type 2 immune cells (e.g., eosinophils) are activated even though there is no infection or allergen. As a result, the immune cells end up damaging the body itself and causing inflammation.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Dupilumab for treating severe chronic rhinosinusitis with nasal polyposis [ID6480]

Clarification questions

17 March 2025

File name	Version	Contains confidential information	Date
ID6480_Dupilumab_ Clarification questions_1703202 5_CIC	Final	Yes [REDACTED]	17/03/2025

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c) Please clarify why the patient numbers in the ‘Subpopulation: Responders at Week 24 - Response at Week 52’ category are so low as it is unclear from the data available to the EAG the reasons for patients not being included (e.g. discontinuation, lost to follow up?). Considering the long-term Markov model transition probabilities are based solely on these data, the EAG considers the small patient numbers introduce considerable uncertainty, particularly as the probability for moving from the controlled disease to the inadequately controlled disease health state for the ECM only arm is based on only █ patients (█ non-responders).....	60
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Transition probabilities	65
B7. Priority question: The EAG was unable to replicate both the 15.1% for the annual probability of surgery for eligible patients and the 42.8% probability of transitioning from post-op controlled to uncontrolled, based on data in Benson <i>et al.</i> 2023.	65
a) The CS states that the 42.8% probability of losing control following surgery was based on “...mean time to third surgery for patients having had >2 surgeries during the follow-up period – adjusted to reflect average wait time for surgery in England”. Please clarify if this means that the company applied a separate adjustment for wait times that was not based on the data in Benson <i>et al.</i> 2023. If so, please provide a scenario analysis in which the annual transition probability is based solely on the data from Benson <i>et al.</i> without any additional adjustments.	65
b) Please provide step by step descriptions to show exactly what data and calculations were performed to obtain both the 15.1% and the 42.8% annual probabilities.	68
B8. Priority question. The economic model includes 23.7% of patient’s ineligible for surgery based on the pooled SINUS 24/52 trials. Please clarify the criteria used to determine ineligibility?	71
B9. Clinical experts to the EAG noted that the proportion of patients who would be deemed ineligible to have revision surgery would be much lower in clinical practice than the 23.7% used in the company’s model as it is rare that patients are not eligible. Please include a scenario analysis which uses a lower proportion of patients based on UK clinical practice. The EAG’s clinical experts expected this to be less than 10%.	72
a) <i>Priority question: In appendix R.2 (UK Health Technology Assessment Consultancy), the company presented the economic model structure to clinical experts, which included the annual transition probabilities (Figure 2). Within this figure the proposed annual proportion of patients receiving revision surgery is [REDACTED]. The document notes that a clinical expert agreed that the number of patients having revision surgery within a year will be small. Please clarify why the company used an alternative annual probability of surgery of 15.1% in the base case as opposed to the value presented to clinical experts? In addition, please confirm which data the value of [REDACTED] was based on and include a scenario analysis in the model using this value instead of the 15.1%.</i>	72
B10. The annual probability used in the economic model for transitioning from the ‘inadequately controlled’ health state to the ‘post-op controlled disease’ is 15.1%. However, both Table 41 and Figure 19 of the CS state that the annual transition probability is 11.5%, which appears to be the annual transition probability (15.1%) multiplied by the proportion of patients eligible for surgery. Please confirm the correct transition probabilities used in the model.	73
B11. In the company’s scenario analysis using the discontinuation rate of [REDACTED] from the AROMA study to inform the annual transition probability of patients on dupilumab moving from ‘controlled’ to ‘inadequately controlled’, the EAG notes that this only captures patients who discontinued but not necessarily patients who would be classed as ‘non-responders’ using the same response criteria as used in the base-case analysis.	73

a) Please clarify if any ‘responder’ status analysis can be undertaken using the AROMA study to inform a more plausible scenario analysis and implement this in the model.....	74
b) The company’s scenario analysis using the [REDACTED] discontinuation rate to inform the transition probability does not make any amendments to the transition probability for the ECM arm, which remains based on only the [REDACTED] patients classed as non-responders in the clinical trial. Please clarify if any alternative data sources based on real-world evidence on the rate at which current patients become ‘inadequately controlled’ could be used to inform an alternative scenario analysis.....	76
B12. Priority question: The company’s base case analysis assumes no treatment waning over time for dupilumab. Clinical experts to the EAG noted that they would expect treatment effectiveness to wane over time, particularly considering their experience of similar biologics in asthma patients.	78
a) Please clarify why the assumption was made in the base-case analysis to assume no treatment waning over time.	78
b) Please include a scenario analysis in which this assumption is relaxed, informed by alternative data. The EAG notes that the AROMA observational study could be used to observe response rates to dupilumab in a real world setting over a longer period than the 52-week trial yet notes that any analysis undertaken should account for any differences in the patient populations, for example, using propensity score matching methods.	81
Mortality	86
B13. The company submission states that “...there is an increased risk of mortality with severe asthma and so a relative risk of increased mortality due to comorbid asthma is applied in the base case”. The EAG notes that the increased risk of mortality is applied to all patients with comorbid asthma (59.1%) and not just patients with severe asthma, which the CS reports as 24.4%. Please clarify why this assumption was made in the model.....	86
B14. The meta-analysis used to inform the relative risk for increased mortality for asthma patients was based on four studies, none of which were UK based and none were published recently. Please clarify if any more relevant and more recently published studies were searched for?	88
B15. Due to the inclusion of increased mortality for asthma patients and the company applying separate rates of uncontrolled asthma for each treatment arm in the model, this results in a difference in mortality between the two treatment arms and therefore in life years (LYs). Please include the total life years for each treatment arm and incremental LYs in the model results sheet.	88
Health related quality of life	89
B16. Priority question: For the general population utility values, the NICE methods guide recommends using the Health Survey for England (HSE) 2014 dataset, as recommended by the DSU (Hernández Alava <i>et al.</i> 2022). Please update the general population utility values used for age adjustment in the model to use the HSE 2014 dataset.	89
B17. Priority question: The Crump <i>et al.</i> 2017 dataset used by the company to inform the mapping between SNOT-22 and EQ-5D uses patients exclusively awaiting ESS, therefore it is likely that there are few or no patients who would be categorised as	

responders. Therefore, please comment on the validity of using the Crump mapping algorithm to accurately quantify responders utility values.	89
B18. Priority question: To limit issues with multicollinearity between SNOT-22 and baseline EQ-5D, please could the company rerun the regression models in section 3.3.3.5 using change from baseline in SNOT-22 score rather than total.	91
B19. Priority question: Please add a scenario using the reported EQ-5D data (crosswalked) to inform health state utility values, in which the responder utility values are capped at general population for the baseline age and a multiplier is applied to subsequent health states to retain the proportional differences between states?	96
B20. The company notes that the utility score for responders is 0.917 if using directly reported EQ-5D, which is higher than the UK general population. Is there any difference in the age of patients who respond, compared to the overall population, that could help explain this?	97
B21. Based on table 27 of the company appendices, health-related quality-of-life studies that use EQ-5D; Tashman <i>et al.</i> 2024, Wahid <i>et al.</i> 2020, Scangas 2018, Scangas 2017a and De Corso <i>et al.</i> 2022 appear to show significantly higher utility values than used in the company's base case. What is the company's explanation for why other health-related quality of life studies appear to show higher utilities for patients?	97
B22. In Table 46 of the CS, the Spearman's rank coefficient for the relationship between EQ-5D and efficacy data at baseline is given using the 'Hernandez 2020 crosswalk method, UK tariffs' whereas the coefficients for the relationship between change from baseline at week 24 is given using the 'Van Hout Crosswalk 2012, UK tariffs'.	98
a) Please clarify why the different crosswalk methods have been used?	98
b) As the NICE methods guide recommends the Hernandez 2020 crosswalk, please provide the results of the equivalent table using only this method.	99
B23. In section 3.3.3.6 the directly observed EQ-5D used for sensitivity analysis is referenced. Please clarify is this EQ-5D-5L data or is this converted into EQ-5D-3L?..	99
B24. What is the justification for using the week 24 response data to inform utility between week 13 and 24 but using an average of week 25-52 to inform utility in week 25-52? Why isn't the same approach used for both periods?	99
B25. Please provide the justification for dupilumab non-responders who receive surgery having a higher utility than ECM non-responders who receive surgery?.....	100
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B27. Please clarify why Dupilumab+ECM responders appear to take significantly more antibiotics than ECM responders (Table 57).	101
B28. Please update the specialist visit cost using NHS schedule of costs 2023/24.....	101
B29. Clinical experts to the EAG noted that if dupilumab were to be recommended for routine clinical practice, the decision to start a patient on treatment would be made as part of a multidisciplinary team (MDT) and that it would only be prescribed through	

specialist centres. Therefore, please include a scenario analysis in the model in which all patients in the dupilumab arm incur the cost of an MDT meeting.	102
B30. An adherence rate to dupilumab of 99.2% is used in the economic model. In the economic model it states that this is based on an ‘average adherence between 300mg q2w-q4w and dupilumab 300mg q2w arms’. As the dosage used in clinical practice in the SmPC is q2w, please include a scenario using the adherence rate from only patients receiving q2w in the economic model.	102
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C2. Priority question: In the economic model in worksheet “Clinical” it states that 14.0% of patients had uncontrolled asthma on dupilumab compared to 59.0% on ECM. This differs from the figures reported for uncontrolled asthma in worksheet “Resource” which corresponds to Table 63 of the CS. Please clarify the discrepancy and amend as needed.	104
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SNOT-22 total score	7
NPS	10
Mapped SNOT-22 to EQ-5D-3L health state utilities (Crump Models 1-3)	1
EQ-5D-5L utilities (Hernandez 2020 crosswalk method, UK tariffs)	1
Patients with ≥ 1 prior NP surgery	5
Baseline characteristics	5
Response rates	6
SNOT-22 total score	7
NPS	10
Mapped SNOT-22 to EQ-5D-3L health state utilities (Crump Models 1-3)	1
EQ-5D-5L utilities (Hernandez 2020 crosswalk method, UK tariffs)	1
Patients with ≥ 1 prior NP surgery and comorbid NSAID-ERD	5
Baseline characteristics	5
Response rates	6
SNOT-22 total score	7
NPS	10
Mapped SNOT-22 to EQ-5D-3L health state utilities (Crump Models 1-3)	1
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Section A: Clarification on effectiveness data

Methods

A1. Priority question: The EAG notes that missing data was imputed using a hybrid approach of WOCF and MI methods. For each relevant outcome in each trial, please clarify how much data was missing (and therefore imputed) for:

- a) the dupilumab arm;**
- b) the ECM arm.**

SINUS-24

The number of patients with missing data which were imputed for NPS, NC score, SNOT-22 total score and EQ-5D at Week 24 in the SINUS-24 trial are presented in [Table 1](#).

Table 1. Patients with missing data imputed by WOCF or MI at Week 24 in SINUS-24 (ITT population)

Endpoint	ECM (N=133)	Dupilumab (N=143)
<i>Bilateral NPS</i>		
Number of patients in the study at baseline	132	143
Number of patients with completed questionnaires (% in relation to ITT population) at baseline	132 (99.2%)	143 (100%)
Number of patients remaining in the study at Week 24	128	141
Number of patients with completed questionnaires regardless SCS use or NP surgery (% in relation to ITT population) at Week 24	125 (94.0%)	135 (94.4%)
Number of patients with completed questionnaires regardless SCS use or NP surgery (% in relation to ITT population remaining in the study regardless SCS use or NP surgery) at Week 24	125 (97.7%)	135 (95.7%)
Patients with data imputed by WOCF at Week 24, n (%)	25 (18.8)	10 (7.0)
Patients with data imputed by MI at Week 24, n (%)	4 (3.0)	5 (3.5)
<i>NC score</i>		
Number of patients in the study at baseline	133	143
Number of patients with completed questionnaires (% in relation to ITT population) at baseline	133 (100%)	143 (100%)

Endpoint	ECM (N=133)	Dupilumab (N=143)
Number of patients remaining in the study at Week 24	128	139
Number of patients with completed questionnaires regardless SCS use or NP surgery (% in relation to ITT population) at Week 24	127 (95.5%)	139 (97.2%)
Number of patients with completed questionnaires regardless SCS use or NP surgery (% in relation to ITT population remaining in the study regardless SCS use or NP surgery) at Week 24	127 (99.2%)	139 (100%)
Patients with data imputed by WOCF at Week 24, n (%)	25 (18.8)	9 (6.3)
Patients with data imputed by MI at Week 24, n (%)	2 (1.5)	1 (0.7)
SNOT-22 total score		
Number of patients in the study at baseline	133	143
Number of patients with completed questionnaires (% in relation to ITT population) at baseline	131 (98.5%)	137 (95.8%)
Number of patients remaining in the study at Week 24	128	141
Number of patients with completed questionnaires regardless SCS use or NP surgery (% in relation to ITT population) at Week 24	127 (95.5%)	137 (95.8%)
Number of patients with completed questionnaires regardless SCS use or NP surgery (% in relation to ITT population remaining in the study regardless SCS use or NP surgery) at Week 24	127 (99.2%)	137 (97.2%)
Patients with data imputed by WOCF at Week 24, n (%)	25 (18.8)	10 (7.0)
Patients with data imputed by MI at Week 24, n (%)	2 (1.5)	2 (1.4)
EQ-5D		
Number of patients in the study at baseline	133	143
Number of patients with completed questionnaires (% in relation to ITT population) at baseline	130 (97.7%)	136 (95.1%)
Number of patients remaining in the study at Week 24	130	142
Number of patients with completed questionnaires regardless SCS use or NP surgery (% in relation to ITT population) at Week 24	129 (97.0%)	138 (96.5%)
Number of patients with completed questionnaires regardless SCS use or NP surgery (% in relation to ITT population remaining in the study regardless SCS use or NP surgery) at Week 24	129 (99.2%)	138 (97.2%)
Patients with data imputed by WOCF at Week 24, n (%)	22 (16.5)	10 (7.0)

Endpoint	ECM (N=133)	Dupilumab (N=143)
Patients with data imputed by MI at Week 24, n (%)	3 (2.3)	3 (2.1)

EQ-5D = EuroQol 5-Dimension; ITT = intention-to-treat; MI: multiple imputation; NC = nasal congestion/obstruction; NP = nasal polyp; NPS = nasal polyp score; SCS = systemic corticosteroids; SNOT-22: 22-item Sino Nasal Outcome Test; WOCF = worst observation carried forward

Source: Sanofi. Data on File, Post-hoc analyses.¹

SINUS-52

The number of patients with missing data which were imputed for EQ-5D score, NPS, NC score and SNOT-22 total score at Week 24 in the SINUS-52 trial are presented in [Table 2](#).

Table 2. Patients with missing NPS, NC score, SNOT-22 total score and EQ-5D data imputed by WOCF or MI at Weeks 24 and 52 in SINUS-52 (ITT population)

Endpoint	ECM (N=153)	Dupilumab Q2W (N=295)
Week 24		
<i>Bilateral NPS</i>		
Number of patients in the study at baseline	152	294
Number of patients with completed questionnaires (% in relation to ITT population) at baseline	152 (99.3%)	294 (99.7%)
Number of patients remaining in the study at Week 24	143	289
Number of patients with completed questionnaires regardless SCS use or NP surgery (% in relation to ITT population) at Week 24	140 (91.5%)	283 (95.9%)
Number of patients with completed questionnaires regardless SCS use or NP surgery (% in relation to ITT population remaining in the study regardless SCS use or NP surgery) at Week 24	140 (97.9%)	283 (97.9%)
Patients with data imputed by WOCF at Week 24, n (%)	44 (28.8)	24 (8.1)
Patients with data imputed by MI at Week 24, n (%)	6 (3.9)	11 (3.7)
<i>NC score</i>		
Number of patients in the study at baseline	153	295
Number of patients with completed questionnaires (% in relation to ITT population) at baseline	153 (100%)	295 (100%)
Number of patients remaining in the study at Week 24	141	289
Number of patients with completed questionnaires regardless SCS use or NP surgery (% in relation to ITT population) at Week 24	141 (92.2%)	289 (98.0%)
Number of patients with completed questionnaires regardless SCS use or NP surgery (% in relation to ITT population remaining in the study regardless SCS use or NP surgery) at Week 24	141 (100%)	289 (100%)

Endpoint	ECM (N=153)	Dupilumab Q2W (N=295)
Patients with data imputed by WOCF at Week 24, n (%)	44 (28.8)	25 (8.5)
Patients with data imputed by MI at Week 24, n (%)	4 (2.6)	5 (1.7)
SNOT-22 total score		
Number of patients in the study at baseline	153	295
Number of patients with completed questionnaires (% in relation to ITT population) at baseline	152 (99.3%)	292 (99.0%)
Number of patients remaining in the study at Week 24	142	289
Number of patients with completed questionnaires regardless SCS use or NP surgery (% in relation to ITT population) at Week 24	138 (90.2%)	284 (96.3%)
Number of patients with completed questionnaires regardless SCS use or NP surgery (% in relation to ITT population remaining in the study regardless SCS use or NP surgery) at Week 24	138 (97.2%)	284 (98.3%)
Patients with data imputed by WOCF at Week 24, n (%)	44 (28.8)	25 (8.5)
Patients with data imputed by MI at Week 24, n (%)	6 (3.9)	9 (3.1)
EQ-5D		
Number of patients in the study at baseline	153	295
Number of patients with completed questionnaires (% in relation to ITT population) at baseline	151 (98.7%)	289 (98.0%)
Number of patients remaining in the study at Week 24	142	289
Number of patients with completed questionnaires regardless SCS use or NP surgery (% in relation to ITT population) at Week 24	137 (89.5%)	282 (95.6%)
Number of patients with completed questionnaires regardless SCS use or NP surgery (% in relation to ITT population remaining in the study regardless SCS use or NP surgery) at Week 24	137 (96.5%)	282 (97.6%)
Patients with data imputed by WOCF at Week 24, n (%)	44 (28.8)	25 (8.5)
Patients with data imputed by MI at Week 24, n (%)	6 (3.9)	11 (3.7)
Week 52		
Bilateral NPS		
Number of patients in the study at baseline	152	294
Number of patients with completed questionnaires (% in relation to ITT population) at baseline	152 (99.3%)	294 (99.7%)

Endpoint	ECM (N=153)	Dupilumab Q2W (N=295)
Number of patients remaining in the study at Week 52	135	288
Number of patients with completed questionnaires regardless SCS use or NP surgery (% in relation to ITT population) at Week 52	130 (85.0%)	277 (93.9%)
Number of patients with completed questionnaires regardless SCS use or NP surgery (% in relation to ITT population remaining in the study regardless SCS use or NP surgery) at Week 52	130 (96.3%)	277 (96.2%)
Patients with data imputed by WOCF at Week 52, n (%)	66 (43.1)	36 (12.2)
Patients with data imputed by MI at Week 52, n (%)	8 (5.2)	14 (4.7)
NC score		
Number of patients in the study at baseline	153	295
Number of patients with completed questionnaires (% in relation to ITT population) at baseline	153 (100%)	295 (100%)
Number of patients remaining in the study at Week 52	133	286
Number of patients with completed questionnaires regardless SCS use or NP surgery (% in relation to ITT population) at Week 52	133 (86.9%)	286 (96.9%)
Number of patients with completed questionnaires regardless SCS use or NP surgery (% in relation to ITT population remaining in the study regardless SCS use or NP surgery) at Week 52	133 (100%)	286 (100%)
Patients with data imputed by WOCF at Week 52, n (%)	66 (43.1)	39 (13.2)
Patients with data imputed by MI at Week 52, n (%)	7 (4.6)	6 (2.0)
SNOT-22 total score		
Number of patients in the study at baseline	153	295
Number of patients with completed questionnaires (% in relation to ITT population) at baseline	152 (99.3%)	292 (99.0%)
Number of patients remaining in the study at Week 52	136	288
Number of patients with completed questionnaires regardless SCS use or NP surgery (% in relation to ITT population) at Week 52	129 (84.3%)	283 (95.9%)
Number of patients with completed questionnaires regardless SCS use or NP surgery (% in relation to ITT population remaining in the study regardless SCS use or NP surgery) at Week 52	129 (94.9%)	283 (98.3%)
Patients with data imputed by WOCF at Week 52, n (%)	66 (43.1)	36 (12.2)

Endpoint	ECM (N=153)	Dupilumab Q2W (N=295)
Patients with data imputed by MI at Week 52, n (%)	8 (5.2)	8 (2.7)
EQ-5D		
Number of patients in the study at baseline	153	295
Number of patients with completed questionnaires (% in relation to ITT population) at baseline	151 (98.7%)	289 (98.0%)
Number of patients remaining in the study at Week 52	136	288
Number of patients with completed questionnaires regardless SCS use or NP surgery (% in relation to ITT population) at Week 52	123 (80.4%)	274 (92.9%)
Number of patients with completed questionnaires regardless SCS use or NP surgery (% in relation to ITT population remaining in the study regardless SCS use or NP surgery) at Week 52	123 (90.4%)	274 (95.1%)
Patients with data imputed by WOCF at Week 52, n (%)	66 (43.1)	36 (12.2)
Patients with data imputed by MI at Week 52, n (%)	9 (5.9)	12 (4.1)

EQ-5D = EuroQol 5-Dimension; ITT = intention-to-treat; MI: multiple imputation; NC = nasal congestion/obstruction; NP = nasal polyp; NPS = nasal polyp score; Q2W = once every two weeks; SCS = systemic corticosteroids; SNOT-22: 22-item Sino Nasal Outcome Test; WOCF = worst observation carried forward
Source: Sanofi. Data on File, Post-hoc analyses.¹

A2. Priority question: Please provide the results from the pooled analysis based on the observed data:

- a) without imputation;
- b) using only multiple imputation.

Results for NPS, NC score, SNOT-22 total score and EQ-5D both without imputation and with only multiple imputation in the pooled SINUS-24 and SINUS-52 ITT population at Week 24 are presented in Table 3.

Table 3. NPS, NC score and SNOT-22 total score results at Week 24 without imputation and using only MI in pooled SINUS-24 and SINUS-52 ITT population

Endpoint	ECM (N=286)		Dupilumab Q2W (N=438)		
	Mean (SD)	LS mean change from baseline (SE)	Mean (SD)	LS mean change from baseline (SE)	LS mean difference vs. ECM (95% CI; p value)
<i>Results without imputation of missing values</i>					
Bilateral NPS	5.859 (1.411)	-0.047 (0.110)	4.122 (1.945)	-1.876 (0.095)	-1.829 (-2.065, -1.592; p<0.0001)
NC score	1.842 (0.794)	-0.552 (0.056)	1.063 (0.833)	-1.349 (0.048)	-0.797 (-0.917, -0.677; p<0.0001)
SNOT-22 total score	38.627 (21.338)	-12.381 (1.179)	20.884 (15.997)	-29.963 (1.029)	-17.583 (-20.137, -15.028; p<0.0001)
EQ-5D* utility index	0.825 (0.156)	0.055 (0.009)	0.874 (0.141)	0.105 (0.008)	0.050 (0.030, 0.071; p<0.0001)
<i>Results using only MI of missing values</i>					
Bilateral NPS	5.859 (1.411)	-0.031 (0.108)	4.122 (1.945)	-1.888 (0.095)	-1.857 (-2.090, -1.624; p<0.0001)
NC score	1.842 (0.794)	-0.538 (0.055)	1.063 (0.833)	-1.347 (0.048)	-0.809 (-0.927, -0.691; p<0.0001)
SNOT-22 total score	38.627 (21.338)	-12.510 (1.167)	20.884 (15.997)	-30.489 (1.021)	-17.978 (-20.488, -15.468; p<0.0001)
EQ-5D* utility index	0.825 (0.156)	0.055 (0.009)	0.874 (0.141)	0.106 (0.008)	0.052 (0.032, 0.072; p<0.0001)

CI = confidence interval; EQ-5D = EuroQol 5-Dimension; ITT = intention-to-treat; LS = least squares; MI: multiple imputation; NC = nasal congestion/obstruction; NPS = nasal polyp score; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test

*Hernandez 2020 crosswalk method, UK tariffs.

Source: Sanofi. Data on File, Post-hoc analyses.¹

Baseline characteristics

A3. Priority question: Please provide the pooled baseline characteristics for the ITT populations in the SINUS-24 and SINUS-52 trials that contribute to the clinical effectiveness results (as provided in Table 17 for the ITT populations for the individual trials).

Baseline characteristics for the SINUS-24 and SINUS-52 pooled ITT population are presented in [Table 4](#).

Table 4. Baseline characteristics of the pooled ITT population

	Dupilumab	ECM
N	438	286
Male, n (%)	272 (62.1)	165 (57.7)
Age, mean (SD)	51.5 (12.8)	51.3 (12.9)
Race, n (%)		
Caucasian/White	382 (87.2)	254 (88.8)
Black/African decent	6 (1.4)	10 (3.5)
Asian/Oriental	37 (8.4)	18 (6.3)

	Dupilumab	ECM
American Indian/Alaska Native	10 (2.3)	3 (1.0)
Native Hawaiian/Other Pacific Islander	1 (0.20)	0
Multiple	1 (0.2)	1 (0.3)
Unknown	1 (0.2)	0
Ethnicity		
Hispanic or Latino	97 (22.2)	41 (14.4)
Not Hispanic or Latino	340 (77.8)	243 (85.6)
Territory		
North America	78 (17.8)	45 (15.7)
European Union	149 (34.0)	115 (40.2)
Rest of the World	211 (48.2)	126 (44.1)
BMI (kg/m ²), mean (SD)	27.81 (5.38)	28.12 (5.61)
Time since first diagnosis of nasal polyps (years), mean (SD)	11.12 (9.73)	10.83 (9.01)
Previous surgeries for nasal polyps, n (%)		
≥1 previous surgery	272 (62.1)	187 (65.4)
≥3 previous surgeries	64 (23.5)	47 (25.1)
Time since most recent surgery for nasal polyps (years), mean (SD)	7.22 (6.52)	7.06 (6.33)
SCS use in the past 2 years, n (%)	329 (75.1)	209 (73.1)
Bilateral endoscopic NPS* (scale 0-8), mean (SD)	6.00 (1.24)	5.91 (1.26)
NC score* (scale 0-3), mean (SD)	2.39 (0.60)	2.41 (0.54)
SNOT-22 total score* (scale 0-110), mean (SD)	50.05 (20.33)	52.27 (21.11)
Smell test (UPSIT) score** (scale 0-40), mean (SD)	13.90 (8.16)	14.09 (8.30)
LoS score* (scale 0-3), mean (SD)	2.74 (0.54)	2.72 (0.52)
LMK-CT total score* (scale 0-24), mean (SD)	18.26 (4.03)	18.53 (4.10)
Rhinosinusitis disease severity* (VAS 0-10cm), mean (SD)	7.82 (2.02)	7.97 (2.14)
Baseline NPIF** (L/min), mean (SD)	88.01 (56.08)	85.63 (56.15)
Baseline blood eosinophils (x10 ⁹ cells/L), mean (SD)	0.43 (0.35)	0.44 (0.34)
Baseline total IgE (IU/mL), mean (SD)	231.73 (347.49)	225.35 (267.60)
Any comorbid type 2 medical history including asthma and NSAID-ERD, n (%)	351 (80.1)	226 (79.0)
Comorbid asthma, n (%)	258 (58.9)	170 (59.4)
Comorbid NSAID-ERD, n (%)	122 (27.9)	82 (28.7)
Any comorbid type 2 medical history excluding asthma and NSAID-ERD, n (%)	276 (63.0)	173 (60.5)
Age of asthma onset in patients with comorbid asthma (years)	35.72 (16.13)	33.35 (15.76)

ERD = exacerbated respiratory disease; ITT = intention-to-treat; LMK-CT = Lund-Mackay computed tomography; LoS = loss-of-smell; NC = nasal congestion/obstruction; NPIF = nasal peak inspiratory flow; NPS = nasal polyp score; NSAID = non-steroidal anti-inflammatory drug; Q2W = every 2 weeks; SD = standard deviation; SNOT-22 = 22-item Sino-Nasal Outcome Test; UPSIT = University of Pennsylvania Smell Identification Test; VAS = visual analogue scale

*Higher scores indicate greater disease severity.

** Higher scores indicate lower disease severity.

Source: Sanofi. Data on File, Summary of Clinical Efficacy.²

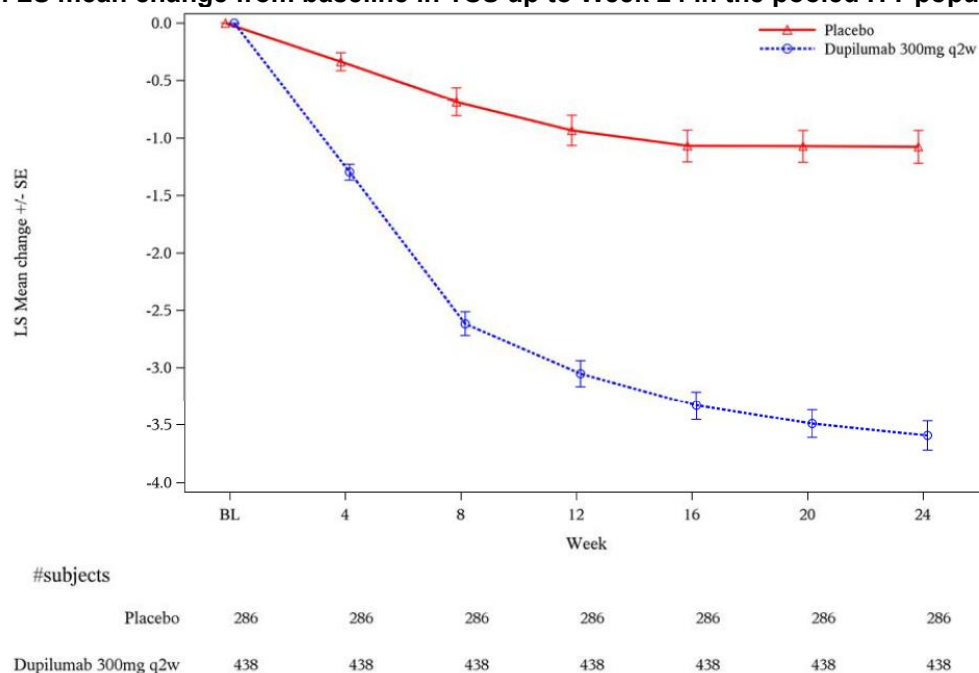
Results

A4. Priority question: Figures 12 and 13 present the pooled results for the change from baseline for the co-primary endpoints (bilateral NPS and NC) for each post-baseline assessment up to Week 24. Please provide the same information for the key secondary outcomes of:

- a) TSS;
- b) SNOT-22 score;
- c) Daily symptoms of decreased/loss of smell; and
- d) UPSIT score.

Results for the changes from baseline in TSS, SNOT-22 total score, daily decreased/loss of smell score and UPSIT score up to Week 24 in the pooled ITT population are presented in [Figure 1](#), [Figure 2](#), [Figure 3](#) and [Figure 4](#), respectively.

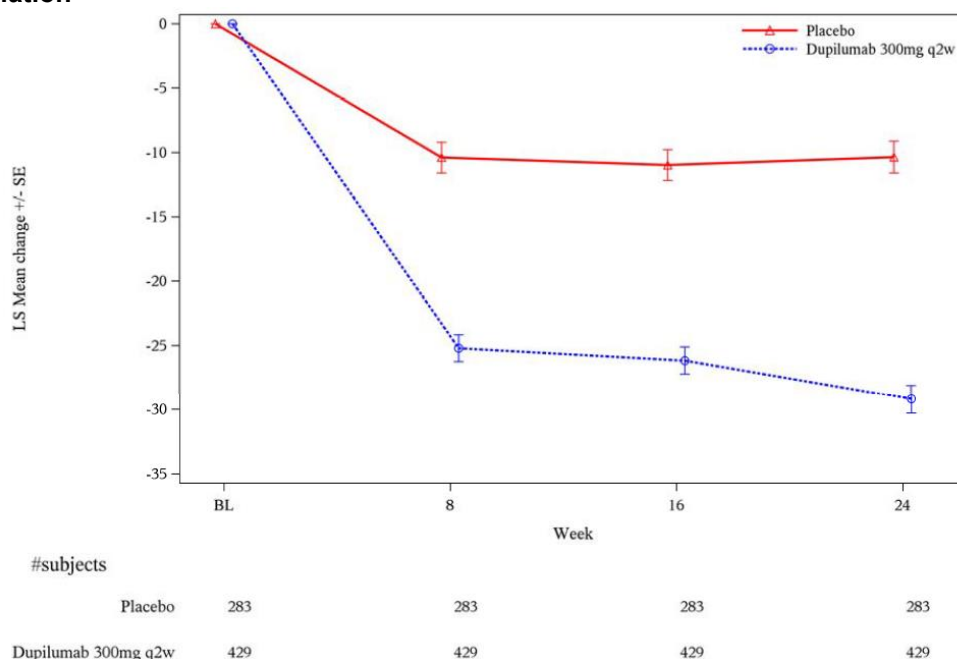
Figure 1. LS mean change from baseline in TSS up to Week 24 in the pooled ITT population



BL = baseline; ITT = intention-to-treat; LS = least squares; Q2W = once every 2 weeks; SE = standard error; TSS = total symptom score.

Source: Sanofi. Data on File, Supporting analyses for summary of clinical efficacy/integrated summary of effectiveness.³

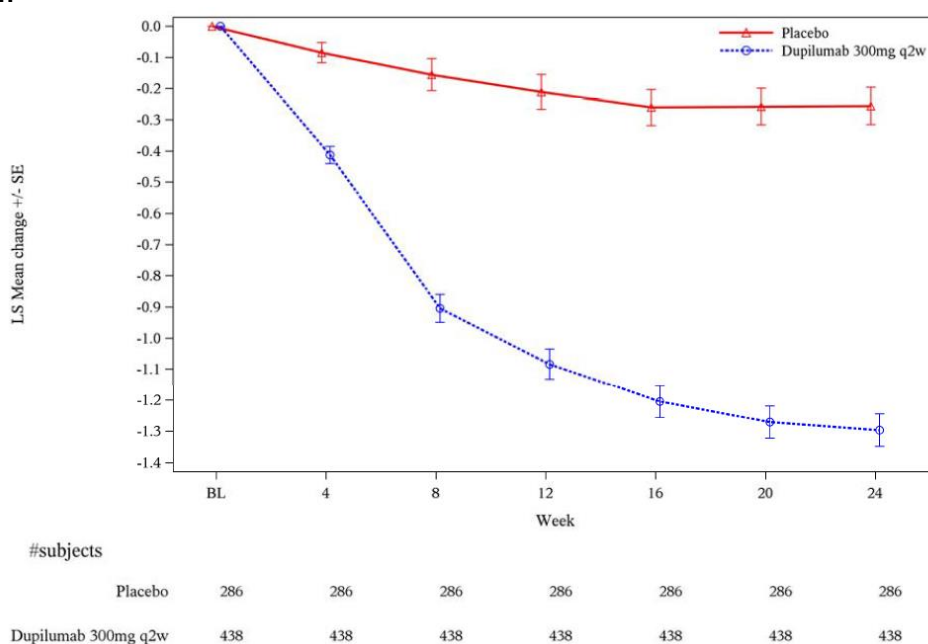
Figure 2. LS mean change from baseline in SNOT-22 total score up to Week 24 in the pooled ITT population



BL = baseline; ITT = intention-to-treat; LS = least squares; Q2W = once every 2 weeks; SE = standard error; SNOT-22 = 22-item Sino-Nasal Outcome Test.

Source: Sanofi. Data on File, Supporting analyses for summary of clinical efficacy/integrated summary of effectiveness.³

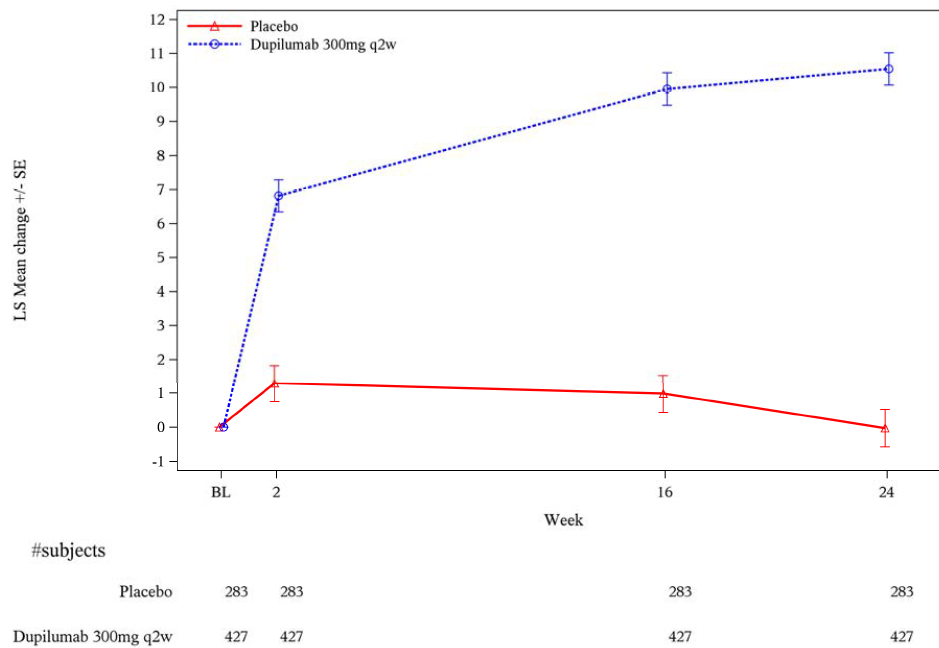
Figure 3. LS mean change from baseline in daily LoS score up to Week 24 in the pooled ITT population



BL = baseline; ITT = intention-to-treat; LoS = loss-of-smell; LS = least squares; Q2W = once every 2 weeks; SE = standard error.

Source: Sanofi. Data on File, Supporting analyses for summary of clinical efficacy/integrated summary of effectiveness.³

Figure 4. LS mean change from baseline in UPSIT score up to Week 24 in the pooled ITT population

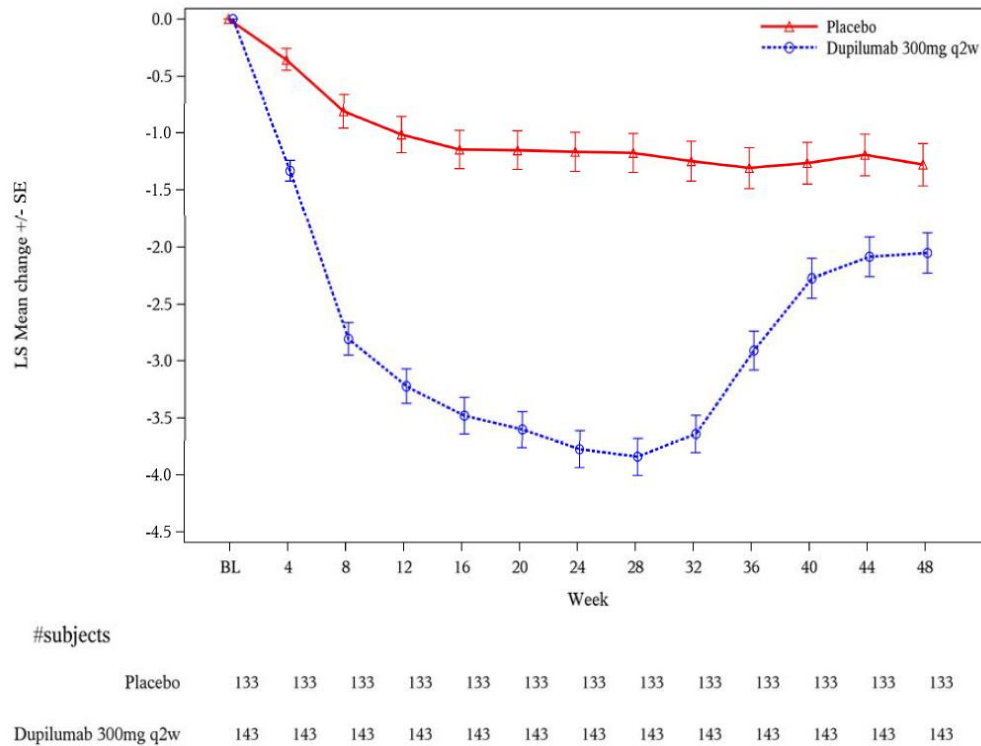


BL = baseline; ITT = intention-to-treat; LS = least squares; Q2W = once every 2 weeks; SE = standard error; UPSIT = University of Pennsylvania Smell Identification Test.
Source: Sanofi. Data on File, Supporting analyses for summary of clinical efficacy/integrated summary of effectiveness.³

A5. Figures 11 and 12 in Appendix N present results for the change from baseline for the co-primary endpoints (bilateral NPS and NC) for SINUS-24 up to Week 48. Please provide the same information for the key secondary outcomes of:

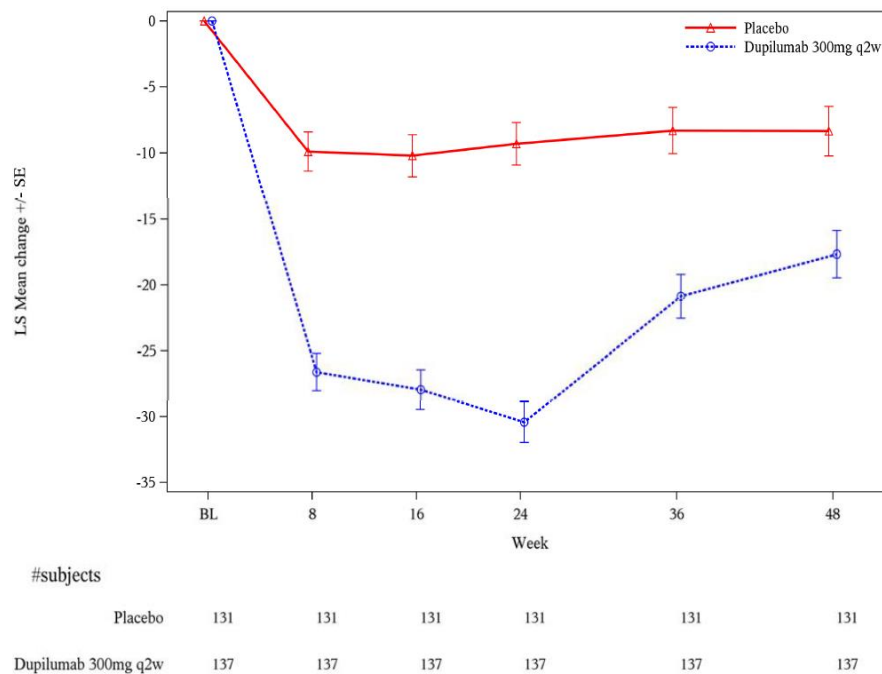
- a) TSS;**
- b) SNOT-22 score;**
- c) Daily symptoms of decreased/loss of smell; and**
- d) UPSIT score.**

Results for the changes from baseline in TSS, SNOT-22 total score, daily decreased/loss of smell score and UPSIT score up to Week 48 in SINUS-24 are presented in [Figure 5](#), [Figure 6](#), [Figure 7](#) and [Figure 8](#), respectively.

Figure 5. LS mean change from baseline in TSS up to Week 48 in SINUS-24 (ITT population)

BL = baseline; ITT = intention-to-treat; LS = least squares; Q2W = once every 2 weeks; SE = standard error; TSS = total symptom score.

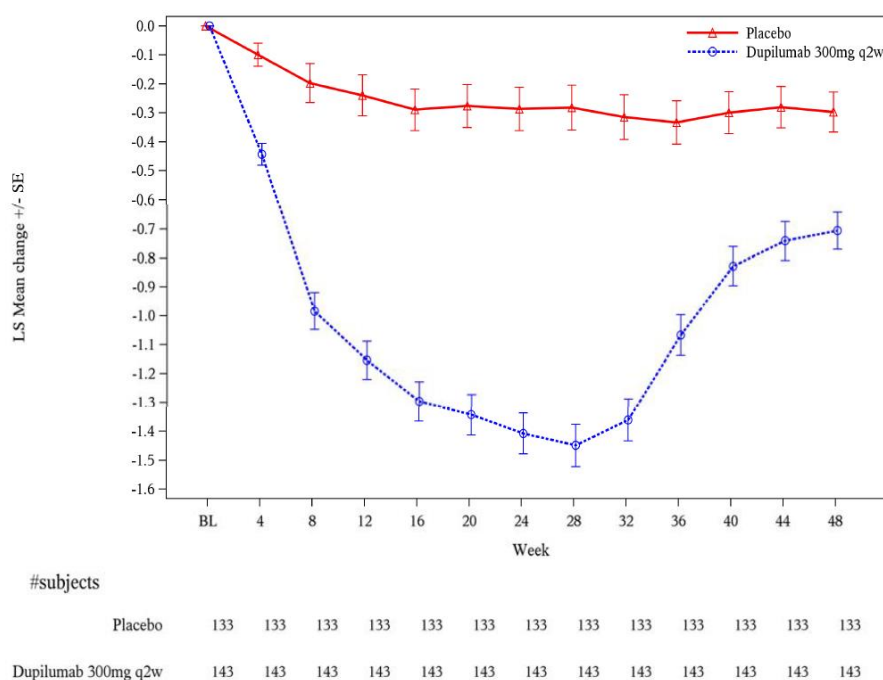
Source: Sanofi. Data on File, Clinical Study Report SINUS-24.⁴

Figure 6. LS mean change from baseline in SNOT-22 total score up to Week 48 in SINUS-24 (ITT population)

BL = baseline; ITT = intention-to-treat; LS = least squares; Q2W = once every 2 weeks; SE = standard error; SNOT-22 = 22-item Sino-Nasal Outcome Test.

Source: Sanofi. Data on File, Clinical Study Report SINUS-24.⁴

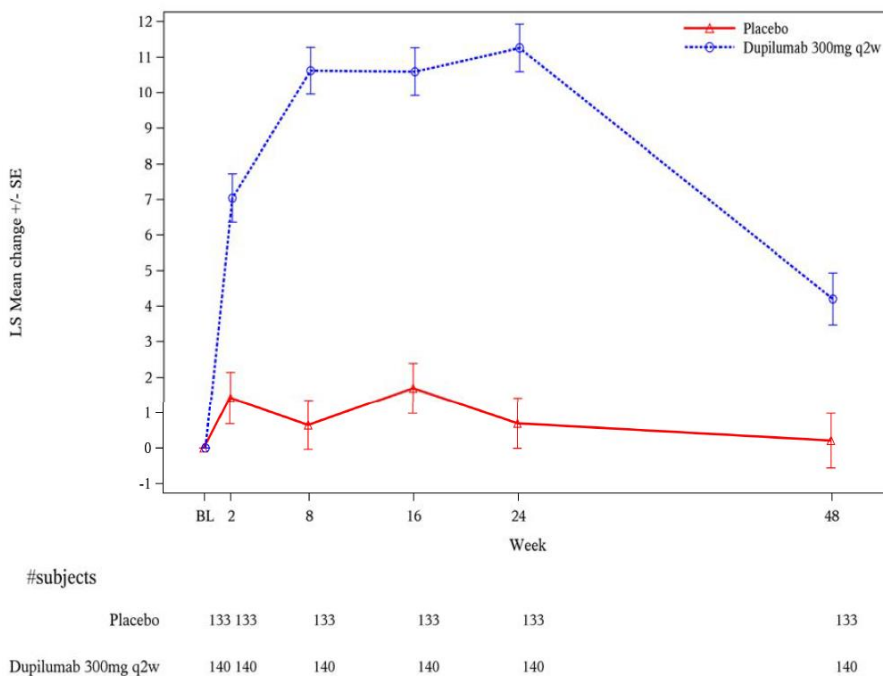
Figure 7. LS mean change from baseline in daily LoS score up to Week 48 in SINUS-24 (ITT population)



BL = baseline; ITT = intention-to-treat; LoS = loss-of-smell; LS = least squares; Q2W = once every 2 weeks; SE = standard error.

Source: Sanofi. Data on File, Clinical Study Report SINUS-24.⁴

Figure 8. LS mean change from baseline in UPSIT score up to Week 48 in SINUS-24 (ITT population)



BL = baseline; ITT = intention-to-treat; LS = least squares; Q2W = once every 2 weeks; SE = standard error; UPSIT = University of Pennsylvania Smell Identification Test.

Source: Sanofi. Data on File, Clinical Study Report SINUS-24.⁴

Subgroup analysis

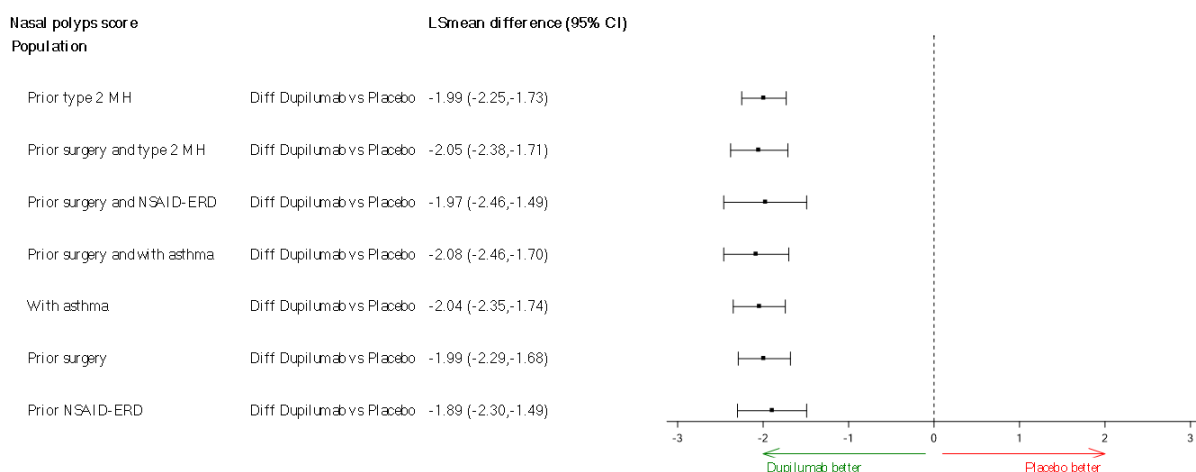
A6. Priority question: The EAG notes that the results of subgroup analyses are only provided for the co-primary endpoints (bilateral NPS and NC in Figures 15 and 16). For each subgroup, please also provide the results for the key secondary outcomes of:

- a) TSS;**
- b) SNOT-22 score;**
- c) Daily symptoms of decreased/loss of smell; and**
- d) UPSIT score.**

Subgroup analyses results for the changes from baseline in NPS, NC score, TSS, SNOT-22 total score, daily decreased/loss of smell score and UPSIT score at Week 24 in the pooled ITT population are presented in [Figure 9](#), [Figure 10](#), [Figure 9](#),

[Figure 12](#), [Figure 13](#) and [Figure 14](#)Figure 14. LS mean change from baseline in UPSIT score at Week 24 in the pooled ITT population by disease characteristic subgroup, respectively.

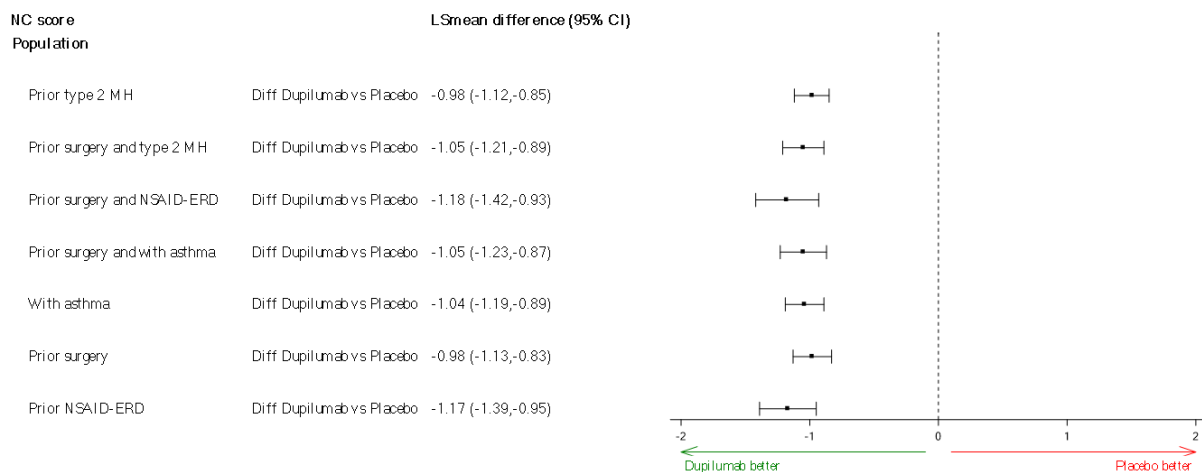
Figure 9. LS mean change from baseline in bilateral NPS score at Week 24 in the pooled ITT population by disease characteristic subgroup



CI = confidence interval; ITT = intention-to-treat; LS = least squares; MH = medical history; NPS = nasal polyp score; NSAID-ERD = nonsteroidal anti-inflammatory drug-exacerbated respiratory disease; Q2W = once every 2 weeks; TSS = total symptom score.

Source: Sanofi. Data on File, Post-hoc analyses.¹

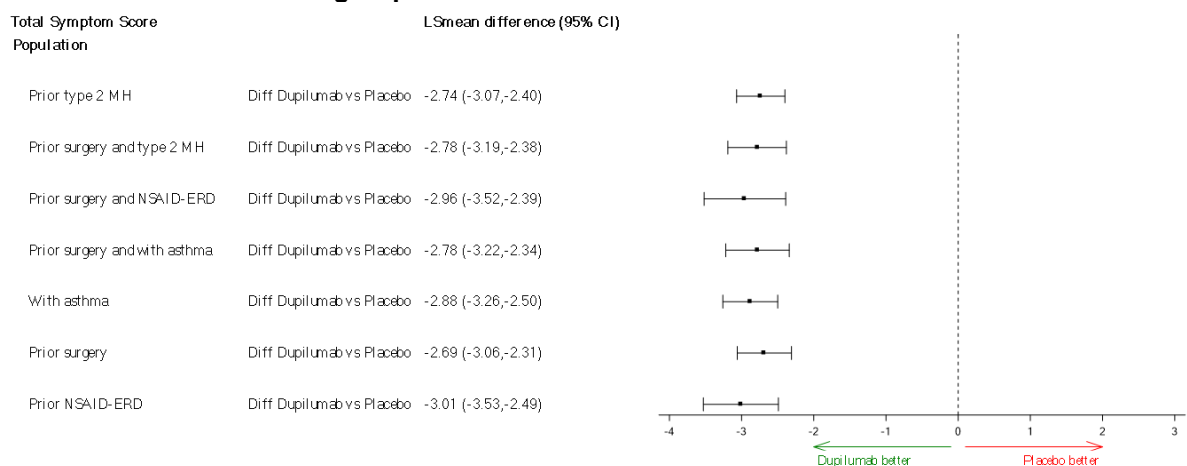
Figure 10. LS mean change from baseline in NC score at Week 24 in the pooled ITT population by disease characteristic subgroup



CI = confidence interval; ITT = intention-to-treat; LS = least squares; MH = medical history; NC = nasal congestion/obstruction; NSAID-ERD = nonsteroidal anti-inflammatory drug-exacerbated respiratory disease; Q2W = once every 2 weeks; TSS = total symptom score.

Source: Sanofi. Data on File, Post-hoc analyses.¹

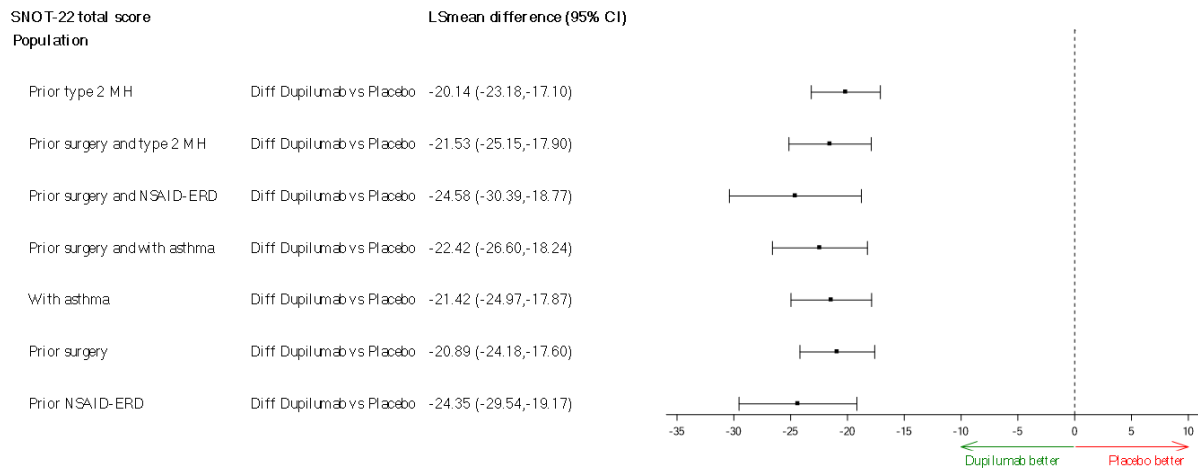
Figure 11. LS mean change from baseline in TSS at Week 24 in the pooled ITT population by disease characteristic subgroup



CI = confidence interval; ITT = intention-to-treat; LS = least squares; MH = medical history; NSAID-ERD = nonsteroidal anti-inflammatory drug-exacerbated respiratory disease; Q2W = once every 2 weeks; TSS = total symptom score.

Source: Sanofi. Data on File, Post-hoc analyses.¹

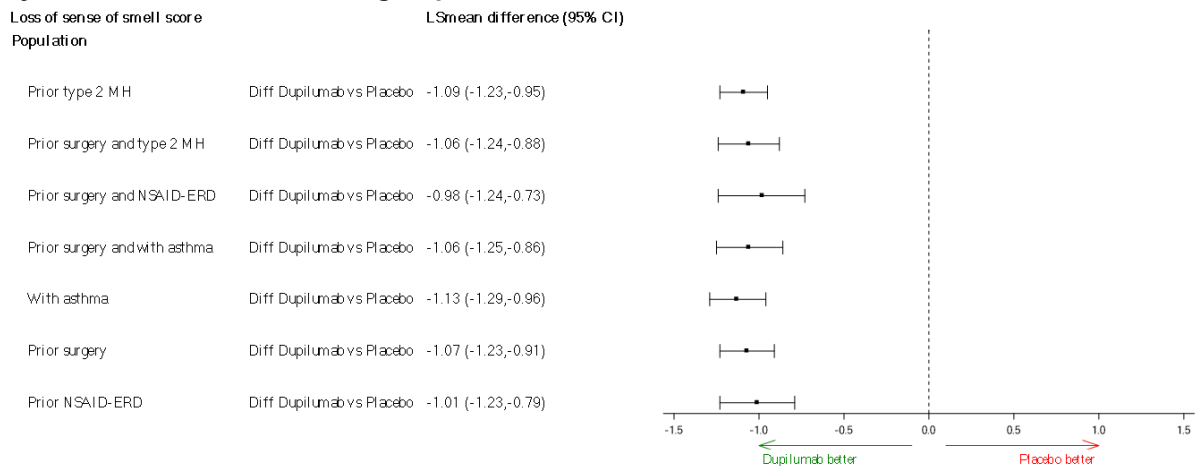
Figure 12. LS mean change from baseline in SNOT-22 total score at Week 24 in the pooled ITT population by disease characteristic subgroup



CI = confidence interval; ITT = intention-to-treat; LS = least squares; MH = medical history; NSAID-ERD = nonsteroidal anti-inflammatory drug-exacerbated respiratory disease; Q2W = once every 2 weeks; SNOT-22 = 22-item Sino-Nasal Outcome Test.

Source: Sanofi. Data on File, Post-hoc analyses.¹

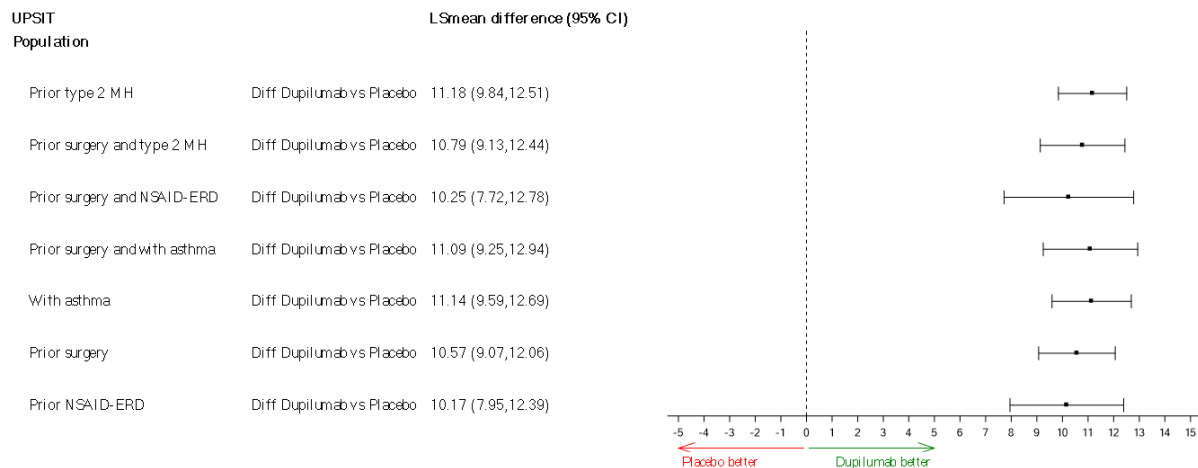
Figure 13. LS mean change from baseline in LoS score at Week 24 in the pooled ITT population by disease characteristic subgroup



CI = confidence interval; ITT = intention-to-treat; LoS = loss-of-smell; LS = least squares; MH = medical history; NSAID-ERD = nonsteroidal anti-inflammatory drug-exacerbated respiratory disease; Q2W = once every 2 weeks.

Source: Sanofi. Data on File, Post-hoc analyses.¹

Figure 14. LS mean change from baseline in UPSIT score at Week 24 in the pooled ITT population by disease characteristic subgroup



CI = confidence interval; ITT = intention-to-treat; LS = least squares; MH = medical history; NSAID-ERD = nonsteroidal anti-inflammatory drug-exacerbated respiratory disease; Q2W = once every 2 weeks; UPSIT = University of Pennsylvania Smell Identification Test.

Source: Sanofi. Data on File, Post-hoc analyses.¹

A7. Priority question [updated]: The EAG notes that two of the subgroups proposed by NICE (patients who have asthma and patients who have NSAID-ERD) have been combined in the company submission. Please provide the results of subgroup analyses for each outcome (bilateral NPS, NC, TSS, SNOT-22 score, daily symptoms of decreased/loss of smell and UPSIT score) for the following subgroups:

- a) Patients who have no comorbidities;**
- b) Patients who have asthma (who do not also have NSAID-ERD); and**
- c) Patients who have NSAID-ERD.**

Please provide this information for the pooled ITT population and the subgroup who had prior surgery for nasal polyps. Please also implement these subgroups as a scenario in the economic model (for the prior surgery patients only).

As requested, Sanofi have conducted additional analyses in the requested subgroups of:

- Patients with comorbid asthma;
- Patients with prior NSAID-ERD;
- Patients with any type-2 prior medical history.

All in the pooled ITT population AND in the population of patients having had at least one prior sinus surgery. These subgroups (baseline characteristics, NPS, SNOT-22 and utility scores) have been added as a user-selectable population in the CEM [Worksheet 'Settings'; Cell F17/ SubgroupDropDown]. Please find details of the SINUS-24/52 post-hoc reports used to inform this at the end of this response document (after section C).

Sanofi have not conducted a subgroup analysis for the population of patients who have asthma (and specifically who do not also have NSAID-ERD) as the presentation of NSAID-ERD includes asthma within its characteristics and, therefore, removing NSAID-ERD patients from the asthma subgroup would introduce a degree bias to the results and is also not in line with the clinical experts opinion or the recognised guidelines for the treatment of CRSwNP. Sanofi have also not conducted a subgroup analysis for the requested subgroup of 'patients who have no comorbidities', as this subgroup was not requested as part of the NICE scope. Moreover, this is not a subgroup the company wishes to pursue reimbursement in and is not in line with the clinical expert's opinion gathered both during the advisory board in June 2024 and the consultancy meetings in November 2024, or the recognised guidelines (such as EUFOREA/EPOS 2020). CRSwNP is driven by type 2 inflammation, which plays a pivotal role in the manifestation of several other inflammatory conditions such as, asthma, NSAID-ERD and AD and therefore, it is clinically not appropriate to investigate results in a subgroup specifically without any of these concomitant pathologies. Furthermore, the number of people with no type-2 comorbidity in SINUS-24/52 was very limited, and would have introduce significant uncertainty especially when calculating the long term response in the Markov model (based on responders throughout, which would be a very small number in the ECM arm).

Additional subgroups:

Patients with NSAID-ERD: Baseline characteristics, clinical outcomes and HRQoL data relevant to the scenario analyses considering patients with prior NSAID-ERD in the pooled ITT population is presented in [Table 38](#) (baseline characteristics) and [Table 5](#) (clinical outcomes and HRQoL). Additionally, we have provided baseline characteristics, clinical outcomes and HRQoL data relevant to the scenario analyses considering patients comorbid NSAID-ERD **and** who had ≥ 1 prior NP surgery in [Table 80](#) (baseline characteristics) and [Table 6](#) (clinical outcomes and HRQoL).

Table 5. Summary of LS mean change from baseline at Week 24 in the subgroup of patients with NSAID-ERD – pooled ITT population

LS mean change from baseline at Week 24	ECM	Dupilumab 300mg Q2W	Difference vs. ECM (p-value)
Bilateral NPS	0.16	-1.73	-1.89 (<0.0001)
NC score	-0.28	-1.45	-1.17 (<0.0001)
Smell test (UPSIT) score	0.56	10.73	10.17 (<0.0001)
SNOT-22 total score	-6.94	-31.30	-24.35 (<0.0001)
Total Symptom Score (TSS)	-0.73	-3.74	-3.01 (<0.0001)
Daily loss of smell score	-0.18	-1.19	-1.01 (<0.0001)

ECM = established clinical management; ITT = intention-to-treat; LS = least squares; NC = nasal congestion/obstruction; NPS = nasal polyp score; NSAID-ERD = non-steroidal anti-inflammatory drug-exacerbated respiratory disease; Q2W = once every two weeks; SNOT-22 = Sino-Nasal Outcome Test-22; UPSIT = University of Pennsylvania Smell Identification Test.

All p-values are nominal.

Sources: Mullol 2022;⁵ Sanofi. Data on File, Summary of Clinical Efficacy.²

Table 6: Summary of LS mean change from baseline at Week 24 in the subgroup of patients with NSAID-ERD and who had prior NP surgery – pooled ITT population

LS mean change from baseline at Week 24	ECM	Dupilumab 300mg Q2W	Difference vs. ECM (p-value)
Bilateral NPS	-0.12	-2.10	-1.97 (<0.0001)
NC score	-0.42	-1.59	-1.18 (<0.0001)
Smell test (UPSIT) score	-0.28	9.97	10.25 (<0.0001)
SNOT-22 total score	-6.59	-31.17	-24.58 (<0.0001)
Total Symptom Score (TSS)	-0.98	-3.94	-2.96 (<0.0001)
Daily loss of smell score	-0.13	-1.11	-0.98 (<0.0001)

ECM = established clinical management; ITT = intention-to-treat; LS = least squares; NC = nasal congestion/obstruction; NP = nasal polyp; NPS = nasal polyp score; NSAID-ERD = non-steroidal anti-inflammatory drug-exacerbated respiratory disease; Q2W = once every two weeks; SNOT-22 = Sino-Nasal Outcome Test-22; UPSIT = University of Pennsylvania Smell Identification Test.

All p-values are nominal.

Source: Sanofi. Data on File, Post-hoc analyses.¹

Patients with asthma: Baseline characteristics, clinical outcomes and HRQoL data relevant to the scenario analyses considering patients with comorbid asthma in the pooled ITT population is presented in [Table 52](#) (baseline characteristics) and [Table 7](#) (clinical outcomes and HRQoL). Additionally, we have provided baseline characteristics, clinical outcomes and HRQoL data relevant to the scenario analyses considering patients comorbid asthma **and** who had ≥ 1 prior NP surgery in [Table 94](#) (baseline characteristics) and [Table 8](#) (clinical outcomes and HRQoL).

Table 7. Summary of LS mean change from baseline at Week 24 in the subgroup of patients with asthma – pooled ITT population

LS mean change from baseline at Week 24	ECM	Dupilumab 300mg Q2W	Difference vs. ECM (p-value)
Bilateral NPS	0.14	-1.90	-2.04 (<0.0001)
NC score	-0.35	-1.39	-1.04 (<0.0001)
Smell test (UPSIT) score	-0.37	10.76	11.14 (<0.0001)
SNOT-22 total score	-9.19	-30.61	-21.42 (<0.0001)
Total Symptom Score (TSS)	-0.91	-2.88	-2.88 (<0.0001)
Daily loss of smell score	-0.18	-1.30	-1.13 (<0.0001)

ECM = established clinical management; ITT = intention-to-treat; LS = least squares; NC = nasal congestion/obstruction; NPS = nasal polyp score; Q2W = once every two weeks; SNOT-22 = Sino-Nasal Outcome Test-22; UPSIT = University of Pennsylvania Smell Identification Test.

Sources: Sanofi. Data on File, Summary of Clinical Efficacy;² Sanofi. Data on File, Supporting analyses for summary of clinical efficacy/integrated summary of effectiveness.³

Table 8: Summary of LS mean change from baseline at Week 24 in the subgroup of patients with asthma and who had prior NP surgery – pooled ITT population

LS mean change from baseline at Week 24	ECM	Dupilumab 300mg Q2W	Difference vs. ECM (p-value)
Bilateral NPS	0.03	-2.05	-2.08 (<0.0001)
NC score	-0.34	-1.39	-1.05 (<0.0001)
Smell test (UPSIT)	-0.76	10.33	11.09 (<0.0001)
SNOT-22 total score	-8.48	-30.90	-22.42 (<0.0001)
Total Symptom Score (TSS)	-0.78	-3.56	-2.78 (<0.0001)
Daily loss of smell score	-0.06	-1.12	-1.06 (<0.0001)

ECM = established clinical management; ITT = intention-to-treat; LS = least squares; NC = nasal congestion/obstruction; NP = nasal polyp; NPS = nasal polyp score; Q2W = once every two weeks; SNOT-22 = Sino-Nasal Outcome Test-22; UPSIT = University of Pennsylvania Smell Identification Test.

Source: Sanofi. Data on File, Post-hoc analyses.¹

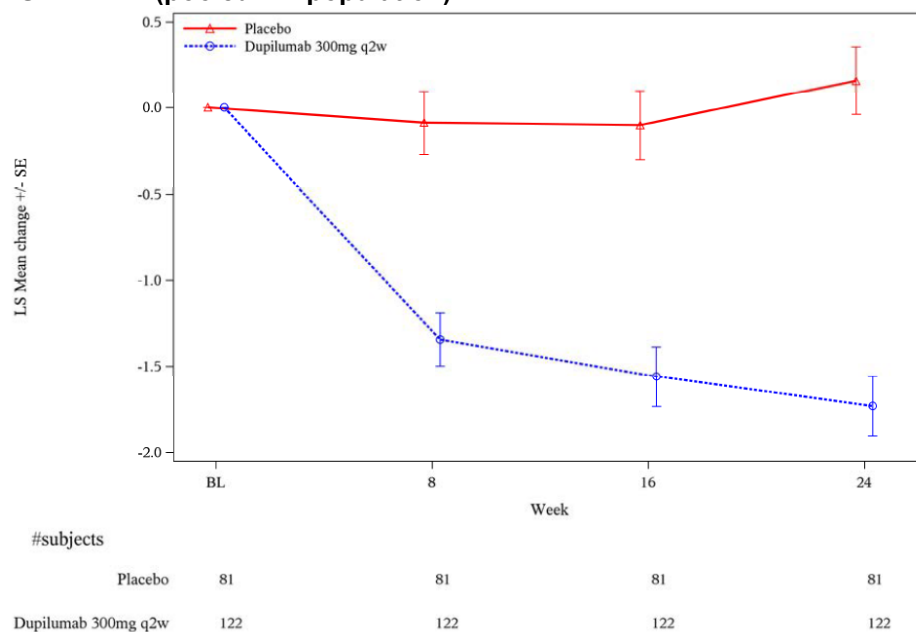
A8. For each subgroup, please provide information on the change from baseline (as provided in Figures 12 and 13 for the overall pooled analysis) for:

- a) Bilateral NPS;**
- b) NC;**
- c) TSS;**
- d) SNOT-22 score;**
- e) Change in daily symptoms of decreased/loss of smell; and**
- f) UPSIT score.**

Patients with comorbid NSAID-ERD

Results for the changes from baseline in bilateral NPS, NC score, TSS, SNOT-22 total score, daily decreased/loss of smell score and UPSIT score up to Week 24 in patients with comorbid NSAID-ERD are presented in [Figure 15](#), [Figure 16](#), [Figure 17](#), [Figure 18](#), [Figure 19](#) and [Figure 20](#), respectively.

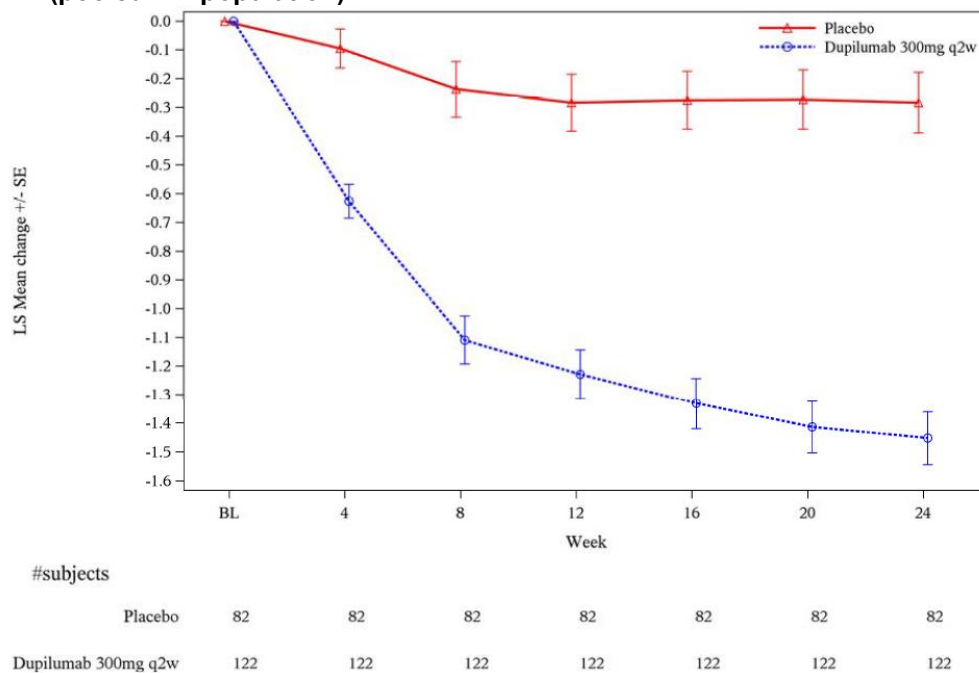
Figure 15. LS mean change from baseline in bilateral NPS up to Week 24 in patients with comorbid NSAID-ERD (pooled ITT population)



BL = baseline; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NSAID = non-steroidal anti-inflammatory drug; NPS = nasal polyp score; Q2W = once every 2 weeks; SE = standard error.

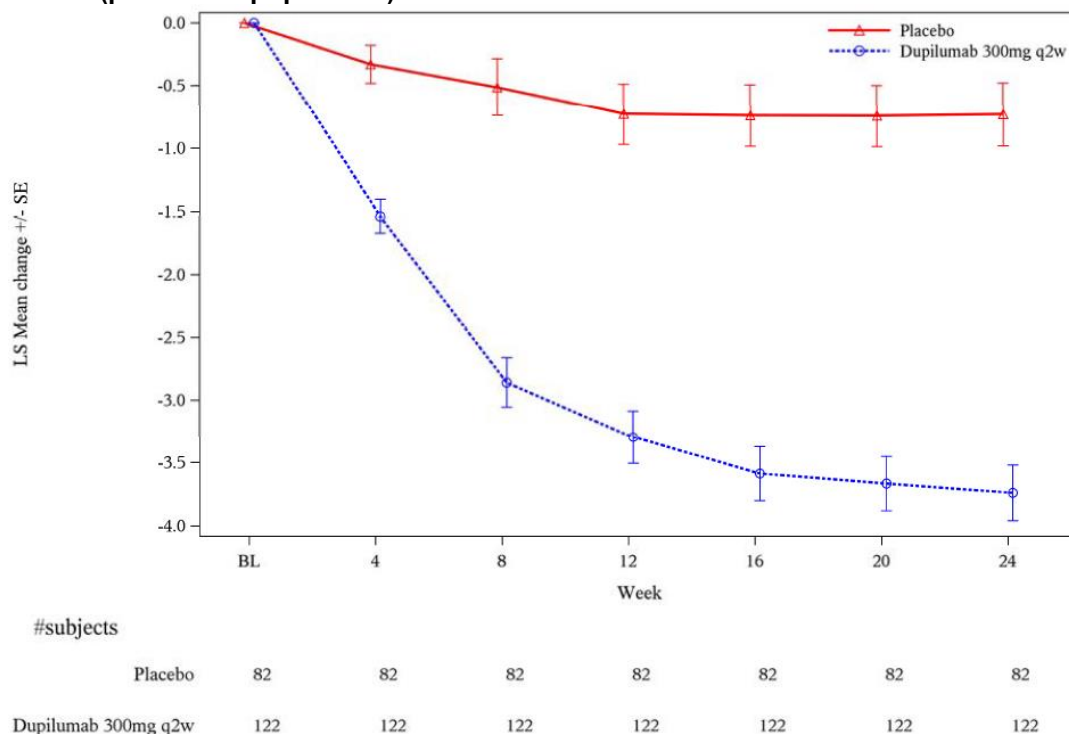
Source: Sanofi. Data on File, Supporting analyses for summary of clinical efficacy/integrated summary of effectiveness.³

Figure 16. LS mean change from baseline in NC score up to Week 24 in patients with comorbid NSAID-ERD (pooled ITT population)



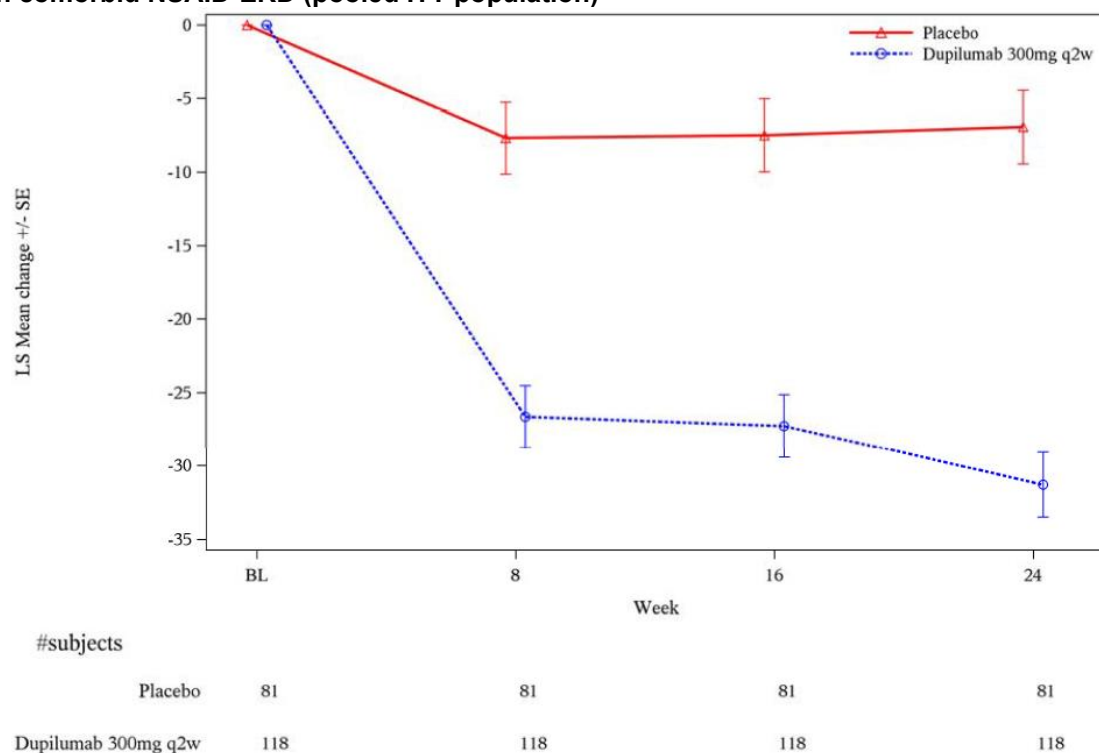
BL = baseline; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NC = nasal congestion/obstruction; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every 2 weeks; SE = standard error. Source: Sanofi. Data on File, Supporting analyses for summary of clinical efficacy/integrated summary of effectiveness.³

Figure 17. LS mean change from baseline in TSS up to Week 24 in patients with comorbid NSAID-ERD (pooled ITT population)



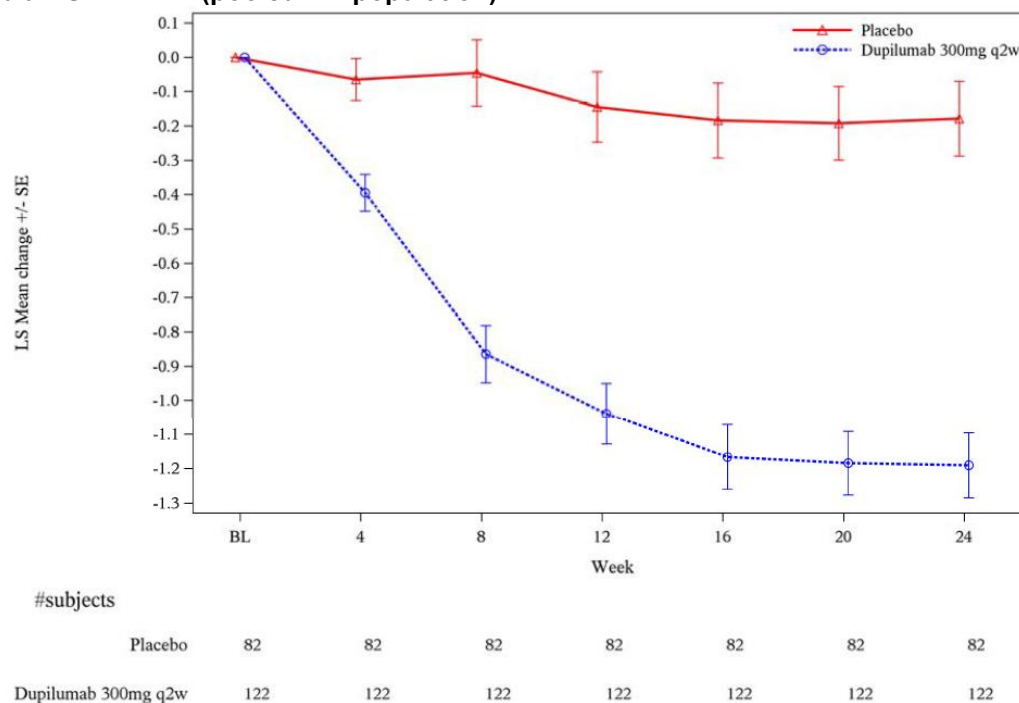
BL = baseline; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every 2 weeks; SE = standard error; TSS = total symptom score. Source: Sanofi. Data on File, Supporting analyses for summary of clinical efficacy/integrated summary of effectiveness.³

Figure 18. LS mean change from baseline in SNOT-22 total score up to Week 24 in patients with comorbid NSAID-ERD (pooled ITT population)



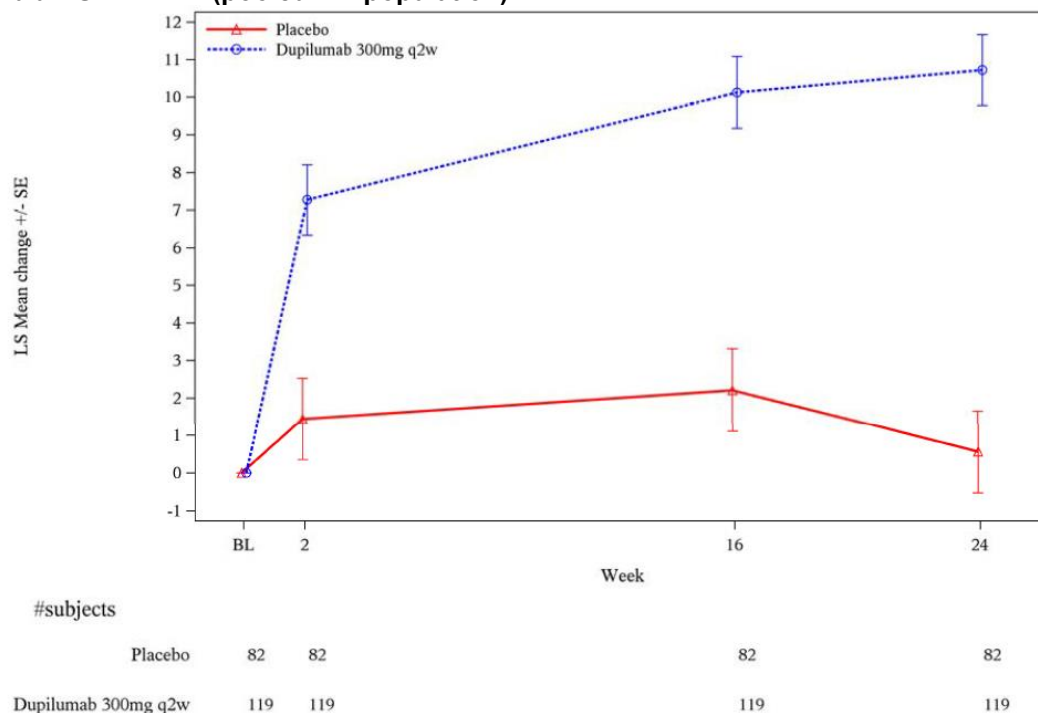
BL = baseline; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every 2 weeks; SE = standard error; SNOT-22 = 22-item Sino-Nasal Outcome Test. Source: Sanofi. Data on File, Supporting analyses for summary of clinical efficacy/integrated summary of effectiveness.³

Figure 19. LS mean change from baseline in LoS score up to Week 24 in patients with comorbid NSAID-ERD (pooled ITT population)



BL = baseline; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LoS = loss-of-smell; LS = least squares; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every 2 weeks; SE = standard error. Source: Sanofi. Data on File, Supporting analyses for summary of clinical efficacy/integrated summary of effectiveness.³

Figure 20. LS mean change from baseline in UPSIT score up to Week 24 in patients with comorbid NSAID-ERD (pooled ITT population)



BL = baseline; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every 2 weeks; SE = standard error; UPSIT = University of Pennsylvania Smell Identification Test.

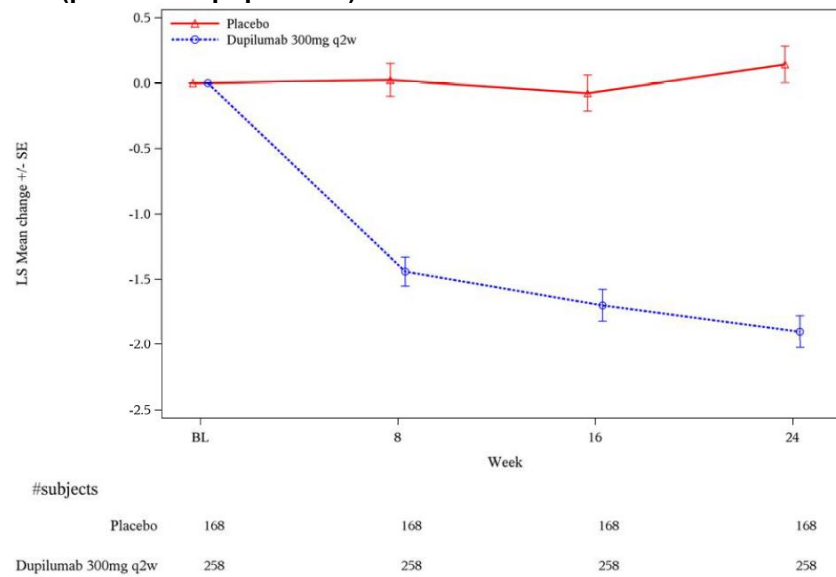
Source: Sanofi. Data on File, Supporting analyses for summary of clinical efficacy/integrated summary of effectiveness.³

Patients with comorbid asthma

Results for the changes from baseline in bilateral NPS, NC score, TSS, SNOT-22 total score, daily decreased/loss of smell score and UPSIT score up to Week 24 in patients with comorbid asthma are presented in [Figure 21](#), [Figure 22](#),

[Figure 23](#), [Figure 24](#), [Figure 25](#) and [Figure 26](#), respectively.

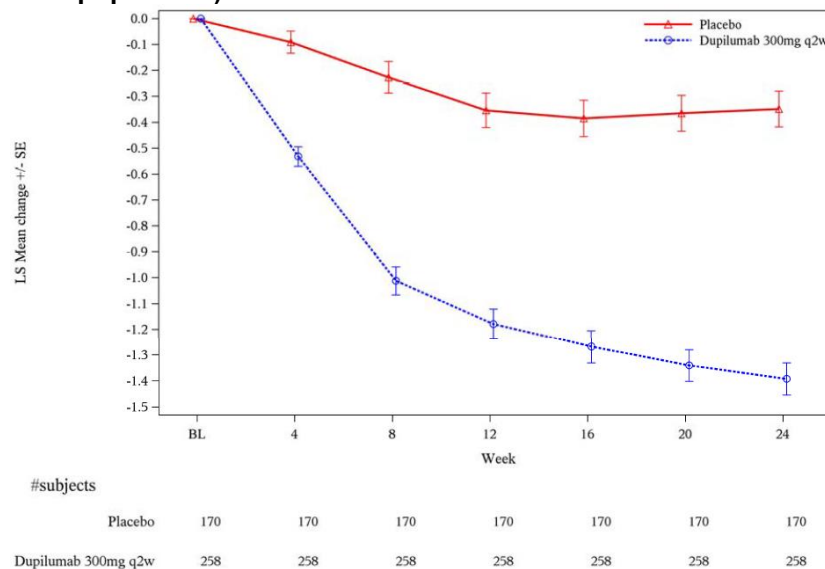
Figure 21. LS mean change from baseline in bilateral NPS up to Week 24 in patients with comorbid asthma (pooled ITT population)



BL = baseline; ITT = intention-to-treat; LS = least squares; NPS = nasal polyp score; Q2W = once every 2 weeks; SE = standard error.

Source: Sanofi. Data on File, Supporting analyses for summary of clinical efficacy/integrated summary of effectiveness.³

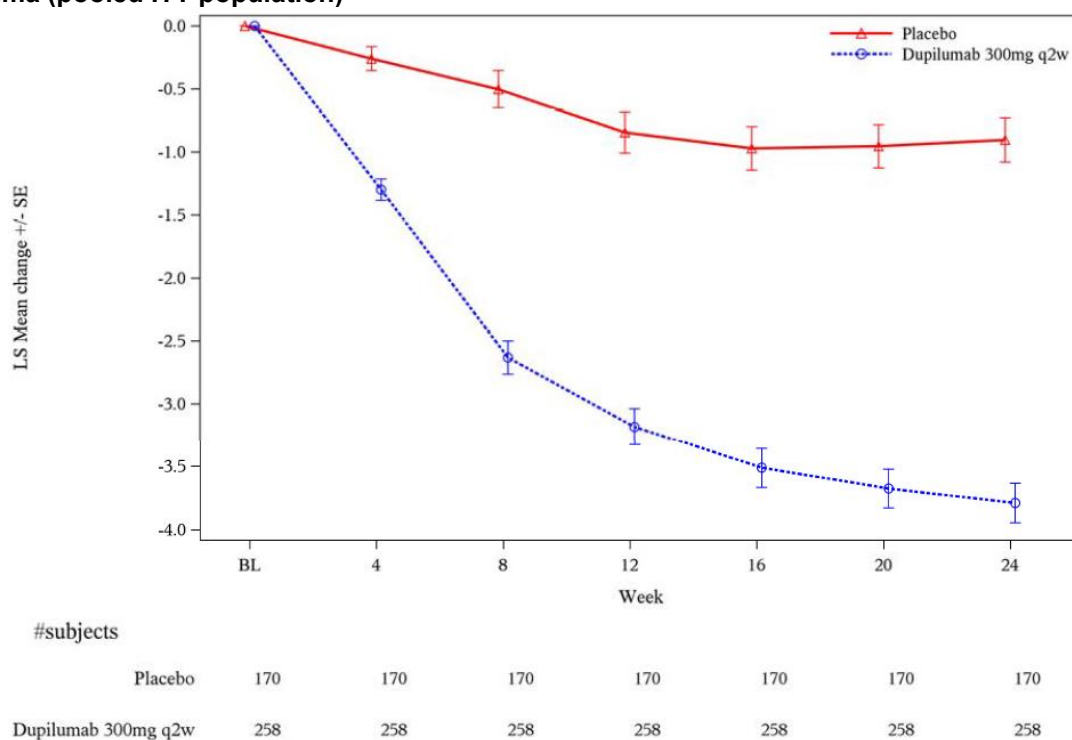
Figure 22. LS mean change from baseline in NC score up to Week 24 in patients with comorbid asthma (pooled ITT population)



BL = baseline; ITT = intention-to-treat; LS = least squares; NC = nasal congestion/obstruction; Q2W = once every 2 weeks; SE = standard error.

Source: Sanofi. Data on File, Supporting analyses for summary of clinical efficacy/integrated summary of effectiveness.³

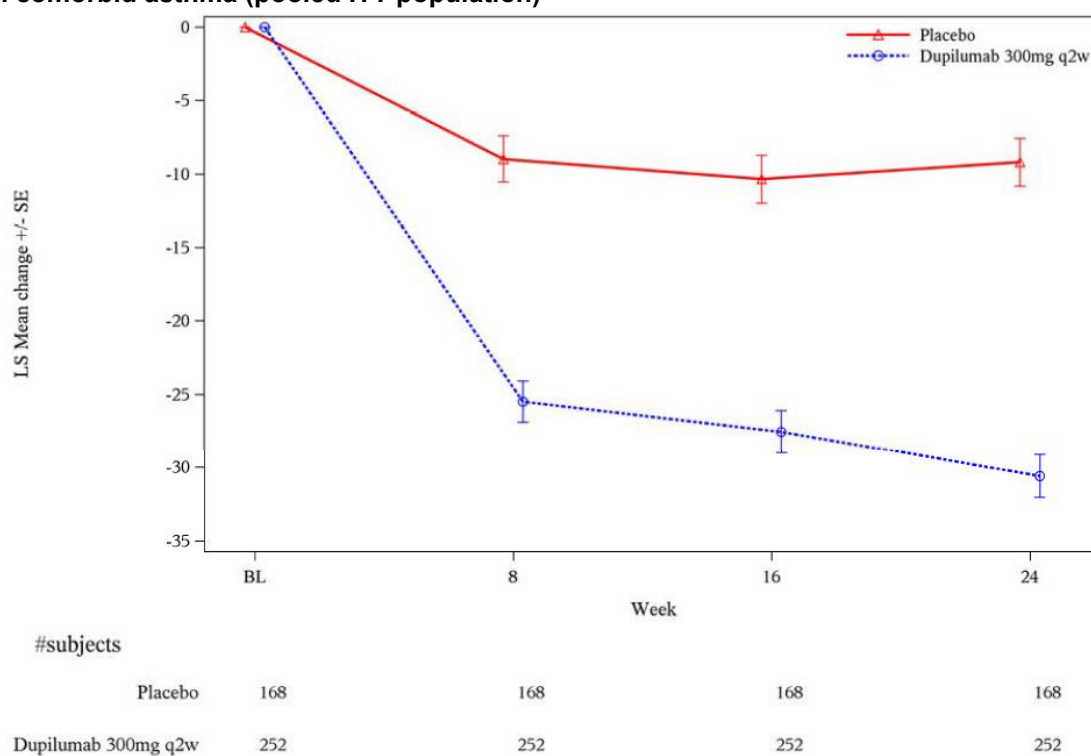
Figure 23. LS mean change from baseline in TSS up to Week 24 in patients with comorbid asthma (pooled ITT population)



BL = baseline; ITT = intention-to-treat; LS = least squares; NP = nasal polyp; Q2W = once every 2 weeks; SE = standard error; TSS = total symptom score.

Source: Sanofi. Data on File, Supporting analyses for summary of clinical efficacy/integrated summary of effectiveness.³

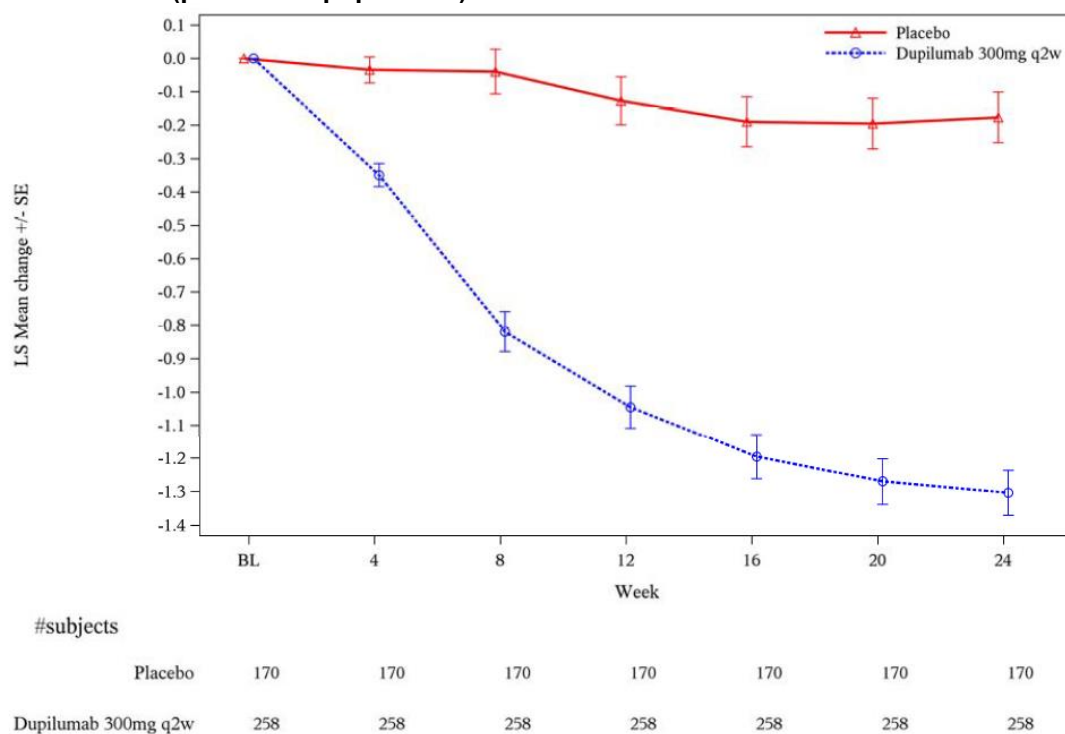
Figure 24. LS mean change from baseline in SNOT-22 total score up to Week 24 in patients with comorbid asthma (pooled ITT population)



BL = baseline; ITT = intention-to-treat; LS = least squares; NP = nasal polyp; Q2W = once every 2 weeks; SE = standard error; SNOT-22 = 22-item Sino-Nasal Outcome Test.

Source: Sanofi. Data on File, Supporting analyses for summary of clinical efficacy/integrated summary of effectiveness.³

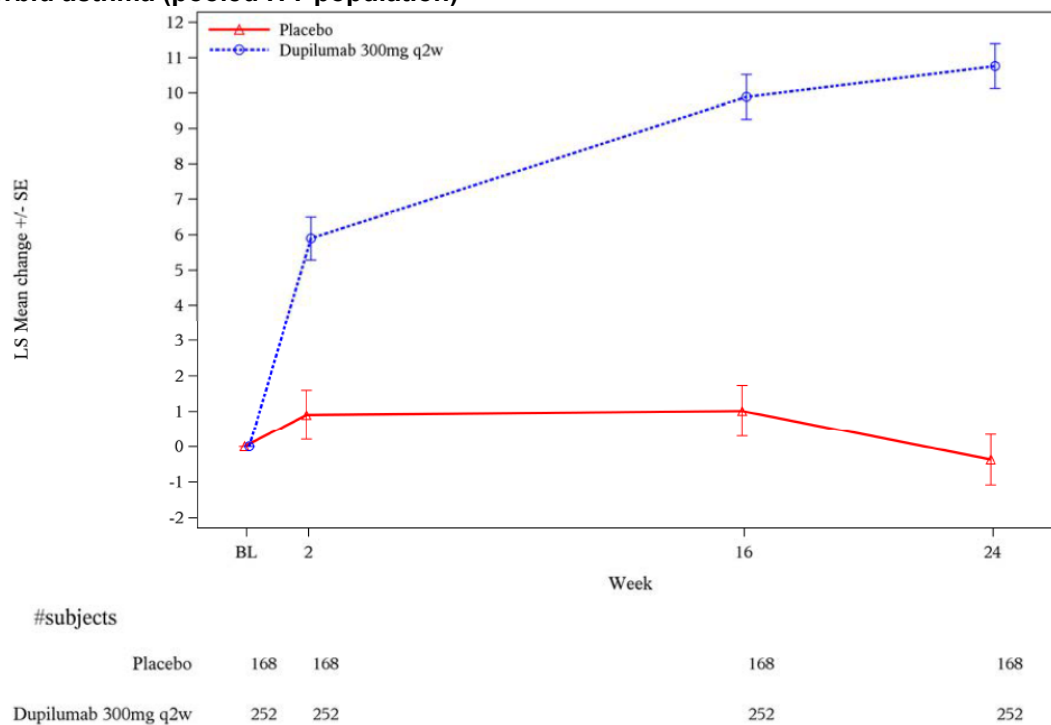
Figure 25. LS mean change from baseline in LoS score up to Week 24 in patients with comorbid asthma (pooled ITT population)



BL = baseline; ITT = intention-to-treat; LoS = loss-of-smell; LS = least squares; NP = nasal polyp; Q2W = once every 2 weeks; SE = standard error.

Source: Sanofi. Data on File, Supporting analyses for summary of clinical efficacy/integrated summary of effectiveness.³

Figure 26. LS mean change from baseline in UPSIT score up to Week 24 in patients with comorbid asthma (pooled ITT population)



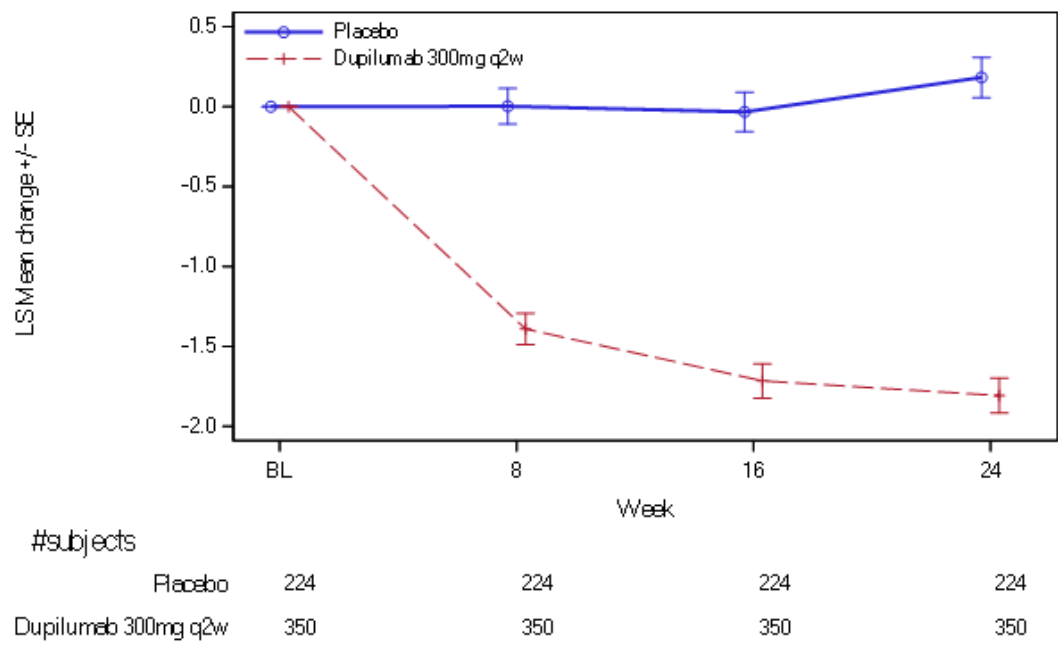
BL = baseline; ITT = intention-to-treat; LS = least squares; NP = nasal polyp; Q2W = once every 2 weeks; SE = standard error; UPSIT = University of Pennsylvania Smell Identification Test.

Source: Sanofi. Data on File, Supporting analyses for summary of clinical efficacy/integrated summary of effectiveness.³

Patients with any comorbid type 2 medical conditions

Results for the changes from baseline in bilateral NPS, NC score, TSS, SNOT-22 total score, daily decreased/loss of smell score and UPSIT score up to Week 24 in patients with any comorbid type 2 medical conditions are presented in [Figure 27](#), [Figure 28](#), [Figure 29](#), [Figure 30](#), [Figure 31](#) and [Figure 32](#), respectively.

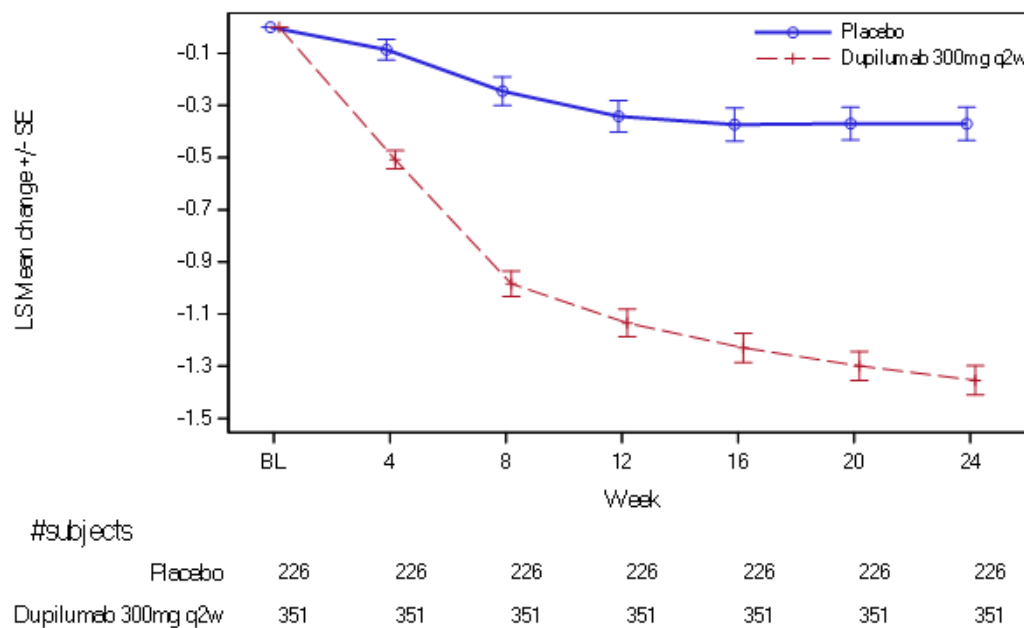
Figure 27. LS mean change from baseline in bilateral NPS up to Week 24 in patients with any comorbid type 2 medical conditions (pooled ITT population)



BL = baseline; ITT = intention-to-treat; LS = least squares; NPS = nasal polyp score; Q2W = once every 2 weeks; SE = standard error.

Source: Sanofi. Data on File, Post-hoc analyses.¹

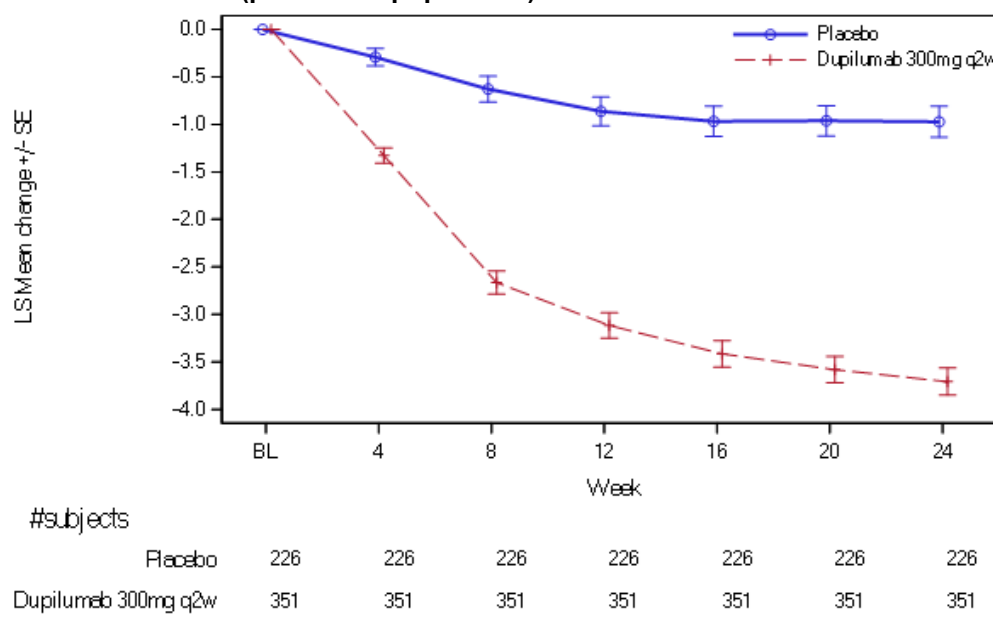
Figure 28. LS mean change from baseline in NC score up to Week 24 in patients with any comorbid type 2 medical conditions (pooled ITT population)



BL = baseline; ITT = intention-to-treat; LS = least squares; NC = nasal congestion/obstruction; Q2W = once every 2 weeks; SE = standard error.

Source: Sanofi. Data on File, Post-hoc analyses.¹

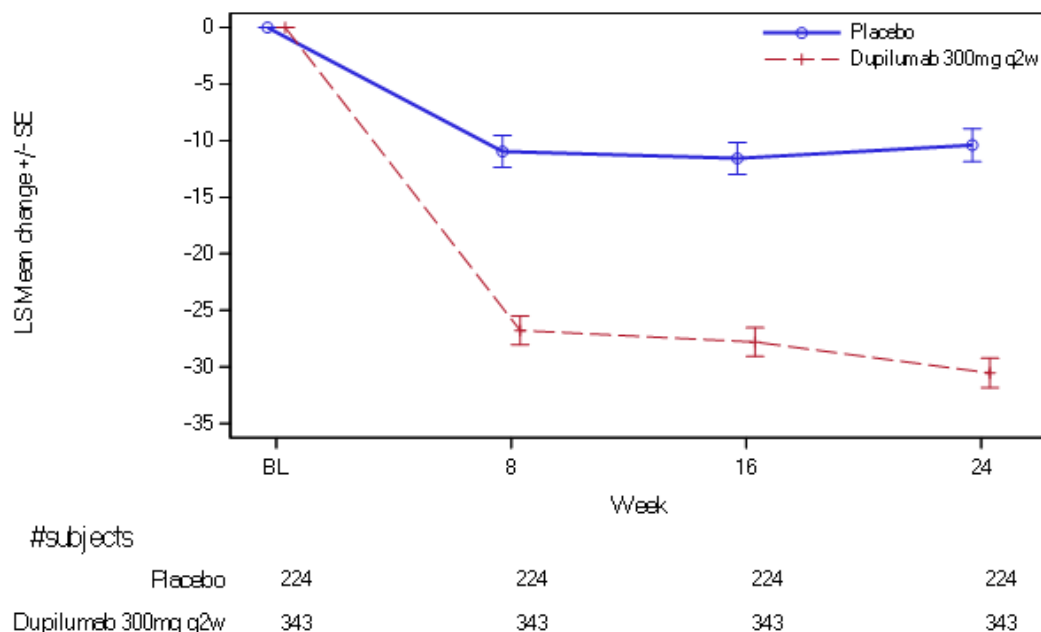
Figure 29. LS mean change from baseline in TSS up to Week 24 in patients with any comorbid type 2 medical conditions (pooled ITT population)



BL = baseline; ITT = intention-to-treat; LS = least squares; Q2W = once every 2 weeks; SE = standard error; TSS = total symptom score.

Source: Sanofi. Data on File, Post-hoc analyses.¹

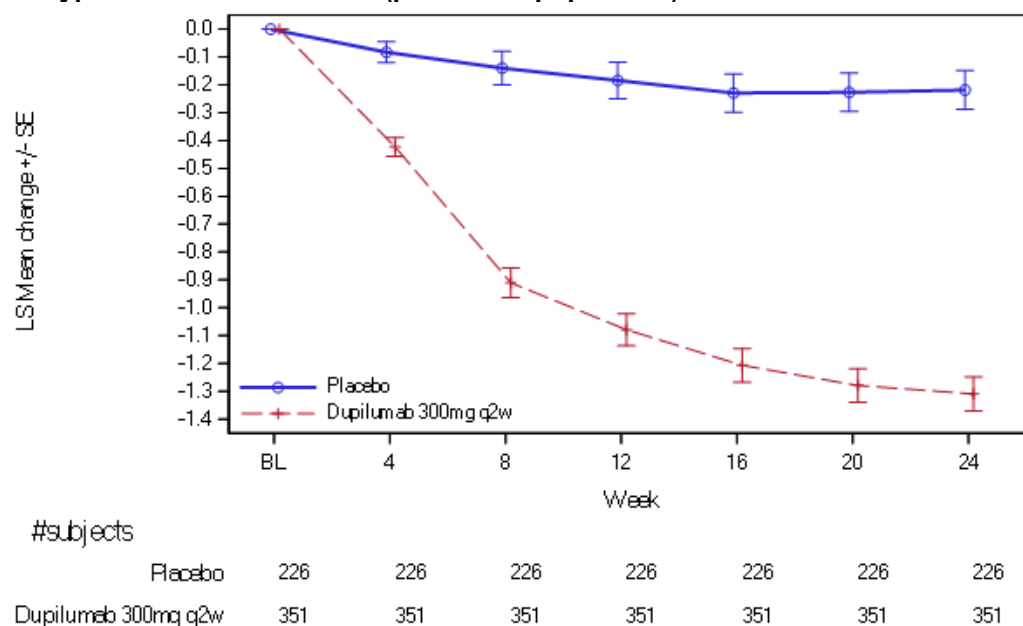
Figure 30. LS mean change from baseline in SNOT-22 total score up to Week 24 in patients with any comorbid type 2 medical conditions (pooled ITT population)



BL = baseline; ITT = intention-to-treat; LS = least squares; Q2W = once every 2 weeks; SE = standard error; SNOT-22 = 22-item Sino Nasal Outcome Test.

Source: Sanofi. Data on File, Post-hoc analyses.¹

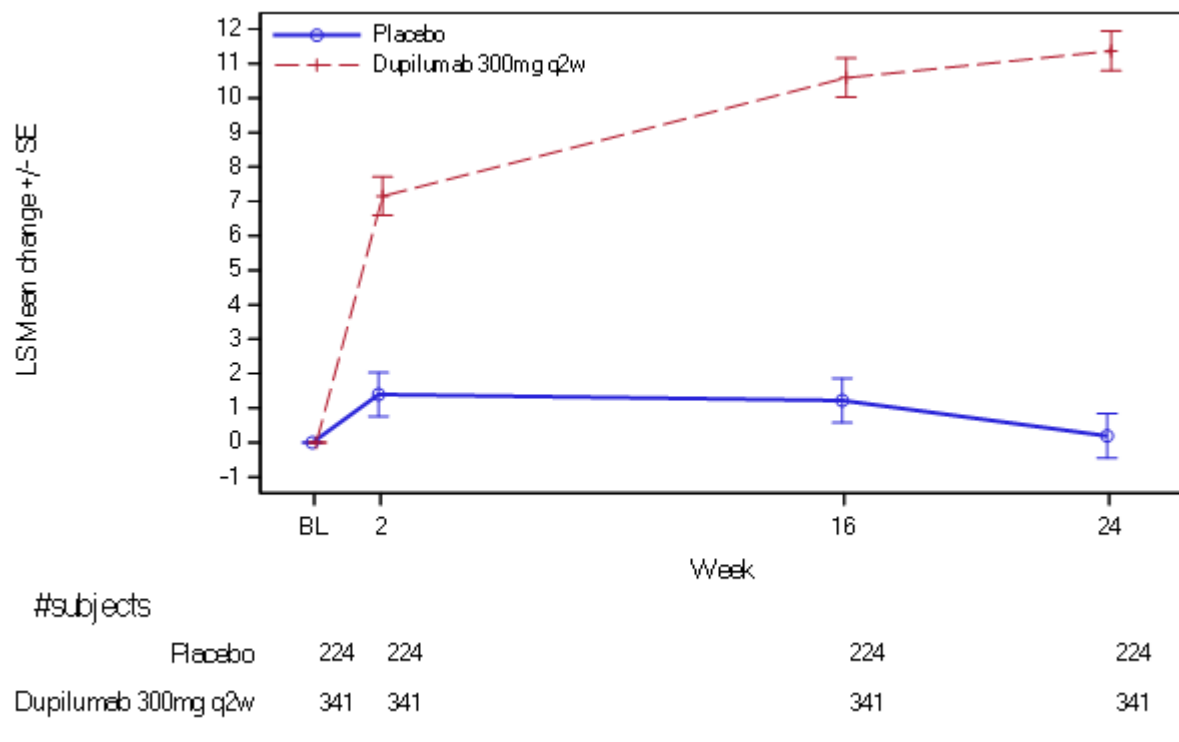
Figure 31. LS mean change from baseline in LoS score up to Week 24 in patients with any comorbid type 2 medical conditions (pooled ITT population)



BL = baseline; ITT = intention-to-treat; LoS = decreased/loss of smell; LS = least squares; Q2W = once every 2 weeks; SE = standard error.

Source: Sanofi. Data on File, Post-hoc analyses.¹

Figure 32. LS mean change from baseline in UPSIT score up to Week 24 in patients with any comorbid type 2 medical conditions (pooled ITT population)



BL = baseline; ITT = intention-to-treat; LS = least squares; Q2W = once every 2 weeks; SE = standard error; UPSIT = University of Pennsylvania Smell Identification Test.
Source: Sanofi. Data on File, Post-hoc analyses.¹

Patients with prior NP surgery

Results for the changes from baseline in bilateral NPS, NC score, TSS, SNOT-22 total score, daily decreased/loss of smell score and UPSIT score up to Week 24 in patients with prior NP surgery are presented in [Figure 33](#), [Figure 34](#), [Figure 35](#), [Figure 36](#), [Figure 37](#) and [Figure 38](#), respectively.

Figure 33. LS mean change from baseline in bilateral NPS up to Week 24 in patients with prior NP surgery (pooled ITT population)

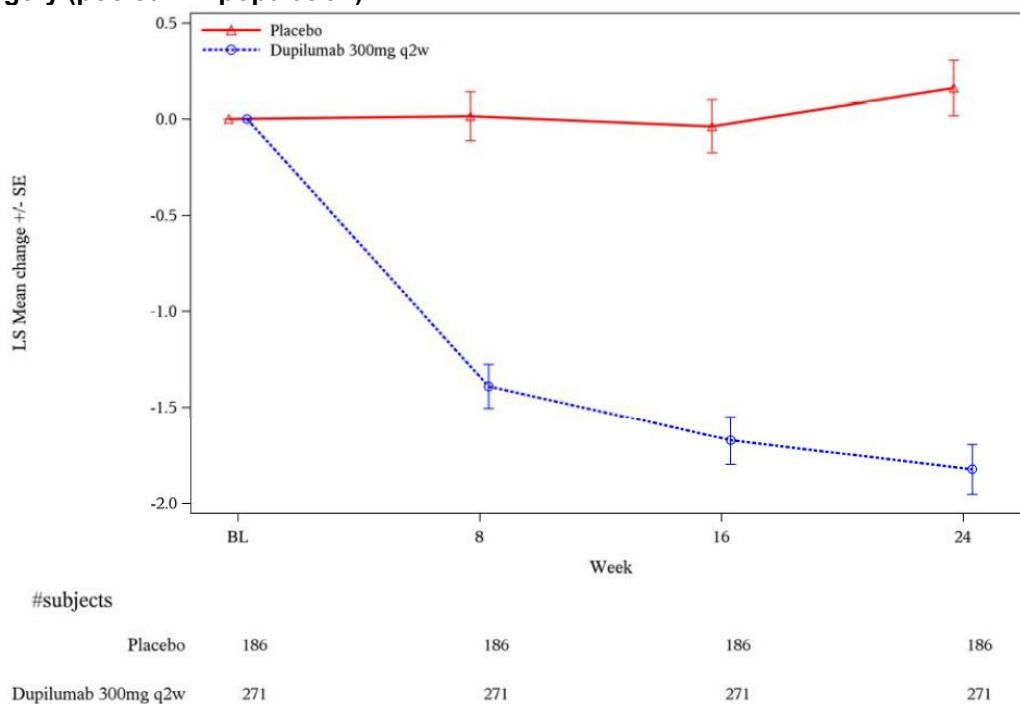


Figure 34. LS mean change from baseline in NC score up to Week 24 in patients with prior NP surgery (pooled ITT population)

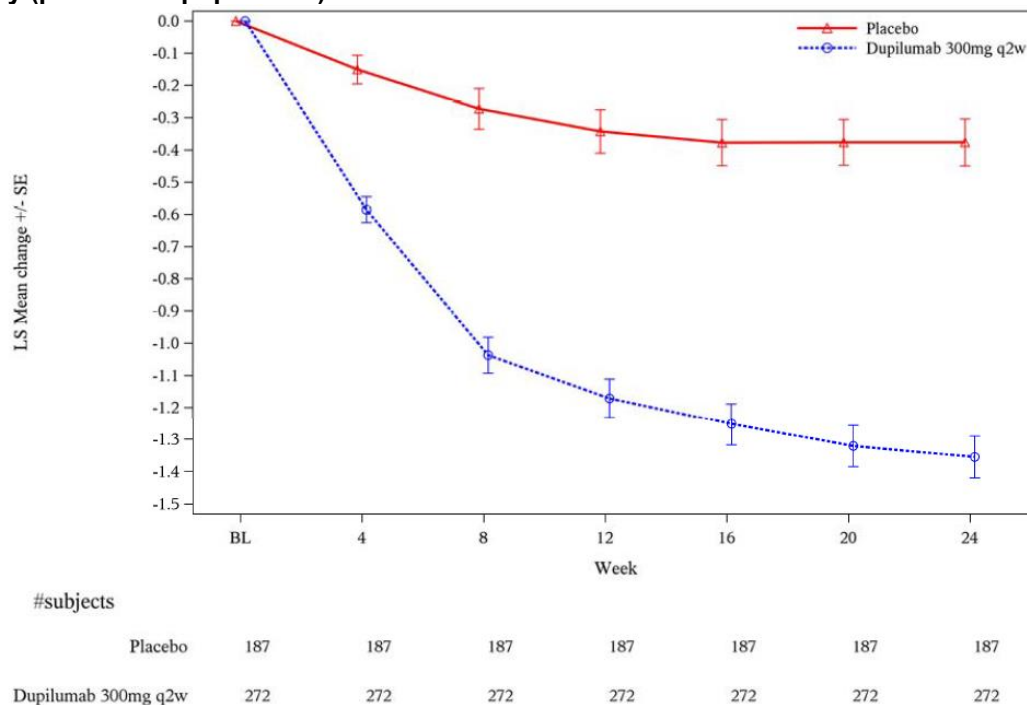
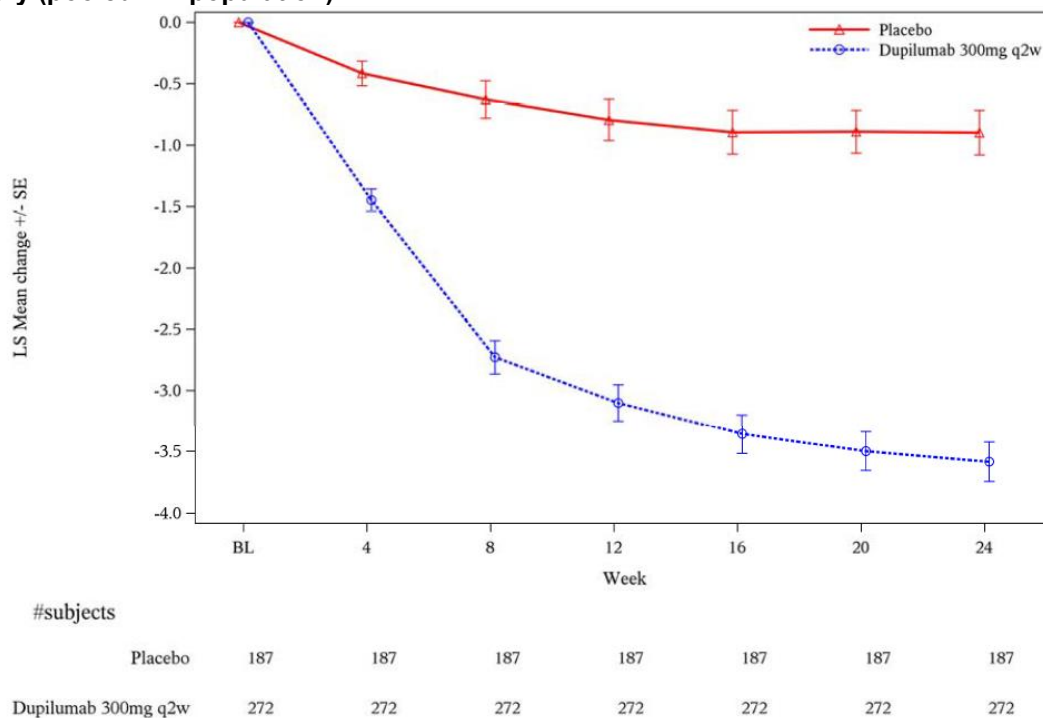


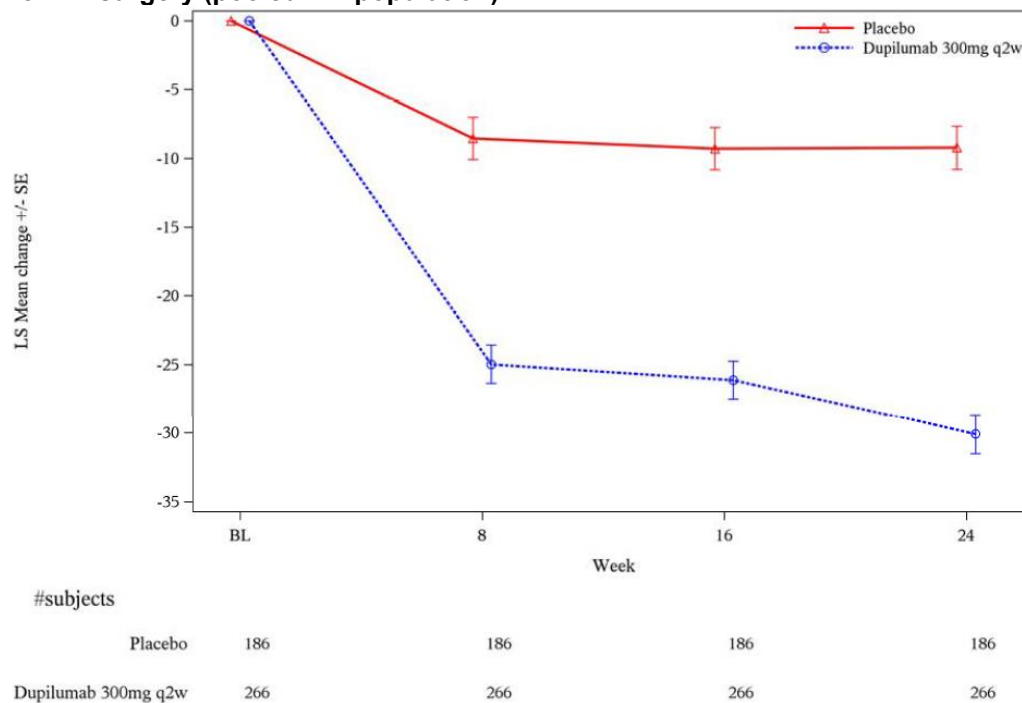
Figure 35. LS mean change from baseline in TSS up to Week 24 in patients with prior NP surgery (pooled ITT population)



BL = baseline; ITT = intention-to-treat; LS = least squares; NP = nasal polyp; Q2W = once every 2 weeks; SE = standard error; TSS = total symptom score.

Source: Sanofi. Data on File, Supporting analyses for summary of clinical efficacy/integrated summary of effectiveness.³

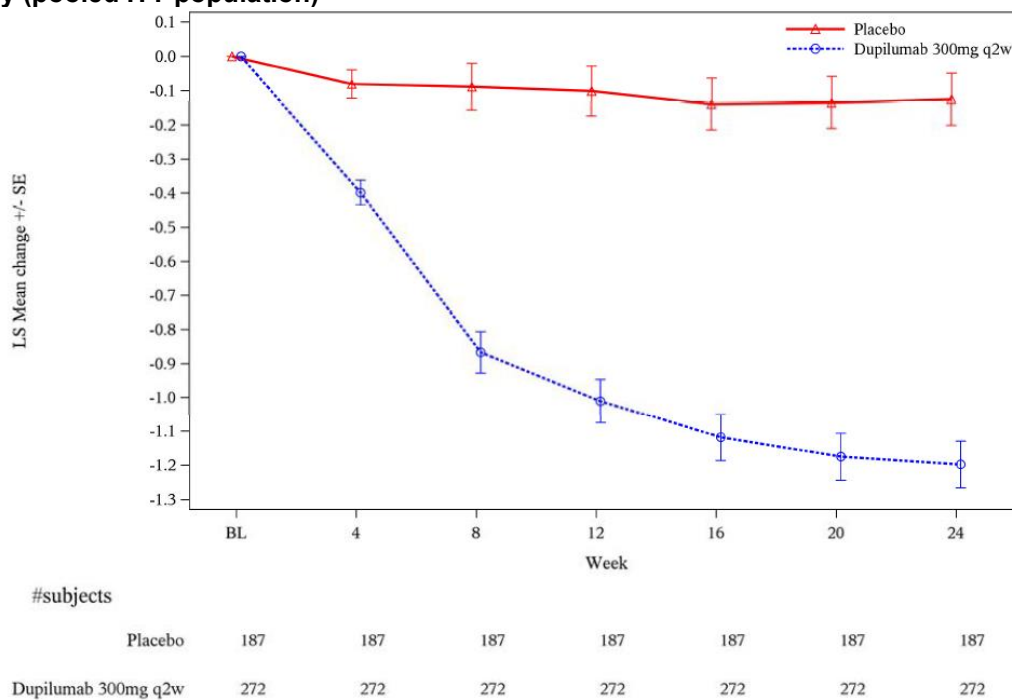
Figure 36. LS mean change from baseline in SNOT-22 total score up to Week 24 in patients with prior NP surgery (pooled ITT population)



BL = baseline; ITT = intention-to-treat; LS = least squares; NP = nasal polyp; Q2W = once every 2 weeks; SE = standard error; SNOT-22 = 22-item Sino-Nasal Outcome Test.

Source: Sanofi. Data on File, Supporting analyses for summary of clinical efficacy/integrated summary of effectiveness.³

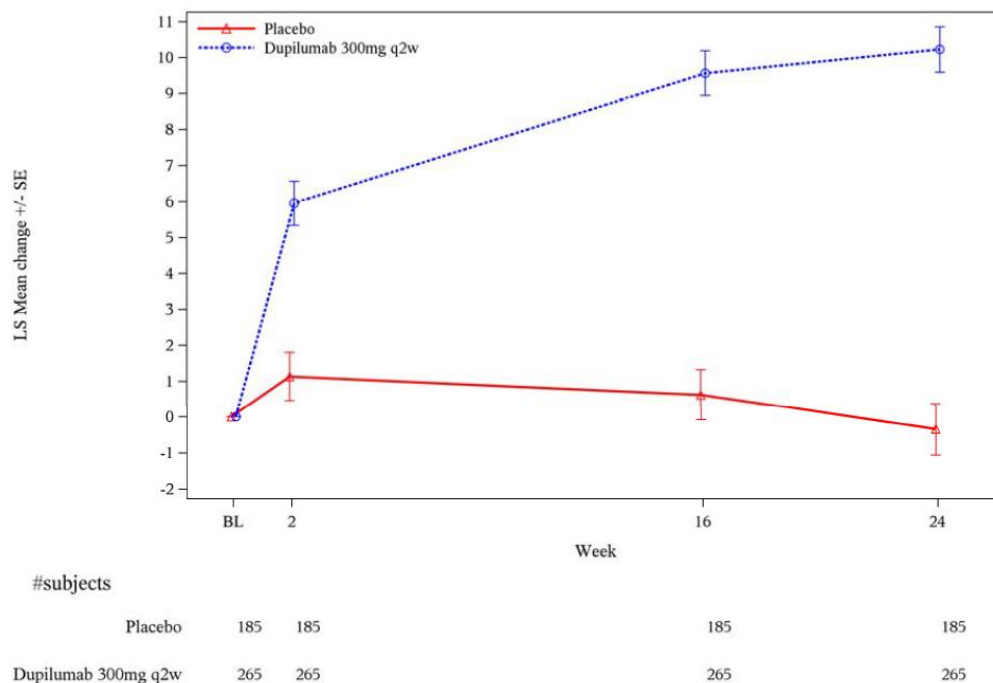
Figure 37. LS mean change from baseline in LoS score up to Week 24 in patients with prior NP surgery (pooled ITT population)



BL = baseline; ITT = intention-to-treat; LoS = loss-of-smell; LS = least squares; NP = nasal polyp; Q2W = once every 2 weeks; SE = standard error.

Source: Sanofi. Data on File, Supporting analyses for summary of clinical efficacy/integrated summary of effectiveness.³

Figure 38. LS mean change from baseline in UPSIT score up to Week 24 in patients with prior NP surgery (pooled ITT population)



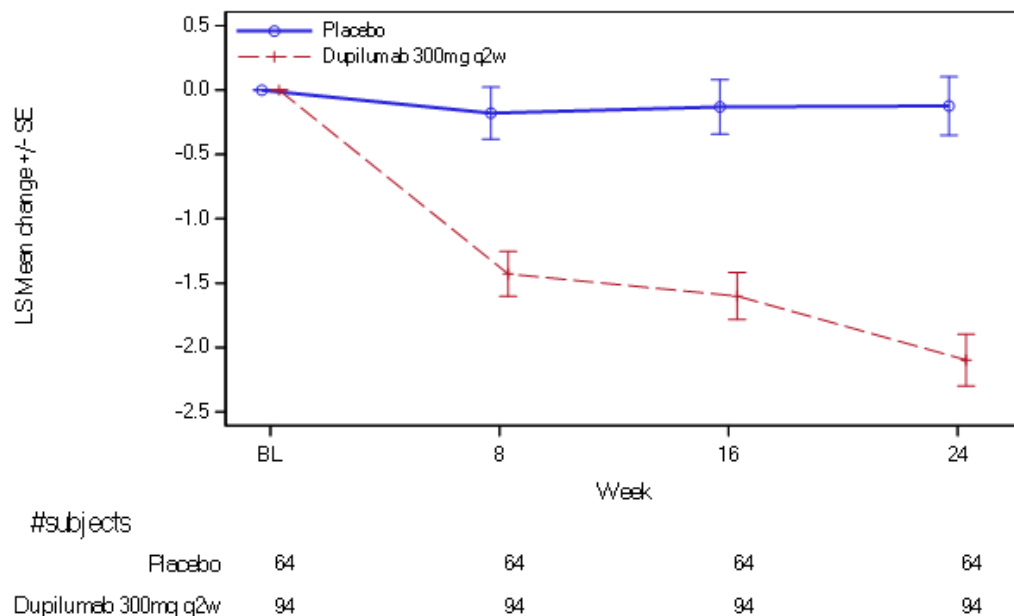
BL = baseline; ITT = intention-to-treat; LS = least squares; NP = nasal polyp; Q2W = once every 2 weeks; SE = standard error; UPSIT = University of Pennsylvania Smell Identification Test.

Source: Sanofi. Data on File, Supporting analyses for summary of clinical efficacy/integrated summary of effectiveness.³

Patients with prior NP surgery and comorbid NSAID-ERD

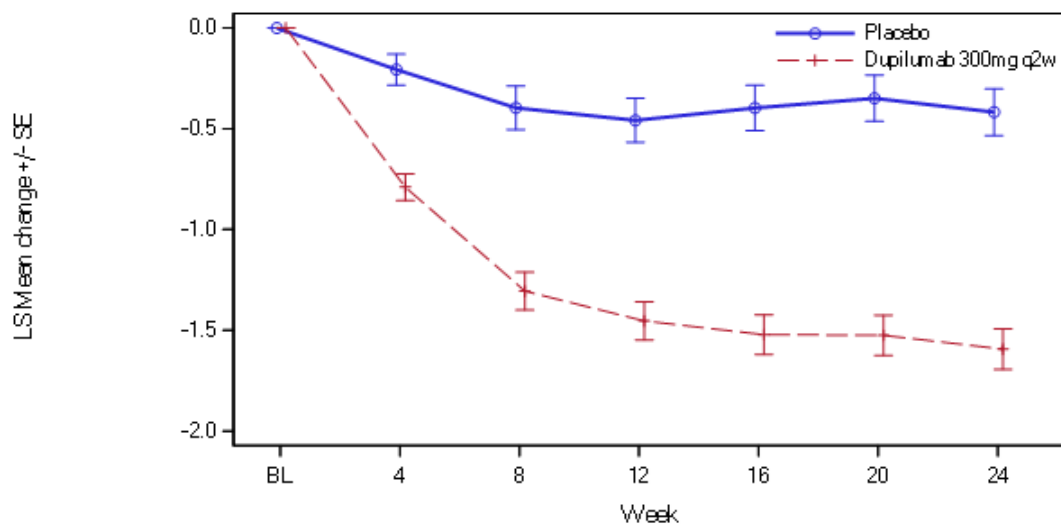
Results for the changes from baseline in bilateral NPS, NC score, TSS, SNOT-22 total score, daily decreased/loss of smell score and UPSIT score up to Week 24 in patients with prior NP surgery and comorbid NSAID-ERD are presented in [Figure 39](#), [Figure 40](#), [Figure 41](#), [Figure 42](#), [Figure 43](#) and [Figure 44](#), respectively.

Figure 39. LS mean change from baseline in bilateral NPS up to Week 24 in patients with prior NP surgery and comorbid NSAID-ERD (pooled ITT population)



BL = baseline; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NP = nasal polyp; NPS = nasal polyp score; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every 2 weeks; SE = standard error.
Source: Sanofi. Data on File, Post-hoc analyses.¹

Figure 40. LS mean change from baseline in NC score up to Week 24 in patients with prior NP surgery and comorbid NSAID-ERD (pooled ITT population)

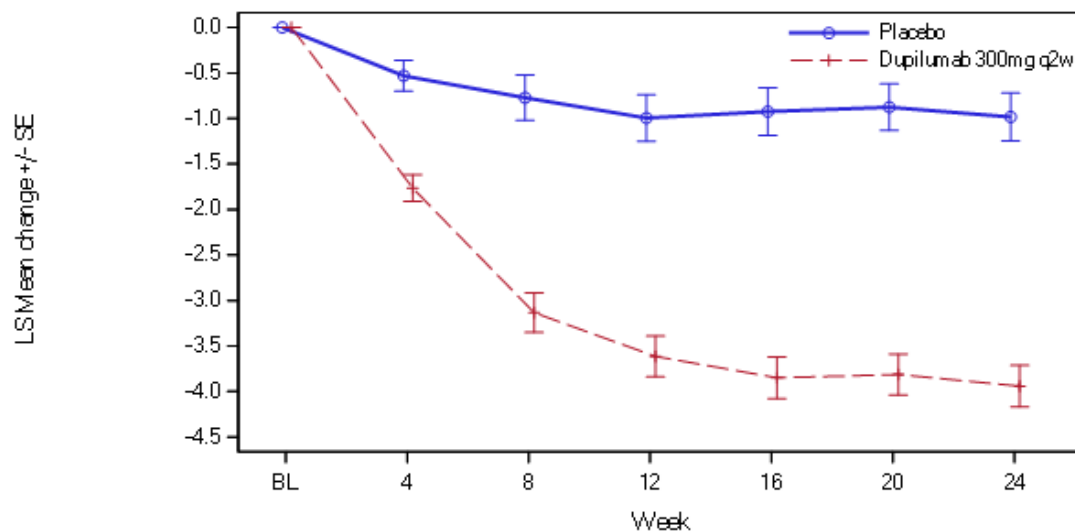


#subjects							
Placebo	65	65	65	65	65	65	65
Dupilumab 300mg q2w	94	94	94	94	94	94	94

BL = baseline; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NC = nasal congestion/obstruction; NP = nasal polyp; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every 2 weeks; SE = standard error.

Source: Sanofi. Data on File, Post-hoc analyses.¹

Figure 41. LS mean change from baseline in TSS up to Week 24 in patients with prior NP surgery and comorbid NSAID-ERD (pooled ITT population)

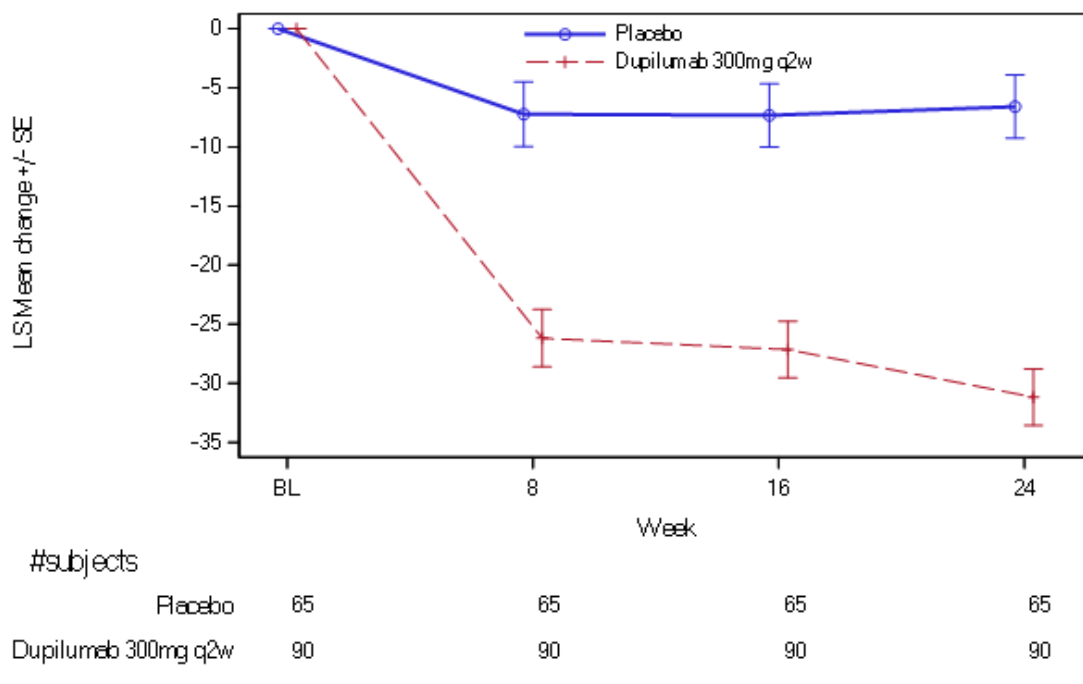


#subjects							
Placebo	65	65	65	65	65	65	65
Dupilumab 300mg q2w	94	94	94	94	94	94	94

BL = baseline; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NP = nasal polyp; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every 2 weeks; SE = standard error; TSS = total symptom score.

Source: Sanofi. Data on File, Post-hoc analyses.¹

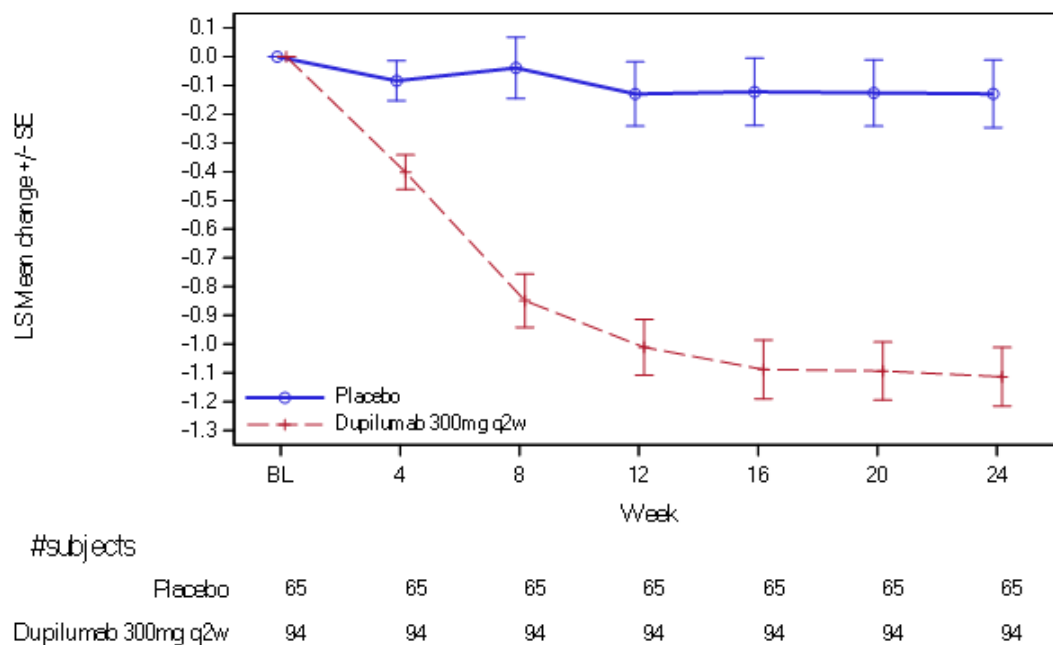
Figure 42. LS mean change from baseline in SNOT-22 total score up to Week 24 in patients with prior NP surgery and comorbid NSAID-ERD (pooled ITT population)



BL = baseline; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NP = nasal polyp; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every 2 weeks; SE = standard error; SNOT-22 = 22-item Sino Nasal Outcome Test.

Source: Sanofi. Data on File, Post-hoc analyses.¹

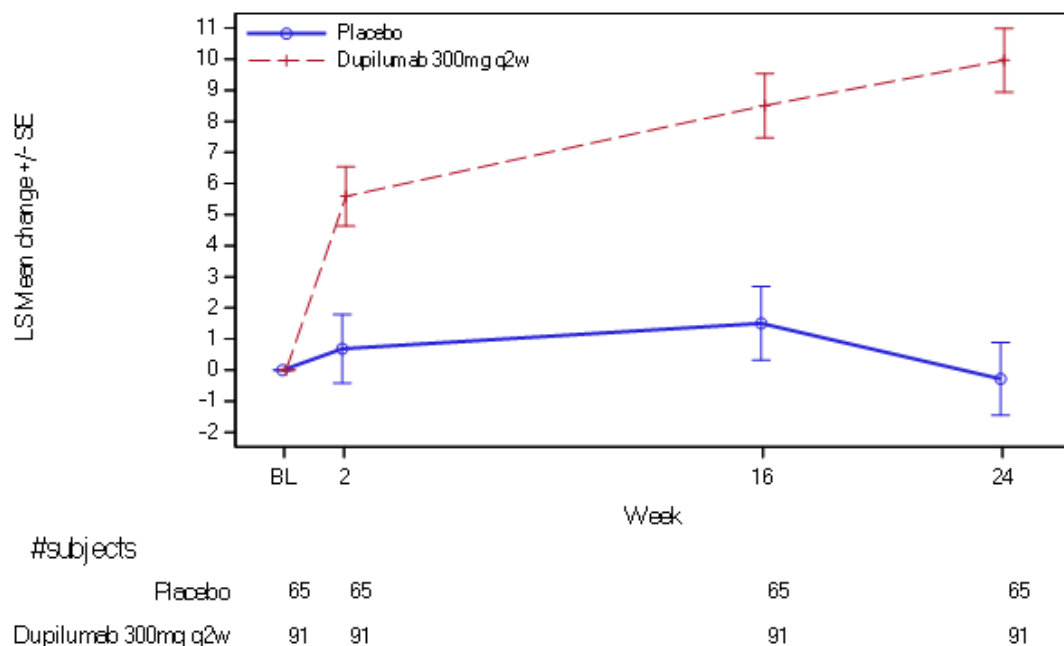
Figure 43. LS mean change from baseline in LoS score up to Week 24 in patients with prior NP surgery and comorbid NSAID-ERD (pooled ITT population)



BL = baseline; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LoS = decreased/loss of smell; LS = least squares; NP = nasal polyp; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every 2 weeks; SE = standard error.

Source: Sanofi. Data on File, Post-hoc analyses.¹

Figure 44. LS mean change from baseline in UPSIT score up to Week 24 in patients with prior NP surgery and comorbid NSAID-ERD (pooled ITT population)



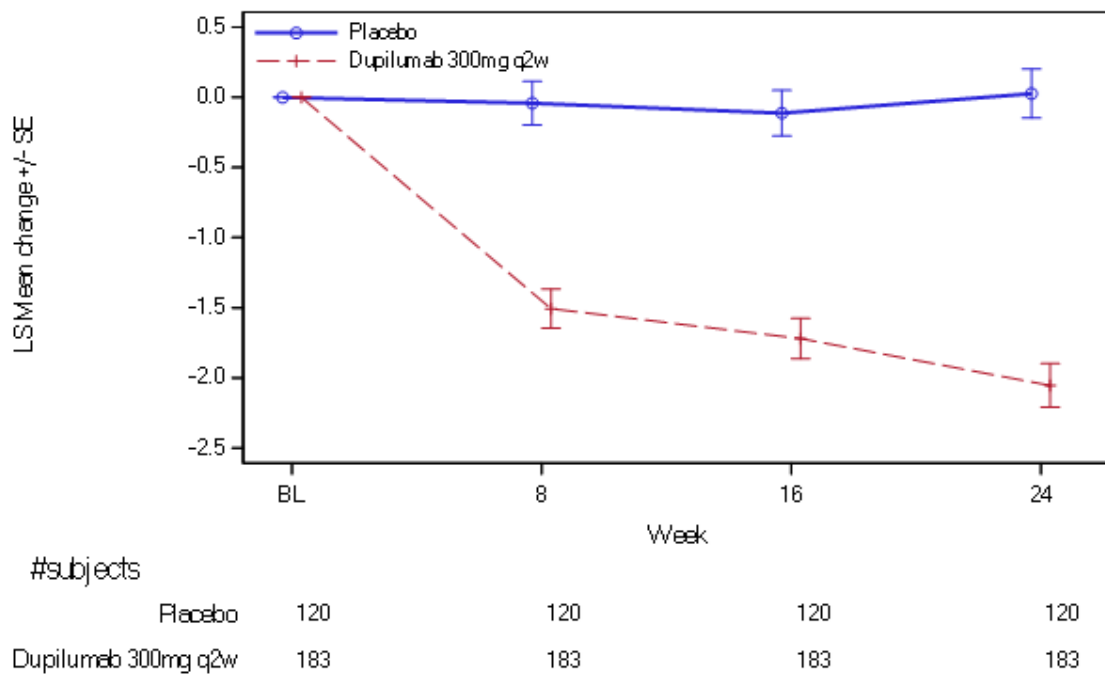
BL = baseline; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NP = nasal polyp; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every 2 weeks; SE = standard error; UPSIT = University of Pennsylvania Smell Identification Test.

Source: Sanofi. Data on File, Post-hoc analyses.¹

Patients with prior NP and comorbid asthma

Results for the changes from baseline in bilateral NPS, NC score, TSS, SNOT-22 total score, daily decreased/loss of smell score and UPSIT score up to Week 24 in patients with prior NP surgery and comorbid asthma are presented in [Figure 45](#), [Figure 46](#), [Figure 47](#), [Figure 48](#), [Figure 49](#) and [Figure 50](#), respectively.

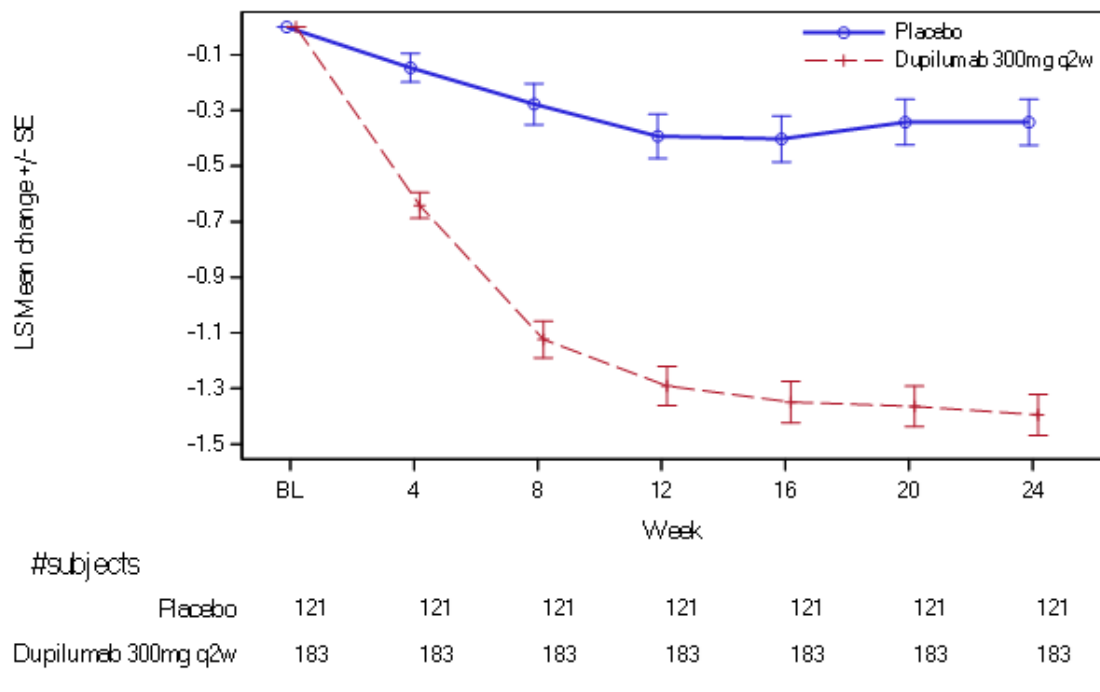
Figure 45. LS mean change from baseline in bilateral NPS up to Week 24 in patients with prior NP surgery and comorbid asthma (pooled ITT population)



BL = baseline; ITT = intention-to-treat; LS = least squares; NP = nasal polyp; NPS = nasal polyp score; Q2W = once every 2 weeks; SE = standard error.

Source: Sanofi. Data on File, Post-hoc analyses.¹

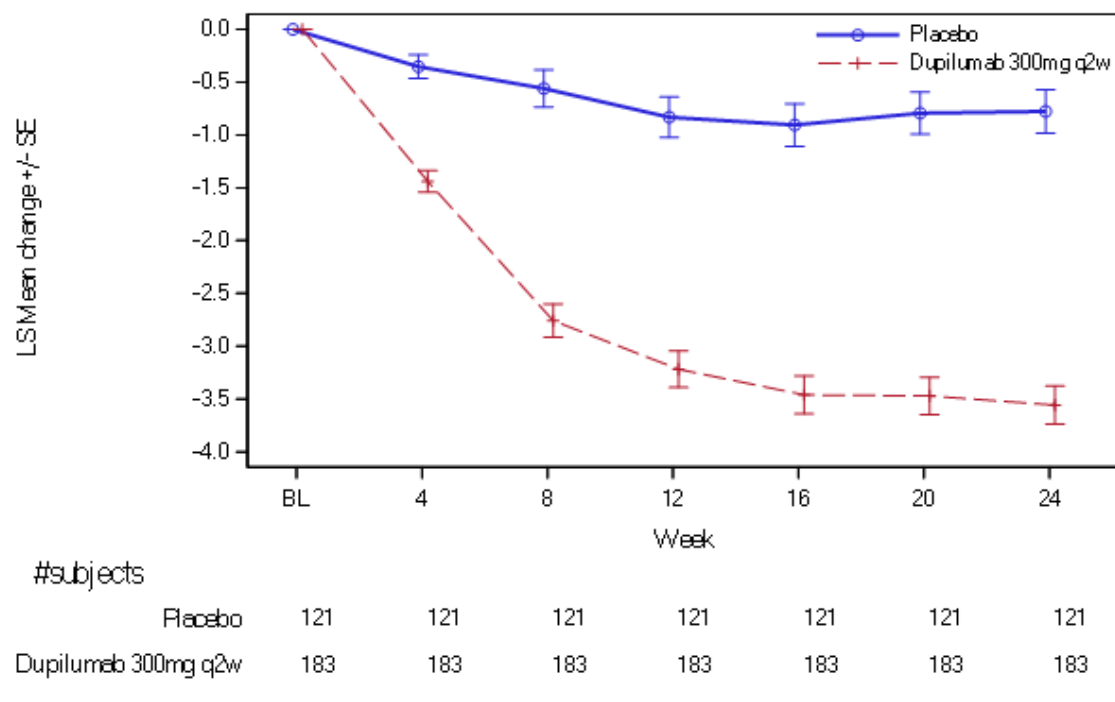
Figure 46. LS mean change from baseline in NC score up to Week 24 in patients with prior NP surgery and comorbid asthma (pooled ITT population)



BL = baseline; ITT = intention-to-treat; LS = least squares; NC = nasal congestion/obstruction; NP = nasal polyp; Q2W = once every 2 weeks; SE = standard error.

Source: Sanofi. Data on File, Post-hoc analyses.¹

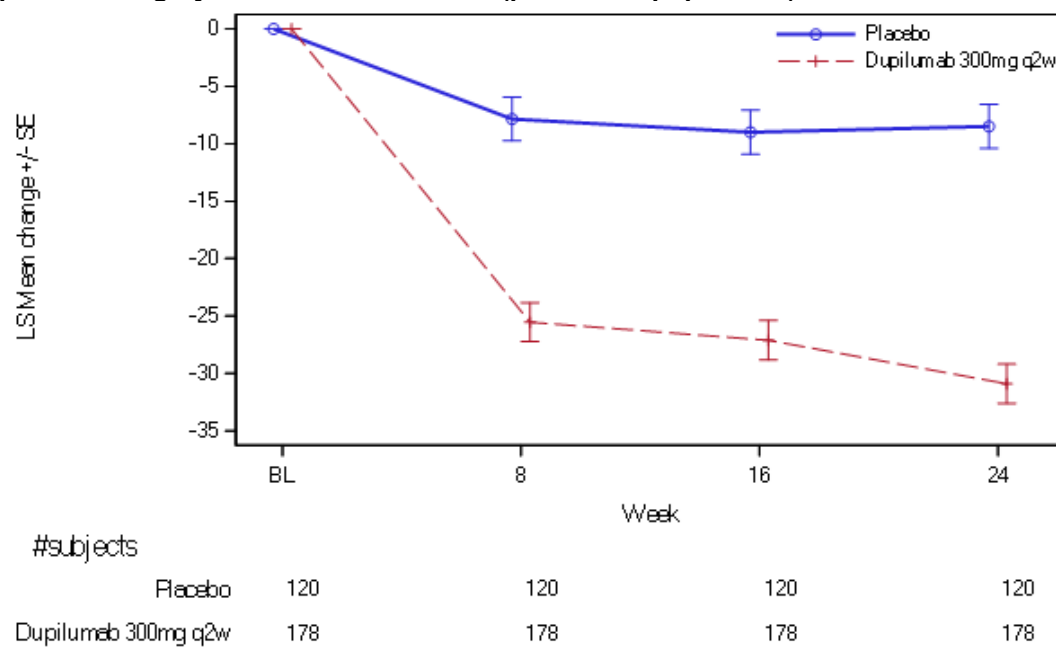
Figure 47. LS mean change from baseline in TSS up to Week 24 in patients with prior NP surgery and comorbid asthma (pooled ITT population)



BL = baseline; ITT = intention-to-treat; LS = least squares; NP = nasal polyp; Q2W = once every 2 weeks; SE = standard error; TSS = total symptom score.

Source: Sanofi. Data on File, Post-hoc analyses.¹

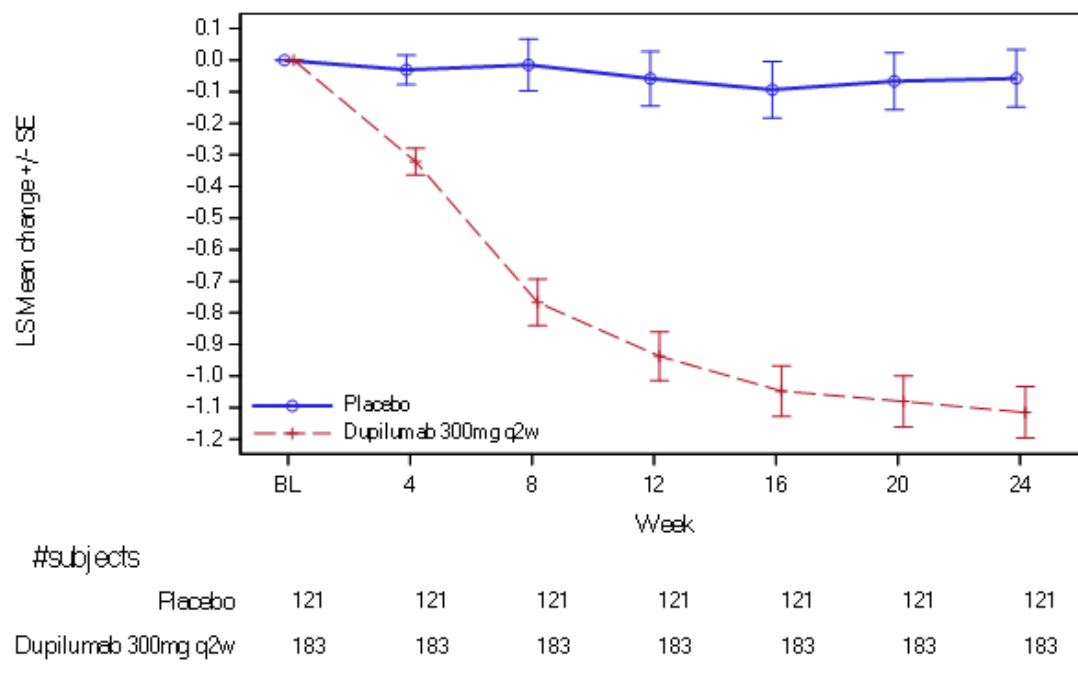
Figure 48. LS mean change from baseline in SNOT-22 total score up to Week 24 in patients with prior NP surgery and comorbid asthma (pooled ITT population)



BL = baseline; ITT = intention-to-treat; LS = least squares; NP = nasal polyp; Q2W = once every 2 weeks; SE = standard error; SNOT-22 = 22-item Sino Nasal Outcome Test.

Source: Sanofi. Data on File, Post-hoc analyses.¹

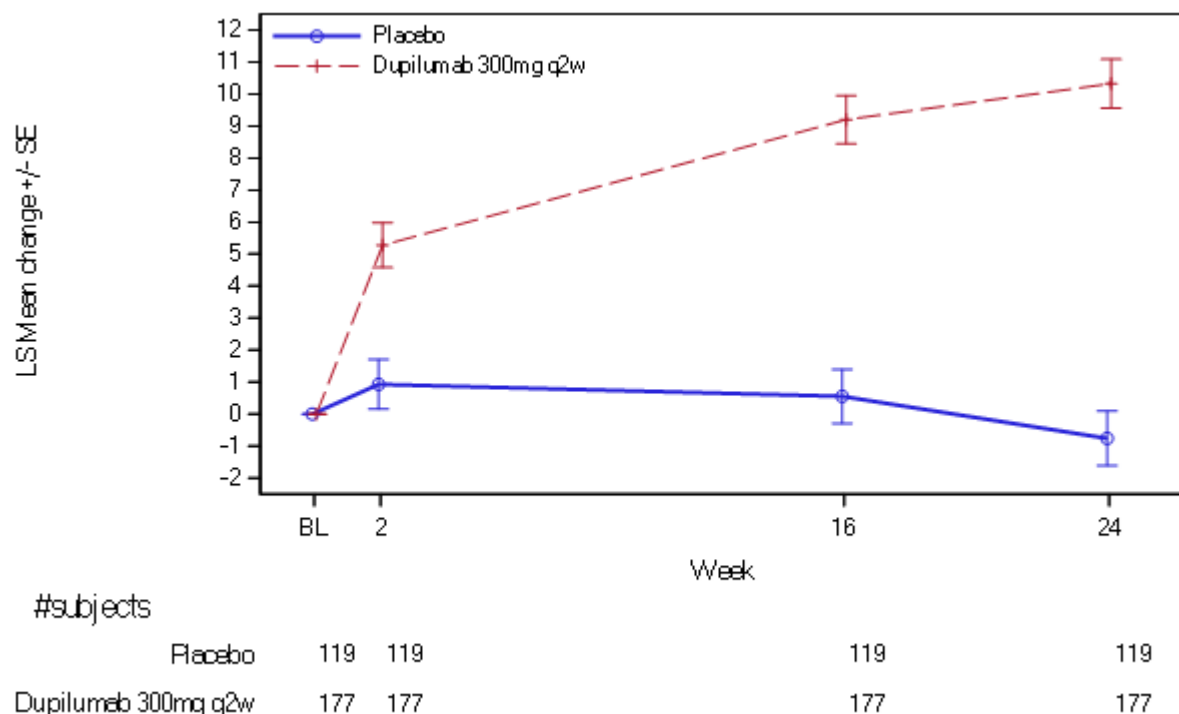
Figure 49. LS mean change from baseline in LoS score up to Week 24 in patients with prior NP surgery and comorbid asthma (pooled ITT population)



BL = baseline; ITT = intention-to-treat; LoS = decreased/loss of smell; LS = least squares; NP = nasal polyp; Q2W = once every 2 weeks; SE = standard error.

Source: Sanofi. Data on File, Post-hoc analyses.¹

Figure 50. LS mean change from baseline in UPSIT score up to Week 24 in patients with prior NP surgery and comorbid asthma (pooled ITT population)



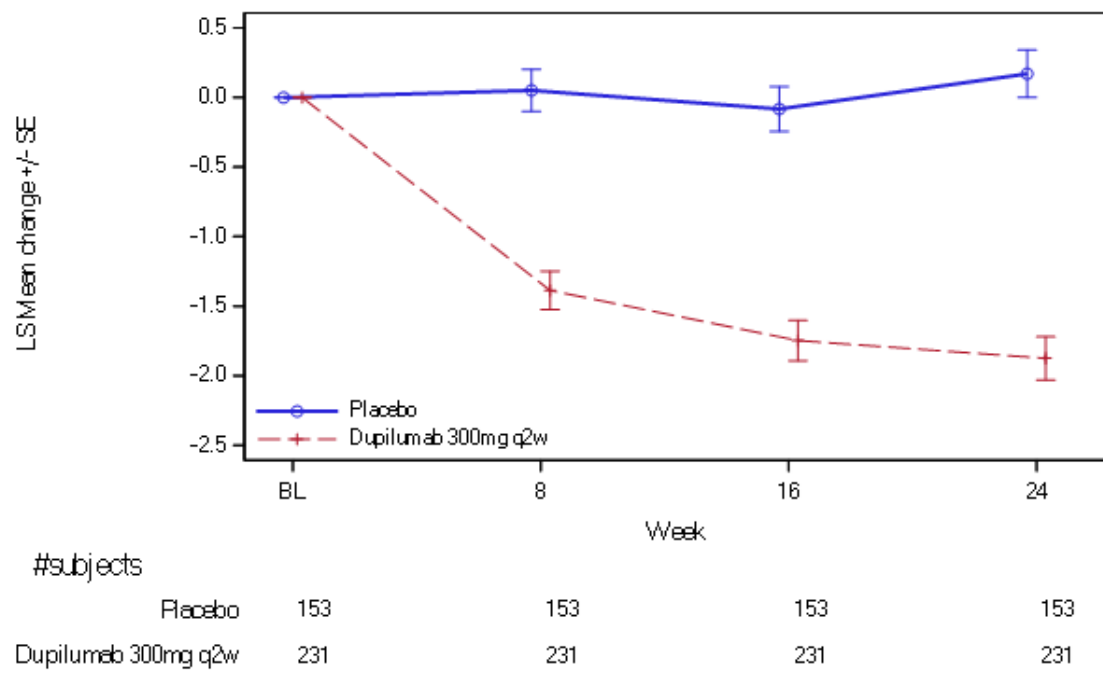
BL = baseline; ITT = intention-to-treat; LS = least squares; NP = nasal polyp; Q2W = once every 2 weeks; SE = standard error; UPSIT = University of Pennsylvania Smell Identification Test.

Source: Sanofi. Data on File, Post-hoc analyses.¹

Patients with prior NP surgery and any comorbid type 2 medical conditions

Results for the changes from baseline in bilateral NPS, NC score, TSS, SNOT-22 total score, daily decreased/loss of smell score and UPSIT score up to Week 24 in patients with prior NP surgery and any comorbid type 2 medical conditions are presented in [Figure 51](#), [Figure 52](#), [Figure 53](#), [Figure 54](#), [Figure 55](#) and [Figure 56](#), respectively.

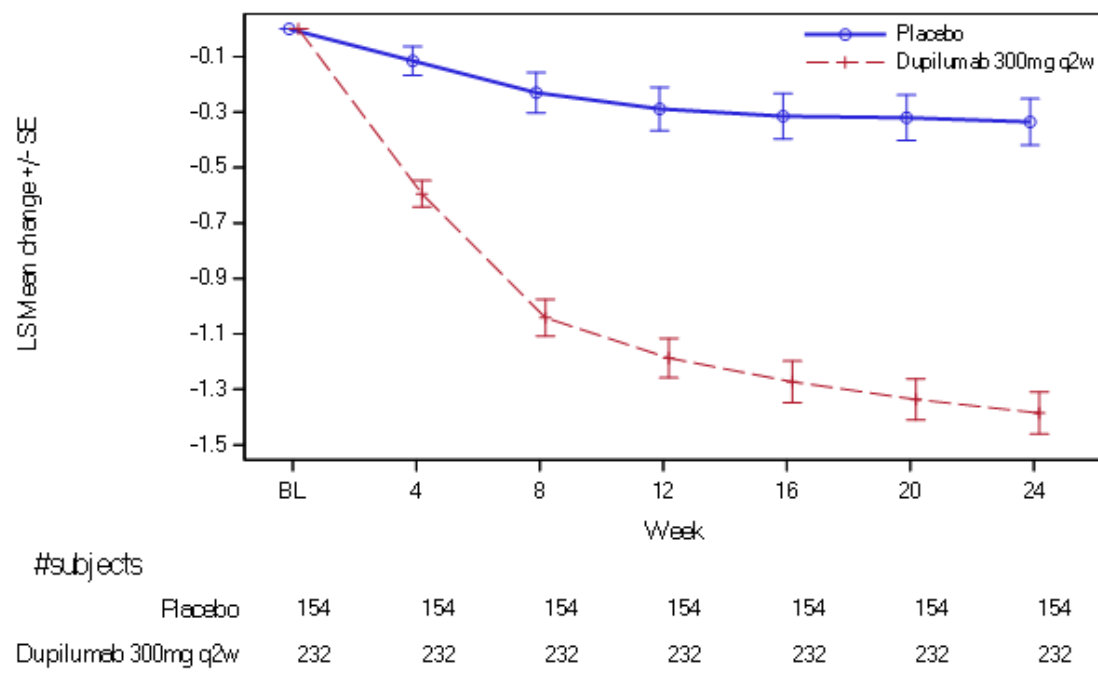
Figure 51. LS mean change from baseline in bilateral NPS up to Week 24 in patients with prior NP surgery and any comorbid type 2 medical conditions (pooled ITT population)



BL = baseline; ITT = intention-to-treat; LS = least squares; NP = nasal polyp; NPS = nasal polyp score; Q2W = once every 2 weeks; SE = standard error.

Source: Sanofi. Data on File, Post-hoc analyses.¹

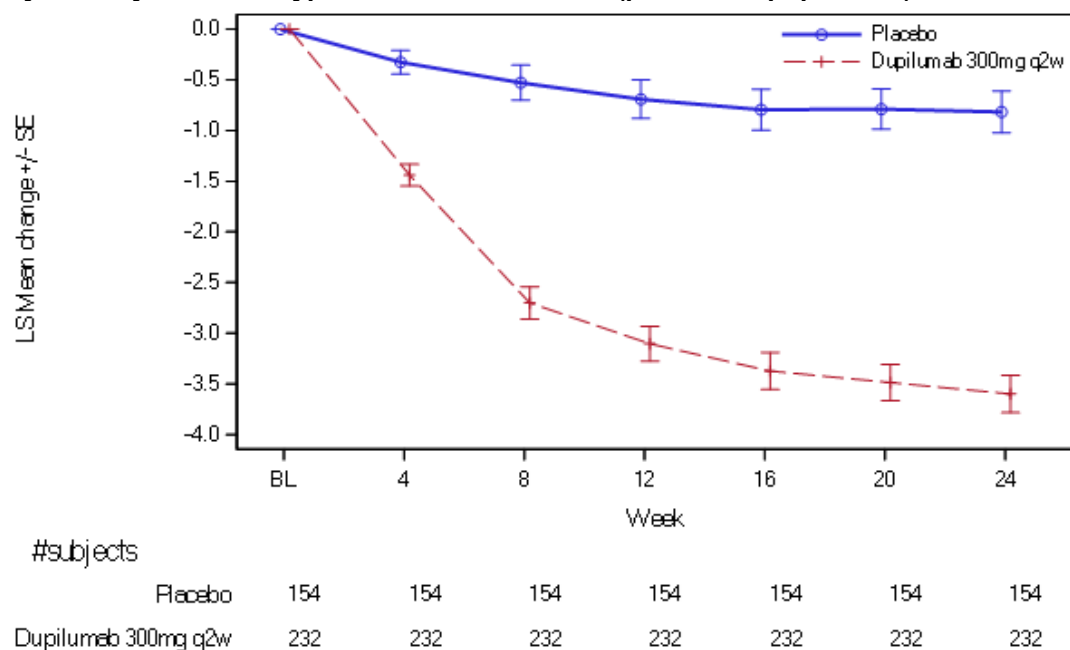
Figure 52. LS mean change from baseline in NC score up to Week 24 in patients with prior NP surgery and any comorbid type 2 medical conditions (pooled ITT population)



BL = baseline; ITT = intention-to-treat; LS = least squares; NC = nasal congestion/obstruction; NP = nasal polyp; Q2W = once every 2 weeks; SE = standard error.

Source: Sanofi. Data on File, Post-hoc analyses.¹

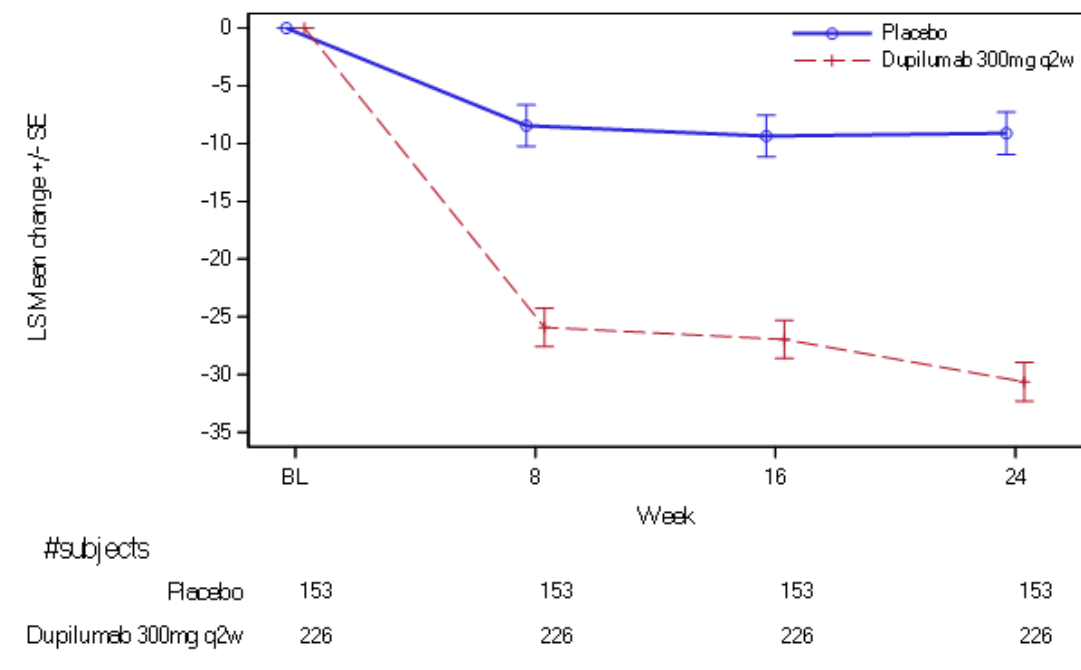
Figure 53. LS mean change from baseline in TSS up to Week 24 in patients with prior NP surgery and any comorbid type 2 medical conditions (pooled ITT population)



BL = baseline; ITT = intention-to-treat; LS = least squares; NP = nasal polyp; Q2W = once every 2 weeks; SE = standard error; TSS = total symptom score.

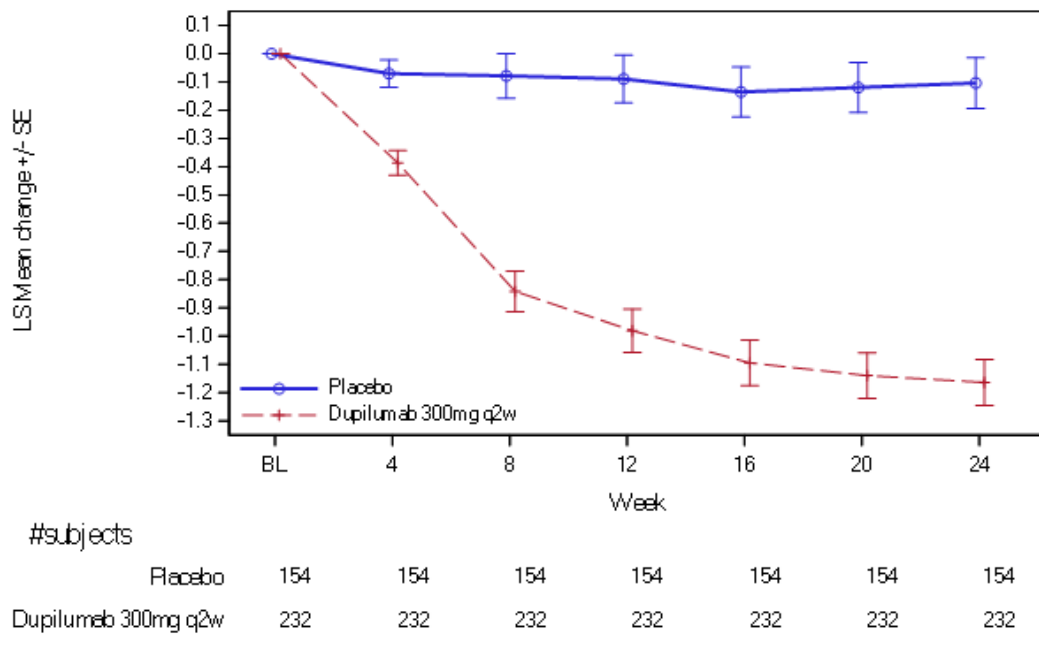
Source: Sanofi. Data on File, Post-hoc analyses.¹

Figure 54. LS mean change from baseline in SNOT-22 total score up to Week 24 in patients with prior NP surgery and any comorbid type 2 medical conditions (pooled ITT population)



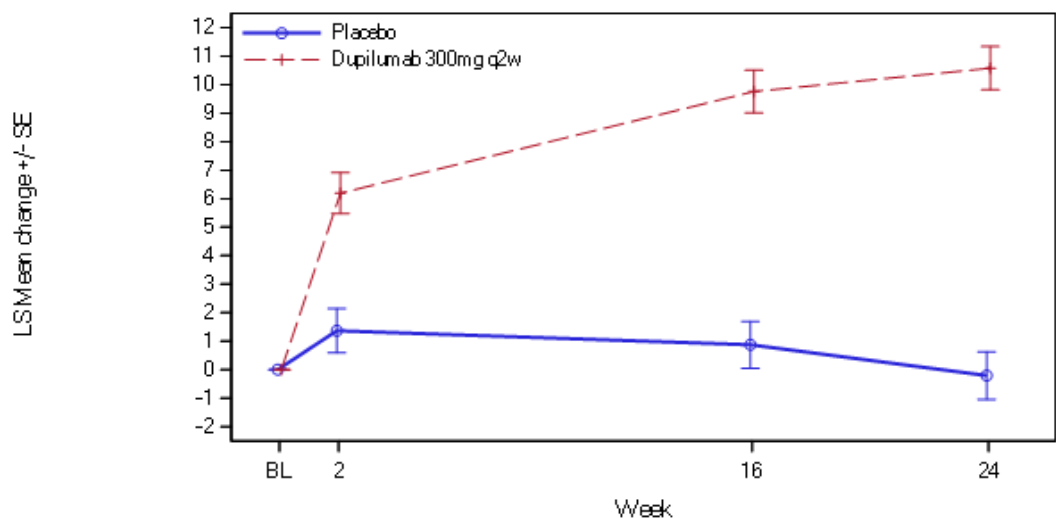
BL = baseline; ITT = intention-to-treat; LS = least squares; NP = nasal polyp; Q2W = once every 2 weeks; SE = standard error; SNOT-22 = 22-item Sino Nasal Outcome Test.
Source: Sanofi. Data on File, Post-hoc analyses.¹

Figure 55. LS mean change from baseline in LoS score up to Week 24 in patients with prior NP surgery and any comorbid type 2 medical conditions (pooled ITT population)



BL = baseline; ITT = intention-to-treat; LoS = decreased/loss of smell; LS = least squares; NP = nasal polyp; Q2W = once every 2 weeks; SE = standard error.
Source: Sanofi. Data on File, Post-hoc analyses.¹

Figure 56. LS mean change from baseline in UPSIT score up to Week 24 in patients with prior NP surgery and any comorbid type 2 medical conditions (pooled ITT population)



#subjects				
Placebo	152	152	152	152
Dupilumab 300mg q2w	225	225	225	225

BL = baseline; ITT = intention-to-treat; LS = least squares; NP = nasal polyp; Q2W = once every 2 weeks; SE = standard error; UPSIT = University of Pennsylvania Smell Identification Test.
Source: Sanofi. Data on File, Post-hoc analyses.¹

AROMA registry study

A9. Priority question: Table 34 reports that results of the first data cut-off for the AROMA study will be available in February/March 2025.

- Please clarify if these are the results reported in the submission, or if longer-term data will be available in February/March 2025;**
- Please provide any additional effectiveness and safety data from the AROMA study if available.**

The phase 4 AROMA study is an ongoing global registry and still generating data. Full-study completion and subsequent finalisation of results will not be available in February/March 2025 as originally suggested. The data provided in the original company submission is currently the most up-to-date interim analysis from the study

based on the most recent data-cut. Further data will become available in 2025, but it is currently unclear if this will be within the timeframe of the submission.

A10. Priority question [new question]: The EAG notes that the main clinical results are presented for the ITT population and not the subgroup which was used for the base case (people who had prior surgery for nasal polyps). Please provide the following information for the subgroup who had prior surgery:

- a) The summary of primary and key secondary endpoints (as presented for the ITT population in Table 21); and
- b) The mean change from baseline up to Week 24 for bilateral NPS, NC, TSS, SNOT-22 score, daily symptoms of decreased/loss of smell and UPSIT score (as presented for the ITT population in Figures 12 and 13).

Results and mean changes from baseline up to Week 24 for the primary and key secondary endpoints (bilateral NPS, NC, TSS, SNOT-22 total score, LoS score and UPSIT score) in the base case population (people who had prior surgery for nasal polyps) are presented in [Table 9](#) and in the figures relevant to patients with prior NP surgery included in question A8 above ([Figure 33](#), [Figure 34](#), [Figure 35](#), [Figure 36](#), [Figure 37](#) and [Figure 38](#)).

Table 9. Summary of results for the primary and key secondary endpoints in patients with prior NP surgery in SINUS-24 and SINUS-52 pooled ITT population

Endpoint	ECM (N=187)		Dupilumab Q2W (N=272)		
	Mean (SD)	LS mean change from baseline (SE)	Mean (SD)	LS mean change from baseline (SE)	LS mean difference vs. ECM (95% CI; P value)
Primary endpoints at Week 24					
Bilateral NPS	0.13 (1.23)	0.16 (0.14)	-1.89 (1.88)	-1.82 (0.13)	-1.99 (-2.29, -1.68)
NC score	-0.47 (0.79)	-0.38 (0.07)	-1.38 (0.92)	-1.36 (0.06)	-0.98 (-1.13, -0.83)
Key secondary endpoints at Week 24					
LMK-CT score	-0.31 (2.24)	-0.05 (0.33)	-6.38 (4.90)	-6.32 (0.30)	-6.27 (-6.97, -5.57)
TSS	-1.13 (1.68)	-0.90 (0.18)	-3.71 (2.30)	-3.58 (0.16)	-2.69 (-3.06, -2.31)
UPSIT score	-0.10 (5.46)	-0.34 (0.71)	10.59 (10.06)	10.23 (0.64)	10.57 (9.07, 12.06)
LoS score	-0.16 (0.52)	-0.12 (0.08)	-1.22 (1.03)	-1.20 (0.07)	-1.07 (-1.23, -0.91)
SNOT-22 score	-9.93 (19.01)	-9.23 (1.57)	-28.89 (21.85)	-30.12 (1.41)	-20.89 (-24.18, -17.60)

CI = confidence interval; ITT = intention-to-treat; LMK-CT = Lund-Mackay computed tomography; LoS = loss-of-smell; LS = least squares; NC = nasal congestion/obstruction; NPS = nasal polyp score; Q2W = every 2 weeks; SD = standard deviation; SE = standard error; SNOT-22 = 22-item Sino-Nasal Outcome Test; TSS = total symptom score; UPSIT = University of Pennsylvania Smell Identification Test.

Source: Sanofi. Data on File, Post-hoc analyses.¹

Adverse events

A11. Priority question: Table 33 provides a breakdown of common TEAEs in the pooled safety population. Please provide the same information for common:

a) Serious TEAEs; and

b) TEAEs leading to treatment discontinuation.

Summaries of common ($\geq 0.5\%$ in any treatment group) serious TEAEs and common TEAEs leading to permanent treatment discontinuation through Week 24 in the SINUS-24 and SINUS-52 pooled safety population are presented in [Table 10](#) and [Table 11](#), respectively.

Table 10. Common serious TEAEs ($\geq 0.5\%$ in any treatment group) through Week 24 in the pooled safety population

TEAE, n (%)	ECM (N=282)	Dupilumab (N=440)
Asthma*	2 (0.7)	0
Facial bones fracture	2 (0.7)	0
Nasal polyps**	2 (0.7)	1 (0.2)

Q2W = once every 2 weeks; SCS = systemic corticosteroid; TEAE = treatment-emergent adverse event

* 'Asthma' refers to a worsening of asthma from baseline.

** 'Nasal polyps' refers to a worsening of nasal polyps resulting in sinonasal surgery or SCS treatment.

Source: Sanofi. Data on File, Summary of Clinical Safety.⁶

Table 11. Common TEAEs leading to permanent treatment discontinuation ($\geq 0.5\%$ in any treatment group) through Week 24 in the pooled safety population

TEAE, n (%)	ECM (N=282)	Dupilumab (N=440)
Nasal polyps*	5 (1.8)	2 (0.5)

Q2W = once every 2 weeks; SCS = systemic corticosteroid; TEAE = treatment-emergent adverse event

* 'Nasal polyps' refers to a worsening of nasal polyps resulting in sinonasal surgery or SCS treatment.

Source: Sanofi. Data on File, Summary of Clinical Safety.⁶

Section B: Clarification on cost-effectiveness data

The results from all the requested scenarios are grouped together in Table following our answers to section C below.

Model structure

B1. The EAG notes that a one-year cycle length is not in line with the regularity of dupilumab administration and may not capture the timings of key clinical events. It is also not in line with how regularly response was assessed in the clinical trials. Please demonstrate that the one-year cycle length captures all relevant events and accounts for them appropriately or please adapt the model to use a shorter cycle length.

We acknowledge the EAG's concerns regarding the appropriateness of a one-year cycle length in our model, particularly in relation to the regularity of treatment administration and clinical event timing. Cycle length, in general, should reflect the frequency of key clinical events that influence patient outcomes. Below, we provide justification for the chosen cycle length:

- **Disease progression and response assessments:** In the clinical trials, patient response was assessed at week 24 and week 52, which aligns with the annual cycle assumption. In line with the clinical trial, the first-year decision tree captures the short-term treatment effect with a first efficacy assessment at week 24 followed by an adjustment based on trial outcomes at week 52. This is also in line with the timings of clinical assessment of CRSwNP response as per the guidelines. EPOS 2020 guidelines endorsed European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA) 2019 consensus on treatment response to biologic treatment in CRSwNP (EPOS, 2020; Fokkens et al., 2019). The EUFOREA states that treatment response should be evaluated after 16 weeks and after 1 year based on 5 criteria: nasal polyp size, need for SCSs, QOL, sense of smell and impact of comorbidities. Patients with no sufficient response in any of the criteria should discontinue treatment. Based on the investigation by Sanofi using the measures included in the SINUS trials, the best representation of the EPOS/EUFOREA response criteria is SNOT-22 CFB ≥ 8.9 and NPS CFB ≥ 1 .

For the Markov section of the model, a one-year time Horizon was preferred because responders at week 24 who continue to respond after week 52 and who enter the

Markov response states are not expected to experience significant change in their response status before one year if they remain on their current treatment. The same assumption is taken for the non-responders.

- **Treatment modifications and adverse events:** Most clinically relevant changes, such as treatment discontinuation or disease progression, occur at a timescale that is consistent with a one-year cycle. Furthermore, even if dupilumab administration is twice a week, its stable long-term treatments effect suggests that no significant changes is expected within the 2 weeks' timeframe. Therefore, we don't expect the outcomes of the CEM to be different with a short cycle length.
- **Consistency with prior health economic evaluations:** Other models for dupilumab submitted for evaluation by NICE have adopted a similar structure but incorporated various cycle lengths to account for different disease outcomes. In the Atopic Dermatitis (TA534) and COPD (ID6235) indications a one-year cycle length was used. For prurigo nodularis (TA955) 3 months was adopted and for Asthma (TA751) 4 weeks was chosen. The dosing schedule is Q2W for all these indications but alignment with the posology was considered less important than aligning with key model inputs, such as future risk of events and the efficacy response criteria. These have been discussed in the first part of this question.

The use of the year cycle length in other models developed for CRsWNP is well established in the literature. For example, Yong 2023 ⁷ and Scangas 2021 ⁸.

- **Half-Cycle Correction Implementation:** To enhance the accuracy of the model and account for the fact that transitions can occur at any point within a cycle, we have implemented a half-cycle correction with the two Markov worksheets. This ensures that the model does not systematically overestimate, or underestimate patient time spent in each health state.

Treatment response

B2. Priority question: As the combined response criteria used in the economic model was not a pre-specified outcome of the clinical trials, the EAG was unable to check the numbers reported in Table 38 of the CS with

data in the CSR. However, the EAG is unclear on some of the numbers reported in Table 38 and the trial data it refers to:

a) Please clarify the exact difference between the ITT population and the base-case population?

Table 38 of the original CS compares response rates between the ITT population, and the company base case population. These response rates are determined based on the observed SINUS-24/52 pooled data, using the primary analysis method and the selected response criteria (in the company base case: according to the response criteria of SNOT 22 total score [8.9 points improvement] and NPS [1-point improvement]). Whilst this data was not provided along with the original CS, response analyses for all requested subgroups and requested criteria have been provided at the end of this document, after section C (all based on non-published post-hoc analyses of the pooled data of SINUS-24/52).

The intention-to-treat (ITT) population of the pooled SINUS-24/52 trials is in line with the phase 3 studies recruitment criteria and the licensed indication: Adults with bilateral nasal polyps and symptoms of CRS despite intranasal corticosteroid therapy before randomisation and who had received systemic corticosteroids in the preceding 2 years (or had a medical contraindication or intolerance to systemic corticosteroids) or previous sinonasal surgery. This corresponds to **patients with uncontrolled CRSwNP despite prior treatment with SCS and/or surgery.**⁹

As this ITT population comprises surgery-naïve patients, and following clinical experts' opinion (advisory board in June 2024 and consultancy meetings in November 2024) the CS base case population is a slightly more restricted subgroup amongst the ITT population of the SINUS-24/52 trials: **patients with uncontrolled CRSwNP following one or more surgery.** Patients who are surgery-naïve (uncontrolled CRSwNP following SCS-use only) are therefore removed from the base case population. The clinical community supports the idea that recurrence of disease after surgery is an appropriate indicator for disease severity and future recurrence, and therefore this population is particularly relevant to be considered in this submission.¹⁰

To cite the original CS, "after consulting with clinicians and people with CRSwNP, the optimal place in therapy for dupilumab is after treatment failure with current standard of care. This includes surgery, which for some people can be a good and lasting option. However, people with more aggressive disease can experience rapid recurrence and for these patients, revision surgery does not provide long term satisfactory outcomes. Therefore, the

base case population focuses on people with uncontrolled disease following one (or more) surgeries. This is a subgroup of the licensed indication”.

b) Please clarify if the data reported under “base case population” and ‘Overall population: Response at Week 52’ is only patients who were in the SINUS-52 trial from the beginning and does not include patients in SINUS-24?

In the CS and the CEM, response analysis at Week 52 in any subgroup population is only calculated amongst SINUS-52 patients who reached Week 52 (ECM Q2W or dupilumab 300mg Q2W) and does not include patients from SINUS-24, as these patients were not on IMP for 52 weeks. Patients from SINUS-24 are only included in the response analysis at Week 24 (pooled ECM Q2W or pooled dupilumab 300mg Q2W).

c) Please clarify why the patient numbers in the ‘Subpopulation: Responders at Week 24 - Response at Week 52’ category are so low as it is unclear from the data available to the EAG the reasons for patients not being included (e.g. discontinuation, lost to follow up?). Considering the long-term Markov model transition probabilities are based solely on these data, the EAG considers the small patient numbers introduce considerable uncertainty, particularly as the probability for moving from the controlled disease to the inadequately controlled disease health state for the ECM only arm is based on only █ patients (█ non-responders).

The reason for ECM Week 52 responders’ numbers being low is due to the primary response analysis method used to inform the CEM. Indeed, during the SINUS-24/52 trial period, patients who were indicated for surgery for NP or received SCS for any reason were considered as non-responders for time points after using SCS or surgery. For patients who discontinue treatment without using SCS or surgery, data collected during the off-treatment period were used to determine the responder/non-responder status. Missing data at the visit of interest were considered as non-responders.

Therefore, any patient assessed “non-responder”, according to the chosen response criteria, at one of the assessments of the trials (either Week 24 or Week 52) was included in the “non-responder” subgroup at Week 52. Non-responders at Week 52 include non-responders at Week 24 OR non-responder at Week 52. In addition to any patient who required rescue therapy during the 52-weeks treatment period.

To the contrary, Week 52 responders needed to be responders throughout the study, according to the defined response criteria, at both assessment points through to Week 52 and not having used any rescue therapy during the 52-weeks treatment period. Week-52 responders only include responders at Week 24 **AND** Week 52.

This analysis method was chosen because the use of rescue therapy was one of the outcomes of SINUS-24/52, and one of the events assessed in the CEM (need for SCS and/or surgery). It could not be replaced with an “all observed” analysis as this would have introduced a bias in the CEM regarding the rate of rescue therapy per treatment arm.

B3. Priority question: Please clarify if all patients who discontinued dupilumab, for whatever reason, during the 24-to-52-week trial period are included in the number of patients reported under “Subpopulation: Responders at Week 24 - Response at Week 52” in Table 38 which informs long-term transition probabilities? If not, please clarify how discontinuations have been incorporated into the model?

As stated above, during the SINUS-24/52 trial period, patients who were indicated for surgery for NP and/or received SCS for any reason were considered as non-responders for any time points after using SCS or surgery. For patients who discontinue treatment without using SCS and/or surgery, data collected during the off-treatment period were used to determine the responder/non-responder status. Missing data at the visit of interest were considered as non-responders. Therefore, all patients who discontinued dupilumab during the 24-to-52-week trial period are included in the number of patients reported under “Subpopulation: Responders at Week 24 - Response at Week 52” in Table 38 in the CS, which informs long-term transition probabilities of the CEM.

B4. Priority question. The EAG notes that the responder criteria used in the economic model is based on a *post-hoc* analysis of the trial data. Please

include scenario analyses in the economic model using alternative response criteria based on:

a) The primary outcome measure of the clinical trials (NPS);

b) SNOT-22 data only.

Response analysis, baseline characteristics, clinical outcomes and HRQoL data relevant to the scenario analyses using only the primary outcome measure of the SINUS-24/52 trials, NPS (cfb > 1) and only SNOT-22 (cfb > 8.9) as response criteria in the different subpopulations are presented in [Table 40](#) through to [Table 107](#).

These additional analyses have also been included in the updated version of the CEM (model data tables in Worksheets 'Baseline Characteristics', 'Response Data', 'Utility Data', 'NPS Score_Observed CFB' and 'SNOT-22 Score_Observed CFB'). It is available as a user-selectable drop-down menu (for each subgroup of the original CS and subgroups requested in the NICE Scope). [Worksheet 'Clinical'; Cell J12/ ResponseDropDown].

B5. Priority question. Please also include an analysis in the economic model in which only data from the SINUS-52 trial is used to inform both clinical outcomes and HRQoL data, as opposed to the pooled trials.

Response analysis, baseline characteristics, clinical outcomes and HRQoL data relevant to the scenario analyses using only data from SINUS-52 are presented in [Table 30](#) through to [Table 37](#).

These analyses has also been included in the updated version of the CEM (model data tables in Worksheets 'Baseline Characteristics', 'Response Data', 'Utility Data', 'NPS Score_Observed CFB' and 'SNOT-22 Score_Observed CFB'). It is available as a user-selectable drop-down menu (for the base-case population and response criteria only). [Worksheet 'Clinical'; Cell J12/ ResponseDropDown].

B6. Priority question. Within the economic model on Sheet "Clinical" it states "The response analysis method determines which trial patients are counted as responders. In the primary response analysis, patients receiving rescue treatment were censored and set to non-responders. In

the observed response method, rescue treatment patients that met the designated response criteria were counted as responders.”

a) Please clarify if the data used in the company’s base case analysis uses the ‘observed response method’ or the ‘primary response method’ and therefore censored patients receiving rescue therapy?

The data used in the company’s base case analysis uses the ‘primary response method’. This means that patients receiving rescue therapy (i.e. SCS and/or sinus surgery) during the 24-to-52 weeks treatment period are set as non-responders for all time points after the rescue therapy usage. It is important to note that the model includes both a controlled Health State and a specific post-op-controlled Health State. This implies that the controlled HS should only include responder patients who didn't undergo surgery and so the primary response method is the most appropriate for analysis.

b) If the base case analysis did censor patients who required rescue therapy and classed them as non-responders, please clarify why this assumption was deemed appropriate, as this differs from the primary outcome of the SINUS 24 and 52 trials?

The base-case analysis is based on the ‘primary response method’. Therefore, patients who required rescue therapy (i.e. SCS and/or sinus surgery) were classed as non-responders. This approach differs from the one used in the SINUS trials, where the two primary endpoints (i.e. NPS and NC) were continuous changes from baseline and post-rescue data were imputed using the WOCF method. This choice reflects a more conservative approach, as applying WOCF to binary outcomes could have led to classifying some patients as responders despite having undergone rescue therapy. Furthermore, the model structure includes separate health states for controlled patients who received dupilumab without rescue therapy and those who underwent surgery so the primary response method is the most appropriate for analysis.

B6a. Table 57 of the CS reports the usage of SCS and antibiotics, split by both treatment arm and responders’ status.

a. In Table 57, the proportion of ECM non-responders having SCS between weeks 0-24 is reported as 45%, however, in the economic model this is 26.7%. Please clarify this discrepancy.

The correct value is 26.7%. The 45% reported in Table 57 of the CS is based on previous calculations that were neither appropriate nor suitable for the decision tree. These have been corrected and the CS should contain the updated value. We are happy to provide an updated CS if requested.

b. In worksheet “Treatment”, cells AA44:AI61 it provides the numbers that the proportions in Table 57 are based on and those used in the base case of the economic model. The EAG note that for week 0-24, these figures appear to be based on the ITT population despite the decision problem being based on those who have had one prior surgery. The EAG was unable to verify the values used as the denominator in the week 25-52 calculations (cells AC58:61 and AH58:61). Please clarify why the ITT population data was used and provide the source of data for week 25-52.

The ITT population was used for these inputs to maintain a higher sample size and improve statistical significance, while considering the minimal impact of ECM medication costs on the results. In the ITT population, no significant difference in antibiotic use between the placebo and dupilumab was observed by response status. Regarding the denominator used for the Week 25-52 calculations, it corresponds to the number of responders or non-responders in the respective arm at Week 24, based on the combined response criterion. The data and the corresponding p-values are presented in Table 12 and

Table13. However, as the use of antibiotics was not statistically significantly different between treatment arms, and its impact on the ICER was extremely limited, the company has decided to remove it from the CEM to only account for the SCS use (statistically significant between treatment arms and by response status).

Table 12. ITT population antibiotic use up to week 52 against responder status.

Time period	Response status*	Drug use in DUP+ECM arm			Drug use in ECM arm			p-value
		<i>x</i>	<i>n</i>	<i>p</i>	<i>x</i>	<i>n</i>	<i>p</i>	
W0-W24 (SINUS24/52)	Responder	46	243	19%	4	31	13%	0.356
	Non-responder	53	195	27%	80	255	31%	0.331
W25-W52 (SINUS52)	Responder	14	77	18%	1	11	9%	0.350
	Non-responder	15	73	21%	40	142	28%	0.208

Table13. ITT population SCS use up to week 52 against responder status.

Time period	Response status*	Drug use in DUP+ECM arm	Drug use in ECM arm	p-value

		<i>x</i>	<i>n</i>	<i>p</i>	<i>x</i>	<i>n</i>	<i>p</i>	
W0-W24 (SINUS24/52)	Responder	0	243	0%	0	31	0%	NA
	Non-responder	35	195	18%	68	255	27%	0.025
W25-W52 (SINUS 52)	Responder	0	77	0%	0	11	0%	NA
	Non-responder	15	73	21%	40	142	28%	0.208

c) Based on the population of the decision problem, please update the proportions requiring each aspect of ECM to use the base case population data (i.e. those with one prior surgery).

As stated above in question B6ab, The ITT population was used for the ECM use calculation to maintain a higher sample size and improve statistical significance, while considering the minimal impact of ECM medication costs on the results. the sample size of the base case population would introduce further uncertainty in terms of usage of ECM medication.

Transition probabilities

B7. Priority question: The EAG was unable to replicate both the 15.1% for the annual probability of surgery for eligible patients and the 42.8% probability of transitioning from post-op controlled to uncontrolled, based on data in Benson *et al.* 2023.

a) The CS states that the 42.8% probability of losing control following surgery was based on “...mean time to third surgery for patients having had >2 surgeries during the follow-up period – adjusted to reflect average wait time for surgery in England”. Please clarify if this means that the company applied a separate adjustment for wait times that was not based on the data in Benson *et al.* 2023. If so, please provide a scenario analysis in which the annual transition probability is based solely on the data from Benson *et al.* without any additional adjustments.

A scenario analysis in which the annual transition probability is based solely on the data from Benson *et al.* 2022¹¹ without any additional adjustments has been provided. However, the company would like to clarify that loss of response or control after surgery for CRSwNP is distinct from the revision surgery rate, as patients do not necessarily access further surgery immediately after losing disease control. This is particularly relevant in the UK, where the average wait time for ESS is 2 to 3 years (as stated during the advisory board held in June

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2024 and the following HCP consultancy meetings held in November 2024), delaying surgical intervention even for those with recurrent or uncontrolled disease. Additionally, insights from clinician experts in our advisory board and HCP consultancy meetings indicated that within our base case population, approximately 40% to 50% of patients would lose control quickly after surgery, aligning with the rate used in our analysis.

In addition, most studies investigating CRSwNP assess patients' revision or recurrence rates regardless of disease severity, number of previous surgeries, or comorbidities such as asthma, which are known to increase the risk of disease recurrence and loss of response. Therefore, we expect the rate of loss of response post-surgery to be higher in our submission base case than in the general CRSwNP population as, according to the CEM structure in the CS base case, this rate apply to patients who have undergone their second (or more) surgery for CRSwNP (as patients need to have had a prior surgery to enter the CEM and they would have cycle once to the post-op-controlled state before being in a position to be applied that rate).

Furthermore, the studies referenced below primarily evaluate disease control based on EUFOREA/EPOS guidelines, which, although relevant, are more restrictive than the criteria used in the CEM to assess response. As a result, the 40% rate used should be viewed as a conservative estimate, reinforcing its suitability in determining the expected yearly loss of response within our base case population. This highlights the importance of distinguishing between loss of control and surgical revision rates, as well as the need for optimised medical management in the interim period before further surgical intervention becomes accessible.

Additional references: According to Bachert et al. (2021) "EUFOREA expert board meeting on uncontrolled severe CRSwNP and biologics: Definitions and management", evaluating the efficacy of sinus surgery for CRSwNP is challenging due to variations in surgical techniques and differing opinions on the extent of surgery required.¹² Procedures range from minimally invasive approaches, such as balloon dilation aimed at opening sinus drainage pathways, to functional ESS focused on removing polyps and diseased mucosal tissue.¹² While experts agree that ESS should involve opening the ostiomeatal complex and addressing the maxillary and ethmoid sinuses, some advocate for more extensive procedures, including creating large openings to all sinuses (e.g., modified Lothrop) or complete removal of sinus mucosa (reboot surgery).¹² This variability, coupled with differences in surgical quality, contributes to the low level of evidence regarding ESS efficacy. Most available data are retrospective or from limited prospective cohort studies with standardised approaches, often centred around single surgeons or institutions, limiting generalisability. For instance, the UK National Sinonasal Audit reported a 21% surgical

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revision rate over five years, while a meta-analysis by Loftus et al. found a revision rate of less than 20% in CRSwNP patients over an average follow-up of 7.4 years, with variations across regions and comorbidities. Given the challenges in conducting high-quality, prospective, multicentre randomised trials on sinus surgery efficacy, international registries may offer valuable real-life evidence. Post-operative management is crucial, as surgery often debulks polyps but does not prevent recurrence.

Despite postoperative medical therapy, such as topical corticosteroids, recurrence rates remain high; a multicentre prospective cohort study, from DeConde et al. (2017), investigated the recurrence rates of nasal polyposis following ESS in patients with CRSwNP of 244 ESS patients reported a **38% polyp recurrence within 12 months**. These findings highlight the need for improved management strategies for nasal polyposis.¹³ The study enrolled 363 CRSwNP patients who underwent ESS involving polypectomy.¹³ Postoperative endoscopic evaluations were conducted on 244 participants (67%) over an average follow-up period of approximately 14.3 months.¹³ The findings revealed that surgery combined with post-operative medical management significantly improved endoscopic scores at 6 months ($p < 0.001$).¹³ However, nasal polyposis recurred in 35% of patients at 6 months (68/197), 38% at 12 months (48/125), and 40% at 18 months (52/129).¹³ Multivariate analysis identified prior ESS (odds ratio [OR]: 2.6; 95% confidence interval [CI]: 1.5-4.6; $p = 0.001$) and greater preoperative polyposis severity (OR: 1.4; 95% CI: 1.1-1.8; $p = 0.016$) as significant risk factors for recurrence.¹³ These results underscore the commonality of polyp recurrence post-ESS and highlight the need for improved surgical and medical management strategies to enhance long-term outcomes.

The study "Comparison of Long-Term Postoperative Outcomes of the Subtypes of Chronic Rhinosinusitis with Nasal Polyps" analysed 202 patients undergoing endoscopic sinus surgery for chronic rhinosinusitis with nasal polyps (CRSwNP).¹⁴ The study compared eosinophilic (ECRSwNP) and non-eosinophilic (NECRSwNP) subtypes, evaluating preoperative clinical characteristics, blood eosinophil and IgE levels, and quality of life using the Sino-Nasal Outcome Test (SNOT-22).¹⁴ Disease control was assessed according to the EUFOREA/EPOS 2020 guidelines.¹⁴ One year after surgery, 23.4% of patients had uncontrolled disease, with a significantly higher rate in the eosinophilic group (39.5%) compared to the non-eosinophilic group (20.3%) ($p = 0.035$).¹⁴ As dupilumab targets type 2 inflammation (eosinophilic type), this further reinforces the rate of approximately 40% of patients losing control according to the EPOS guidelines, 1 year after undergoing sinus surgery.¹⁴

Furthermore, the study titled "Real-life study showing uncontrolled rhinosinusitis after sinus surgery in a tertiary referral centre" evaluated 560 adult patients who had undergone bilateral functional endoscopic sinus surgery (FESS) for CRS 3–5 years prior.¹⁵ The research was conducted across multiple centres across the Benelux region.¹⁵ Using the EUFOREA/EPOS control criteria, the study found that 41.8% of patients with CRSwNP were uncontrolled at 3 to 5 years post-FESS.¹⁵

Finally, the meta-analysis titled "Revision surgery rates in chronic rhinosinusitis with nasal polyps: A meta-analysis of risk factors" analysed 45 studies encompassing 34,220 subjects to determine revision surgery rates in patients with CRSwNP.¹⁶ The findings revealed an overall revision rate of 18.6% (95% confidence interval, 14.1%-23.6%).¹⁶ Separate rates were analysed for patients undergoing their first surgical procedure vs. a subsequent one. For those undergoing revision surgery (second surgery or greater), the subsequent revision rate was 26.4% ($p < 0.0001$).¹⁶ This suggests that patients requiring repeat revision surgeries are at a significantly higher risk of needing further surgical interventions.¹⁶ Additionally, the study identified asthma, aspirin-exacerbated respiratory disease (AERD), and allergy as key risk factors associated with increased revision rates.¹⁶

b) Please provide step by step descriptions to show exactly what data and calculations were performed to obtain both the 15.1% and the 42.8% annual probabilities.

These rates above-mentioned have been calculated based on the study from Benson et al. (2023)¹¹ titled "Real-world characterisation of patients with chronic rhinosinusitis with nasal polyps with and without surgery in England" aimed to assess the burden of CRSwNP in the UK, focusing on patients who underwent surgery compared to those who did not.¹¹ Utilising data from the UK Clinical Practice Research Datalink Aurum database linked with Hospital Episodes Statistics (2007–2019), the retrospective cohort study included 33,107 adults diagnosed with nasal polyps, with a mean follow-up of 5.3 years.¹¹ Table 4 of the study presents the time intervals between surgeries among patients who underwent multiple surgical procedures.¹¹ The data indicate that the time between surgeries decreased with each subsequent procedure, suggesting a trend towards shorter intervals between surgeries for patients requiring multiple interventions.¹¹ This information was derived from the linked datasets, providing insights into the surgical patterns and healthcare utilisation of CRSwNP patients in England.¹¹ (Table 14).

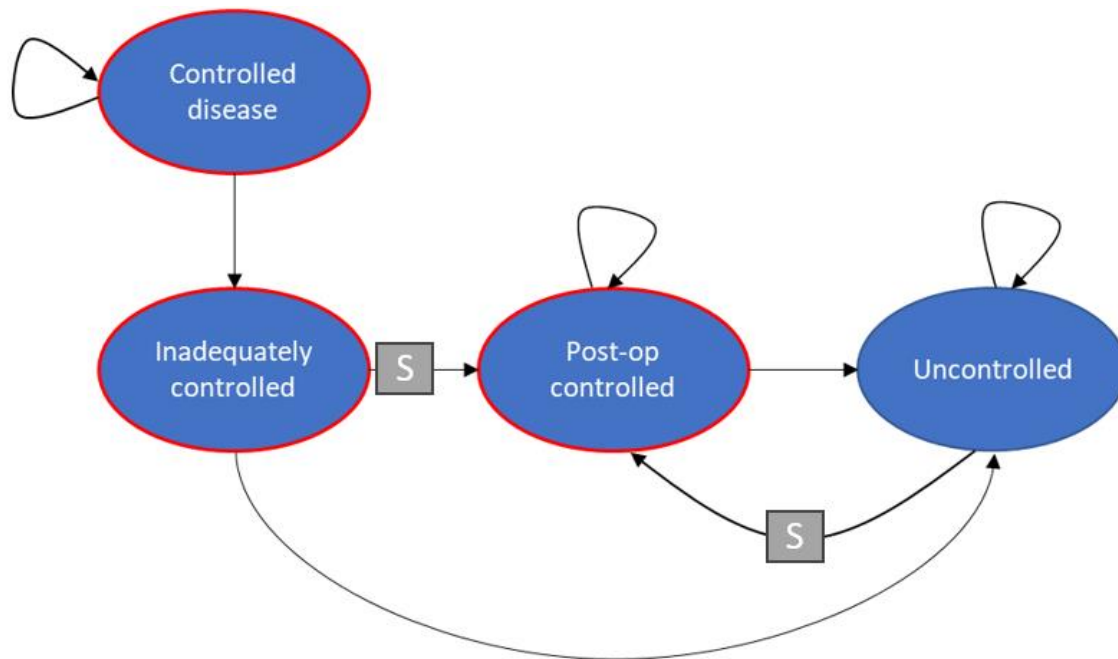
Table 14. Time between NP surgeries and proportion of patients with surgery failure amongst the CPRD database

Overall study population, N =	33,107

Patients with ≥ 1 surgery during follow-up, N =	7,793
Time between index and first surgery, days	
Mean (SD)	430 (564)
Median (Q1, Q3)	219 (106, 485)
Surgery failure, n (%) =	136 (1.8%)
Patients with ≥ 2 surgeries during follow-up, N =	722
Time between index and first surgery, days	
Mean (SD)	312 (384)
Median (Q1, Q3)	189 (95, 358)
Time between first and second surgery, days	
Mean (SD)	1191 (770)
Median (Q1, Q3)	1032 (567, 1646)
Surgery failure, n (%) =	36 (5.0%)
Patients with ≥ 3 surgeries during follow-up, N =	122
Time between index and first surgery, days	
Mean (SD)	234 (279)
Median (Q1, Q3)	169 (81, 277)
Time between first and second surgery, days	
Mean (SD)	755 (397)
Median (Q1, Q3)	704 (445, 1039)
Time between second and third surgery, days	
Mean (SD)	875 (535)
Median (Q1, Q3)	719 (462, 1271)
Surgery failure, n (%) =	11 (9.0%)
Patients with ≥ 4 surgeries during follow-up, N =	33
Time between index and first surgery, days	
Mean (SD)	150 (132)
Median (Q1, Q3)	107 (63, 189)
Time between first and second surgery, days	
Mean (SD)	710 (307)
Median (Q1, Q3)	721 (445, 994)
Time between second and third surgery, days	
Mean (SD)	602 (255)
Median (Q1, Q3)	553 (422, 722)
Time between third and fourth surgery, days	
Mean (SD)	777 (489)
Median (Q1, Q3)	598 (481, 996)
Surgery failure, n (%) =	7 (21.2%)

The annual transition probabilities from 'post-op controlled' to 'uncontrolled' HS (patients losing response post revision surgery), as well as from 'uncontrolled' and 'inadequately controlled' HS to 'post-op controlled' (annual surgery rate) were calculated using adjusted data from this study.

Since the CS and CEM base case population includes patients with at least one prior surgery and given that patients cycle through the 'post-op controlled' health state (HS) at least once before being in the position to be losing response and requiring another intervention, we identified that patients with at least two surgeries (N = 722) were relevant to calculate our transition probabilities. Specifically, patients with three or more surgeries (N = 122) would allow us to identify patients who already cycled once through the 'post-op controlled' HS and back.



****Red outlined states indicated where patients enter from the decision tree**

Surgery is denoted by: **S**

We considered the mean time between the second and third surgery amongst these patients (875 days) and adjusted for the average 2-year wait time for surgery in the UK (two cycles of 365.25 days). This adjustment accounts for patients who became uncontrolled and remained on the surgical waitlist before receiving their next procedure. Additionally, since the cycle length in the CEM is one year, patients would require two cycles (i.e., two years) to transition back to the 'post-op controlled' HS following their third surgery.

Thus, the annual transition probability from 'post-op controlled' to 'uncontrolled' HS was calculated as follows:

$$- X = 122 / 722 \div (875 - (365.25 \times 2) / 365.25) = 42.8\%.$$

This estimate is consistent with previously published data on post-surgical loss of control rates in CRSwNP. DeConde et al. (2017) reported that 40% of patients experienced nasal polyp recurrence within 18 months post-ESS despite medical therapy. These findings also align with insights from our advisory board and HCP consultancy meetings, where experts estimated that 40% of the base case population would lose control quickly, reinforcing the clinical relevance of this assumption in the CEM model.

Furthermore, the annual surgery rate (15.1%) was also based on patients with ≥ 2 surgeries during follow-up ion Benson et al. 2023 and was derived by calculating a simple annual probability—specifically, dividing the number of surgeries (52) by the total eligible population (344) after accounting for the average wait time in the UK.

This denominator (344 patients eligible for revision surgery yearly) was obtained by dividing the 122 observed surgeries by the adjusted mean follow-up period (875 days minus 2-year wait = 145 days, or 0.3963 years), resulting in approximately 308 patients, and then adding 36 additional eligible patients (failed second surgery).

The numerator (52 surgeries per year) was similarly calculated by dividing the 122 surgeries by the original mean follow-up duration (875 days, or approximately 2.3956 years; $Y = 122 / (875 / 365.25) = 52$). Dividing this annualised event number by the total eligible population results in a simple annual probability of 15.1% included in the CEM.

$$- X2 = 52 / 344 = 15.1\%$$

Conversely, using the log-based hazard approach, the calculation involves converting the observed probability ($122/722 = 16.9\%$) into an instantaneous annual event rate by applying the formula: annual rate = $-\ln(1-\text{probability})/\text{mean time}$, yielding a slightly higher annual hazard rate of 16.5%.

B8. Priority question. The economic model includes 23.7% of patient's ineligible for surgery based on the pooled SINUS 24/52 trials. Please clarify the criteria used to determine ineligibility?

In the SINUS-24/52 trials, eligibility for surgery was assessed as part of the baseline screening visits. This assessment was solely based on the clinician expert opinion and not based on a specific pre-defined threshold or criteria (CSR of both SINUS-24/52: "At baseline (V1 and V2) eligibility to surgery based on Investigator opinion was to be assessed."

The 23.7% rate included in the original CEM is the observed rate of surgery ineligibility amongst the CS base case population (patients with prior surgery). As an alternative, the

company proposes to use the observed rate of surgery ineligibility in the ITT population of the pooled SINUS-24/52 trials (15.1%) as this might reduce the uncertainty. However, the company would like to emphasise that surgery ineligibility increases with age (mostly linked to anaesthesia risks for patients) and that the CEM offers the possibility to apply a lower starting rate with an age-adjusted polynomial or linear increase.

B9. Clinical experts to the EAG noted that the proportion of patients who would be deemed ineligible to have revision surgery would be much lower in clinical practice than the 23.7% used in the company's model as it is rare that patients are not eligible. Please include a scenario analysis which uses a lower proportion of patients based on UK clinical practice. The EAG's clinical experts expected this to be less than 10%.

The company did not find supporting publications providing a specific rate of ineligibility for surgery amongst CRSwNP patients, specifically in our base case population. However, to comply with the EAG request, we have added in the CEM the option to use a user-defined rate, currently set at 10%. [Worksheet 'clinical'; Cell J65/ Percentage_Eligible_Surgery] This scenario is provided in Table after our answers to Section C).

a) Priority question: In appendix R.2 (UK Health Technology Assessment Consultancy), the company presented the economic model structure to clinical experts, which included the annual transition probabilities (Figure 2). Within this figure the proposed annual proportion of patients receiving revision surgery is [REDACTED]. The document notes that a clinical expert agreed that the number of patients having revision surgery within a year will be small. Please clarify why the company used an alternative annual probability of surgery of 15.1% in the base case as opposed to the value presented to clinical experts? In addition, please confirm which data the value of [REDACTED] was based on and include a scenario analysis in the model using this value instead of the 15.1%.

The rate of [REDACTED] presented during the consultancy meetings was part of the draft CEM and derived from the French hospital discharge database (Programme de médicalisation des systèmes d'information [PMSI], 2019)¹⁷. However, this data is now six years old and, not specific to the UK or to our base case population of patients have already undergone at least one prior sinus surgery. The clinical experts agreed that a rate of revision within a year would be small. However, they did not specifically validate the number of [REDACTED]. Based on

clinical opinion gathered, and literature review (Benson et al. 2023¹¹), we estimated this rate to be closer to 15%. However, we have provided a scenario analysis in which this rate is set at ■■■, as requested by the EAG.

B10. The annual probability used in the economic model for transitioning from the ' inadequately controlled' health state to the 'post-op controlled disease' is 15.1%. However, both Table 41 and Figure 19 of the CS state that the annual transition probability is 11.5%, which appears to be the annual transition probability (15.1%) multiplied by the proportion of patients eligible for surgery. Please confirm the correct transition probabilities used in the model.

In the CEM, the transition probability from 'inadequately controlled' to 'post-op controlled' HS and from 'uncontrolled' to 'post-op controlled' HS are based on the same annual surgery rate (15.1% in the CS base case scenario but can be a user-selectable input) ¹¹. As this annual rate is only applied to surgery-eligible patients in the 'uncontrolled' and 'inadequately controlled' HS, the resulting rate of surgery on the HS is lower and equal to:

- Annual surgery rate * (1 – rate of surgery ineligibility).

Which, in the CS base case corresponds to the above-mentioned rate:

- 15.1% * (1 – 23.7%) = 11.5%.

Therefore, the annual transition probability to 'post-op controlled' is aligned between the CEM and the CS, and based on these two inputs (annual surgery rate and percentage of patients ineligible for surgery) which can both be varied in sensitivity analyses.

B11. In the company's scenario analysis using the discontinuation rate of ■■■ from the AROMA study to inform the annual transition probability of patients on dupilumab moving from 'controlled' to 'inadequately controlled', the EAG notes that this only captures patients who discontinued but not necessarily patients who would be classed as 'non-

responders' using the same response criteria as used in the base-case analysis.

a) Please clarify if any 'responder' status analysis can be undertaken using the AROMA study to inform a more plausible scenario analysis and implement this in the model.

As NPS was not collected in the AROMA phase 4 registry ¹⁸, we have carried out a responder analysis based on SNOT-22 alone (cfb >8.9; [Table 15](#)). This has been included in the CEM. [Worksheet 'Clinical'; Cells AC43 to AD46]

The calculation of discontinuation rates, including non-response and dropouts from AROMA, was conducted in three steps:

- 1) First, the response rate among responders at previous visits was calculated at each visit. The analysis was performed in both the base case population and the ITT population. Since the objective was to best inform the model beyond SINUS trials and given the number of observations between month 12 and 30, the ITT population was used for the subsequent calculations. Moreover, the differences between the two populations appeared negligible.
- 2) Then, non-response rates were calculated, and an exponential trendline was applied to the data. The resulting equation was then used to generate the discontinuation rates over three months during the first 5 years. As a next step, the discontinuation rates were annualized, considering the decrease in the size of the responder cohort every three months over the course of a year.
- 3) Finally, the dropout rate was added to the discontinuation rates based on response.

Table 15. Responder analysis based on SNOT-22 CFB > 8.9

Visit	Patients with prior surgery	ITT population	Non-response rate
Visit 2 (Baseline) *	413/512	552/691	
Visit 3 (Month 3)	260/334 (77.8%)	335/443 (75.6%)	24.4%
Visit 4 (Month 6)	209/227 (92.1%)	256/285 (89.8%)	10.2%
Visit 5 (Month 9)	141/152 (92.8%)	191/204 (93.6%)	6.4%
Visit 6 (Month 12)	114/120 (95.0%)	148/155 (95.5%)	4.5%
Visit 7 (Month 15)	63/66 (95.5%)	87/91 (95.6%)	4.4%

Visit 8 (Month 18)	45/45 (100.0%)	61/61 (100.0%)	0.0%
Visit 9 (Month 21)	24/24 (100.0%)	37/38 (97.4%)	2.6%
Visit 10 (Month 24)	11/11 (100.0%)	16/16 (100.0%)	0.0%
Visit 11 (Month 30)	0	1/1 (100.0%)	0.0%
Visit 12 EOS (Month 36)	0	0	NR

cfb = change from baseline; EOS = end of study; MCID = minimal clinically important difference; SNOT-22 = Sino-Nasal Outcome Test-22.

Source: Sanofi. Data on File, Post-hoc analyses.¹

*Number of Patients who had baseline SNOT-22, n/N

Figure 57. Discontinuation rate of dupilumab over 24 months, based on SNOT-22 response analysis in the AROMA registry (RAS).

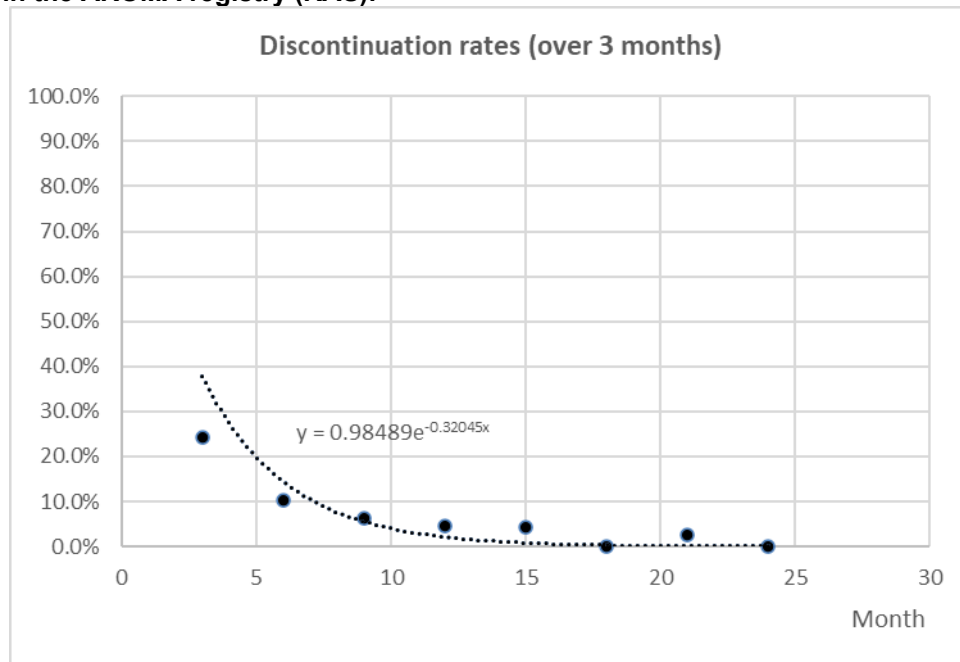


Table 16. Overall discontinuation rate of dupilumab over 5 years, including dropouts, based on AROMA (RAS).

Month	Discontinuation		Annual discontinuation including dropouts
	Over the last 3 months	Annual discontinuation	
3	37.66%		
6	14.40%		
9	5.51%		
12	2.11%		
15	0.81%	■	■
18	0.31%		
21	0.12%		
24	0.05%		
27	0.02%	■	■
30	0.01%		
33	0.00%		
36	0.00%		
39	0.00%	■	■
42	0.00%		

45	0.00%		
48	0.00%		
51	0.00%		
54	0.00%		
57	0.00%		
60	0.00%		

The proportion of patients who discontinued treatment in AROMA for any reason (dropouts) is presented in [Table 17](#).

Table 17. Proportion of patients who discontinued treatment in AROMA, by reason (registry analysis set and previous sinonasal surgery ≥1)

	Total (N=512)
Patients in the study >12 Months, n (%)	498 (97.3%)
Discontinuation rate over 12 months (Month 12 to Month 24) & 24 Months, n (%)	
Adverse Event	
Sponsor Request	
Death	
Lost To Follow-Up	
Subject Decision	
Ongoing	0/487

ITT = intention-to-treat; NPS = nasal polyp score; SNOT-22 = Sino-Nasal Outcome Test-22.
Source: Sanofi. Data on File, Post-hoc analyses.¹

- b) The company's scenario analysis using the [REDACTED] discontinuation rate to inform the transition probability does not make any amendments to the transition probability for the ECM arm, which remains based on only the [REDACTED] patients classed as non-responders in the clinical trial. Please clarify if any alternative data sources based on real-world evidence on the rate at which current patients become 'inadequately controlled' could be used to inform an alternative scenario analysis.**

As discussed in question B9 above, the company would like to distinguish that loss of response or control for CRSwNP is distinct from the revision surgery rate, as patients do not necessarily access further surgery immediately after losing disease control. This is particularly relevant in the UK, where the average wait time for ESS is 2 to 3 years, delaying surgical intervention even for those with recurrent or uncontrolled disease. Additionally, insights from clinician experts in our advisory board and HCP consultancy meetings indicated that within our base case population, approximately 40% to 50% of patients would lose control quickly after surgery, aligning with the rate used in our analysis.

In addition, most studies investigating CRSwNP assess patients' revision or recurrence rates regardless of disease severity, number of previous surgeries, or comorbidities such as asthma, which are known to increase the risk of disease recurrence and loss of response. Therefore, we expect the rate of loss of response post-surgery to be higher in our submission base case than in the general CRSwNP population as, according to the CEM structure in the CS base case, this rate apply to patients who have undergone their second (or more) surgery for CRSwNP (as patients need to have had a prior surgery to enter the CEM and they would have cycle once to the post-op-controlled state before being in a position to be applied that rate). Furthermore, the studies referenced below primarily evaluate disease control based on EUFOREA/EPOS guidelines, which, although relevant, are more restrictive than the criteria used in the CEM to assess response.

Additional references:

Despite postoperative medical therapy, such as topical corticosteroids, recurrence rates remain high; a multicentre prospective cohort study, from DeConde et al. (2017), investigated the recurrence rates of nasal polyposis following ESS in patients with CRSwNP of 244 ESS patients reported a **38% polyp recurrence within 12 months**. These findings highlight the need for improved management strategies for nasal polyposis.¹⁹ The study enrolled 363 CRSwNP patients who underwent ESS involving polypectomy.¹⁹ Postoperative endoscopic evaluations were conducted on 244 participants (67%) over an average follow-up period of approximately 14.3 months.¹⁹ The findings revealed that surgery combined with post-operative medical management significantly improved endoscopic scores at 6 months ($p < 0.001$).¹⁹ However, nasal polyposis recurred in 35% of patients at 6 months (68/197), 38% at 12 months (48/125), and 40% at 18 months (52/129).¹⁹ Multivariate analysis identified prior ESS (odds ratio [OR]: 2.6; 95% confidence interval [CI]: 1.5-4.6; $p = 0.001$) and greater preoperative polyposis severity (OR: 1.4; 95% CI: 1.1-1.8; $p = 0.016$) as significant risk factors for recurrence.¹⁹ These results underscore the commonality of polyp recurrence post-ESS and highlight the need for improved surgical and medical management strategies to enhance long-term outcomes.

Furthermore, the study titled "Real-life study showing uncontrolled rhinosinusitis after sinus surgery in a tertiary referral centre" evaluated 560 adult patients who had undergone bilateral functional endoscopic sinus surgery (FESS) for CRS 3–5 years prior.¹⁵ The research was conducted across multiple centres across the Benelux region.¹⁵ Using the EUFOREA/EPOS control criteria, the study found that 41.8% of patients with CRSwNP were uncontrolled at 3 to 5 years post-FESS.¹⁵

Finally, the meta-analysis titled "Revision surgery rates in chronic rhinosinusitis with nasal polyps: A meta-analysis of risk factors" analysed 45 studies encompassing 34,220 subjects to determine revision surgery rates in patients with CRSwNP.¹⁶ The findings revealed an overall revision rate of 18.6% (95% confidence interval, 14.1%-23.6%).¹⁶ Separate rates were analysed for patients undergoing their first surgical procedure vs. a subsequent one. For those undergoing revision surgery (second surgery or greater), the subsequent revision rate was 26.4% ($p < 0.0001$).¹⁶ This suggests that patients requiring repeat revision surgeries are at a significantly higher risk of needing further surgical interventions.¹⁶ Additionally, the study identified asthma, aspirin-exacerbated respiratory disease (AERD), and allergy as key risk factors associated with increased revision rates.¹⁶

B12. Priority question: The company's base case analysis assumes no treatment waning over time for dupilumab. Clinical experts to the EAG noted that they would expect treatment effectiveness to wane over time, particularly considering their experience of similar biologics in asthma patients.

a) Please clarify why the assumption was made in the base-case analysis to assume no treatment waning over time.

Patients treated with dupilumab demonstrated statistically significant and clinically meaningful improvements in the co-primary endpoints of NPS and NC score at Week 24 compared with the placebo arm in both SINUS 24 and 52. In the longer-term SINUS 52 study there was no evidence of plateauing of effect for dupilumab treatment on these key symptom measures. (Figure 58 and Figure 59).

Figure 58 LS mean change from baseline bilateral nasal polyps score (NPS) by visit to week 52 – ITT population.

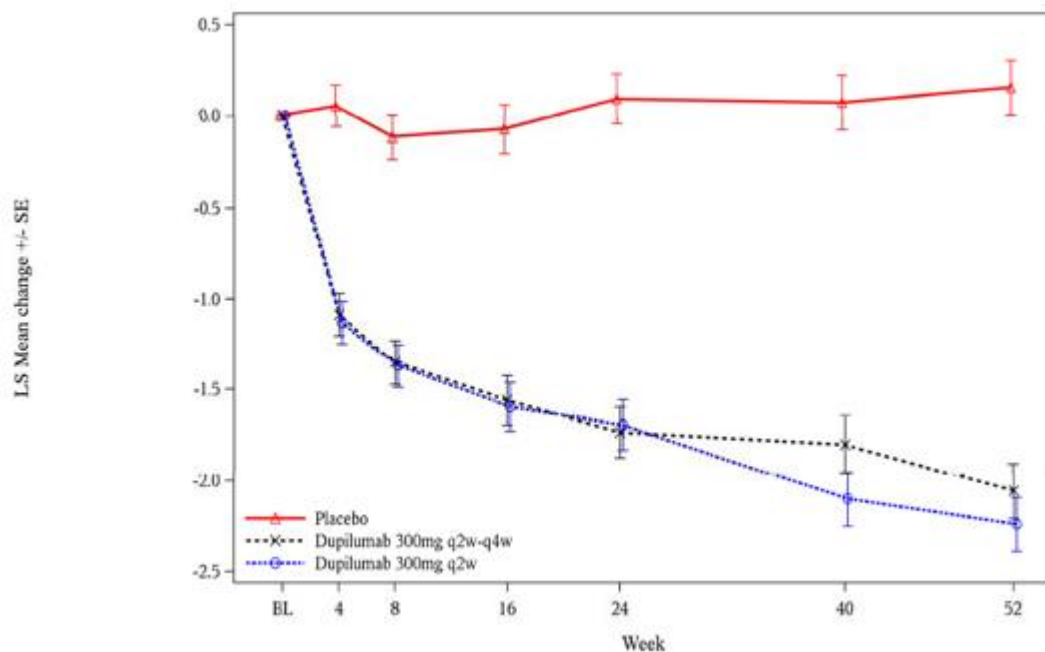
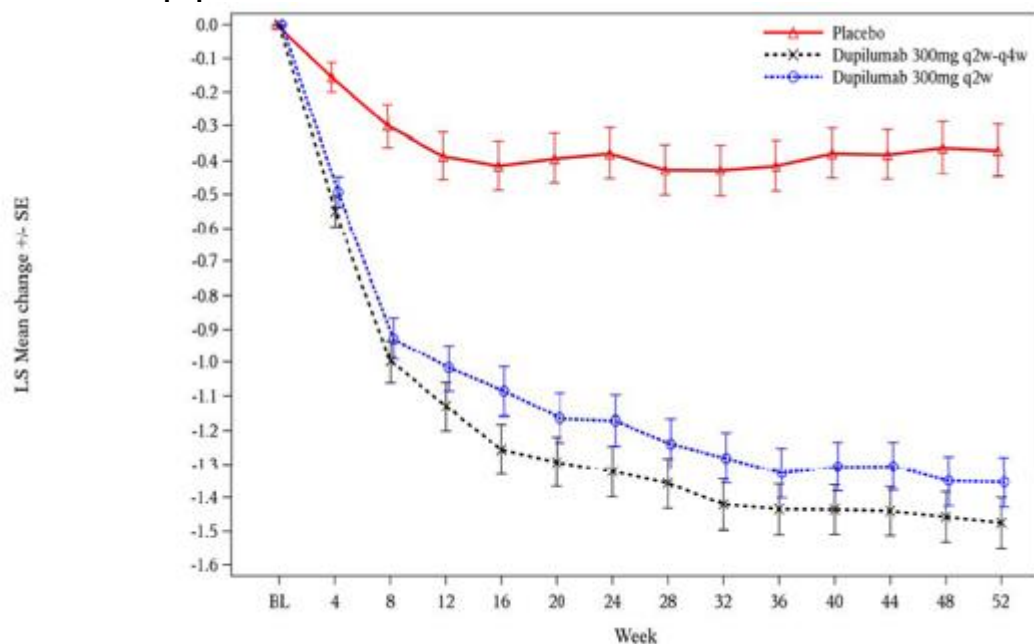


Figure 59 LS mean change from baseline in nasal congestion/obstruction (NC) by month to week 52 – ITT population.

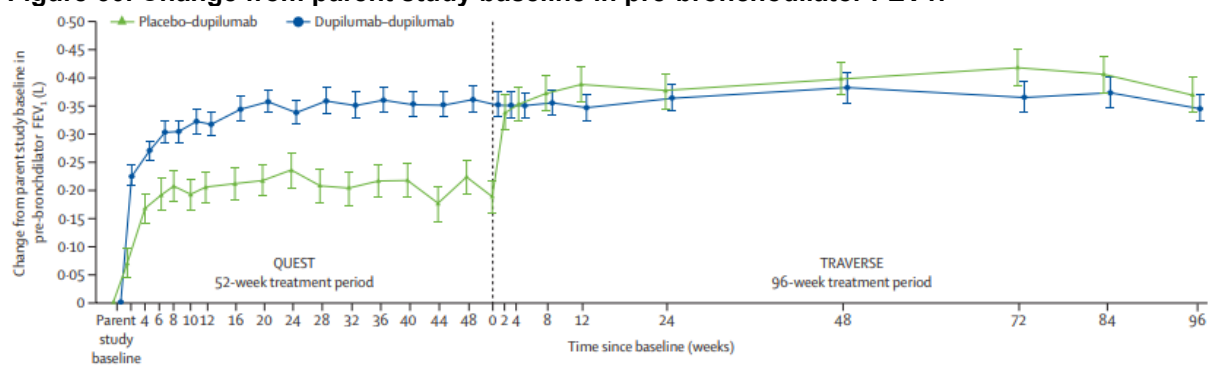


We note the concerns raised by the EAG experts who cited their experience in asthma with biologics. In the long-term real world open-label extension study TRAVERSE, in moderate-to-severe asthma, sustained FEV₁ treatment effect of up to 148 weeks (52 weeks for the parent studies + 96 week extension) for dupilumab was observed.²⁰

TRAVERSE was an open-label extension study involving 362 hospitals and clinical centres across 27 countries that assessed the safety and efficacy of dupilumab 300 mg every 2

weeks for up to 96 weeks in adults and adolescents (aged 12–84 years) with moderate-to-severe or oral-corticosteroid-dependent severe asthma who had completed a previous dupilumab asthma study (phase 2A EXPEDITION, phase 2B DRI [P2b], phase 3 QUEST, or VENTURE). The primary endpoint was the number and percentage of patients with any treatment emergent adverse events (TEAE); secondary endpoints included the annualised exacerbation rate over the treatment period and the change from parent study baseline in pre-bronchodilator FEV₁ and anti-drug antibodies (ADAs). The maintenance of treatment effect is illustrated in the plot of change from baseline in pre-bronchodilator FEV₁ for 3 years since the start of the parent study. (Figure 60).

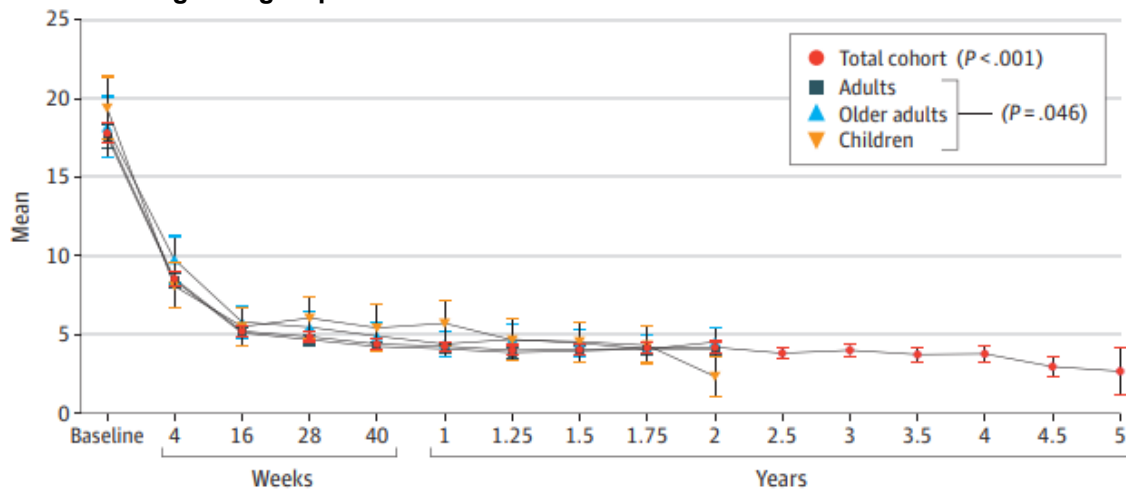
Figure 60. Change from parent study baseline in pre-bronchodilator FEV₁.



CRSwNP while associated with asthma is not a disease with known exacerbating factors such as viral infection and environmental exposures playing a role in long term disease control. This suggests that treatment effect in CRSwNP may be even more durable than observed for the asthma indication.

Results from the long-term open label extension study for Atopic Dermatitis over five years show sustained treatment effect. The outcomes for the key primary endpoint of Eczema Area and Severity Index (EASI) are presented in Figure 61 below.

Figure 61 Primary continuous outcome for Eczema Area and Severity Index (EASI) amongst 1286 Patients with atopic dermatitis during 5 Years of dupilumab treatment, stratified by the total cohort and age subgroup.



The supportive data above suggest that treatment with dupilumab in CRSwNP and other Type 2 inflammatory conditions results in sustained longer term outcomes, nonetheless we recognise that patients do discontinue biologic therapies for many reasons amongst which may be loss of efficacy and so a discontinuation rate is included in the model to account for all cause discontinuation based on the rate observed (annualised rate of Week 24 responders becoming uncontrolled at Week 52 of the dupilumab arm, in the base case scenario) in the SINUS studies (■■■■). The observed rate of discontinuation in the real-world AROMA study was very low (■■■■) indicating strong persistence on treatment and this tested in sensitivity analysis in the longer-term Markov model. (Added to the annual rate of loss of response based on SNOT-22, see Question B11).

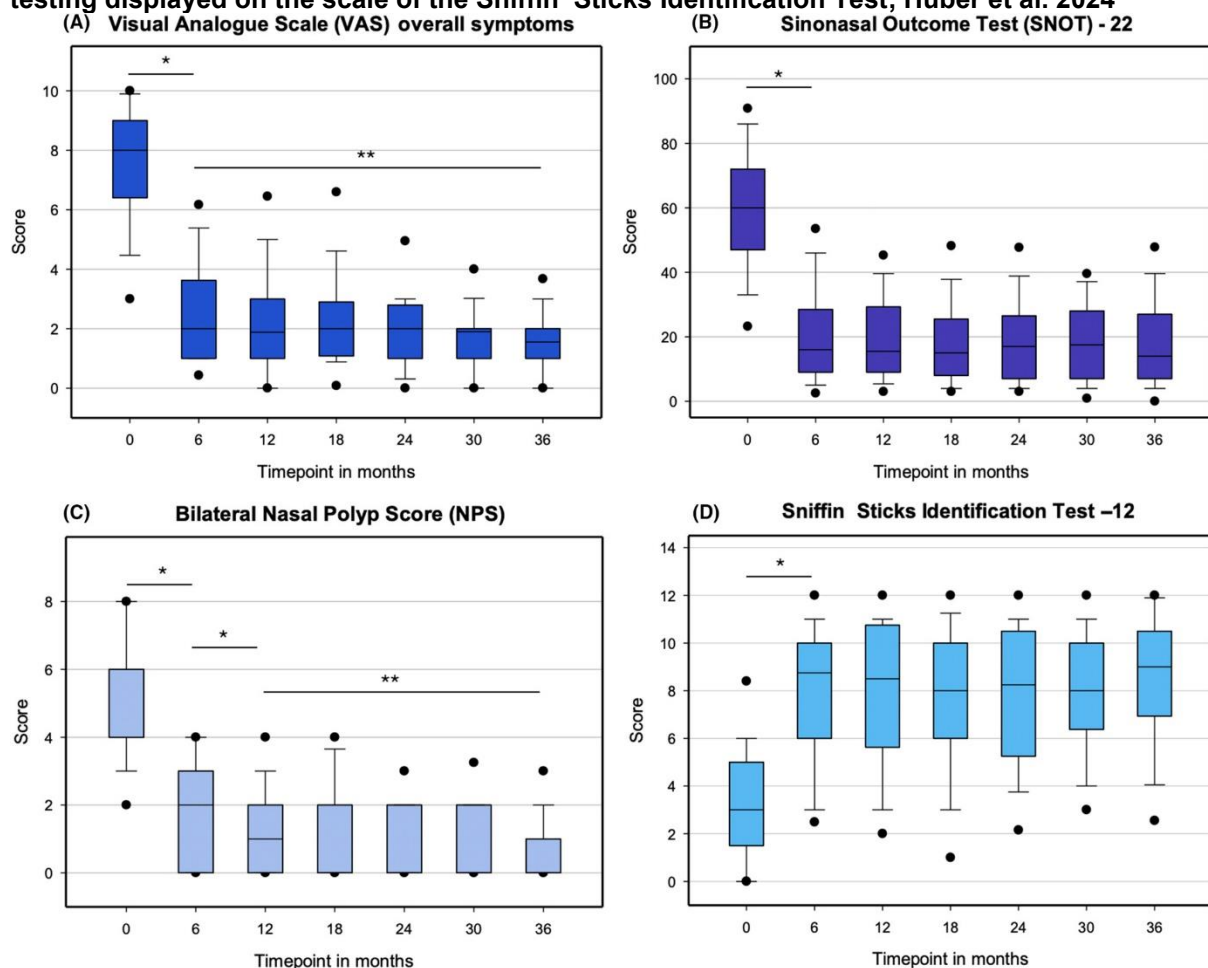
- b) Please include a scenario analysis in which this assumption is relaxed, informed by alternative data. The EAG notes that the AROMA observational study could be used to observe response rates to dupilumab in a real world setting over a longer period that the 52-week trial yet notes that any analysis undertaken should account for any differences in the patient populations, for example, using propensity score matching methods.**

In addition to the arguments provided above (question B12a), we did not find publications supporting the assumption that the efficacy of biologics, specifically dupilumab, would wane over time in its CRSwNP and/or asthma indications. To the contrary, several studies have assessed the long-term efficacy of dupilumab and

other biologics in patients with CRSwNP, with findings consistently demonstrating sustained improvements without waning effects.

In a real-world, multicentre study, Huber et al. (Real-world data show sustained therapeutic effects of dupilumab in CRSwNP over 3 years, 2024) evaluated 150 patients with severe CRSwNP treated with dupilumab over a 36-month period.²¹ The study reported significant and sustained improvements in disease-related impairment, rhinosinusitis symptoms, and nasal polyp burden throughout the treatment duration, with no signs of loss of efficacy.

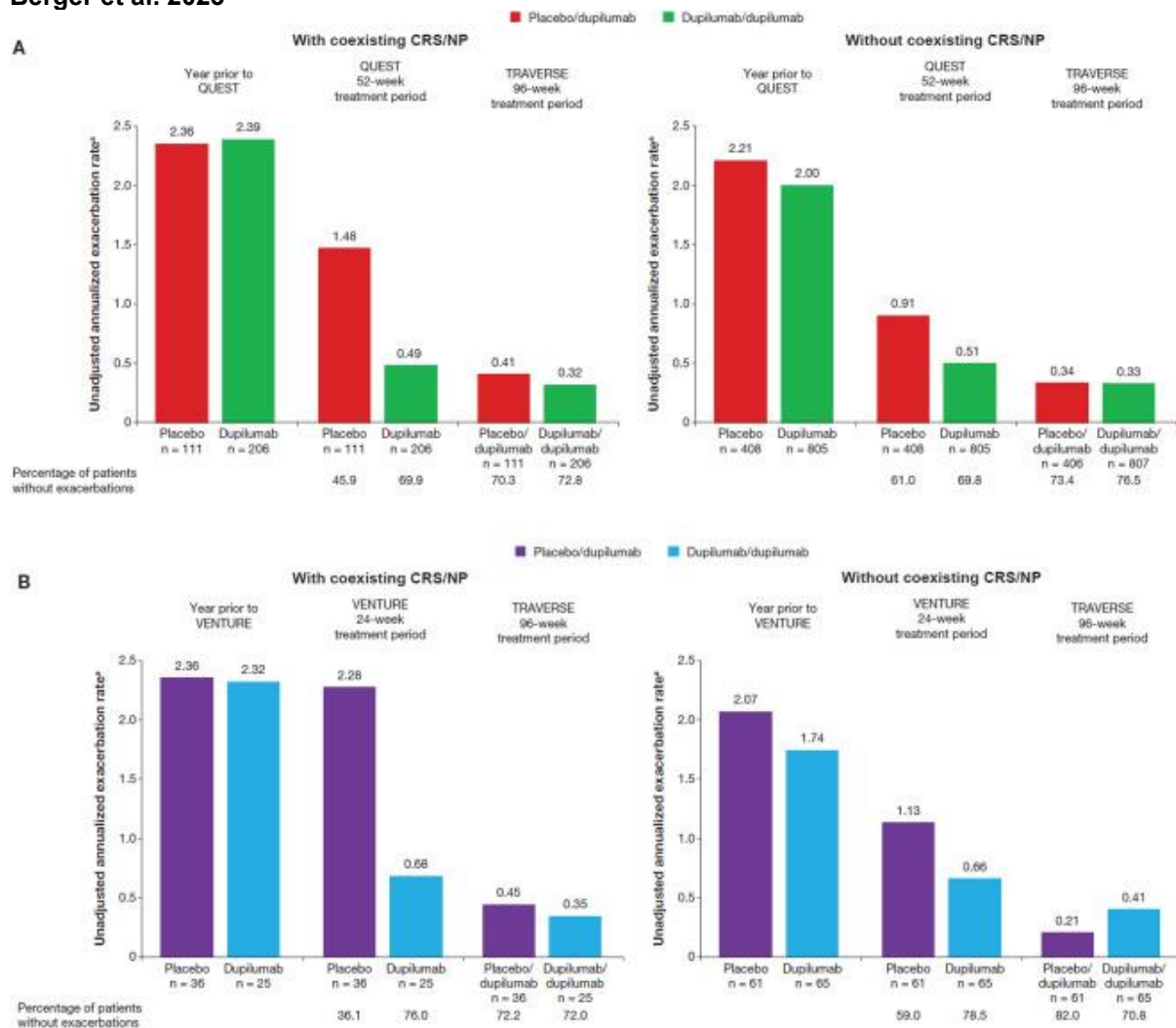
Figure 62. Boxplots displaying the changes of VAS, SNOT-22, bilateral NPS and olfactory testing displayed on the scale of the Sniffin' Sticks Identification Test, Huber et al. 2024



Similarly, a post hoc analysis of the TRAVERSE study, Berger et al. (Long-term efficacy of dupilumab in asthma with or without chronic rhinosinusitis and nasal polyps, 2023), assessed long-term efficacy in patients with moderate-to-severe asthma with or without CRSwNP.²² The study found that improvements in lung

function, asthma control, and quality of life scores observed in the parent studies were maintained in TRAVERSE, with 71% of oral corticosteroid-dependent patients with CRSwNP able to discontinue oral corticosteroids by week 96.

Figure 63. Annualized rate of severe asthma exacerbations in the TRAVERSE in patients enrolled from (A) QUEST and (B) VENTURE. CRSwNP, chronic rhinosinusitis and nasal polyp, Berger et al. 2023



Additionally, a systematic review and meta-analysis by Cai et al. (Efficacy and Safety of Biologics for Chronic Rhinosinusitis With Nasal Polyps: A Meta-Analysis of Real-World Evidence 2024) examined real-world data on biologic therapies, including dupilumab, omalizumab, mepolizumab, and benralizumab.²³ The study demonstrated significant clinical improvements at most follow-up time points, with dupilumab showing particularly strong effects. The efficacy of biologics in real-world settings was found to be greater than that reported in phase 3 randomised controlled trials, and all biologics exhibited low discontinuation rates due to adverse events,

further supporting their sustained efficacy and favourable safety profiles. Collectively, these studies provide strong evidence that dupilumab and other biologics maintain their clinical benefits over extended treatment periods, with no signs of waning efficacy.

Finally, in the study titled "The use of biologics in patients suffering from chronic rhinosinusitis with nasal polyps—a 4-year real-life observation,"²⁴ Frankenberger et al. conducted a retrospective analysis of 191 patients with CRSwNP treated with biologics such as dupilumab, mepolizumab, or omalizumab over a period of up to four years. The study reported significant symptom improvements with few side effects, and no loss of efficacy or tolerability was noted during the 4-year period ("After four years of therapy, there was no evidence of symptom control deterioration following an initial good response or increased side effects after good tolerability."). Patients reported high satisfaction compared to previous therapies, with overall improved quality of life. Notably, the need for revision surgery or oral steroid use during biologic therapy was rare. Some patients were able to prolong injection intervals or discontinue steroid nasal sprays. Biologic switching occurred infrequently due to side effects or inadequate response and was generally well tolerated. Many patients reported additional positive effects, such as improvements in asthma or allergy symptoms and reduced medication intake. These findings confirm the potency and tolerability of biologics for CRSwNP treatment, with sustained efficacy over four years (Frankenberger et al., 2024).

Collectively, these studies provide strong evidence that dupilumab and other biologics maintain their clinical benefits over long-term treatment periods, with no signs of waning efficacy and reduced need for additional medical or surgical interventions.

Figure 64. Development of NPS, SNOT-22 and olfactory test over time (polynomial regression with $n=5$, $R^2=0,95/0,94/0,92$), Frankenberger et al. 2024.

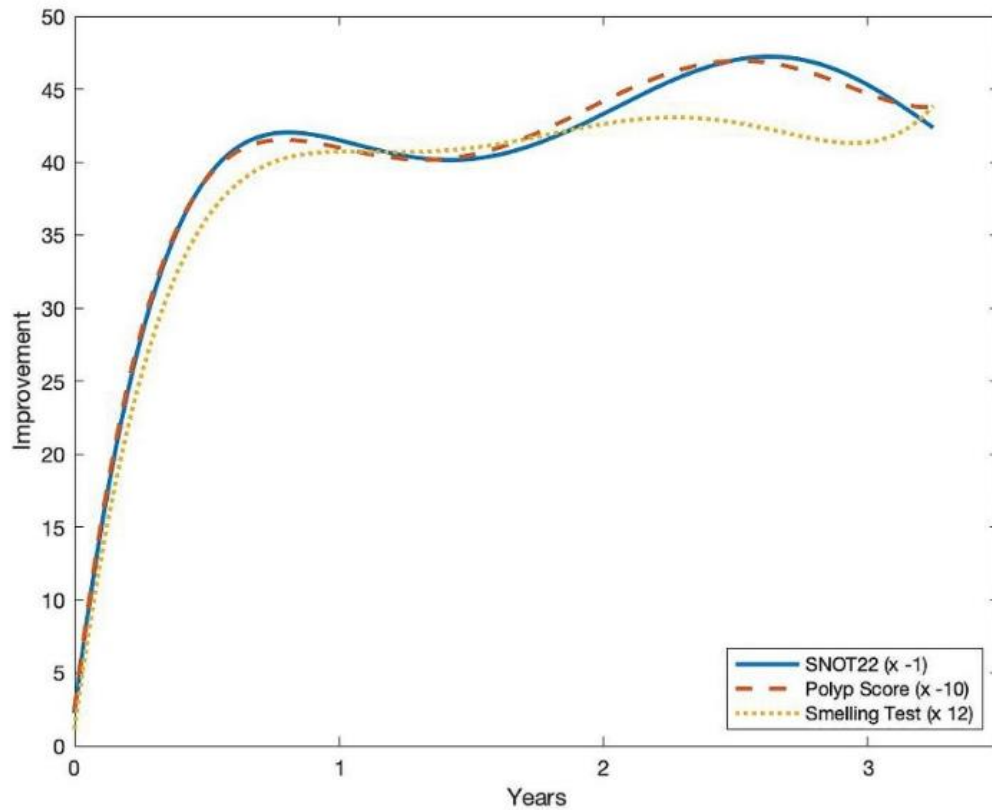


Fig. 1 Development of NPS, SNOT-22 and olfactory test over time (polynomial regression with $n=5$, $R^2=0,95/0,94/0,92$). In order to make the 3 parameters comparable, a scaling was used as shown in the box at the bottom right

Figure 65. Progress of the nasal polyp score under biological therapy measured quarterly by rhinoscopy, Frankenberger et al. 2024.

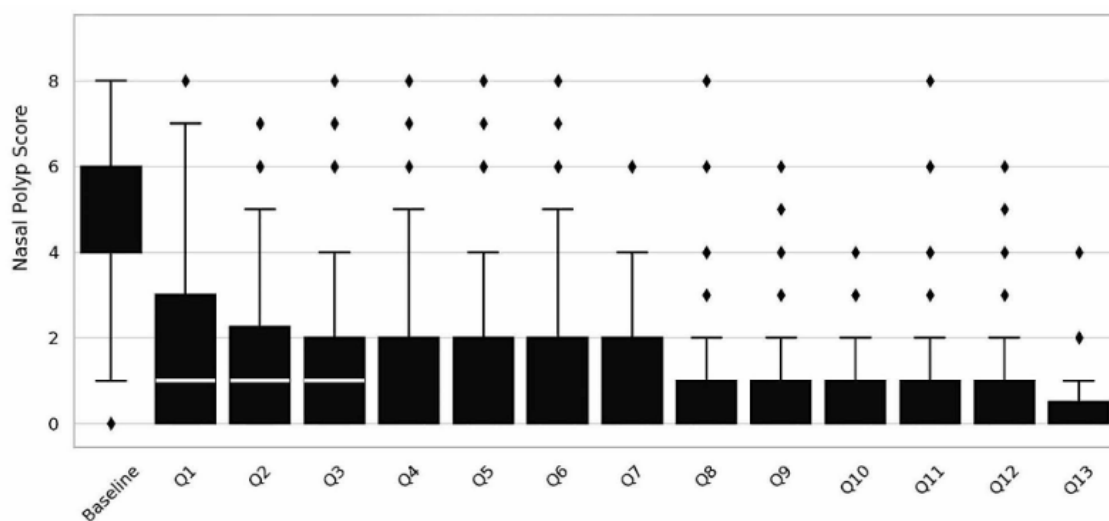


Fig. 3 Progress of the nasal polyp score (0–4 per side, 0–8 both sides combined) under biological therapy measured quarterly (Q1, 2....) by rhinoscopy

Table 18. SNOT-22 total score in AROMA (RAS), from baseline to month 24

	AROMA dupilumab Q2W (N=691)
Baseline SNOT-22, Mean (SD) N=552	45.9 (21.4)
Month 6 SNOT-22, Mean (SD) N=453	19.7 (15.6)
Month 12 SNOT-22, Mean (SD) N=272	17.1 (14.3)
Month 24 SNOT-22, Mean (SD) N=37	19.8 (19.2)

SD = Standard deviation; SNOT-22 = Sino-Nasal Outcome Test-22; RAS = Registry analysis set
Source: Sanofi. Data on File, Post-hoc analyses.¹

Dupilumab Patient Testimony (Video):

Finally, one of the major key opinion leaders (KOLs) in the field of rhinology in the UK has provided the company with a patient's video testimony. This patient has severe uncontrolled CRSwNP and was part of the SINUS trials. They continued treatment with dupilumab for CRSwNP (compassionate use) for several years until now and are providing a detailed testimony of the efficacy of dupilumab, its advantages over surgery, and moreover the sustained efficacy and response over numerous years. The video will be provided by the company along with the clarification questions response and the updated CEM.

Mortality

B13. The company submission states that “...there is an increased risk of mortality with severe asthma and so a relative risk of increased mortality due to comorbid asthma is applied in the base case”. The EAG notes that the increased risk of mortality is applied to all patients with comorbid asthma (59.1%) and not just patients with severe asthma, which the CS reports as 24.4%. Please clarify why this assumption was made in the model.

The percentages of asthma patients differ between worksheets 'Clinical' and 'Resource' as they are referring to different subpopulations and are applied differently in the CEM:

- In [Worksheet 'Clinical'; cell J99/ Mortality_UncontrolledAsthma], the relative risk of mortality linked to asthma (any severity) versus general population is applied to all

asthma patients of the relevant subgroup (picked up in the 'Baseline Characteristics' Worksheet).

- In [Worksheet 'Resource'; Cell F205/ AsthmaPercentage_ResourceSheet] asthma-related costs are only applied to severe asthma patients (GINA 4 or 5), to follow the referenced publication (picked up in the 'Baseline Characteristics' Worksheet), Willson et al. 2014.²⁵

The mention of "severe" asthma in the citation above was a typing error. The increased mortality calculate in the meta-analysis applies to all asthma patients versus general population, therefore should apply to all comorbid asthma patients in the model. This relative mortality risk has therefore been maintained in the CEM to all patients with comorbid asthma. In addition, further details have been added in the company's response to question B14.

B13a. The CS states that 24.4% of patients had comorbid severe asthma at baseline in the pooled population. On worksheet "Resource" it details the calculation used to derive this number $((126+32)/428*0.662 = 24.4\%)$. Please clarify what data each of these numbers represents as the EAG was unable to verify them. In addition, please clarify the exact data used to calculate the proportions of patients with controlled, partially controlled and uncontrolled as it is unclear to the EAG if this is based on the ITT or base-case population.

In the original CS, a detailed analysis of asthma in each subgroup by asthma severity level was not yet available. Therefore, the company had calculated the percentage of severe asthma patients (126 patients GINA 4 and 32 patients GINA 5) amongst the asthma population only (428 patients with comorbid asthma) and applied this factor to the asthma population of the base case. This value was hard-coded in the original CEM. The company has taken the opportunity to update baseline characteristics of all subgroups to include both asthma and severe asthma numbers from the relevant post-hoc analysis reports of SINUS-24/52, now available in [Worksheet 'Baseline Characteristics Data'; Lines 75-86].

B13b. The CS regularly refers to the source of data as "Sanofi data on file, 2019b (pooled trial data from SINUS-24 and SINUS-52)". Please provide any relevant documentation or reports that correspond with this source.

All data used in the CEM and referred to "Sanofi data on file, 2019b (pooled trial data from SINUS-24 and SINUS-52)" is based on post-hoc analysis of the pooled SINUS-24/52 trials, non-published and run by the company global biostatistics team. To comply with the EAG

request, the company has provided, at the end of this response document (after section C), all post-hoc analysis tables used to inform the model, for all requested subgroups and requested response criteria.

B14. The meta-analysis used to inform the relative risk for increased mortality for asthma patients was based on four studies, none of which were UK based and none were published recently. Please clarify if any more relevant and more recently published studies were searched for?

To comply with the EAG request, we have carried out an updated targeted literature review and selected a more recent meta-analysis by Zhang B et al. (2022),²⁶ which investigated the association between asthma and all-cause mortality. This study included 18 studies,²⁶ compared to the 4 studies utilized in Xu et al. (2017). Despite the increased number of studies, the results remained consistent, showing a statistically significant risk of increased all-cause mortality for asthma patients: 1.38 (95% CI: 1.07 – 1.77) in Zhang B et al. (2022)²⁶ vs. 1.36 (95% CI: 1.01 – 1.83) in Xu et al. (2017).²⁷

Zhang B et al. included a study conducted by Markowe et al. (1987) in England and Wales, which reported a relative risk of 1.64 (95% CI: 1.34 – 2.00). More recent studies, including He et al. (2021), Osvald et al. (2020), and Ng et al. (2020), reported relative risks of 1.38 (95% CI: 1.20 – 1.58), 1.46 (95% CI: 1.33 – 1.60), and 1.02 (95% CI: 0.60 – 1.73), respectively. It is important to note that the relative risk of 1.02 in Ng et al. (2020) was evaluated in childhood asthma, which may not align with the population of interest. To capture the full spectrum of patients with asthma, we recommend using the relative risk of 1.38 (95% CI: 1.07 – 1.77) from the meta-analysis by Zhang B et al. (2022).

Additionally, data from Alt et al. (2017) indicated a significant difference in mortality risk between patients with CRSwNP versus CRSsNP (HR = 1.39, 95% CI: 1.09 – 1.77), highlighting the higher mortality risk for patients with CRSwNP.²⁸

The relative risk of mortality related to asthma (in comparison to general population mortality) has therefore been updated in the CEM to 1.38 in the CEM, [Worksheet 'Clinical'; cell J99/ Mortality_UncontrolledAsthma]

B15. Due to the inclusion of increased mortality for asthma patients and the company applying separate rates of uncontrolled asthma for each treatment arm in the model, this results in a difference in mortality between the two treatment arms and therefore in life years (LYs). Please include the

total life years for each treatment arm and incremental LYs in the model results sheet.

Total life years (LYs) for each treatment arm, as well as incremental LYs have been included in the CEM results worksheet, [Worksheet 'Tabular'; Lines 46-58]

Health related quality of life

B16. Priority question: For the general population utility values, the NICE methods guide recommends using the Health Survey for England (HSE) 2014 dataset, as recommended by the DSU (Hernández Alava *et al.* 2022). Please update the general population utility values used for age adjustment in the model to use the HSE 2014 dataset.

The general population utility values used for age and sex adjustment in the CEM have been updated in [Worksheet 'Utility Calcs'; Lines 194-350] to use the Health Survey for England (HSE) 2014 dataset, as recommended by the DSU (Hernández Alava *et al.* 2022). And can be selected in [Worksheet 'Utility'; Cell I75/Utility_Source_Population_Norms].

B17. Priority question: The Crump *et al.* 2017 dataset used by the company to inform the mapping between SNOT-22 and EQ-5D uses patients exclusively awaiting ESS, therefore it is likely that there are few or no patients who would be categorised as responders. Therefore, please comment on the validity of using the Crump mapping algorithm to accurately quantify responders utility values.

As discussed in the CS (Section 3.3.3.3) a search of the HERC database of mapping studies and a targeted literature review which aimed to include any publications with chronic rhinosinusitis with information on mapping algorithms or models for mapping not restricted by intervention was carried out. These searches identified the study by Crump *et al.* from 2017 as the only published algorithm for mapping SNOT-22 onto EQ5D.²⁹

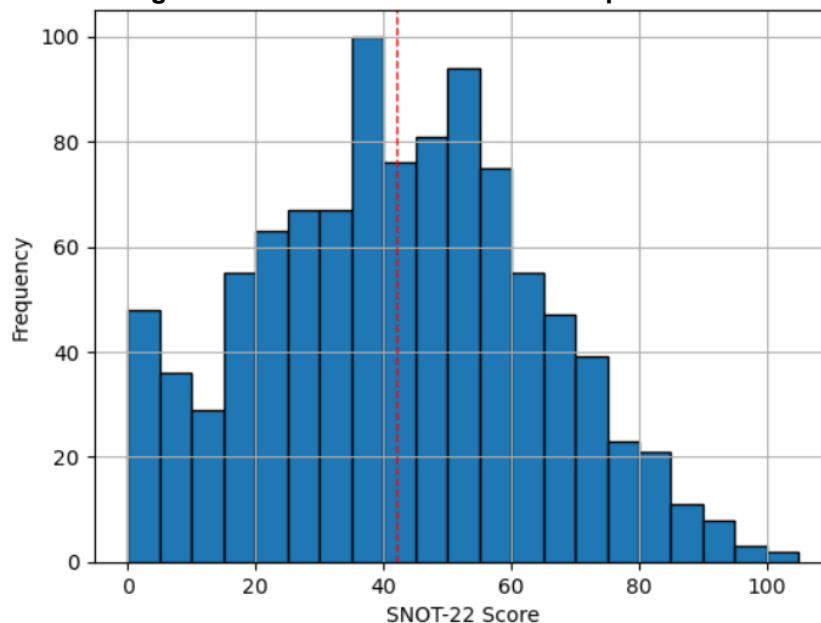
This study used data from CRS patients at the time they were enrolled onto the Canadian patient registry for elective surgery. However, patients were excluded if their surgery was considered emergent or cancer-related, or if their surgery was scheduled within 2 weeks of being enrolled on the waitlist.

We recognise that these patients cannot be considered 'responders' under the definition used in our modelling and that this is therefore an imperfect dataset with incomplete overlap

with the patient populations modelled in our submission. However as this is the only available published algorithm it is informative to consider the spread of SNOT22 values collected from the included patients.

According to the characteristics of the study sample the mean $\pm$ SD SNOT-22 global score was 42.5 ± 22.2 and the median was 42.0 (0-103). There is no histogram of SNOT-22 total score published in the paper by Crump et al. but for illustrative purposes we have simulated this according to the published scores above. This is presented in [Figure 66](#) below.

Figure 66. Simulated histogram of SNOT-22 scores from Crump et al. 2017

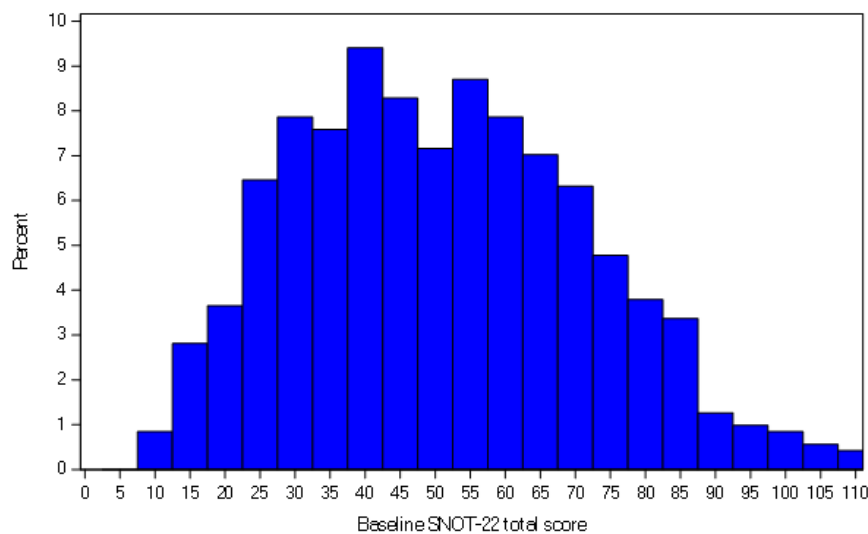


SNOT-22 = 22-item Sino Nasal Outcome Test
Source: Crump et al. 2017.

The published standard deviation in the SNOT-22 global score was ± 22 and [Figure 66](#) above illustrates this spread of results covering almost the entire domain of SNOT-22 (which runs from 0 to 110).

In the pooled data from the SINUS studies at baseline the mean $\pm$ SD SNOT-22 global score was 50.94 ± 20.66 and the median was 50.00 (8.0-110). We have provided the observed SNOT-22 scores at baseline from the pooled SINUS studies plotted as a histogram in [Figure 67](#) for comparative purposes below.

Figure 67. Histogram of baseline SNOT-22 total score overall treatment groups – Pooled ITT population



ITT = intention-to-treat; SNOT-22 = 22-item Sino Nasal Outcome Test
Source: Crump et al. 2017

Patients in the SINUS studies had slightly higher total SNOT-22 scores at baseline but there is likely to have been considerable overlap of scores with the patient population used to derive the Crump algorithms.

To derive a robust mapping algorithm, it is important to ensure that there is a wide spread of data to inform all points across the span of expected use. Responders are likely to have low SNOT-22 scores, and it is clear from [Figure 66](#) above that the Crump dataset is likely to contain low and very SNOT-22 scores.

The SNOT-22 total score and change from baseline for the base case population according to response from the SINUS studies is provided in table 47 in the CS. For the population with response the mean $\pm$ SD scores are 22.800 (± 16.536) and 17.545 (± 14.368) for ECM and dupilumab patients respectively at 24 weeks and 20.500 (17.678) and 13.795 (15.740) at 52 weeks. Inspection of [Figure 66](#) above suggests that these scores will have been well represented in the dataset used to derive the algorithm.

Whilst we recognise the limitations with the application of the published data to our economic model, for the reasons above it remains the best (and only) source to derive the required utility data for the model, even in the responder patient population.

B18. Priority question: To limit issues with multicollinearity between SNOT-22 and baseline EQ-5D, please could the company rerun the regression

models in section 3.3.3.5 using change from baseline in SNOT-22 score rather than total.

The regression models in section 3.3.3.5 and in the CEM [Worksheet 'Utility Calcs'; Lines 58-107] have been re-run using change from baseline (CFB) in both SNOT-22 and NPS rather than total score, to limit issues with multicollinearity between SNOT-22 and baseline EQ-5D.

Table 19 Covariates included in the regression models

	Model 5	Model 6	Model 7	Model 8
Covariates included in the models				
Female gender	✓	✓	✓	✓
Age	✓	✓	✓	✓
Baseline EQ-5D score	✓	✓	✓	✓
Cfb in SNOT-22 total score	✓	✓	✓	✓
Cfb in NPS total score	x	✓	✓	✓
Interaction between CFB in SNOT-22 and CFB in total NPS total score	x	x	✓	✓
Treatment	x	x	x	✓
Selection criteria				
AIC	-3071.7	-2984.6	-2969.6	-2959.2
AICC	-3071.7	-2984.6	-2969.6	-2959.2
BIC	-3062.6	-2975.5	-2960.5	-2950.2

The individual models are described in more detail below.

'Model 5'

Table 20. Estimates for the covariates for 'Model 5' (Hernandez Alva crosswalk)

Effect	Sex	Estimate	Standard Error	Pr > t	Lower	Upper
Intercept		0.3588	0.02751	<.0001	0.3048	0.4128
SEX	F	-0.01604	0.009107	0.0786	-0.03392	0.001838
SEX	M	0	.	.	.	.
AGE		-0.00075	0.000345	0.0302	-0.00143	-0.00007
EQUKHBL		0.5942	0.02302	<.0001	0.5489	0.6394
SNTOTAL_chg		-0.00317	0.000167	<.0001	-0.00350	-0.00284

Figure 68. Conditional residuals for 'Model 5'

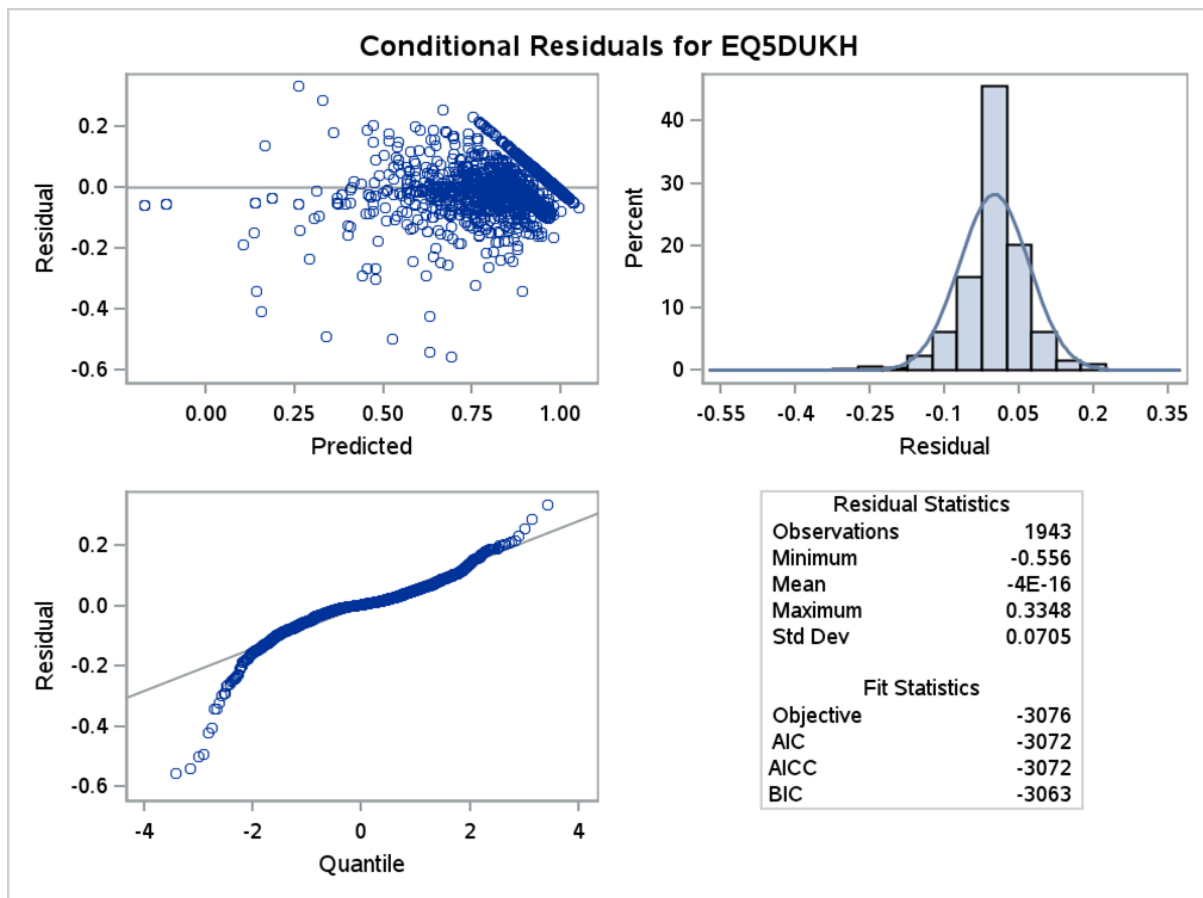
**'Model 6'**

Table 21. Estimates for the covariates for 'Model 6' (Hernandez Alva crosswalk)

Effect	Sex	Estimate	Standard Error	Pr > t	Lower	Upper
Intercept		0.3584	0.02783	<.0001	0.3038	0.4130
SEX	F	-0.01617	0.009216	0.0798	-0.03427	0.001924
SEX	M	0	.	.	.	.
AGE		-0.00078	0.000349	0.0251	-0.00147	-0.00010
EQUKHBL		0.5973	0.02334	<.0001	0.5514	0.6431
SNTOTAL_chg		-0.00323	0.000182	<.0001	-0.00358	-0.00287
NPS0203_chg		0.001168	0.001996	0.5585	-0.00275	0.005082

Figure 69. Conditional residuals for 'Model 6'

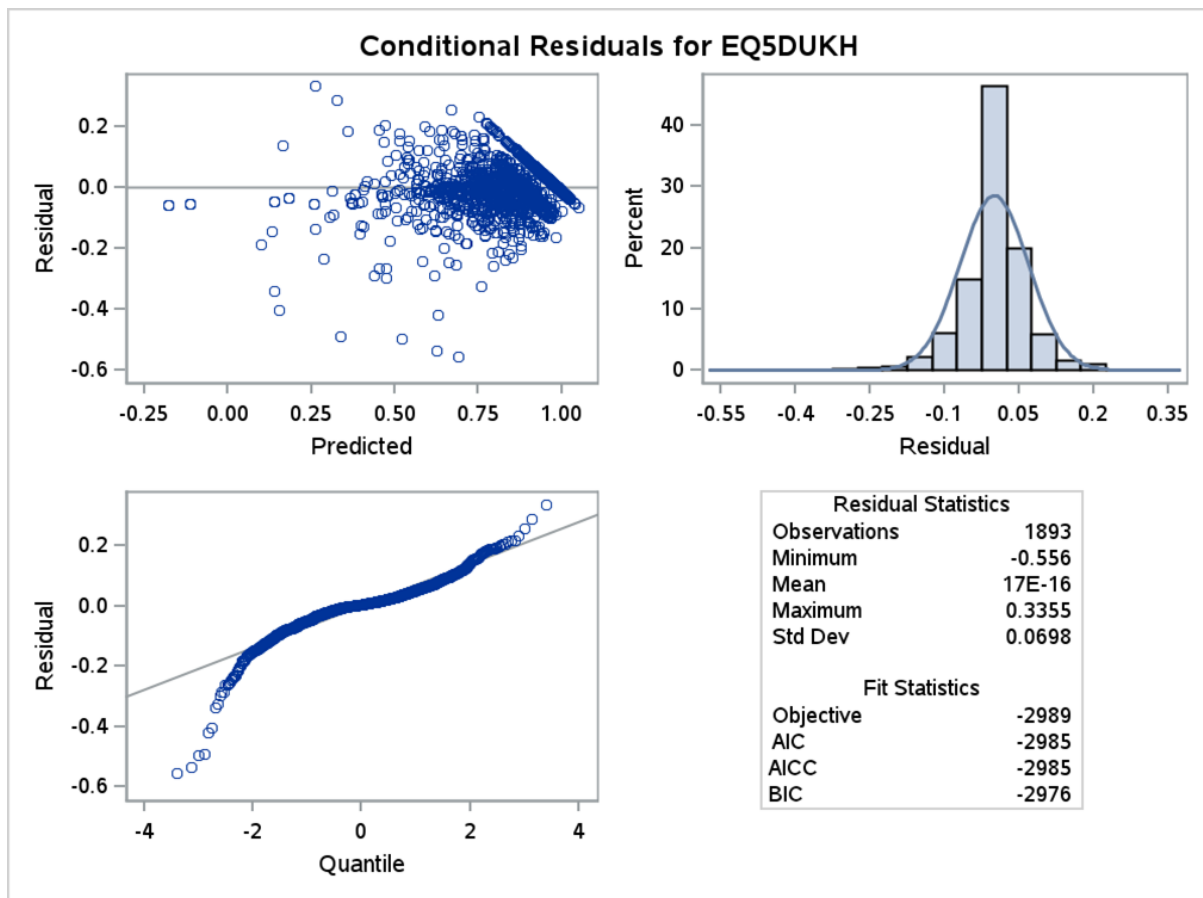
**'Model 7'**

Table 22. Estimates for the covariates for 'Model 7' (Hernandez Alva crosswalk)

Effect	Sex	Estimate	Standard Error	Pr > t	Lower	Upper
Intercept		0.3570	0.02792	<.0001	0.3022	0.4118
SEX	F	-0.01603	0.009242	0.0832	-0.03418	0.002111
SEX	M	0	.	.	.	.
AGE		-0.00076	0.000350	0.0302	-0.00145	-0.00007
EQUKHBL		0.5991	0.02344	<.0001	0.5531	0.6451
SNTOTAL_chg		-0.00310	0.000201	<.0001	-0.00350	-0.00271
NPS0203_chg		0.003997	0.002776	0.1502	-0.00145	0.009442
SNTOTAL_c*NPS0203_ch		0.000110	0.000075	0.1442	-0.00004	0.000257

Figure 70. Conditional residuals for 'Model 7'

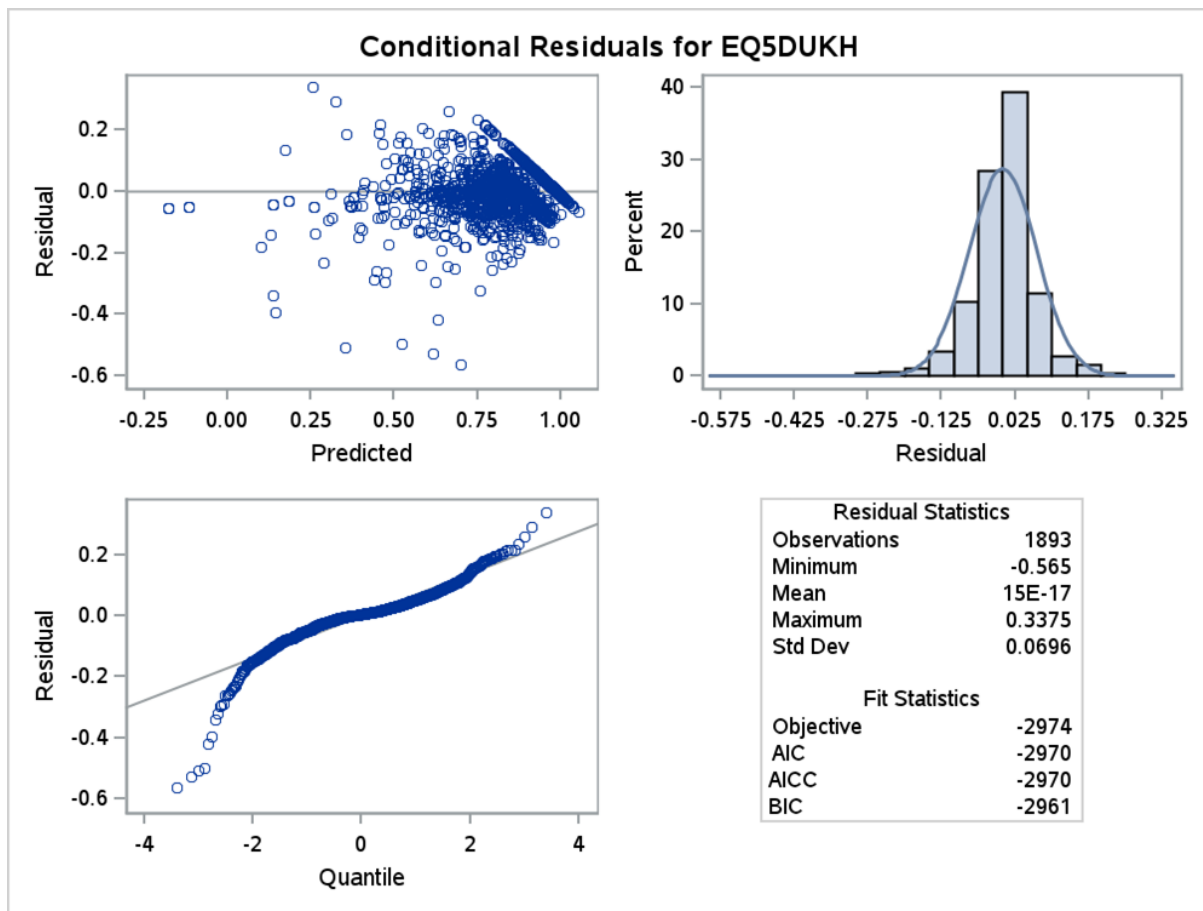
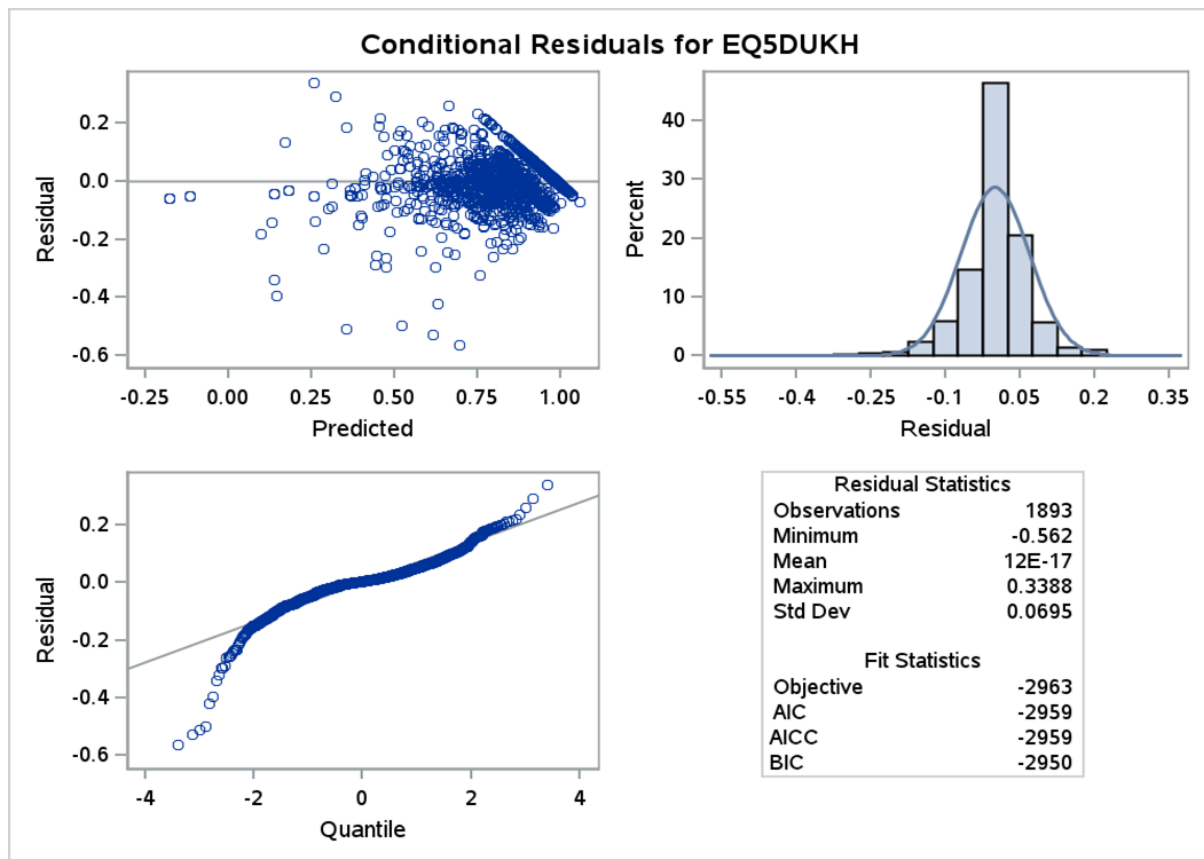
**'Model 8'**

Table 23. Estimates for the covariates for 'Model 8' (Hernandez Alva crosswalk)

Effect	Sex	Planned Treatment for Period 01	Estimate	Standard Error	Pr > t	Lower	Upper
Intercept			0.3527	0.02807	<.0001	0.2976	0.4078
SEX	F		-0.01545	0.009240	0.0949	-0.03359	0.002687
SEX	M		0	.	.	.	.
AGE			-0.00076	0.000350	0.0306	-0.00145	0.00007
EQUKHBL			0.5983	0.02345	<.0001	0.5523	0.6444
SNTOTAL_chg			-0.00307	0.000207	<.0001	-0.00347	-0.00266
NPS0203_chg			0.004737	0.002890	0.1014	-0.00093	0.01041
TRT01P		Dupilumab 300 mg q2w	0.01763	0.01116	0.1145	-0.00427	0.03954

TRT01P		Dupilumab 300 mg q2w up to Week 24 and 300 q4w from Week 24 to Week 52	-0.00308	0.01264	0.8078	-0.02790	0.02174
TRT01P		Placebo q2w	0	.	.	.	.
SNTOTAL_c*NPS0203_ch			0.000113	0.000075	0.1337	-0.00003	0.000261

Figure 71. Conditional residuals for 'Model 8'



B19. Priority question: Please add a scenario using the reported EQ-5D data (crosswalked) to inform health state utility values, in which the responder utility values are capped at general population for the baseline age and a multiplier is applied to subsequent health states to retain the proportional differences between states?

The option to cap utility values at general population for the baseline age has been implemented in the CEM [Worksheet 'Utility'; Cell I84/UtilityCapping], and a multiplier has been applied to subsequent health states to retain the proportional differences between states. The multiplier is located in the [Worksheet 'Utility'; Cells P12, AB12 or AN12] depending on the utility scenario selected. The multiplier factor has been calculated from Clarification questions

utility of DUP+ECM responders at week 52 vs. utility at population norm at baseline age. This scenario is included in the wider Table of all scenarios presented after Section C.

B20. The company notes that the utility score for responders is 0.917 if using directly reported EQ-5D, which is higher than the UK general population. Is there any difference in the age of patients who respond, compared to the overall population, that could help explain this?

Data for the age of responders versus non-responders in the pooled SINUS-24/52 ITT population is provided in Table 24 below. As can be seen, there is no statistically significant difference in the mean age of responder patients versus non-responder patients. Therefore, age is unlikely to explain the observed high utility scores. This high utility value is more likely to be due to the poor performance of the EQ-5D instrument to assess quality of life in CRSwNP. (See our answer to question B21 below and Section 3.3.3.2 of the CS).

Table 24 Age of responders versus non-responders in pooled SINUS-24 and SINUS-52 ITT population

	Responders (N=174)	Non-responders (N=285)
	Improvement from baseline ≥8.9 in SNOT-22 and improvement by at least 1 point in NPS from baseline at Week 24	
Age (years)		
Number	174	285
Mean (SD)	50.70 (11.51)	51.79 (13.24)
Median	51.00	52.00
Q1 : Q3	42.00 : 60.00	41.00 : 61.00
Min : Max	23.0 : 79.0	22.0 : 85.0
Age group (years) [n (%)]		
Number	174	285
18 – 64	154 (88.5%)	229 (80.4%)
65 – 74	18 (10.3%)	45 (15.8%)
75 - 84	2 (1.1%)	10 (3.5%)
≥85	0	1 (0.4%)

ITT = intention-to-treat; NPS = nasal polyp score; SNOT-22 = Sino-Nasal Outcome Test-22.
Source: Sanofi. Data on File, Post-hoc analyses.¹

B21. Based on table 27 of the company appendices, health-related quality-of-life studies that use EQ-5D; Tashman *et al.* 2024, Wahid *et al.* 2020, Scangas 2018, Scangas 2017a and De Corso *et al.* 2022 appear to show significantly higher utility values than used in the company's base case.

What is the company's explanation for why other health-related quality of life studies appear to show higher utilities for patients?

In Section 3.3.3.2 of the CS we discussed the poor performance of the EQ-5D instrument in capturing the quality of life of patients with CRSwNP. We noted that EQ-5D is a generic instrument which does not include items specifically related to the key domains of HRQoL impact for these patients in particular for anosmia and sleep.

In all the studies cited in question B21 the baseline EQ-5D was high (Tashman 2024: 0.820, Wahid: 0.797, Scangas 2017: 0.842 (regardless of asthma) and Scangas 2017a: 0.832 to 0.839) and close to or above EQ-5D population norms.

The DeCorso study takes its evidence from the SINUS trials. In the CS we highlighted the poor correlation between several disease specific measures and EQ-5D from the pooled SINUS data at baseline. In all cases the correlation coefficients are between 0.3 and -0.3 indicating poor correlation for these objective and subjective measures and providing more evidence for the poor performance of EQ-5D in this disease area.

The high mental, physical and emotional burden that CRSwNP places on patients cannot be ignored and this came across strongly in the patient testimonies at the SINUS UK roundtable held in January 2025, details of which are provided in Appendix S to the CS.

The consistently high scores for EQ-5D, approaching population norm or above it, across the literature supports the assertion that EQ-5D cannot robustly capture the burden of CRSwNP (or sufficiently describe changes to that burden). This would very likely be common to any study in CRSwNP that uses this instrument and good reason to ensure disease specific measures are used in clinical trials that can be mapped to utility scores.

B22. In Table 46 of the CS, the Spearman's rank coefficient for the relationship between EQ-5D and efficacy data at baseline is given using the 'Hernandez 2020 crosswalk method, UK tariffs' whereas the coefficients for the relationship between change from baseline at week 24 is given using the 'Van Hout Crosswalk 2012, UK tariffs'.

a) Please clarify why the different crosswalk methods have been used?

We apologise for the incorrect labelling of table 46 in the CS. The data in table 46 exclusively uses the Hernandez crosswalk method.

b) As the NICE methods guide recommends the Hernandez 2020 crosswalk, please provide the results of the equivalent table using only this method.

We have reproduced table 46 from the CS below with the correct label for the change from baseline data.

Table 25. Exploration of the relationship between EQ-5D-5L utilities and efficacy data

Score	Spearman correlation coefficient	P value
Relationship between baseline EQ-5D-5L utilities (Hernandez 2020 crosswalk method, UK tariffs) and baseline efficacy		
Decreased/loss of sense of smell score	-0.06	0.143
UPSIT smell test score	0.13	<0.001
Nasal polyposis score	-0.07	0.055
Nasal congestion/ obstruction score	-0.13	<0.001
Lund-Mackay score	-0.04	0.241
Relationship between change from baseline in EQ-5D-5L utilities (Hernandez 2020 crosswalk method, UK tariffs) at Week 24 and change from baseline in efficacy at Week 24		
Decreased/loss of sense of smell score	-0.23	<0.001
UPSIT smell test score	0.21	<0.001
Nasal polyposis score	-0.19	<0.001
Nasal congestion /obstruction score	-0.26	<0.001
Lund-Mackay score	-0.18	<0.001

EQ-5D-5L = EuroQol -5 Dimensions 5-Levels; UPSIT = University of Pennsylvania Smell Identification Test

B23. In section 3.3.3.6 the directly observed EQ-5D used for sensitivity analysis is referenced. Please clarify is this EQ-5D-5L data or is this converted into EQ-5D-3L?

All utility values (HUVs) in the CS and the CEM are EQ-5D-3L, based on either:

- Observed EQ-5D-5L in SINUS-24/52, converted into EQ-5D-3L using a crosswalk method (either Van Hout or Hernandez depending on scenarios).
- Observed SNOT-22 in SINUS-24/52, mapped into EQ-5D-3L using Crump et al. 2017 models 1 to 3.

Some titles in the CEM may have been misleading and have been updated appropriately.

B24. What is the justification for using the week 24 response data to inform utility between week 13 and 24 but using an average of week 25-52 to inform utility in week 25-52? Why isn't the same approach used for both periods?

In SINUS-24/52, EQ-5D utility values were collected at baseline, week 24, and week 52. To account for utility changes over time, the approach taken in the analysis was to apply baseline utility values from baseline to week 12, and week 24 utility values from week 13 to

24. This method is mathematically equivalent to applying the average utility between baseline and week 24 over the entire 24-week period. Similarly, for the week 25 to 52 period, the average utility from week 25 to 52 was applied by responder status and by treatment arm. This is consistent in the approach (even if the calculation seems different). The key distinction is that this method allows differentiation by response status, which was not assessed before week 24, while ultimately leading to the same overall utility outcomes per treatment arm.

B25. Please provide the justification for dupilumab non-responders who receive surgery having a higher utility than ECM non-responders who receive surgery?

Two key studies, Soler et al. (2011)³⁰ and Remenschneider et al. (2015)³¹, provide evidence of a one-off health utility value (HUV) gain following ESS in patients with CRS, including those with nasal polyps (CRSwNP). Soler et al. (2011) conducted a prospective, multicentre study evaluating SF-6D-derived health utility values in 110 CRS patients undergoing ESS. The study found a significant improvement in health-related quality of life, with a mean SF-6D utility gain of +0.051 (0.099), $p < 0.001$, specifically in the nasal polyposis subgroup. Remenschneider et al. (2015) assessed EQ-5D utility values in 190 patients undergoing ESS for CRS, with preoperative, 3-month, and 12-month follow-up assessments. The study demonstrated a mean HUV increase from 0.81 (0.13) preoperatively to 0.89 (0.12) at 3 months, with stabilisation at 0.88 (0.10) at 1 year, resulting in a one-off utility gain of +0.080.

Both studies confirm that ESS leads to a one-off quality of life improvement post-surgery, from the utility value before surgery. Therefore, this utility gain has been applied to the utility value of the patient's health state of origin, reflecting the improvement from the pre-surgical condition. Furthermore, studies cited in questions B above show that response post-surgery is not well maintained, confirming the rationale for a one-off utility gain. As this is applied to the HS or origin of patients in the Markov model, there are four different utility values possible in that HS, all within close range.

B26. Given NPS was not a statistically significant coefficient to include in the QoL regression analysis (as shown in table 41 of the company appendix) and it was not a component of the Crump model, please clarify why it was maintained as a definition for response?

The Crump et al. 2017²⁹ mapping exercise was based on patient-reported outcome data collected by the Vancouver Coastal Health Authority (VCH). This study was designed to understand the health of patients waiting for elective surgery, and prospectively collected

PROs (including general health, pain, and depression status) on a longitudinal basis from community-dwelling patients waiting, receiving, and recovering from a range of elective surgeries. The NPS score was not collected in the dataset and the Crump mapping algorithm does not include it as a covariate.

In our regression models (See also Q18 above) NPS did not emerge as a statistically significant covariate and has not been included in the model of choice. However, our base-case response criterion is defined as improvement (reduction) from baseline ≥ 8.9 in SNOT-22 and improvement from baseline ≥ 1 point in NPS.

Whilst the NPS score does not feature in the calculation of utility it does not mean it is not a useful instrument for the assessment of response by clinicians. This was clear in the opinions of the experts we consulted at an advisory board who emphasised a combined approach resonates with clinical practice which seeks to determine the impact of treatment on patients' quality of life and objectively assess nasal polyp size.

Cost and resource use

B27. Please clarify why Dupilumab+ECM responders appear to take significantly more antibiotics than ECM responders (Table 57).

The data presented in Table 57 has been further analysed by calculating the p-values for the difference in antibiotic use between Dupilumab+ECM responders and ECM responders during week 0-week 24 and week 25-week 52. As shown in Table, no statistically significant difference was observed in the ITT population. In addition, given its minimal impact on the results, antibiotic use was removed from the CEM, to reduce uncertainty.

Table 26. Difference in antibiotic use by arm

	Response status*	Drug use in DUP+ECM arm			Drug use in ECM arm			p-value
		<i>x</i>	<i>n</i>	<i>p</i>	<i>x</i>	<i>n</i>	<i>p</i>	
W0-W24 (SINUS24/52)	Response	46	243	18.9%	4	31	12.9%	0.356
W25-W52 (SINUS52)	Response among responders at W24	14	77	18.2%	1	11	9.1%	0.350

B28. Please update the specialist visit cost using NHS schedule of costs 2023/24

The specialist visit cost included in the CEM has been extracted, using the NHS schedule of costs 2023/24³². The average consultant-led unit cost was £168.16,³² which has been updated in the appropriate sections of the CEM [Worksheet 'Resource'; cell H112/

UnitCost_Item2]. Please note that other costs have also been updated throughout worksheet 'Resource' to reflect the most recent version of the PSSRU 2023³².

- Specialist visit: 2023/24 National Cost Collection – Ear, Nose and Throat (ENT) service [120] Outpatient Care national average unit cost (consultant Led)
- Nurse visit: Hospital based nurse band 5 including qualification costs, 1 hour of initial patient training, £48 inflated to 2024. ³² (Table 11.2.2: Annual and unit costs for hospital-based nurses).
- Inflation factor: 1.029 inflation factor between 2023 and 2024 based on the 2016-2023 annual inflation rates were derived from PSSRU, 2023 and the 2023-2024 annual inflation rate based on annual CPIH annual rate, as of September 2024 (ONS).

B29. Clinical experts to the EAG noted that if dupilumab were to be recommended for routine clinical practice, the decision to start a patient on treatment would be made as part of a multidisciplinary team (MDT) and that it would only be prescribed through specialist centres. Therefore, please include a scenario analysis in the model in which all patients in the dupilumab arm incur the cost of an MDT meeting.

A scenario analysis in which all patients in the dupilumab arm incur the cost of a multidisciplinary team (MDT, multiprofessional consultant-led) meeting has been added in the updated version of the CEM with a cost of £220.78 of the CEM, based on ³²:

- 2023/24 National Cost Collection – Ear, Nose and Throat (ENT) service [120] Outpatient Care national average unit cost (multiprofessional - consultant Led).

B30. An adherence rate to dupilumab of 99.2% is used in the economic model. In the economic model it states that this is based on an 'average adherence between 300mg q2w-q4w and dupilumab 300mg q2w arms'. As the dosage used in clinical practice in the SmPC is q2w, please include a scenario using the adherence rate from only patients receiving q2w in the economic model.

The proportion of dupilumab injections with compliance to Investigational Medicinal Product (IMP) administration in the pooled SINUS-24/52 trials, for patients receiving Q2W only (Dupilumab and ECM), is reported in the Summary of Clinical Efficacy of dupilumab for

CRSwNP, as shown below in Table 26 below. The weighted average of Q2W treatment compliance across both arms was therefore 99.26%. This number has been updated in the CEM in [Worksheet 'Treatment'; cell K38/'DUPComplianceRate_1stCycle'; cell 39/'DUPComplianceRate_SubCycle'].

Table 26: Proportion of dupilumab injections in compliance with IMP administration (pooled ITT population)

% injections with compliance to IMP administration	ECM (N=286)	Dupilumab Q2W (N=438)
Mean (SD)	99.14 (3.13)	99.34 (2.44)

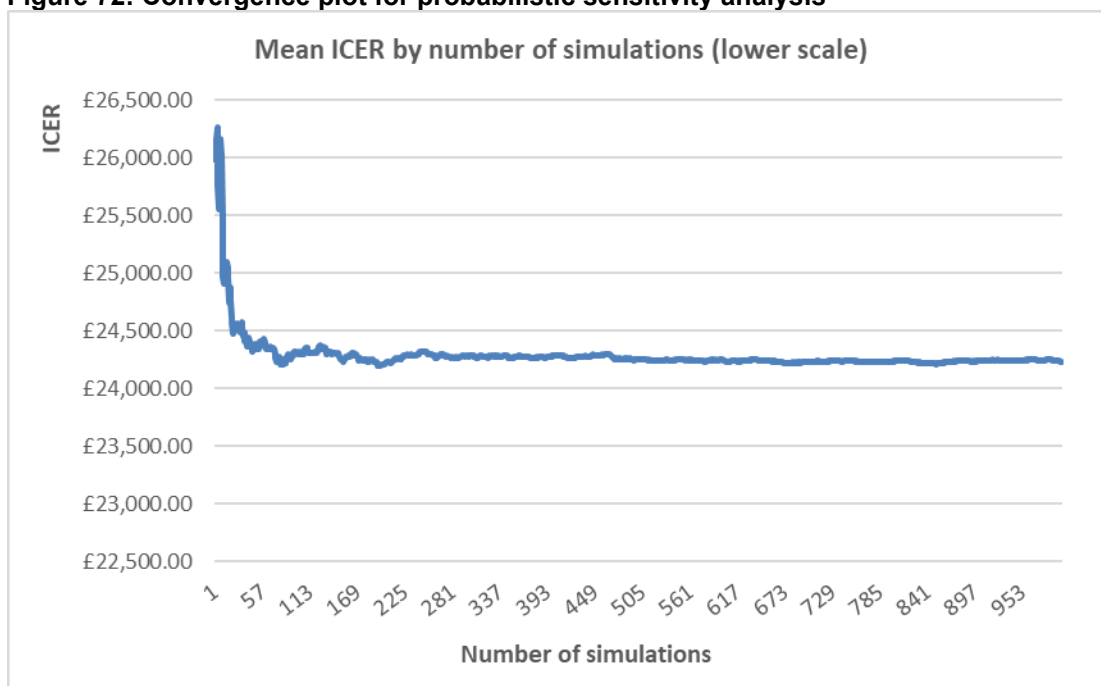
IMP = Investigational Medicinal Products; SD = standard deviation; Q2W = once every 2 weeks
Source: Sanofi. Data on File, Summary of Clinical Efficacy - Table 28.²

Section C: Textual clarification and additional points

C1. Priority question: Please provide a convergence plot for the probabilistic sensitivity analysis and ensure this is included in the economic model.

A convergence plot for the probabilistic sensitivity analysis (Figure 72) has been added to the CEM in [Worksheet 'Probabilistic SA'; Cells 95-115]. In the company base case, this convergence plot shows a clear convergence of the average probabilistic ICER towards the deterministic ICER of £23,410 after 300 iterations of the PSA, which supports its robustness.

Figure 72: Convergence plot for probabilistic sensitivity analysis



ICER = incremental cost-effectiveness ratio.

C2. Priority question: In the economic model in worksheet “Clinical” it states that 14.0% of patients had uncontrolled asthma on dupilumab compared to 59.0% on ECM. This differs from the figures reported for uncontrolled asthma in worksheet “Resource” which corresponds to Table 63 of the CS. Please clarify the discrepancy and amend as needed.

The percentages of controlled, partially controlled and uncontrolled asthma patients used in the CEM were determined based on the distribution of ACQ-6 level, per treatment arm, after 52 weeks of treatment in SINUS-52 (SINUS-52 ITT population with asthma GINA 4 or 5), as reported in Table 27 below. The company could not use the base case population (patients

with prior surgery) to inform these specific inputs, as the sample sizes would be too small, and had to resort to using the ITT population numbers.

Before the submission, there was a calculation error in the CEM, where the percentage of uncontrolled patients in the 'clinical' sheet was calculated based on the total number of patients with asthma GINA 4 or 5 in the ECM arm (39), when it should have been using the number of patients with ACQ-6 data at week 52 (36). This error was corrected in the CEM ahead of the CS in [Worksheet 'Resource'] and [Worksheet 'Baseline Characteristics'], but it seems that the input in [Worksheet 'Clinical'; cell J104/

Percentage_UncontrolledAsthma_Comparator] was hard-coded and not corrected. This input has now been updated in the CEM to reflect the appropriate 63.9% of ECM patients with uncontrolled asthma at week 52:

- DUP+ECM uncontrolled asthma: 14.0%.
- ECM uncontrolled asthma: 63.9%.

Table 27 Distribution of ACQ-6 categories at Week 52 (SINUS-52 ITT population with asthma GINA 4 or 5)

ACQ-6 at week 52	ECM (N=39)	Dupilumab (N=50)
Number	36	50
ACQ-6 <1 (controlled asthma)	6 (16.7%)	38 (76.0%)
ACQ-6 ≥1 to <1.5 (partially controlled asthma)	7 (19.4%)	5 (10.0%)
ACQ-6 ≥1.5 (uncontrolled asthma)	23 (63.9%)	7 (14.0%)

ACQ-6 = 6-item Asthma Control Questionnaire; ECM = established clinical management; GINA = Global Initiative for Asthma; ITT = intention-to-treat.

Source: Sanofi. Data on File, Post-hoc analyses.¹

Base case and scenario analyses results

- Base-case incremental cost-effectiveness analysis results**

Table 28 Base-case deterministic results

Treatments	TOTAL QALYs	TOTAL costs	Incr. QALYs	Incr. costs	ICER
Dupilumab + ECM	■	■	■	■	£23,410
ECM	■	■			

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

- Probabilistic sensitivity analysis**

Table 29. Summary of the base case PSA results

Treatments	TOTAL QALYs	TOTAL costs	Incr. QALYs	Incr. costs	ICER
Dupilumab + ECM	■	■	■	■	£23,793
ECM	■	■			

ICER = incremental cost-effectiveness ratio; Incr = incremental; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year; ECM Established Clinical Management

Figure 73 Scatter plot for incremental cost-effectiveness results (1,000 iterations)

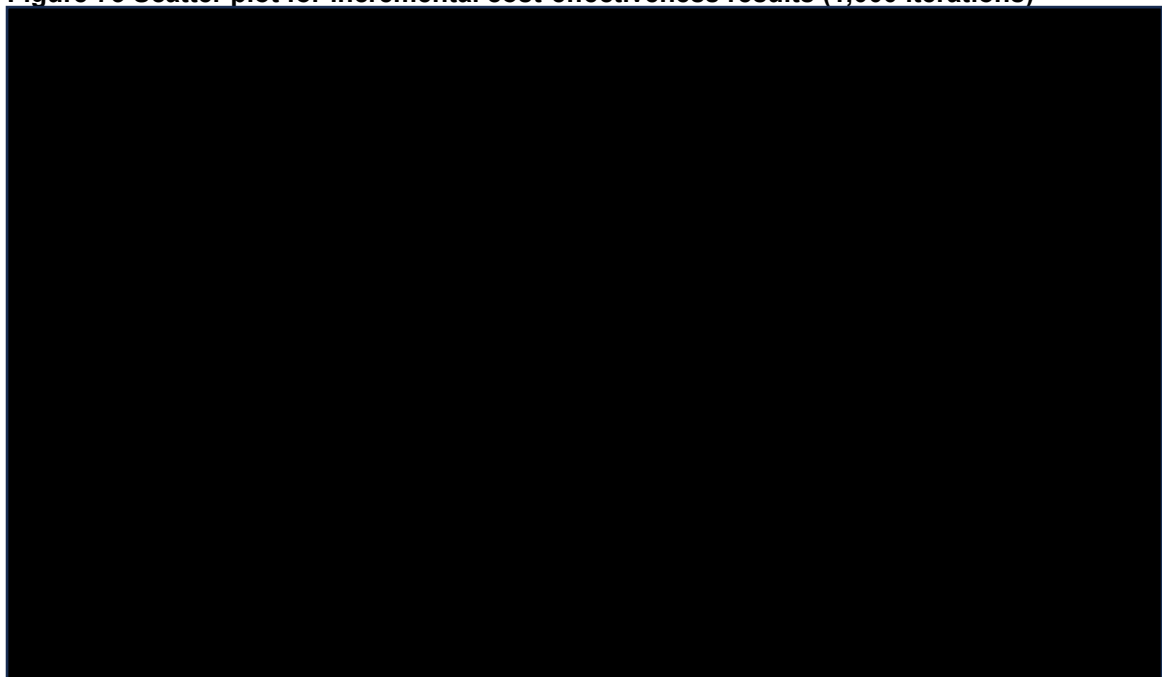
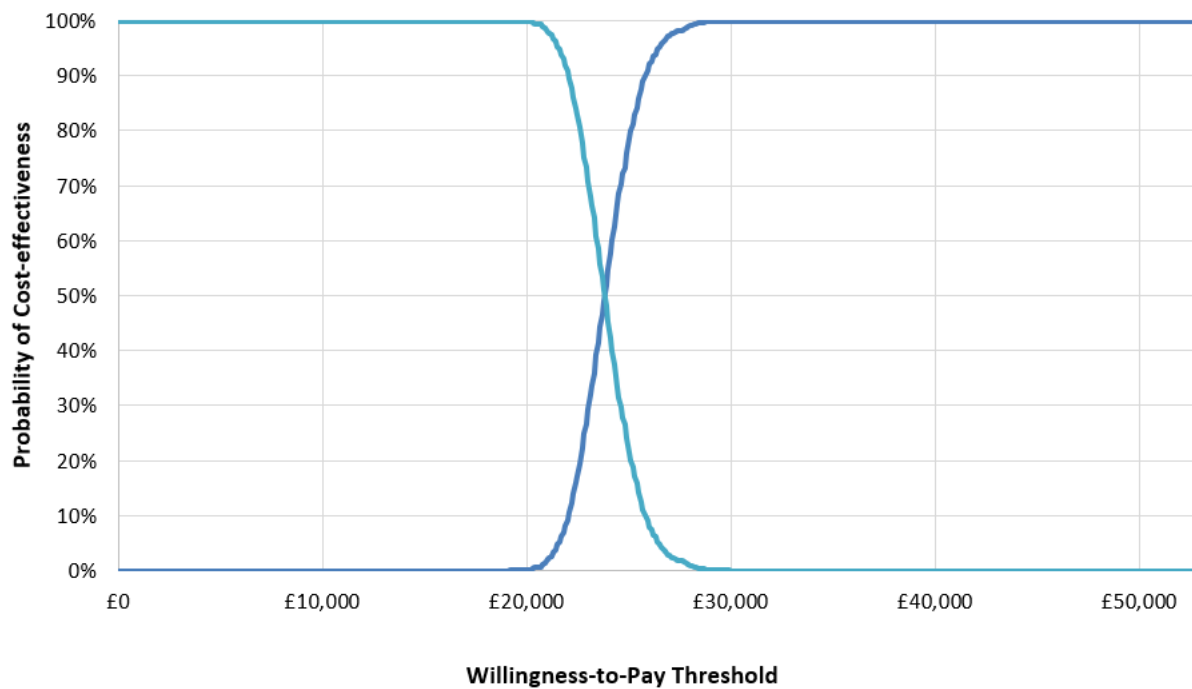
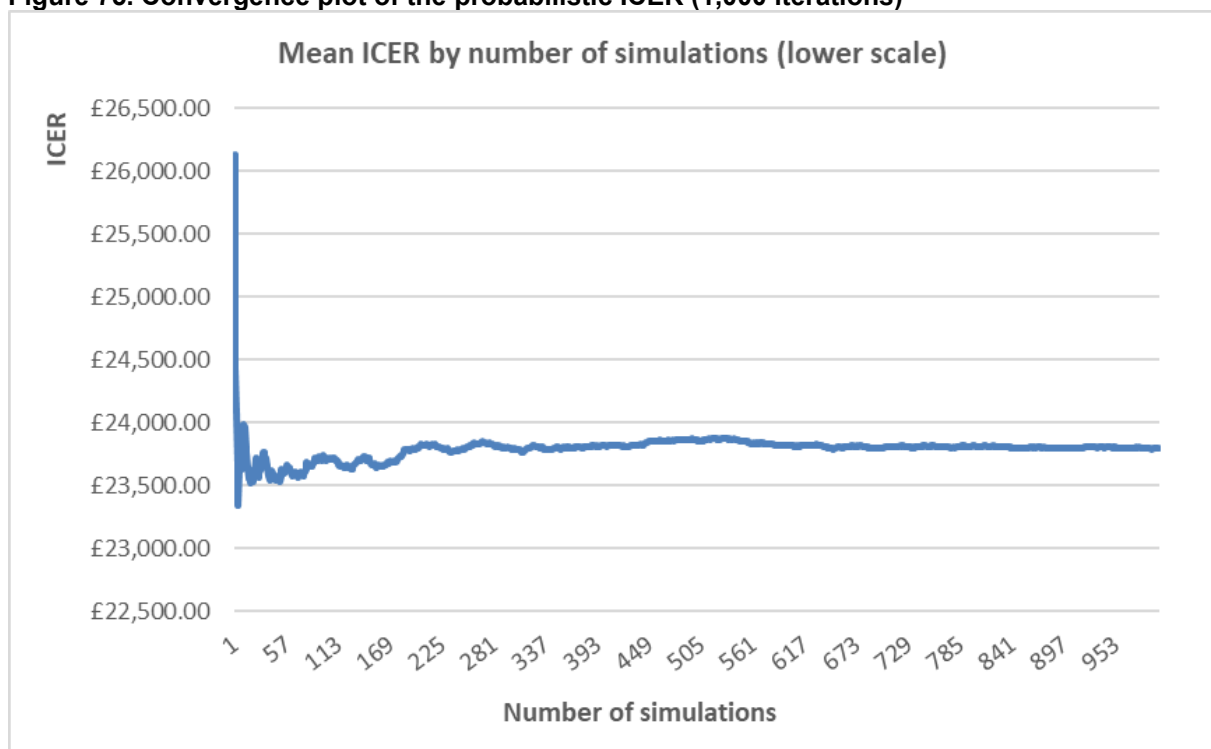
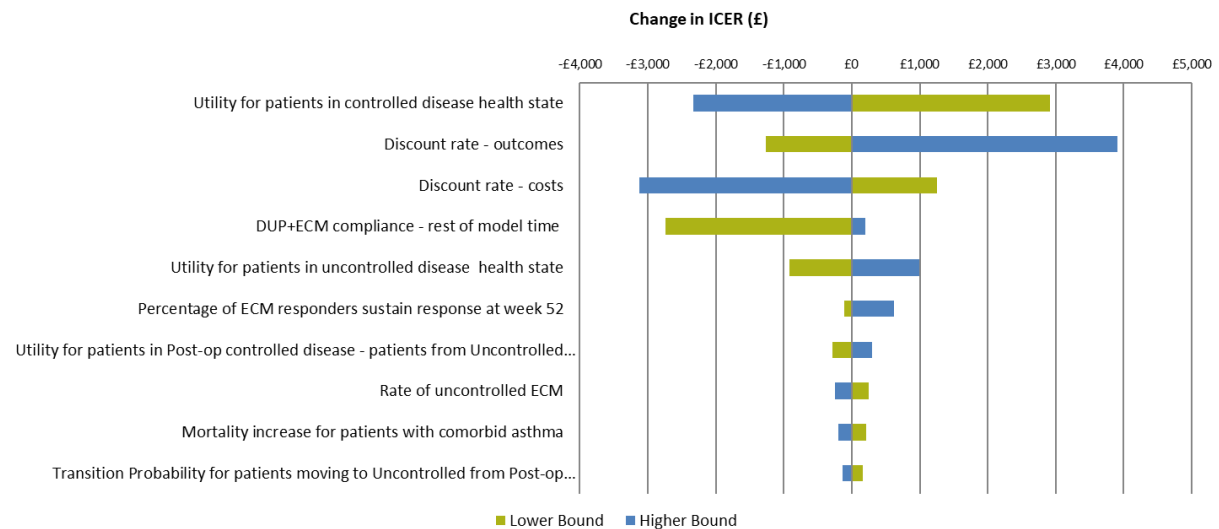


Figure 74. Cost-effectiveness acceptability curve (1,000 iterations)**Figure 75. Convergence plot of the probabilistic ICER (1,000 iterations)**

- Deterministic sensitivity analysis**

Figure 76. Tornado diagram of ICER (incremental cost per QALY gained) of DUP + ECM vs. ECM



DUP = dupilumab; ECM = established clinical management; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

Table 31. Top 10 drivers of the ICER results

Rank	Parameter	ICER - Lower Bound	ICER - Upper Bound	Difference
Base case ICER (Deterministic)		£23,410		
1	Utility for patients in controlled disease health state			£5,249
2	Discount rate - outcomes			£5,173
3	Discount rate - costs			£4,367
4	DUP+ECM compliance - rest of model time			£2,943
5	Utility for patients in uncontrolled disease health state			£1,918
6	Percentage of ECM responders sustain response at week 52			£742
7	Utility for patients in post-op-controlled disease - patients from Uncontrolled health state			£583
8	Rate of uncontrolled ECM			£492
9	Mortality increases for patients with comorbid asthma			£411
10	Transition Probability for patients moving to Uncontrolled from Post-op Controlled			£296

DUP = dupilumab; ECM = established clinical management; HS = health state; ICER = incremental cost-effectiveness ratio

- Sensitivity and scenario analysis**

To test the sensitivity of the cost-effectiveness results due to uncertainty in key parameters and assumptions, various analyses have been explored ([Table](#)).

Table 32. Sensitivity analysis results – Base case population, PAS price (Deterministic ICERs)

Parameter	Scenario	Incr. QALYs	Incr. costs	ICER*	Rationale
Base case	N/A	■	■	£23,410	N/A
Discount	3%	■	■	£24,658	Alternative input to the NICE reference case.
	5%	■	■	£23,675	
Time horizon	5 years	■	■	£27,485	
	10 years	■	■	£24,814	
	20 years	■	■	£23,784	
Subgroup	Patients with asthma comorbidity	■	■	£25,445	Alternative to subgroup "Patients with prior surgery"
	Patients with NSAID-ERD	■	■	£25,534	
	Patients with prior surgery (SINUS-52 only)	■	■	£23,261	
	Patients with prior surgery and with asthma comorbidity	■	■	£26,009	
	Patients with prior surgery and with NSAID-ERD	■	■	£26,217	
	Patients with prior surgery and with prior type 2 medical history including asthma/NSAID-ERD	■	■	£23,258	
	Patients with prior prior type 2 medical history including asthma/NSAID-ERD	■	■	£24,955	
Response criteria	NPS cfb ≥1	■	■	£25,885	Alternative response criteria to SNOT-22 cfb ≥8.9 AND NPS cfb ≥1
	SNOT-22 cfb ≥8.9	■	■	£28,128	
Utility: Crump models	Crump model 2	■	■	£37,990	Alternative to Crump model 1. These regressions include the individual items of the SNOT-22 score
	Crump model 3	■	■	£38,306	
Utility: regression	Utility = Gender + Age + Baseline Utility + Cfb in SNOT-22 Score + Cfb in NPS Score	■	■	£50,042	Use of EQ-5D with regression from the studies with the Hernandez mapping algorithm (5L to 3L)
	Regression: Utility = Gender + Age + Baseline Utility + Cfb in SNOT-22 Score	■	■	£50,042	

Parameter	Scenario	Incr. QALYs	Incr. costs	ICER*	Rationale
	Regression: Utility = Gender + Age + Baseline Utility + SNOT-22 Score	■	■	£50,430	
	Regression: Utility = Gender + Age + Baseline Utility + SNOT-22 Score + NPS Score	■	■	£51,751	
	Observed change from baseline (Hernandez)	■	■	£48,956	
	Utility gain from surgery (Remenschneider, 2015)	■	■	23,997	
	Remove disutility associated with surgery	■	■	22,443	
Utility norms	Ara et al. (2011)	■	■	£23,438	
Long term discontinuation rate	RCT-based discontinuation	■	■	£24,028	Discontinuation source from RCT instead of RW
Short and long term compliance rate	Rate changed from 99.3% to 95%	■	■	£22,234	Reduced compliance for dupilumab patients
Nurse administration	Nurse administered doses = 5%	■	■	£23,578	A very small number of patients may require assistance in injecting
Asthma related costs	Remove asthma related costs	■	■	£24,321	Testing the impact of asthma related costs
Asthma related mortality	Remove asthma related mortality	■	■	£24,029	No direct evidence in the SINUS studies
Eligibility for surgery	Change from no increase to linear increase	■	■	£23,424	Eligibility for surgery may not remain constant over time as patients age
	Change from no increase to polynomial increase	■	■	£23,415	
Transition probability for eligible patients	Receive surgery and move to Post-op Controlled: 15.1% to ■	■	■	£23,343	Ad-board and consultancy report
HCRU	Wahid et al. 2020: Non-responder GP appointments increased to 7.64, Consultant appointments decreased to 2.0	■	■	23,657	Alternative suggestions from clinicians at the ad boards
	1 nurse visit instead of 1	■	■	23,381	

Parameter	Scenario	Incr. QALYs	Incr. costs	ICER*	Rationale
	consultant visit for responders				
Societal perspective	Include indirect costs associated with presenteeism and absenteeism	■	■	£17,839	It is important to appreciate that CRSwNP has a profound effect on patients' lives including work

Baseline characteristics, clinical outcomes and HRQoL used in the additional scenario analyses

SINUS-52 data only

Baseline characteristics

Table 30. Baseline characteristics of patients with ≥1 prior NP surgery in SINUS-52 ITT population

	ECM	Dupilumab Q2W	All
N	88	88	261
Male, n (%)	52 (59.1)	59 (67.0)	161 (61.7)
Age, mean (SD)	51.01 (12.90)	50.95 (11.45)	51.72 (12.09)
Race, n (%)			
Caucasian/White	75 (85.2)	72 (81.8)	216 (82.8)
Black/African decent	0	1 (1.1)	3 (1.1)
Asian/Oriental	12 (13.6)	11 (12.5)	36 (13.8)
American Indian/Alaska Native	1 (1.1)	4 (4.5)	5 (1.9)
Native Hawaiian/Other Pacific Islander	0	0	0
Multiple	0	0	1 (0.4)
Unknown	0	0	0
Ethnicity			
Hispanic or Latino	14 (15.9)	22 (25.0)	46 (17.7)
Not Hispanic or Latino	74 (84.1)	66 (75.0)	214 (82.3)
Territory			
North America	19 (21.6)	22 (25.0)	63 (24.1)
European Union	17 (19.3)	17 (19.3)	51 (19.5)
Rest of the World	52 (59.1)	49 (55.7)	147 (56.3)
BMI (kg/m ²), mean (SD)	27.56 (5.75)	27.63 (4.99)	27.64 (5.47)
Time since first diagnosis of nasal polyps (years), mean (SD)	15.10 (9.90)	15.27 (10.63)	14.90 (10.01)
≥3 previous surgeries for nasal polyps, n (%)	18 (20.5)	22 (25.0)	49 (18.8)
Time since most recent surgery for nasal polyps (years), mean (SD)	8.77 (7.15)	7.54 (7.02)	8.24 (7.00)
SCS use in the past 2 years, n (%)	62 (70.5)	63 (71.6)	186 (71.3)
Bilateral endoscopic NPS* (scale 0-8), mean (SD)	5.81 (1.17)	6.08 (1.22)	6.05 (1.20)
NC score* (scale 0-3), mean (SD)	2.45 (0.52)	2.46 (0.63)	2.48 (0.57)
SNOT-22 total score* (scale 0-110), mean (SD)	55.36 (21.20)	49.93 (19.52)	52.81 (20.58)
Smell test (UPSIT) score** (scale 0-40), mean (SD)	12.44 (7.84)	12.45 (7.87)	12.20 (7.25)
LoS score* (scale 0-3), mean (SD)	2.78 (0.54)	2.81 (0.51)	2.81 (0.54)
LMK-CT total score* (scale 0-24), mean (SD)	18.35 (3.80)	19.51 (3.40)	18.86 (3.62)
Rhinosinusitis disease severity* (VAS 0-10cm), mean (SD)	8.18 (2.06)	8.25 (1.70)	8.16 (1.97)
Baseline NPIF** (L/min), mean (SD)	89.27 (54.61)	80.61 (49.66)	87.76 (57.87)

	ECM	Dupilumab Q2W	All
Baseline blood eosinophils (x10 ⁹ cells/L), mean (SD)	0.49 (0.32)	0.55 (0.44)	0.48 (0.36)
Any comorbid type 2 medical history including asthma and NSAID-ERD, n (%)	80 (90.9)	77 (87.5)	235 (90.0)
Comorbid asthma, n (%)	61 (69.3)	57 (64.8)	180 (69.0)
Comorbid NSAID-ERD, n (%)	35 (39.8)	25 (28.4)	91 (34.9)
Any comorbid type 2 medical history excluding asthma and NSAID-ERD, n (%)	60 (68.2)	59 (67.0)	181 (69.3)
Age of asthma onset in patients with comorbid asthma (years), mean (SD)	33.00 (15.08)	31.60 (15.13)	33.22 (15.94)
Baseline ACQ-6 score* in patients with comorbid asthma, mean (SD)	1.53 (1.04)	1.41 (1.05)	1.49 (1.08)

ACQ-6 = 6-item Asthma Control Questionnaire; BMI: body mass index; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LMK-CT = Lund-Mackay computed tomography; LoS = loss-of-smell; NC = nasal congestion/obstruction; NPIF = peak nasal inspiratory flow; NP = nasal polyp; NPS = nasal polyp score; NSAID = non-steroidal anti-inflammatory drug; Q2W = every 2 weeks; SD = standard deviation; SNOT-22 = 22-item Sino-Nasal Outcome Test; UPSIT = University of Pennsylvania Smell Identification Test; VAS = visual analogue scale

*Higher scores indicate greater disease severity.

** Higher scores indicate lower disease severity.

Source: Sanofi. Data on File, Post-hoc analyses.¹

Response rates

Table 31. Response rates for patients with ≥1 prior NP surgery in SINUS-52 ITT population according to the response criteria of SNOT-22 total score (≥8.9-point improvement) and NPS (≥1-point improvement)

	ECM (N=88)	Dupilumab Q2W (N=173)
Overall response at Week 24		
Responders, n (%)	5 (5.7)	100 (57.8)
Non-responders, n (%)	83 (94.3)	73 (42.2)

ITT = intention-to-treat; NP = nasal polyp; NPS = nasal polyp score; Q2W = once every two weeks; SNOT-22: 22-item Sino Nasal Outcome Test

Source: Sanofi. Data on File, Post-hoc analyses.¹

SNOT-22 total score

Table 32. SNOT-22 total score and change from baseline in patients with ≥1 prior NP surgery in SINUS-52 ITT population according to the response criteria of SNOT-22 total score (≥8.9-point improvement) and NPS (≥1-point improvement)

	ECM (N=88)	Dupilumab Q2W (N=173)
Baseline		
<i>All</i>		
Number	88	170
Mean (SD)	55.364 (21.204)	51.482 (20.190)
Responders at Week 24		
Number	5	100
Mean (SD)	45.000 (6.205)	56.170 (19.573)
Non-responders at Week 24		
Number	83	70
Mean (SD)	55.988 (21.638)	44.786 (19.271)
Week 24		
<i>All</i>		
Number	82	164
Mean (SD)	45.524 (21.833)	23.073 (17.313)

Clarification questions

	ECM (N=88)	Dupilumab Q2W (N=173)
Change from baseline		
Number	82	164
Mean (SD)	-9.512 (19.505)	-28.860 (22.518)
LS mean (SE)	-8.254 (2.097)	-28.804 (1.662)
LS mean diff (95% CI)	NA	-20.550 (-25.061, -16.039)
p value vs. ECM	NA	<0.0001
Responders at Week 24		
Number	5	100
Mean (SD)	19.200 (12.133)	18.920 (15.574)
Change from baseline		
Number	5	100
Mean (SD)	19.200 (12.133)	18.920 (15.574)
LS mean (SE)	-25.800 (6.797)	-37.250 (19.932)
LS mean diff (95% CI)	NA	-4.162 (-17.833, 9.509)
p value vs. ECM	NA	0.5471
Non-responders at Week 24		
Number	77	64
Mean (SD)	47.234 (21.255)	29.563 (18.006)
Change from baseline		
Number	77	64
Mean (SD)	-8.455 (19.607)	-15.750 (20.033)
LS mean (SE)	-6.430 (2.257)	-18.923 (2.433)
LS mean diff (95% CI)	NA	-12.493 (-18.237, -6.749)
p value vs. ECM	NA	<0.0001

CI = confidence interval; ITT = intention-to-treat; LS = least squares; NA = not applicable; NP = nasal polyp; NPS = nasal polyp score; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test

Source: Sanofi. Data on File, Post-hoc analyses.¹

NPS

Table 33. NPS and change from baseline in patients with ≥1 prior NP surgery in SINUS-52 ITT population according to the response criteria of SNOT-22 total score (≥8.9-point improvement) and NPS (≥1-point improvement)

	ECM (N=88)	Dupilumab Q2W (N=173)
Baseline		
<i>All</i>		
Number	88	172
Mean (SD)	5.813 (1.173)	6.169 (1.200)
Responders at Week 24		
Number	5	100
Mean (SD)	6.100 (1.084)	6.410 (1.111)
Non-responders at Week 24		
Number	83	72
Mean (SD)	5.795 (1.182)	5.833 (1.245)
Week 24		
<i>All</i>		
Number	83	164
Mean (SD)	5.988 (1.166)	4.262 (1.878)
Change from baseline		
Number	83	164

	ECM (N=88)	Dupilumab Q2W (N=173)
Mean (SD)	0.163 (0.976)	-1.905 (1.885)
LS mean (SE)	0.223 (0.189)	-729 (0.151)
LS mean diff (95% CI)	NA	-1.953 (-2.361, -1.545)
p value vs. ECM	NA	<0.0001
Responders at Week 24		
Number	5	100
Mean (SD)	4.700 (1.304)	3.425 (1.721)
Change from baseline		
Number	5	100
Mean (SD)	-1.400 (0.418)	-2.985 (1.353)
LS mean (SE)	-1.282 (0.636)	-2.807 (0.189)
LS mean diff (95% CI)	NA	-1.525 (-2.769, -0.281)
p value vs. ECM	NA	0.0168
Non-responders at Week 24		
Number	78	64
Mean (SD)	6.071 (1.116)	5.570 (1.272)
Change from baseline		
Number	78	64
Mean (SD)	0.263 (0.914)	-0.219 (1.256)
LS mean (SE)	0.363 (0.152)	-0.398 (0.165)
LS mean diff (95% CI)	NA	-0.760 (-1.138, -0.382)
p value vs. ECM	NA	<0.0001

CI = confidence interval; ITT = intention-to-treat; LS = least squares; NA = not applicable; NP = nasal polyp; NPS = nasal polyp score; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test

Source: Sanofi. Data on File, Post-hoc analyses.¹

Mapped SNOT-22 to EQ-5D-3L health state utilities (Crump Models 1-3)

Table 34. Mapped SNOT-22 to EQ-5D-3L health state utilities (Crump Model 1) in patients with ≥1 prior NP surgery in SINUS-52 ITT population according to the response criteria of SNOT-22 total score (≥8.9-point improvement) and NPS (≥1-point improvement)

	ECM (N=88)	Dupilumab Q2W (N=173)	All (N=261)
Baseline			
<i>All</i>			
Number	88	170	258
Mean (SD)	0.498 (0.144)	0.525 (0.137)	0.516 (0.140)
Responders at Week 24			
Number	5	100	105
Mean (SD)	0.569 (0.042)	0.493 (0.133)	0.496 (0.131)
Non-responders at Week 24			
Number	83	70	153
Mean (SD)	0.494 (0.147)	0.570 (0.131)	0.529 (0.145)
Week 24			
<i>All</i>			
Number	82	164	246
Mean (SD)	0.584 (0.150)	0.720 (0.115)	0.674 (0.143)
Change from baseline			
Number	82	164	246
Mean (SD)	0.083 (0.133)	0.198 (0.152)	0.160 (0.155)
LS mean (SE)	0.070 (0.014)	0.195 (0.011)	NA

	ECM (N=88)	Dupilumab Q2W (N=173)	All (N=261)
LS mean diff (95% CI)	NA	0.125 (0.095, 0.156)	NA
p value vs. ECM	NA	<0.0001	NA
Responders at Week 24			
Number	5	100	105
Mean (SD)	0.744 (0.083)	0.746 (0.106)	0.746 (0.105)
Change from baseline			
Number	5	100	105
Mean (SD)	0.175 (0.046)	0.253 (0.136)	0.250 (0.134)
LS mean (SE)	0.226 (0.047)	0.254 (0.014)	NA
LS mean diff (95% CI)	NA	0.028 (-0.065, 0.121)	NA
p value vs. ECM	NA	0.5471	NA
Non-responders at Week 24			
Number	77	64	141
Mean (SD)	0.573 (0.148)	0.678 (0.118)	0.621 (0.145)
Change from baseline			
Number	77	64	141
Mean (SD)	0.077 (0.135)	0.112 (0.136)	0.093 (0.136)
LS mean (SE)	0.056 (0.015)	0.128 (0.016)	NA
LS mean diff (95% CI)	NA	0.071 (0.033, 0.110)	NA
p value vs. ECM	NA	0.0003	NA

CI = confidence interval; EQ-5D-3L = EuroQol 5-Dimension 3-Level; ITT = intention-to-treat; LS = least squares; NA = not applicable; NP = nasal polyp; NPS = nasal polyp score; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test
Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 35. Mapped SNOT-22 to EQ-5D-3L health state utilities (Crump Model 2) in patients with ≥1 prior NP surgery in SINUS-52 ITT population according to the response criteria of SNOT-22 total score (≥8.9-point improvement) and NPS (≥1-point improvement)

	ECM (N=88)	Dupilumab Q2W (N=173)	All (N=261)
Baseline			
<i>All</i>			
Number	88	170	258
Mean (SD)	0.614 (0.201)	0.654 (0.181)	0.640 (0.188)
Responders at Week 24			
Number	5	100	105
Mean (SD)	0.706 (0.189)	0.618 (0.188)	0.623 (0.188)
Non-responders at Week 24			
Number	83	70	153
Mean (SD)	0.609 (0.202)	0.705 (0.158)	0.653 (0.188)
Week 24			
<i>All</i>			
Number	82	164	246
Mean (SD)	0.678 (0.188)	0.760 (0.112)	0.733 (0.147)
Change from baseline			
Number	82	164	246
Mean (SD)	0.058 (0.170)	0.110 (0.161)	0.093 (0.165)
LS mean (SE)	0.050 (0.015)	0.116 (0.011)	NA
LS mean diff (95% CI)	NA	0.066 (0.035, 0.098)	NA
p value vs. ECM	NA	<.0001	NA
Responders at Week 24			
Number	5	100	105

	ECM (N=88)	Dupilumab Q2W (N=173)	All (N=261)
Mean (SD)	0.820 (0.082)	0.764 (0.110)	0.767 (0.109)
Change from baseline			
Number	5	100	105
Mean (SD)	0.114 (0.130)	0.146 (0.167)	0.144 (0.165)
LS mean (SE)	0.194 (0.046)	0.155 (0.014)	NA
LS mean diff (95% CI)	NA	-0.039 (-0.130, 0.052)	NA
p value vs. ECM	NA	0.3965	NA
Non-responders at Week 24			
Number	77	64	141
Mean (SD)	0.669 (0.189)	0.753 (0.115)	0.707 (0.165)
Change from baseline			
Number	77	64	141
Mean (SD)	0.054 (0.172)	0.054 (0.133)	0.054 (0.155)
LS mean (SE)	0.037 (0.017)	0.075 (0.018)	NA
LS mean diff (95% CI)	NA	0.039 (-0.004, 0.082)	NA
p value vs. ECM	NA	0.0761	NA

CI = confidence interval; EQ-5D-3L = EuroQol 5-Dimension 3-Level; ITT = intention-to-treat; LS = least squares; NA = not applicable; NP = nasal polyp; NPS = nasal polyp score; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test
Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 36. Mapped SNOT-22 to EQ-5D-3L health state utilities (Crump Model 3) in patients with ≥1 prior NP surgery in SINUS-52 ITT population according to the response criteria of SNOT-22 total score (≥8.9-point improvement) and NPS (≥1-point improvement)

	ECM (N=88)	Dupilumab Q2W (N=173)	All (N=261)
Baseline			
<i>All</i>			
Number	88	170	258
Mean (SD)	0.617 (0.201)	0.657 (0.184)	0.643 (0.190)
<i>Responders at Week 24</i>			
Number	5	100	105
Mean (SD)	0.699 (0.165)	0.621 (0.191)	0.625 (0.190)
<i>Non-responders at Week 24</i>			
Number	83	70	153
Mean (SD)	0.612 (0.203)	0.708 (0.161)	0.656 (0.190)
Week 24			
<i>All</i>			
Number	82	164	246
Mean (SD)	0.681 (0.189)	0.763 (0.116)	0.736 (0.149)
Change from baseline			
Number	82	164	246
Mean (SD)	0.059 (0.169)	0.111 (0.161)	0.093 (0.165)
LS mean (SE)	0.051 (0.015)	0.117 (0.012)	NA
LS mean diff (95% CI)	NA	0.066 (0.034, 0.098)	NA
p value vs. ECM	NA	<0.0001	NA
<i>Responders at Week 24</i>			
Number	5	100	105
Mean (SD)	0.824 (0.069)	0.767 (0.114)	0.770 (0.113)
Change from baseline			
Number	5	100	105
Mean (SD)	0.125 (0.124)	0.146 (0.168)	0.145 (0.166)

	ECM (N=88)	Dupilumab Q2W (N=173)	All (N=261)
LS mean (SE)	0.194 (0.047)	0.155 (0.014)	NA
LS mean diff (95% CI)	NA	-0.039 (-0.132, 0.053)	NA
p value vs. ECM	NA	0.4027	NA
Non-responders at Week 24			
Number	77	64	141
Mean (SD)	0.672 (0.191)	0.757 (0.119)	0.711 (0.167)
Change from baseline			
Number	77	64	141
Mean (SD)	0.054 (0.171)	0.056 (0.133)	0.055 (0.155)
LS mean (SE)	0.038 (0.017)	0.077 (0.018)	NA
LS mean diff (95% CI)	NA	0.039 (-0.004, 0.082)	NA
p value vs. ECM	NA	0.0787	NA

CI = confidence interval; EQ-5D-3L = EuroQol 5-Dimension 3-Level; ITT = intention-to-treat; LS = least squares; NA = not applicable; NP = nasal polyp; NPS = nasal polyp score; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test
Source: Sanofi. Data on File, Post-hoc analyses.¹

EQ-5D-5L utilities (Hernandez 2020 crosswalk method, UK tariffs)

Table 37. EQ-5D-5L utilities (Hernandez 2020 crosswalk method, UK tariffs) in patients with ≥1 prior NP surgery in SINUS-52 ITT population according to the response criteria of SNOT-22 total score (≥8.9-point improvement) and NPS (≥1-point improvement)

	ECM (N=88)	Dupilumab Q2W (N=173)
Baseline		
<i>All</i>		
Number	87	167
Mean (SD)	0.763 (0.189)	0.791 (0.195)
Responders at Week 24		
Number	5	99
Mean (SD)	0.829 (0.088)	0.768 (0.187)
Non-responders at Week 24		
Number	82	68
Mean (SD)	0.759 (0.193)	0.825 (0.203)
Week 24		
<i>All</i>		
Number	82	162
Mean (SD)	0.798 (0.182)	0.861 (0.169)
Change from baseline		
Number	82	162
Mean (SD)	0.037 (0.161)	0.073 (0.179)
LS mean (SE)	0.044 (0.018)	0.091 (0.014)
LS mean diff (95% CI)	NA	0.047 (0.010, 0.085)
p value vs. ECM	NA	0.0140
Responders at Week 24		
Number	5	99
Mean (SD)	0.925 (0.056)	0.875 (0.147)
Change from baseline		
Number	5	99
Mean (SD)	0.096 (0.072)	0.107 (0.178)
LS mean (SE)	0.154 (0.060)	0.134 (0.018)
LS mean diff (95% CI)	NA	-0.020 (-0.139, 0.098)

	ECM (N=88)	Dupilumab Q2W (N=173)
p value vs. ECM	NA	0.7332
Non-responders at Week 24		
Number	77	63
Mean (SD)	0.790 (0.185)	0.840 (0.197)
Change from baseline		
Number	77	63
Mean (SD)	0.033 (0.164)	0.021 (0.168)
LS mean (SE)	0.035 (0.019)	0.045 (0.021)
LS mean diff (95% CI)	NA	0.010 (-0.039, 0.059)
p value vs. ECM	NA	0.6874

CI = confidence interval; EQ-5D-5L = EuroQol 5-Dimension 5-Level; ITT = intention-to-treat; LS = least squares; NA = not applicable; NP = nasal polyp; NPS = nasal polyp score; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test
Source: Sanofi. Data on File, Post-hoc analyses.¹

Patients with comorbid NSAID-ERD

Baseline characteristics

Table 38. Baseline characteristics of patients with comorbid NSAID-ERD in SINUS-24 and SINUS-52 pooled ITT population

	ECM	Dupilumab Q2W	All
N	82	81	204
Male, n (%)	29 (35.4)	40 (49.4)	88 (43.1)
Age, mean (SD)	49.68 (13.61)	50.90 (12.95)	50.30 (12.87)
Race, n (%)			
Caucasian/White	72 (87.8)	72 (88.9)	180 (88.2)
Black/African decent	3 (3.7)	1 (1.2)	4 (2.0)
Asian/Oriental	6 (7.3)	6 (7.4)	16 (7.8)
American Indian/Alaska Native	1 (1.2)	2 (2.5)	3 (1.5)
Native Hawaiian/Other Pacific Islander	0	0	0
Multiple	0	0	1 (0.5)
Unknown	0	0	0
Ethnicity			
Hispanic or Latino	11 (13.6)	10 (12.3)	31 (15.3)
Not Hispanic or Latino	70 (86.4)	71 (87.7)	172 (84.7)
Territory			
North America	13 (15.9)	13 (16.0)	36 (17.6)
European Union	30 (36.6)	32 (39.5)	71 (34.8)
Rest of the World	39 (47.6)	36 (44.4)	97 (47.5)
BMI (kg/m ²), mean (SD)	28.01 (6.20)	27.29 (4.79)	27.43 (5.39)
Time since first diagnosis of nasal polyps (years), mean (SD)	12.11 (8.47)	14.18 (9.85)	12.85 (9.20)
Previous surgery for nasal polyps, n (%)	65 (79.3)	63 (77.8)	159 (77.9)
Time since most recent surgery for nasal polyps (years), mean (SD)	6.06 (4.26)	6.42 (4.69)	6.34 (4.70)
SCS use in the past 2 years, n (%)	64 (78.0)	54 (66.7)	148 (72.5)
Bilateral endoscopic NPS* (scale 0-8), mean (SD)	5.87 (1.27)	5.75 (1.39)	5.92 (1.32)
NC score* (scale 0-3), mean (SD)	2.52 (0.49)	2.31 (0.62)	2.43 (0.58)

	ECM	Dupilumab Q2W	All
SNOT-22 total score* (scale 0-110), mean (SD)	56.27 (20.48)	47.62 (18.43)	52.86 (19.63)
Smell test (UPSIT) score** (scale 0-40), mean (SD)	11.71 (6.35)	12.65 (7.50)	11.88 (6.47)
LoS score* (scale 0-3), mean (SD)	2.85 (0.33)	2.82 (0.45)	2.83 (0.43)
LMK-CT total score* (scale 0-24), mean (SD)	19.85 (3.52)	18.94 (4.37)	19.33 (3.83)
Rhinosinusitis disease severity* (VAS 0-10cm), mean (SD)	8.19 (2.14)	7.79 (1.72)	7.99 (2.09)
Baseline NPIF** (L/min), mean (SD)	84.60 (55.91)	89.46 (54.26)	84.86 (54.75)
Baseline blood eosinophils (x10 ⁹ cells/L), mean (SD)	0.48 (0.39)	0.50 (0.43)	0.48 (0.39)
Comorbid asthma, n (%)	74 (90.2)	70 (86.4)	181 (88.7)
Any comorbid type 2 medical history excluding asthma and NSAID-ERD, n (%)	57 (69.5)	57 (70.4)	146 (71.6)
Age of asthma onset in patients with comorbid asthma (years), mean (SD)	32.59 (15.14)	35.61 (12.22)	34.18 (14.00)
Baseline ACQ-6 score* in patients with comorbid asthma, mean (SD)	1.64 (1.08)	1.36 (1.02)	1.56 (1.12)
Baseline GINA 4 or 5, n (%)	31 (37.8)	40 (32.8)	71 (34.8)

ACQ-6 = 6-item Asthma Control Questionnaire; BMI = body mass index; ERD = exacerbated respiratory disease; GINA = Global Initiative for Asthma; ITT = intention-to-treat; LMK-CT = Lund-Mackay computed tomography; LoS = loss-of-smell; NC = nasal congestion/obstruction; NPIF = peak nasal inspiratory flow; NPS = nasal polyp score; NSAID = non-steroidal anti-inflammatory drug; Q2W = every 2 weeks; SD = standard deviation; SNOT-22 = 22-item Sino-Nasal Outcome Test; UPSIT = University of Pennsylvania Smell Identification Test; VAS = visual analogue scale

*Higher scores indicate greater disease severity.

** Higher scores indicate lower disease severity.

Source: Sanofi. Data on File, Post-hoc analyses.¹

Response rates

Table 39. Response rates for patients with comorbid NSAID-ERD in SINUS-24 and SINUS-52 pooled ITT population according to the different response criteria

	ECM (N=82)	Dupilumab Q2W (N=122)
Overall response at Week 24		
NPS (≥1-point improvement)		
Responders, n (%)	8 (9.8)	80 (65.6)
Non-responders, n (%)	74 (90.2)	42 (34.4)
SNOT-22 total score (≥8.9-point improvement)		
Responders, n (%)	30 (36.6)	90 (73.8)
Non-responders, n (%)	52 (63.4)	32 (26.2)
SNOT-22 total score (≥8.9-point improvement) and NPS (≥1-point improvement)		
Responders, n (%)	7 (8.5)	70 (57.4)
Non-responders, n (%)	75 (91.5)	52 (42.6)
Overall response at Week 52		
All		
NPS (≥1-point improvement)		
Responders, n (%)	6 (13.6)	28 (80.0)
Non-responders, n (%)	38 (86.4)	7 (20.0)
SNOT-22 total score (≥8.9-point improvement)		
Responders, n (%)	8 (18.2)	26 (74.3)
Non-responders, n (%)	36 (81.8)	9 (25.7)

	ECM (N=82)	Dupilumab Q2W (N=122)
SNOT-22 total score (≥8.9-point improvement) and NPS (≥1-point improvement)		
Responders, n (%)	2 (4.5)	24 (68.6)
Non-responders, n (%)	42 (95.5)	11 (31.4)
Responders at Week 24		
NPS (≥1-point improvement)	ECM (N=1)	Dupilumab Q2W (N=21)
Responders, n (%)	0	19 (90.5)
Non-responders, n (%)	1 (100)	2 (9.5)
SNOT-22 total score (≥8.9-point improvement)	ECM (N=12)	Dupilumab Q2W (N=24)
Responders, n (%)	6 (50.0)	22 (91.7)
Non-responders, n (%)	6 (50.0)	2 (8.3)
SNOT-22 total score (≥8.9-point improvement) and NPS (≥1-point improvement)	ECM (N=1)	Dupilumab Q2W (N=17)
Responders, n (%)	0	14 (82.4)
Non-responders, n (%)	1 (100)	3 (17.6)
Non-responders at Week 24		
NPS (≥1-point improvement)	ECM (N=43)	Dupilumab Q2W (N=14)
Responders, n (%)	6 (14.0)	9 (64.3)
Non-responders, n (%)	37 (86.0)	5 (35.7)
SNOT-22 total score (≥8.9-point improvement)	ECM (N=32)	Dupilumab Q2W (N=11)
Responders, n (%)	2 (6.3)	4 (36.4)
Non-responders, n (%)	30 (93.8)	7 (63.6)
SNOT-22 total score (≥8.9-point improvement) and NPS (≥1-point improvement)	ECM (N=43)	Dupilumab Q2W (N=18)
Responders, n (%)	2 (4.7)	10 (55.6)
Non-responders, n (%)	41 (95.3)	8 (44.4)

ERD = exacerbated respiratory disease; ITT = intention-to-treat; NPS = nasal polyp score NSAID = non-steroidal anti-inflammatory drug; Q2W = once every two weeks; SNOT-22: 22-item Sino Nasal Outcome Test
Source: Sanofi. Data on File, Post-hoc analyses.¹

SNOT-22 total score

Table 40. SNOT-22 total score and change from baseline in patients with comorbid NSAID-ERD in SINUS-24 and SINUS-52 ITT population according to the response criteria of NPS (≥1-point improvement)

	ECM (N=82)	Dupilumab Q2W (N=122)
Baseline		
<i>All</i>		
Number	81	118
Mean (SD)	56.272 (20.476)	50.525 (18.757)
Responders at Week 24		
Number	8	77
Mean (SD)	50.000 (11.263)	51.143 (18.260)
Non-responders at Week 24		
Number	73	41
Mean (SD)	56.959 (21.181)	49.366 (19.838)
Week 24		
<i>All</i>		
Number	80	116
Mean (SD)	47.500 (23.176)	21.974 (16.955)
Change from baseline		

	ECM (N=82)	Dupilumab Q2W (N=122)
Number	80	116
Mean (SD)	-8.700 (20.411)	-28.483 (21.406)
LS mean (SE)	-6.945 (2.509)	-31.300 (2.186)
LS mean diff (95% CI)	NA	-24.355 (-29.537, -19.173)
p value vs. ECM	NA	<0.0001
Responders at Week 24		
Number	8	76
Mean (SD)	28.500 (21.334)	17.816 (11.801)
Change from baseline		
Number	8	76
Mean (SD)	-21.500 (17.525)	-33.618 (20.049)
LS mean (SE)	-23.956 (5.162)	-35.143 (2.149)
LS mean diff (95% CI)	NA	-11.188 (-21.201, -1.174)
p value vs. ECM	NA	0.0285
Non-responders at Week 24		
Number	72	40
Mean (SD)	49.611 (22.529)	29.875 (21.958)
Change from baseline		
Number	72	40
Mean (SD)	-7.278 (20.316)	-18.725 (20.717)
LS mean (SE)	-6.311 (3.059)	-24.062 (3.615)
LS mean diff (95% CI)	NA	-17.750 (-25.160, -10.341)
p value vs. ECM	NA	<.0001
Week 52		
Responders at Week 24 AND Week 52		
Number	0	18
Mean (SD)	NA	15.611 (13.426)
Change from baseline		
Number	0	18
Mean (SD)	NA	-30.389 (19.874)
LS mean (SE)	NE	-36.485 (3.479)
LS mean diff (95% CI)	NA	NE
p value vs. ECM	NA	NE
Non-responders at Week 24 OR Week 52		
Number	42	16
Mean (SD)	50.452 (22.460)	28.250 (25.255)
Change from baseline		
Number	42	16
Mean (SD)	-6.238 (17.736)	-23.625 (25.324)
LS mean (SE)	-3.595 (3.531)	-25.629 (5.014)
LS mean diff (95% CI)	NA	-22.034 (-33.413, -10.655)
p value vs. ECM	NA	0.0001

CI = confidence interval; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NPS = nasal polyp score; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test

Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 41. SNOT-22 total score and change from baseline in patients with comorbid NSAID-ERD in SINUS-24 and SINUS-52 ITT population according to the response criteria of SNOT-22 total score (≥ 8.9 -point improvement)

	ECM (N=82)	Dupilumab Q2W (N=122)
Baseline		
<i>Responders at Week 24</i>		
Number	30	90
Mean (SD)	58.967 (17.580)	52.678 (17.475)
<i>Non-responders at Week 24</i>		
Number	51	28
Mean (SD)	54.686 (22.014)	43.607 (21.284)
Week 24		
<i>Responders at Week 24</i>		
Number	30	90
Mean (SD)	33.400 (19.795)	16.756 (11.183)
Change from baseline		
Number	30	90
Mean (SD)	-25.567 (12.743)	-35.922 (17.525)
LS mean (SE)	-22.599 (0.409)	-38.082 (0.276)
LS mean diff (95% CI)	NA	-15.483 (-16.290, -14.676)
p value vs. ECM	NA	<0.0001
<i>Non-responders at Week 24</i>		
Number	50	26
Mean (SD)	55.960 (20.960)	40.038 (20.971)
Change from baseline		
Number	50	26
Mean (SD)	1.420 (17.230)	-2.731 (11.206)
LS mean (SE)	0.965 (3.122)	-10.004 (3.913)
LS mean diff (95% CI)	NA	-10.969 (-19.171, -2.767)
p value vs. ECM	NA	0.0088
Week 52		
<i>Responders at Week 24 AND Week 52</i>		
Number	6	22
Mean (SD)	44.667 (28.395)	14.000 (10.699)
Change from baseline		
Number	6	22
Mean (SD)	-27.333 (11.928)	-38.636 (17.358)
LS mean (SE)	-15.765 (5.469)	-41.539 (2.832)
LS mean diff (95% CI)	NA	-25.774 (-38.932, -12.617)
p value vs. ECM	NA	<0.0001
<i>Non-responders at Week 24 OR Week 52</i>		
Number	36	12
Mean (SD)	51.417 (21.658)	35.417 (27.000)
Change from baseline		
Number	36	12
Mean (SD)	-2.722 (16.099)	-6.250 (14.303)
LS mean (SE)	-0.292 (3.076)	-7.556 (5.186)
LS mean diff (95% CI)	NA	-7.264 (-18.130, 3.601)
p value vs. ECM	NA	0.1901

CI = confidence interval; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NA = not applicable; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test

Source: Sanofi. Data on File, Post-hoc analyses.¹**Table 42. SNOT-22 total score and change from baseline in patients with comorbid NSAID-ERD in SINUS-24 and SINUS-52 ITT population according to the response criteria of SNOT-22 total score (≥ 8.9 -point improvement) and NPS (≥ 1 -point improvement)**

	ECM (N=82)	Dupilumab Q2W (N=122)
Baseline		
<i>Responders at Week 24</i>		
Number	7	70
Mean (SD)	51.714 (10.981)	53.071 (17.834)
<i>Non-responders at Week 24</i>		
Number	74	48
Mean (SD)	56.703 (21.151)	46.813 (19.627)
Week 24		
<i>Responders at Week 24</i>		
Number	7	70
Mean (SD)	25.857 (21.583)	16.700 (11.508)
Change from baseline		
Number	7	70
Mean (SD)	-25.857 (13.459)	-36.371 (18.306)
LS mean (SE)	-28.032 (0.771)	-38.429 (0.317)
LS mean diff (95% CI)	NA	-10.397 (-11.895, -8.899)
p value vs. ECM	NA	<0.0001
<i>Non-responders at Week 24</i>		
Number	73	46
Mean (SD)	49.575 (22.374)	30.000 (20.555)
Change from baseline		
Number	73	46
Mean (SD)	-7.055 (20.264)	-16.478 (20.325)
LS mean (SE)	-5.268 (2.965)	-22.143 (3.399)
LS mean diff (95% CI)	NA	-16.875 (-23.913, -9.837)
p value vs. ECM	NA	<0.0001
Week 52		
<i>Responders at Week 24 AND Week 52</i>		
Number	0	14
Mean (SD)	NA	13.143 (10.136)
Change from baseline		
Number	0	14
Mean (SD)	NA	-37.000 (15.655)
LS mean (SE)	NE	-40.565 (3.190)
LS mean diff (95% CI)	NA	NE
p value vs. ECM	NA	NE
<i>Non-responders at Week 24 OR Week 52</i>		
Number	42	20
Mean (SD)	50.452 (22.460)	27.450 (24.021)
Change from baseline		
Number	42	20
Mean (SD)	-6.238 (17.736)	-20.350 (24.336)
LS mean (SE)	-3.367 (3.445)	-23.444 (4.619)
LS mean diff (95% CI)	NA	-20.077 (-30.503, -9.651)
p value vs. ECM	NA	0.0002

CI = confidence interval; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NPS = nasal polyp score; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test
Source: Sanofi. Data on File, Post-hoc analyses.¹

NPS

Table 43. NPS and change from baseline in patients with comorbid NSAID-ERD in SINUS-24 and SINUS-52 ITT population according to the response criteria of NPS (≥ 1 -point improvement)

	ECM (N=82)	Dupilumab Q2W (N=122)
Baseline		
<i>All</i>		
Number	81	122
Mean (SD)	5.870 (1.274)	5.955 (1.347)
<i>Responders at Week 24</i>		
Number	8	80
Mean (SD)	6.000 (0.845)	6.163 (1.130)
<i>Non-responders at Week 24</i>		
Number	73	42
Mean (SD)	5.856 (1.316)	5.560 (1.628)
Week 24		
<i>All</i>		
Number	81	116
Mean (SD)	5.988 (1.337)	4.211 (1.766)
Change from baseline		
Number	81	116
Mean (SD)	0.117 (1.122)	-1.733 (1.754)
LS mean (SE)	0.158 (0.198)	-1.733 (0.172)
LS mean diff (95% CI)	NA	-1.891 (-2.296, -1.486)
p value vs. ECM	NA	<0.0001
<i>Responders at Week 24</i>		
Number	8	80
Mean (SD)	4.188 (1.413)	3.569 (1.556)
Change from baseline		
Number	8	80
Mean (SD)	-1.813 (1.335)	-2.594 (1.225)
LS mean (SE)	-1.552 (0.072)	-2.456 (0.030)
LS mean diff (95% CI)	NA	-0.904 (-1.044, -0.765)
p value vs. ECM	NA	<.0001
<i>Non-responders at Week 24</i>		
Number	73	36
Mean (SD)	6.185 (1.180)	5.639 (1.318)
Change from baseline		
Number	73	36
Mean (SD)	0.329 (0.875)	0.181 (1.122)
LS mean (SE)	0.326 (0.183)	-0.429 (0.226)
LS mean diff (95% CI)	NA	-0.755 (-1.218, -0.291)
p value vs. ECM	NA	0.0014
Week 52		
<i>Responders at Week 24 AND Week 52</i>		
Number	0	19
Mean (SD)	NA	2.684 (1.366)

	ECM (N=82)	Dupilumab Q2W (N=122)
Change from baseline		
Number	0	19
Mean (SD)	NA	-3.474 (1.136)
LS mean (SE)	NE	-3.574 (0.336)
LS mean diff (95% CI)	NA	NE
p value vs. ECM	NA	NE
Non-responders at Week 24 OR Week 52		
Number	42	16
Mean (SD)	6.000 (1.770)	4.094 (2.417)
Change from baseline		
Number	42	16
Mean (SD)	-0.095 (1.201)	-1.438 (1.834)
LS mean (SE)	0.070 (0.286)	-1.511 (0.394)
LS mean diff (95% CI)	NA	-1.582 (-2.512, -0.652)
p value vs. ECM	NA	0.0009

CI = confidence interval; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NPS = nasal polyp score; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every two weeks; SD = standard deviation; SE = standard error
Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 44. NPS and change from baseline in patients with comorbid NSAID-ERD in SINUS-24 and SINUS-52 ITT population according to the response criteria of SNOT-22 total score (≥8.9-point improvement)

	ECM (N=82)	Dupilumab Q2W (N=122)
Baseline		
Responders at Week 24		
Number	29	90
Mean (SD)	5.483 (0.940)	5.950 (1.349)
Non-responders at Week 24		
Number	52	32
Mean (SD)	6.087 (1.389)	5.969 (1.362)
Week 24		
Responders at Week 24		
Number	29	87
Mean (SD)	5.103 (1.256)	3.868 (1.692)
Change from baseline		
Number	29	87
Mean (SD)	-0.379 (1.208)	-2.069 (1.774)
LS mean (SE)	-0.396 (0.321)	-1.877 (0.217)
LS mean diff (95% CI)	NA	-1.480 (-2.110, -0.851)
p value vs. ECM	NA	<0.0001
Non-responders at Week 24		
Number	52	29
Mean (SD)	6.481 (1.116)	5.241 (1.596)
Change from baseline		
Number	52	29
Mean (SD)	0.394 (0.977)	-0.724 (1.251)
LS mean (SE)	0.280 (0.214)	-1.121 (0.265)
LS mean diff (95% CI)	NA	-1.401 (-1.934, -0.869)
p value vs. ECM	NA	<0.0001

	ECM (N=82)	Dupilumab Q2W (N=122)
Week 52		
<i>Responders at Week 24 AND Week 52</i>		
Number	6	22
Mean (SD)	4.917 (2.558)	2.773 (1.681)
Change from baseline		
Number	6	22
Mean (SD)	-0.667 (1.835)	-3.114 (1.610)
LS mean (SE)	-0.748 (0.714)	-3.046 (0.366)
LS mean diff (95% CI)	NA	-2.298 (-3.791, -0.806)
p value vs. ECM	NA	0.0025
<i>Non-responders at Week 24 OR Week 52</i>		
Number	36	13
Mean (SD)	6.181 (1.582)	4.269 (2.251)
Change from baseline		
Number	36	13
Mean (SD)	0.000 (1.069)	-1.577 (1.730)
LS mean (SE)	0.077 (0.294)	-1.608 (0.455)
LS mean diff (95% CI)	NA	-1.685 (-2.650, -0.720)
p value vs. ECM	NA	0.0006

CI = confidence interval; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NA = not applicable; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test
Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 45. NPS and change from baseline in patients with comorbid NSAID-ERD in SINUS-24 and SINUS-52 ITT population according to the response criteria of SNOT-22 total score (≥8.9-point improvement) and NPS (≥1-point improvement)

	ECM (N=82)	Dupilumab Q2W (N=122)
Baseline		
<i>Responders at Week 24</i>		
Number	7	70
Mean (SD)	5.929 (0.886)	6.171 (1.157)
<i>Non-responders at Week 24</i>		
Number	74	52
Mean (SD)	5.865 (1.309)	5.663 (1.530)
Week 24		
<i>Responders at Week 24</i>		
Number	7	70
Mean (SD)	4.071 (1.484)	3.493 (1.585)
Change from baseline		
Number	7	70
Mean (SD)	-1.857 (1.435)	-2.679 (1.237)
LS mean (SE)	-1.534 (0.078)	-2.495 (0.032)
LS mean diff (95% CI)	NA	-0.962 (-1.113, -0.810)
p value vs. ECM	NA	<0.0001
<i>Non-responders at Week 24</i>		
Number	74	46
Mean (SD)	6.169 (1.180)	5.304 (1.447)
Change from baseline		
Number	74	46
Mean (SD)	0.304 (0.894)	-0.293 (1.416)

	ECM (N=82)	Dupilumab Q2W (N=122)
LS mean (SE)	0.314 (0.188)	-0.708 (0.217)
LS mean diff (95% CI)	NA	-1.023 (-1.466, -0.580)
p value vs. ECM	NA	0<.0001
Week 52		
<i>Responders at Week 24 AND Week 52</i>		
Number	0	14
Mean (SD)	NA	2.500 (1.240)
Change from baseline		
Number	0	14
Mean (SD)	NA	-3.750 (1.033)
LS mean (SE)	NE	-3.684 (0.364)
LS mean diff (95% CI)	NA	NE
p value vs. ECM	NA	NE
<i>Non-responders at Week 24 OR Week 52</i>		
Number	42	21
Mean (SD)	6.000 (1.770)	3.881 (2.263)
Change from baseline		
Number	42	21
Mean (SD)	-0.095 (1.201)	-1.738 (1.758)
LS mean (SE)	0.068 (0.282)	-1.735 (0.354)
LS mean diff (95% CI)	NA	-1.804 (-2.630, -0.978)
p value vs. ECM	NA	<0.0001

CI = confidence interval; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NPS = nasal polyp score; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test
Source: Sanofi. Data on File, Post-hoc analyses.¹

Mapped SNOT-22 to EQ-5D-3L health state utilities (Crump Models 1-3)

Table 46. Mapped SNOT-22 to EQ-5D-3L health state utilities (Crump Models 1-3) in patients with comorbid NSAID-ERD in SINUS-24 and SINUS-52 ITT pooled population according to the response criteria of NPS (≥ 1 -point improvement)

	ECM (N=82)			Dupilumab Q2W (N=122)			All (N=204)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Baseline									
<i>All</i>									
Number	81	81	81	118	118	118	199	199	199
Mean (SD)	0.492 (0.139)	0.612 (0.190)	0.612 (0.188)	0.531 (0.128)	0.656 (0.161)	0.658 (0.166)	0.515 (0.133)	0.638 (0.174)	0.639 (0.176)
<i>Responders at Week 24</i>									
Number	8	8	8	77	77	77	85	85	85
Mean (SD)	0.535 (0.077)	0.661 (0.097)	0.652 (0.085)	0.527 (0.124)	0.652 (0.158)	0.654 (0.163)	0.528 (0.120)	0.653 (0.153)	0.654 (0.157)
<i>Non-responders at Week 24</i>									
Number	73	73	73	41	41	41	114	114	114
Mean (SD)	0.487 (0.144)	0.607 (0.197)	0.607 (0.196)	0.539 (0.135)	0.665 (0.169)	0.664 (0.175)	0.506 (0.142)	0.628 (0.189)	0.628 (0.190)
Week 24									
<i>All</i>									
Number	80	80	80	116	116	116	196	196	196
Mean (SD)	0.565 (0.157)	0.653 (0.180)	0.652 (0.179)	0.729 (0.110)	0.769 (0.124)	0.771 (0.131)	0.662 (0.154)	0.721 (0.159)	0.722 (0.163)
<i>Change from baseline</i>									
Number	80	80	80	116	116	116	196	196	196
Mean (SD)	0.072 (0.142)	0.040 (0.176)	0.040 (0.175)	0.197 (0.142)	0.113 (0.144)	0.114 (0.144)	0.146 (0.155)	0.083 (0.162)	0.084 (0.161)
LS mean (SE)	0.064 (0.017)	0.040 (0.018)	0.040 (0.018)	0.218 (0.015)	0.136 (0.016)	0.137 (0.016)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.154 (0.119, 0.189)	0.096 (0.059, 0.133)	0.097 (0.060, 0.134)	NA	NA	NA
p value vs. ECM	NA	NA	NA	<0.0001	<0.0001	<0.0001	NA	NA	NA
<i>Responders at Week 24</i>									
Number	8	8	8	76	76	76	84	84	84
Mean (SD)	0.681 (0.145)	0.728 (0.140)	0.719 (0.134)	0.754 (0.080)	0.778 (0.097)	0.781 (0.101)	0.747 (0.090)	0.773 (0.102)	0.775 (0.105)
<i>Change from baseline</i>									
Number	8	8	8	76	76	76	84	84	84
Mean (SD)	0.146 (0.119)	0.067 (0.143)	0.067 (0.141)	0.229 (0.136)	0.129 (0.146)	0.130 (0.146)	0.221 (0.136)	0.124 (0.146)	0.124 (0.146)

	ECM (N=82)			Dupilumab Q2W (N=122)			All (N=204)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
LS mean (SE)	0.162 (0.035)	0.092 (0.037)	0.082 (0.038)	0.239 (0.015)	0.144 (0.015)	0.144 (0.016)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.076 (0.008, 0.145)	0.052 (-0.020, 0.124)	0.062 (-0.011, 0.136)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.0286	0.1572	0.0960	NA	NA	NA
Non-responders at Week 24									
Number	72	72	72	40	40	40	112	112	112
Mean (SD)	0.552 (0.153)	0.644 (0.182)	0.645 (0.183)	0.682 (0.142)	0.751 (0.164)	0.750 (0.175)	0.598 (0.161)	0.682 (0.183)	0.682 (0.186)
Change from baseline									
Number	72	72	72	40	40	40	112	112	112
Mean (SD)	0.064 (0.142)	0.037 (0.180)	0.037 (0.179)	0.138 (0.136)	0.081 (0.136)	0.082 (0.137)	0.090 (0.144)	0.053 (0.166)	0.053 (0.166)
LS mean (SE)	0.063 (0.021)	0.040 (0.024)	0.041 (0.024)	0.175 (0.025)	0.118 (0.028)	0.118 (0.028)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.112 (0.061, 0.163)	0.078 (0.020, 0.135)	0.076 (0.019, 0.134)	NA	NA	NA
p value vs. ECM	NA	NA	NA	<.0001	0.0078	0.0093	NA	NA	NA
Week 52									
Responders at Week 24 AND Week 52									
Number	0	0	0	18	18	18	43	43	43
Mean (SD)	NA	NA	NA	0.769 (0.091)	0.794 (0.109)	0.802 (0.111)	0.770 (0.078)	0.787 (0.097)	0.792 (0.100)
Change from baseline									
Number	0	0	0	18	18	18	43	43	43
Mean (SD)	NA	NA	NA	0.207 (0.135)	0.106 (0.144)	0.105 (0.145)	0.249 (0.138)	0.130 (0.163)	0.130 (0.163)
LS mean (SE)	NE	NE	NE	0.248 (0.024)	0.144 (0.028)	0.145 (0.028)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	NE	NE	NA	NA	NA	NA
p value vs. ECM	NA	NA	NA	NE	NE	NA	NA	NA	NA
Non-responders at Week 24 AND Week 52									
Number	35	35	35	5	5	5	47	47	47
Mean (SD)	0.553 (0.152)	0.656 (0.188)	0.656 (0.192)	0.563 (0.211)	0.642 (0.250)	0.625 (0.253)	0.569 (0.162)	0.665 (0.192)	0.663 (0.197)
Change from baseline									
Number	35	35	35	5	5	5	47	47	47
Mean (SD)	0.083 (0.137)	0.069 (0.167)	0.068 (0.165)	0.117 (0.153)	0.117 (0.166)	0.116 (0.167)	0.094 (0.133)	0.071 (0.155)	0.070 (0.154)
LS mean (SE)	0.074 (0.027)	0.067 (0.029)	0.066 (0.030)	0.087 (0.064)	0.061 (0.070)	0.053 (0.071)	NA	NA	NA

	ECM (N=82)			Dupilumab Q2W (N=122)			All (N=204)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
LS mean diff (95% CI)	NA	NA	NA	0.013 (-0.118, 0.145)	-0.006 (-0.149, 0.137)	-0.012 (-0.157, 0.132)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.8425	0.9299	0.8671	NA	NA	NA
<i>Non-responders at Week 24 OR Week 52</i>									
Number	42	42	42	16	16	16	73	73	73
Mean (SD)	0.570 (0.160)	0.667 (0.193)	0.666 (0.195)	0.701 (0.165)	0.721 (0.174)	0.721 (0.185)	0.630 (0.170)	0.701 (0.183)	0.700 (0.188)
<i>Change from baseline</i>									
Number	42	42	42	16	16	16	73	73	73
Mean (SD)	0.081 (0.140)	0.059 (0.172)	0.058 (0.169)	0.179 (0.169)	0.086 (0.199)	0.088 (0.200)	0.131 (0.165)	0.081 (0.176)	0.081 (0.175)
LS mean (SE)	0.065 (0.025)	0.052 (0.028)	0.050 (0.028)	0.189 (0.036)	0.091 (0.039)	0.091 (0.039)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.125 (0.044, 0.206)	0.039 (-0.049, 0.128)	0.041 (-0.049, 0.130)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.0026	0.3849	0.3721	NA	NA	NA

CI = confidence interval; EQ-5D-3L = EuroQol 5-Dimension 3-Level; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NA = not applicable; NP = nasal polyp; NPS = nasal polyp score; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every two weeks; SD = standard deviation; SE = standard error
Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 47. Mapped SNOT-22 to EQ-5D-3L health state utilities (Crump Models 1-3) in patients with comorbid NSAID-ERD in SINUS-24 and SINUS-52 ITT pooled population according to the response criteria of SNOT-22 total score (≥8.9-point improvement)

	ECM (N=82)			Dupilumab Q2W (N=122)			All (N=204)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Baseline									
<i>Responders at Week 24</i>									
Number	30	30	30	90	90	90	120	120	120
Mean (SD)	0.474 (0.120)	0.580 (0.166)	0.576 (0.165)	0.517 (0.119)	0.650 (0.158)	0.651 (0.161)	0.506 (0.120)	0.632 (0.162)	0.632 (0.164)
<i>Non-responders at Week 24</i>									
Number	51	51	51	28	28	28	79	79	79
Mean (SD)	0.503 (0.150)	0.631 (0.202)	0.633 (0.199)	0.578 (0.145)	0.677 (0.174)	0.680 (0.185)	0.530 (0.151)	0.647 (0.192)	0.649 (0.194)
Week 24									
<i>Responders at Week 24</i>									

	ECM (N=82)			Dupilumab Q2W (N=122)			All (N=204)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Number	30	30	30	90	90	90	120	120	120
Mean (SD)	0.648 (0.135)	0.726 (0.145)	0.722 (0.146)	0.761 (0.076)	0.790 (0.095)	0.792 (0.100)	0.733 (0.106)	0.774 (0.112)	0.774 (0.116)
Change from baseline									
Number	30	30	30	90	90	90	120	120	120
Mean (SD)	0.174 (0.087)	0.146 (0.109)	0.146 (0.108)	0.244 (0.119)	0.140 (0.143)	0.141 (0.142)	0.227 (0.116)	0.141 (0.135)	0.142 (0.134)
LS mean (SE)	0.154 (0.003)	0.120 (0.003)	0.117 (0.003)	0.259 (0.002)	0.160 (0.002)	0.160 (0.002)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.105 (0.100, 0.111)	0.040 (0.034, 0.046)	0.043 (0.037, 0.050)	NA	NA	NA
p value vs. ECM	NA	NA	NA	<0.0001	<0.0001	<0.0001	NA	NA	NA
Non-responders at Week 24									
Number	50	50	50	26	26	26	76	76	76
Mean (SD)	0.515 (0.149)	0.608 (0.185)	0.610 (0.186)	0.619 (0.138)	0.696 (0.179)	0.697 (0.191)	0.551 (0.153)	0.638 (0.187)	0.640 (0.191)
Change from baseline									
Number	50	50	50	26	26	26	76	76	76
Mean (SD)	0.011 (0.134)	-0.024 (0.179)	-0.024 (0.177)	0.035 (0.086)	0.019 (0.105)	0.019 (0.108)	0.019 (0.119)	-0.009 (0.158)	-0.009 (0.157)
LS mean (SE)	0.019 (0.023)	-0.003 (0.028)	-0.003 (0.028)	0.081 (0.029)	0.052 (0.034)	0.051 (0.034)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.062 (0.002, 0.123)	0.055 (-0.014, 0.125)	0.054 (-0.016, 0.124)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.0440	0.1194	0.1322	NA	NA	NA
Week 52									
Responders at Week 24 AND Week 52									
Number	6	6	6	22	22	22	60	60	60
Mean (SD)	0.571 (0.193)	0.620 (0.253)	0.609 (0.253)	0.780 (0.073)	0.791 (0.089)	0.797 (0.100)	0.756 (0.105)	0.770 (0.122)	0.773 (0.128)
Change from baseline									
Number	6	6	6	22	22	22	60	60	60
Mean (SD)	0.186 (0.081)	0.179 (0.040)	0.177 (0.044)	0.263 (0.118)	0.148 (0.158)	0.148 (0.159)	0.272 (0.128)	0.158 (0.159)	0.159 (0.159)
LS mean (SE)	0.107 (0.037)	0.054 (0.049)	0.050 (0.050)	0.282 (0.019)	0.167 (0.024)	0.168 (0.025)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.175 (0.086, 0.265)	0.113 (-0.004, 0.229)	0.119 (0.000, 0.237)	NA	NA	NA
p value vs. ECM	NA	NA	NA	<0.0001	0.0389	0.0320	NA	NA	NA
Non-responders at Week 24 AND Week 52									

	ECM (N=82)			Dupilumab Q2W (N=122)			All (N=204)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Number	29	29	29	6	6	6	40	40	40
Mean (SD)	0.545 (0.160)	0.655 (0.192)	0.657 (0.194)	0.535 (0.172)	0.577 (0.237)	0.570 (0.236)	0.549 (0.158)	0.648 (0.198)	0.648 (0.202)
Change from baseline									
Number	29	29	29	6	6	6	40	40	40
Mean (SD)	0.041 (0.144)	0.021 (0.183)	0.021 (0.180)	0.015 (0.127)	-0.010 (0.208)	-0.011 (0.210)	0.037 (0.132)	0.023 (0.176)	0.023 (0.174)
LS mean (SE)	0.038 (0.028)	0.040 (0.036)	0.038 (0.036)	0.008 (0.060)	-0.023 (0.075)	-0.028 (0.075)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	-0.031 (-0.152, 0.091)	-0.063 (-0.215, 0.089)	-0.067 (-0.220, 0.087)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.6218	0.4167	0.3953	NA	NA	NA
Non-responders at Week 24 OR Week 52									
Number	36	36	36	12	12	12	56	56	56
Mean (SD)	0.570 (0.157)	0.675 (0.184)	0.676 (0.187)	0.658 (0.182)	0.703 (0.208)	0.703 (0.214)	0.602 (0.166)	0.692 (0.188)	0.692 (0.192)
Change from baseline									
Number	36	36	36	12	12	12	56	56	56
Mean (SD)	0.063 (0.141)	0.038 (0.178)	0.039 (0.174)	0.066 (0.119)	0.002 (0.155)	0.002 (0.155)	0.070 (0.133)	0.036 (0.164)	0.036 (0.163)
LS mean (SE)	0.048 (0.026)	0.038 (0.031)	0.037 (0.031)	0.079 (0.044)	0.026 (0.050)	0.022 (0.050)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.032 (-0.062, 0.125)	-0.012 (-0.117, 0.093)	-0.015 (-0.120, 0.090)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.5071	0.8238	0.7850	NA	NA	NA

CI = confidence interval; EQ-5D-3L = EuroQol 5-Dimension 3-Level; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NA = not applicable; NP = nasal polyp; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test
Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 48. Mapped SNOT-22 to EQ-5D-3L health state utilities (Crump Models 1-3) in patients with comorbid NSAID-ERD in SINUS-24 and SINUS-52 ITT pooled population according to the response criteria of SNOT-22 total score (≥ 8.9 -point improvement) and NPS (≥ 1 -point improvement)

	ECM (N=82)			Dupilumab Q2W (N=102)			All (N=204)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Baseline									
<i>Responders at Week 24</i>									

	ECM (N=82)			Dupilumab Q2W (N=102)			All (N=204)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Number	7	7	7	70	70	70	77	77	77
Mean (SD)	0.523 (0.075)	0.653 (0.101)	0.646 (0.090)	0.514 (0.121)	0.642 (0.159)	0.644 (0.164)	0.515 (0.117)	0.643 (0.155)	0.644 (0.158)
<i>Non-responders at Week 24</i>									
Number	74	74	74	48	48	48	122	122	122
Mean (SD)	0.489 (0.144)	0.608 (0.196)	0.608 (0.195)	0.556 (0.133)	0.677 (0.164)	0.678 (0.170)	0.516 (0.143)	0.635 (0.186)	0.636 (0.188)
Week 24									
<i>Responders at Week 24</i>									
Number	7	7	7	70	70	70	77	77	77
Mean (SD)	0.699 (0.147)	0.757 (0.122)	0.751 (0.108)	0.761 (0.078)	0.785 (0.094)	0.788 (0.099)	0.756 (0.087)	0.783 (0.096)	0.784 (0.100)
Change from baseline									
Number	7	7	7	70	70	70	77	77	77
Mean (SD)	0.176 (0.092)	0.104 (0.103)	0.105 (0.099)	0.247 (0.124)	0.143 (0.144)	0.144 (0.143)	0.241 (0.123)	0.139 (0.140)	0.140 (0.140)
LS mean (SE)	0.191 (0.005)	0.124 (0.005)	0.116 (0.006)	0.261 (0.002)	0.161 (0.002)	0.161 (0.002)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.071 (0.061, 0.081)	0.037 (0.026, 0.048)	0.045 (0.035, 0.056)	NA	NA	NA
p value vs. ECM	NA	NA	NA	<0.0001	<0.0001	<.0001	NA	NA	NA
<i>Non-responders at Week 24</i>									
Number	73	73	73	46	46	46	119	119	119
Mean (SD)	0.552 (0.152)	0.643 (0.182)	0.643 (0.182)	0.680 (0.133)	0.744 (0.157)	0.745 (0.167)	0.601 (0.157)	0.682 (0.179)	0.682 (0.183)
Change from baseline									
Number	73	73	73	46	46	46	119	119	119
Mean (SD)	0.062 (0.142)	0.034 (0.181)	0.034 (0.179)	0.121 (0.135)	0.067 (0.134)	0.068 (0.135)	0.085 (0.142)	0.047 (0.165)	0.047 (0.164)
LS mean (SE)	0.055 (0.020)	0.035 (0.023)	0.036 (0.023)	0.161 (0.023)	0.104 (0.026)	0.104 (0.026)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.105 (0.057, 0.154)	0.068 (0.014, 0.122)	0.068 (0.014, 0.122)	NA	NA	NA
p value vs. ECM	NA	NA	NA	<0.0001	0.0129	0.0143	NA	NA	NA

	ECM (N=82)			Dupilumab Q2W (N=102)			All (N=204)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Week 52									
<i>Responders at Week 24 AND Week 52</i>									
Number	0	0	0	14	14	14	38	38	38
Mean (SD)	NA	NA	NA	0.785 (0.069)	0.809 (0.078)	0.817 (0.083)	0.777 (0.069)	0.791 (0.086)	0.795 (0.091)
Change from baseline									
Number	0	0	0	14	14	14	38	38	38
Mean (SD)	NA	NA	NA	0.252 (0.106)	0.142 (0.133)	0.140 (0.135)	0.274 (0.122)	0.151 (0.158)	0.151 (0.159)
LS mean (SE)	NE	NE	NE	0.276 (0.022)	0.171 (0.027)	0.174 (0.028)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	NE	NE	NE	NA	NA	NA
p value vs. ECM	NA	NA	NA	NE	NE	NE	NA	NA	NA
<i>Non-responders at Week 24 AND Week 52</i>									
Number	39	39	39	7	7	7	54	54	54
Mean (SD)	0.560 (0.157)	0.660 (0.194)	0.660 (0.197)	0.562 (0.173)	0.593 (0.220)	0.584 (0.218)	0.575 (0.161)	0.661 (0.194)	0.661 (0.199)
Change from baseline									
Number	39	39	39	7	7	7	54	54	54
Mean (SD)	0.071 (0.139)	0.050 (0.176)	0.050 (0.173)	0.057 (0.162)	0.023 (0.210)	0.022 (0.210)	0.075 (0.137)	0.048 (0.167)	0.047 (0.165)
LS mean (SE)	0.067 (0.026)	0.060 (0.030)	0.059 (0.030)	0.047 (0.056)	-0.010 (0.065)	-0.016 (0.065)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	-0.020 (-0.135, 0.095)	-0.070 (-0.204, 0.063)	-0.075 (-0.208, 0.059)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.7287	0.3010	0.2715	NA	NA	NA
<i>Non-responders at Week 24 OR Week 52</i>									
Number	42	42	42	20	20	20	78	78	78
Mean (SD)	0.570 (0.160)	0.667 (0.193)	0.666 (0.195)	0.702 (0.157)	0.725 (0.172)	0.727 (0.181)	0.635 (0.168)	0.704 (0.181)	0.705 (0.186)
Change from baseline									
Number	42	42	42	20	20	20	78	78	78
Mean (SD)	0.081 (0.140)	0.059 (0.172)	0.058 (0.169)	0.153 (0.165)	0.065 (0.188)	0.066 (0.189)	0.127 (0.162)	0.074 (0.174)	0.074 (0.173)
LS mean (SE)	0.063 (0.025)	0.048 (0.027)	0.047 (0.027)	0.173 (0.033)	0.079 (0.036)	0.078 (0.036)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.111 (0.036, 0.185)	0.030 (-0.051, 0.111)	0.031 (-0.050, 0.113)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.0035	0.4633	0.4531	NA	NA	NA

CI = confidence interval; EQ-5D-3L = EuroQol 5-Dimension 3-Level; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NPS = nasal polyp score; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test
Source: Sanofi. Data on File, Post-hoc analyses.¹

EQ-5D-5L utilities (Hernandez 2020 crosswalk method, UK tariffs)

Table 49. EQ-5D-5L utilities (Hernandez 2020 crosswalk method, UK tariffs) in patients with comorbid NSAID-ERD in SINUS-24 and SINUS-52 ITT pooled population according to the response criteria of NPS (≥1-point improvement)

	ECM (N=82)	Dupilumab Q2W (N=122)
Baseline		
<i>All</i>		
Number	81	115
Mean (SD)	0.739 (0.197)	0.781 (0.183)
<i>Responders at Week 24</i>		
Number	8	75
Mean (SD)	0.790 (0.118)	0.804 (0.149)
<i>Non-responders at Week 24</i>		
Number	73	40
Mean (SD)	0.734 (0.203)	0.737 (0.229)
Week 24		
<i>All</i>		
Number	79	113
Mean (SD)	0.768 (0.221)	0.854 (0.190)
Change from baseline		
Number	79	113
Mean (SD)	0.030 (0.139)	0.074 (0.150)
LS mean (SE)	0.022 (0.019)	0.084 (0.017)
LS mean diff (95% CI)	NA	0.062 (0.022, 0.101)
p value vs. ECM	NA	0.0022
<i>Responders at Week 24</i>		
Number	8	74
Mean (SD)	0.889 (0.119)	0.883 (0.143)
Change from baseline		
Number	8	74
Mean (SD)	0.099 (0.190)	0.081 (0.142)
LS mean (SE)	0.105 (0.049)	0.098 (0.021)
LS mean diff (95% CI)	NA	-0.007 (-0.103, 0.090)
p value vs. ECM	NA	0.8931
<i>Non-responders at Week 24</i>		
Number	71	39
Mean (SD)	0.755 (0.227)	0.800 (0.250)
Change from baseline		
Number	71	39
Mean (SD)	0.022 (0.131)	0.060 (0.165)
LS mean (SE)	0.020 (0.023)	0.066 (0.027)
LS mean diff (95% CI)	NA	0.047 (-0.008, 0.102)
p value vs. ECM	NA	0.0946
Week 52		
<i>Responders at Week 24 AND Week 52</i>		
Number	0	17
Mean (SD)	NA	0.911 (0.116)
Change from baseline		
Number	0	17
Mean (SD)	NA	0.067 (0.095)

	ECM (N=82)	Dupilumab Q2W (N=122)
LS mean (SE)	NE	0.099 (0.024)
LS mean diff (95% CI)	NA	NE
p value vs. ECM	NA	NE
Non-responders at Week 24 AND Week 52		
Number	35	5
Mean (SD)	0.720 (0.295)	0.595 (0.484)
Change from baseline		
Number	35	5
Mean (SD)	-0.009 (0.210)	0.115 (0.165)
LS mean (SE)	-0.039 (0.038)	0.056 (0.094)
LS mean diff (95% CI)	NA	0.095 (-0.097, 0.288)
p value vs. ECM	NA	0.3327
Non-responders at Week 24 OR Week 52		
Number	42	16
Mean (SD)	0.748 (0.282)	0.826 (0.313)
Change from baseline		
Number	42	16
Mean (SD)	0.003 (0.201)	0.115 (0.152)
LS mean (SE)	-0.015 (0.033)	0.101 (0.046)
LS mean diff (95% CI)	NA	0.116 (0.010, 0.223)
p value vs. ECM	NA	0.0324

CI = confidence interval; EQ-5D-5L = EuroQol 5-Dimension 5-Level; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NPS = nasal polyp score; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every two weeks; SD = standard deviation; SE = standard error
Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 50. EQ-5D-5L utilities (Hernandez 2020 crosswalk method, UK tariffs) in patients with comorbid NSAID-ERD in SINUS-24 and SINUS-52 ITT pooled population according to the response criteria of SNOT-22 total score (≥8.9-point improvement)

	ECM (N=82)	Dupilumab Q2W (N=122)
Baseline		
Responders at Week 24		
Number	30	89
Mean (SD)	0.766 (0.139)	0.790 (0.149)
Non-responders at Week 24		
Number	51	26
Mean (SD)	0.724 (0.224)	0.749 (0.270)
Week 24		
Responders at Week 24		
Number	30	89
Mean (SD)	0.857 (0.132)	0.882 (0.147)
Change from baseline		
Number	30	89
Mean (SD)	0.091 (0.139)	0.092 (0.153)
LS mean (SE)	0.069 (0.004)	0.099 (0.003)
LS mean diff (95% CI)	NA	0.030 (0.022, 0.038)
p value vs. ECM	NA	<0.0001
Non-responders at Week 24		
Number	49	24
Mean (SD)	0.714 (0.247)	0.750 (0.281)
Change from baseline		

	ECM (N=82)	Dupilumab Q2W (N=122)
Number	49	24
Mean (SD)	-0.007 (0.126)	0.007 (0.121)
LS mean (SE)	0.009 (0.026)	0.026 (0.031)
LS mean diff (95% CI)	NA	0.017 (-0.048, 0.082)
p value vs. ECM	NA	0.6040
Week 52		
<i>Responders at Week 24 AND Week 52</i>		
Number	6	21
Mean (SD)	0.724 (0.292)	0.908 (0.120)
Change from baseline		
Number	6	21
Mean (SD)	0.032 (0.159)	0.107 (0.111)
LS mean (SE)	0.008 (0.055)	0.117 (0.028)
LS mean diff (95% CI)	NA	0.109 (-0.021, 0.239)
p value vs. ECM	NA	0.0703
<i>Non-responders at Week 24 AND Week 52</i>		
Number	29	6
Mean (SD)	0.707 (0.299)	0.646 (0.462)
Change from baseline		
Number	29	6
Mean (SD)	-0.022 (0.223)	0.045 (0.156)
LS mean (SE)	-0.038 (0.041)	-0.017 (0.088)
LS mean diff (95% CI)	NA	0.021 (-0.159, 0.200)
p value vs. ECM	NA	0.8220
<i>Non-responders at Week 24 OR Week 52</i>		
Number	36	12
Mean (SD)	0.751 (0.284)	0.803 (0.353)
Change from baseline		
Number	36	12
Mean (SD)	-0.002 (0.208)	0.061 (0.150)
LS mean (SE)	-0.016 (0.035)	0.027 (0.056)
LS mean diff (95% CI)	NA	0.043 (-0.074, 0.160)
p value vs. ECM	NA	0.4748

CI = confidence interval; EQ-5D-5L = EuroQol 5-Dimension 5-Level; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NA = not applicable; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test
Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 51. EQ-5D-5L utilities (Hernandez 2020 crosswalk method, UK tariffs) in patients with comorbid NSAID-ERD in SINUS-24 and SINUS-52 ITT pooled population according to the response criteria of SNOT-22 total score (≥8.9-point improvement) and NPS (≥1-point improvement)

	ECM (N=82)	Dupilumab Q2W (N=122)
Baseline		
<i>Responders at Week 24</i>		
Number	7	69
Mean (SD)	0.795 (0.126)	0.798 (0.150)
<i>Non-responders at Week 24</i>		

	ECM (N=82)	Dupilumab Q2W (N=122)
Number	74	46
Mean (SD)	0.734 (0.202)	0.754 (0.222)
Week 24		
<i>Responders at Week 24</i>		
Number	7	69
Mean (SD)	0.886 (0.128)	0.884 (0.144)
Change from baseline		
Number	7	69
Mean (SD)	0.091 (0.203)	0.085 (0.145)
LS mean (SE)	0.102 (0.008)	0.105 (0.003)
LS mean diff (95% CI)	NA	0.004 (-0.012, 0.019)
p value vs. ECM	NA	0.6337
<i>Non-responders at Week 24</i>		
Number	72	44
Mean (SD)	0.757 (0.226)	0.808 (0.240)
Change from baseline		
Number	72	44
Mean (SD)	0.024 (0.131)	0.057 (0.158)
LS mean (SE)	0.020 (0.022)	0.062 (0.025)
LS mean diff (95% CI)	NA	0.042 (-0.010, 0.094)
p value vs. ECM	NA	0.1149
Week 52		
<i>Responders at Week 24 AND Week 52</i>		
Number	0	13
Mean (SD)	NA	0.922 (0.094)
Change from baseline		
Number	0	13
Mean (SD)	NA	0.089 (0.087)
LS mean (SE)	NE	0.117 (0.024)
LS mean diff (95% CI)	NA	NE
p value vs. ECM	NA	NE
<i>Non-responders at Week 24 AND Week 52</i>		
Number	39	7
Mean (SD)	0.736 (0.287)	0.652 (0.422)
Change from baseline		
Number	39	7
Mean (SD)	-0.011 (0.201)	0.071 (0.157)
LS mean (SE)	-0.031 (0.035)	0.014 (0.076)
LS mean diff (95% CI)	NA	0.046 (-0.112, 0.204)
p value vs. ECM	NA	0.5711
<i>Non-responders at Week 24 OR Week 52</i>		
Number	42	20
Mean (SD)	0.748 (0.282)	0.836 (0.288)
Change from baseline		
Number	42	20
Mean (SD)	0.003 (0.201)	0.091 (0.148)
LS mean (SE)	-0.011 (0.032)	0.080 (0.042)
LS mean diff (95% CI)	NA	0.090 (-0.005, 0.185)
p value vs. ECM	NA	0.0627

CI = confidence interval; EQ-5D-5L = EuroQol 5-Dimension 5-Level; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NPS = nasal polyp score; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test

Source: Sanofi. Data on File, Post-hoc analyses.¹

Patients with comorbid asthma

Baseline characteristics

Table 52. Baseline characteristics of patients with comorbid asthma in SINUS-24 and SINUS-52 pooled ITT population

	ECM	Dupilumab Q2W	All
N	170	167	428
Male, n (%)	76 (44.7)	86 (51.5)	210 (49.1)
Age, mean (SD)	50.60 (13.30)	52.30 (12.46)	51.54 (12.89)
Race, n (%)			
Caucasian/White	149 (87.6)	149 (89.2)	372 (86.9)
Black/African decent	8 (4.7)	3 (1.8)	12 (2.8)
Asian/Oriental	12 (7.1)	9 (5.4)	35 (8.2)
American Indian/Alaska Native	1 (0.6)	5 (3.0)	7 (1.6)
Native Hawaiian/Other Pacific Islander	0	0	0
Multiple	0	0	1 (0.2)
Unknown	0	1 (0.6)	1 (0.2)
Ethnicity			
Hispanic or Latino	20 (11.9)	27 (16.2)	67 (15.7)
Not Hispanic or Latino	148 (88.1)	140 (83.8)	359 (84.3)
Territory			
North America	30 (17.6)	29 (17.4)	79 (18.5)
European Union	67 (39.4)	65 (38.9)	149 (34.8)
Rest of the World	73 (42.9)	73 (43.7)	200 (46.7)
BMI (kg/m ²), mean (SD)	28.01 (6.09)	27.58 (5.35)	27.72 (5.64)
Time since first diagnosis of nasal polyps (years), mean (SD)	12.06 (9.43)	13.06 (10.61)	12.14 (9.75)
Previous surgery for nasal polyps, n (%)	121 (71.2)	121 (72.5)	304 (71.0)
Time since most recent surgery for nasal polyps (years), mean (SD)	7.23 (6.43)	6.61 (5.37)	6.91 (5.74)
SCS use in the past 2 years, n (%)	130 (76.5)	122 (73.1)	324 (75.7)
Bilateral endoscopic NPS* (scale 0-8), mean (SD)	5.82 (1.32)	5.89 (1.26)	5.97 (1.26)
NC score* (scale 0-3), mean (SD)	2.43 (0.53)	2.40 (0.61)	2.42 (0.57)
SNOT-22 total score* (scale 0-110), mean (SD)	56.72 (20.61)	50.96 (19.74)	53.98 (20.21)
Smell test (UPSIT) score** (scale 0-40), mean (SD)	12.79 (7.17)	12.22 (7.18)	12.39 (6.97)
LoS score* (scale 0-3), mean (SD)			
LMK-CT total score* (scale 0-24), mean (SD)	19.15 (3.85)	19.26 (3.83)	19.14 (3.77)
Rhinosinusitis disease severity* (VAS 0-10cm), mean (SD)	8.18 (2.08)	8.05 (1.71)	8.04 (2.03)
Baseline NPIF** (L/min), mean (SD)	84.57 (55.78)	90.32 (55.79)	87.02 (57.26)
Baseline blood eosinophils (x10 ⁹ cells/L), mean (SD)	0.51 (0.38)	0.54 (0.43)	0.51 (0.39)

	ECM	Dupilumab Q2W	All
Comorbid NSAID-ERD, n (%)	74 (43.5)	70 (41.9)	181 (42.3)
Any comorbid type 2 medical history excluding asthma and NSAID-ERD, n (%)	122 (71.8)	114 (68.3)	308 (72.0)
Age of asthma onset (years), mean (SD)	33.35 (15.76)	36.89 (14.82)	34.78 (16.01)
Baseline ACQ-6 score*, mean (SD)	1.66 (1.09)	1.49 (1.05)	1.59 (1.10)
Baseline GINA 4 or 5, n (%)	75 (44.1)	83 (32.2)	158 (36.9)

ACQ-6 = 6-item Asthma Control Questionnaire; BMI = body mass index; GINA = Global Initiative for Asthma; ITT = intention-to-treat; LMK-CT = Lund-Mackay computed tomography; LoS = loss-of-smell; NC = nasal congestion/obstruction; NPIF = peak nasal inspiratory flow; NPS = nasal polyp score; Q2W = every 2 weeks; SD = standard deviation; SNOT-22 = 22-item Sino-Nasal Outcome Test; UPSIT = University of Pennsylvania Smell Identification Test; VAS = visual analogue scale

*Higher scores indicate greater disease severity.

** Higher scores indicate lower disease severity.

Source: Sanofi. Data on File, Post-hoc analyses.¹

Response rates

Table 53. Response rates for patients with comorbid asthma in SINUS-24 and SINUS-52 pooled ITT population according to the different response criteria

	ECM (N=170)	Dupilumab Q2W (N=258)
Overall response at Week 24		
NPS (≥1-point improvement)		
Responders, n (%)	23 (13.5)	170 (65.9)
Non-responders, n (%)	147 (86.5)	88 (34.1)
SNOT-22 total score (≥8.9-point improvement)		
Responders, n (%)	68 (40.0)	194 (75.2)
Non-responders, n (%)	102 (60.0)	64 (24.8)
SNOT-22 total score (≥8.9-point improvement) and NPS (≥1-point improvement)		
Responders, n (%)	18 (10.6)	148 (57.4)
Non-responders, n (%)	152 (89.4)	110 (42.6)
Overall response at Week 52		
All		
NPS (≥1-point improvement)		
Responders, n (%)	9 (9.9)	57 (67.1)
Non-responders, n (%)	82 (90.1)	28 (32.9)
SNOT-22 total score (≥8.9-point improvement)		
Responders, n (%)	20 (22.0)	61 (71.8)
Non-responders, n (%)	71 (78.0)	24 (28.2)
SNOT-22 total score (≥8.9-point improvement) and NPS (≥1-point improvement)		
Responders, n (%)	5 (5.5)	50 (58.8)
Non-responders, n (%)	86 (94.5)	35 (41.2)
Responders at Week 24		
NPS (≥1-point improvement)		
Responders, n (%)	ECM (N=9) 1 (11.1)	Dupilumab Q2W (N=50) 46 (92.0)
Non-responders, n (%)	8 (88.9)	4 (8.0)
SNOT-22 total score (≥8.9-point improvement)		
Responders, n (%)	ECM (N=12) 15 (45.5)	Dupilumab Q2W (N=24) 57 (95.0)
Non-responders, n (%)	18 (54.5)	3 (5.0)
SNOT-22 total score (≥8.9-point improvement) and NPS (≥1-point improvement)		
Responders, n (%)	ECM (N=1) 0	Dupilumab Q2W (N=17) 39 (88.6)

	ECM (N=170)	Dupilumab Q2W (N=258)
Non-responders, n (%)	6 (100)	5 (11.4)
Non-responders at Week 24		
NPS (≥1-point improvement)	ECM (N=82)	Dupilumab Q2W (N=35)
Responders, n (%)	8 (.8)	11 (31.4)
Non-responders, n (%)	74 (90.2)	24 (68.6)
SNOT-22 total score (≥8.9-point improvement)	ECM (N=32)	Dupilumab Q2W (N=11)
Responders, n (%)	5 (8.6)	4 (16.0)
Non-responders, n (%)	53 (91.4)	21 (84.0)
SNOT-22 total score (≥8.9-point improvement) and NPS (≥1-point improvement)	ECM (N=43)	Dupilumab Q2W (N=18)
Responders, n (%)	5 (5.9)	11 (26.8)
Non-responders, n (%)	80 (94.1)	30 (73.2)

ITT = intention-to-treat; NPS = nasal polyp score; Q2W = once every two weeks; SNOT-22: 22-item Sino Nasal Outcome Test
Source: Sanofi. Data on File, Post-hoc analyses.¹

SNOT-22 total score

Table 54. SNOT-22 total score and change from baseline in patients with comorbid asthma in SINUS-24 and SINUS-52 ITT population according to the response criteria of NPS (≥1-point improvement)

	ECM (N=170)	Dupilumab Q2W (N=258)
Baseline		
<i>All</i>		
Number	168	252
Mean (SD)	56.720 (20.608)	52.155 (19.768)
<i>Responders at Week 24</i>		
Number	23	166
Mean (SD)	50.304 (16.907)	53.175 (19.295)
<i>Non-responders at Week 24</i>		
Number	145	86
Mean (SD)	57.738 (21.005)	50.186 (20.622)
Week 24		
<i>All</i>		
Number	160	247
Mean (SD)	45.319 (23.589)	22.713 (17.820)
Change from baseline		
Number	160	247
Mean (SD)	-10.813 (19.148)	-29.636 (21.415)
LS mean (SE)	-9.193 (1.625)	-30.612 (1.449)
LS mean diff (95% CI)	NA	-21.418 (-24.966, -17.871)
p value vs. ECM	NA	<0.0001
<i>Responders at Week 24</i>		
Number	23	164
Mean (SD)	31.000 (21.418)	18.646 (13.943)
Change from baseline		
Number	23	164
Mean (SD)	-19.304 (14.686)	-34.640 (20.475)
LS mean (SE)	-21.788 (3.134)	-35.740 (1.539)
LS mean diff (95% CI)	NA	-13.952 (-20.336, -7.569)
p value vs. ECM	NA	<0.0001

	ECM (N=170)	Dupilumab Q2W (N=258)
Non-responders at Week 24		
Number	137	83
Mean (SD)	47.723 (23.148)	30.747 (21.628)
Change from baseline		
Number	137	83
Mean (SD)	-9.387 (19.482)	-19.747 (19.833)
LS mean (SE)	-7.249 (1.999)	-21.014 (2.389)
LS mean diff (95% CI)	NA	-13.765 (-18.829, -8.701)
p value vs. ECM	NA	<0.0001
Week 52		
Responders at Week 24 AND Week 52		
Number	1	45
Mean (SD)	26.000 (NC)	15.711 (14.686)
Change from baseline		
Number	1	45
Mean (SD)	-8.000 (NC)	-34.222 (20.068)
LS mean (SE)	-24.240 (14.249)	-35.571 (2.423)
LS mean diff (95% CI)	NA	-11.331 (-40.928, 18.267)
p value vs. ECM	NA	0.4328
Non-responders at Week 24 OR Week 52		
Number	83	36
Mean (SD)	49.229 (21.984)	31.556 (22.437)
Change from baseline		
Number	83	36
Mean (SD)	-8.096 (16.516)	-21.528 (20.682)
LS mean (SE)	-7.199 (2.258)	-23.723 (3.249)
LS mean diff (95% CI)	NA	-16.525 (-23.794, -9.256)
p value vs. ECM	NA	<0.0001

CI = confidence interval; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NPS = nasal polyp score; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test

Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 55. SNOT-22 total score and change from baseline in patients with comorbid asthma in SINUS-24 and SINUS-52 ITT population according to the response criteria of SNOT-22 total score (≥8.9-point improvement)

	ECM (N=170)	Dupilumab Q2W (N=258)
Baseline		
Responders at Week 24		
Number	68	194
Mean (SD)	56.368 (19.583)	55.072 (18.661)
Non-responders at Week 24		
Number	100	58
Mean (SD)	56.960 (21.370)	42.397 (20.392)
Week 24		
Responders at Week 24		
Number	68	194
Mean (SD)	30.662 (18.138)	18.340 (14.007)
Change from baseline		
Number	68	194
Mean (SD)	-25.706 (14.538)	-36.732 (17.906)

	ECM (N=170)	Dupilumab Q2W (N=258)
LS mean (SE)	-24.841 (0.279)	-37.357 (0.194)
LS mean diff (95% CI)	NA	-12.517 (-13.089, -11.945)
p value vs. ECM	NA	<0.0001
Non-responders at Week 24		
Number	92	53
Mean (SD)	56.152 (21.232)	38.717 (21.015)
Change from baseline		
Number	92	53
Mean (SD)	0.196 (14.028)	-3.660 (10.194)
LS mean (SE)	0.633 (1.915)	-6.789 (2.443)
LS mean diff (95% CI)	NA	-7.422 (-12.584, -2.261)
p value vs. ECM	NA	0.0048
Week 52		
Responders at Week 24 AND Week 52		
Number	15	57
Mean (SD)	37.400 (22.693)	15.860 (14.891)
Change from baseline		
Number	15	57
Mean (SD)	-28.467 (11.940)	-37.596 (16.345)
LS mean (SE)	-22.297 (3.487)	-38.222 (1.908)
LS mean diff (95% CI)	NA	-15.924 (-24.361, -7.488)
p value vs. ECM	NA	<0.0001
Non-responders at Week 24 OR Week 52		
Number	69	24
Mean (SD)	51.464 (21.184)	39.125 (21.438)
Change from baseline		
Number	69	24
Mean (SD)	-3.667 (13.716)	-7.167 (15.199)
LS mean (SE)	-2.421 (2.034)	-8.094 (3.385)
LS mean diff (95% CI)	NA	-5.673 (-12.790, 1.444)
p value vs. ECM	NA	0.1182

CI = confidence interval; ITT = intention-to-treat; LS = least squares; NA = not applicable; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test
Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 56. SNOT-22 total score and change from baseline in patients with comorbid asthma in SINUS-24 and SINUS-52 ITT population according to the response criteria of SNOT-22 total score (≥8.9-point improvement) and NPS (≥1-point improvement)

	ECM (N=82)	Dupilumab Q2W (N=122)
Baseline		
Responders at Week 24		
Number	18	148
Mean (SD)	52.778 (16.398)	55.851 (17.875)
Non-responders at Week 24		
Number	150	104
Mean (SD)	57.193 (21.052)	46.894 (21.182)
Week 24		
Responders at Week 24		
Number	18	148
Mean (SD)	27.944 (21.759)	17.730 (13.590)
Change from baseline		

	ECM (N=82)	Dupilumab Q2W (N=122)
Number	18	148
Mean (SD)	-24.833 (10.918)	-38.122 (18.354)
LS mean (SE)	-27.125 (0.523)	-38.950 (0.238)
LS mean diff (95% CI)	NA	-11.825 (-12.880, -10.770)
p value vs. ECM	NA	<0.0001
Non-responders at Week 24		
Number	142	99
Mean (SD)	47.521 (22.956)	30.162 (20.652)
Change from baseline		
Number	142	99
Mean (SD)	-9.035 (19.257)	-16.949 (19.353)
LS mean (SE)	-6.601 (1.881)	-19.476 (2.174)
LS mean diff (95% CI)	NA	-12.875 (-17.573, -8.177)
p value vs. ECM	NA	<0.0001
Week 52		
Responders at Week 24 AND Week 52		
Number	0	39
Mean (SD)	NA	14.513 (14.205)
Change from baseline		
Number	0	39
Mean (SD)	NA	-38.846 (16.677)
LS mean (SE)	NE	-39.101 (2.432)
LS mean diff (95% CI)	NA	NE
p value vs. ECM	NA	NE
Non-responders at Week 24 OR Week 52		
Number	84	42
Mean (SD)	48.952 (21.998)	30.405 (21.727)
Change from baseline		
Number	84	42
Mean (SD)	-8.095 (16.416)	-19.048 (20.611)
LS mean (SE)	-6.651 (2.186)	-21.946 (3.000)
LS mean diff (95% CI)	NA	-15.295 (-22.154, -8.436)
p value vs. ECM	NA	<0.0001

CI = confidence interval; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NPS = nasal polyp score; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test

Source: Sanofi. Data on File, Post-hoc analyses.¹

NPS

Table 57. NPS and change from baseline in patients with comorbid asthma in SINUS-24 and SINUS-52 ITT population according to the response criteria of NPS (≥1-point improvement)

	ECM (N=170)	Dupilumab Q2W (N=258)
Baseline		
<i>All</i>		
Number	168	258
Mean (SD)	5.818 (1.319)	6.070 (1.220)
Responders at Week 24		
Number	23	170
Mean (SD)	6.022 (0.859)	6.165 (1.141)
Non-responders at Week 24		

	ECM (N=170)	Dupilumab Q2W (N=258)
Number	145	88
Mean (SD)	5.786 (1.378)	5.886 (1.349)
Week 24		
<i>All</i>		
Number	162	249
Mean (SD)	5.926 (1.341)	4.102 (1.999)
Change from baseline		
Number	162	249
Mean (SD)	0.127 (1.220)	-1.970 (1.777)
LS mean (SE)	0.143 (0.140)	-1.902 (0.124)
LS mean diff (95% CI)	NA	-2.045 (-2.350, -1.740)
p value vs. ECM	NA	<0.0001
<i>Responders at Week 24</i>		
Number	23	170
Mean (SD)	4.413 (1.459)	3.285 (1.716)
Change from baseline		
Number	23	170
Mean (SD)	-1.609 (1.097)	-2.879 (1.327)
LS mean (SE)	-1.567 (0.044)	-2.897 (0.021)
LS mean diff (95% CI)	NA	-1.330 (-1.420, -1.240)
p value vs. ECM	NA	<0.0001
<i>Non-responders at Week 24</i>		
Number	139	79
Mean (SD)	6.176 (1.147)	5.861 (1.315)
Change from baseline		
Number	139	79
Mean (SD)	0.414 (0.980)	-0.013 (0.734)
LS mean (SE)	0.490 (0.104)	-0.098 (0.126)
LS mean diff (95% CI)	NA	-0.589 (-0.861, -0.316)
p value vs. ECM	NA	<0.0001
Week 52		
<i>Responders at Week 24 AND Week 52</i>		
Number	1	46
Mean (SD)	4.500 (NC)	2.446 (1.651)
Change from baseline		
Number	1	46
Mean (SD)	-2.500 (NC)	-3.685 (1.423)
LS mean (SE)	-1.557 (1.463)	-3.294 (0.219)
LS mean diff (95% CI)	NA	-2.098 (-5.144, 0.948)
p value vs. ECM	NA	0.1598
<i>Non-responders at Week 24 OR Week 52</i>		
Number	83	34
Mean (SD)	6.108 (1.562)	5.368 (2.016)
Change from baseline		
Number	83	34
Mean (SD)	0.247 (1.255)	-0.750 (1.463)
LS mean (SE)	0.342 (0.173)	-0.871 (0.242)
LS mean diff (95% CI)	NA	-1.213 (-1.760, -0.667)
p value vs. ECM	NA	<0.0001

CI = confidence interval; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NPS = nasal polyp score; Q2W = once every two weeks; SD = standard deviation; SE = standard error
Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 58. NPS and change from baseline in patients with comorbid asthma in SINUS-24 and SINUS-52 ITT population according to the response criteria of SNOT-22 total score (≥8.9-point improvement)

	ECM (N=82)	Dupilumab Q2W (N=122)
Baseline		
<i>Responders at Week 24</i>		
Number	66	194
Mean (SD)	5.765 (1.216)	6.049 (1.219)
<i>Non-responders at Week 24</i>		
Number	102	64
Mean (SD)	5.853 (1.387)	6.133 (1.232)
Week 24		
<i>Responders at Week 24</i>		
Number	65	189
Mean (SD)	5.477 (1.509)	3.730 (1.881)
Change from baseline		
Number	65	189
Mean (SD)	-0.269 (1.332)	-2.317 (1.726)
LS mean (SE)	-0.291 (0.218)	-2.302 (0.149)
LS mean diff (95% CI)	NA	-2.011 (-2.458, -1.563)
p value vs. ECM	NA	<0.0001
<i>Non-responders at Week 24</i>		
Number	97	60
Mean (SD)	6.227 (1.127)	5.275 (1.917)
Change from baseline		
Number	97	60
Mean (SD)	0.392 (1.066)	-0.875 (1.475)
LS mean (SE)	0.458 (0.154)	-0.782 (0.187)
LS mean diff (95% CI)	NA	-1.240 (-1.624, -0.855)
p value vs. ECM	NA	<0.0001
Week 52		
<i>Responders at Week 24 AND Week 52</i>		
Number	14	54
Mean (SD)	5.536 (1.985)	3.009 (1.912)
Change from baseline		
Number	14	54
Mean (SD)	-0.393 (1.559)	-3.056 (1.860)
LS mean (SE)	-0.084 (0.469)	-2.811 (0.249)
LS mean diff (95% CI)	NA	-2.726 (-3.730, -1.723)
p value vs. ECM	NA	<0.0001
<i>Non-responders at Week 24 OR Week 52</i>		
Number	70	26
Mean (SD)	6.200 (1.456)	5.096 (2.478)
Change from baseline		
Number	70	26
Mean (SD)	0.336 (1.197)	-1.154 (1.826)
LS mean (SE)	0.314 (0.211)	-1.216 (0.325)
LS mean diff (95% CI)	NA	-1.530 (-2.211, -0.849)

	ECM (N=82)	Dupilumab Q2W (N=122)
p value vs. ECM	NA	<0.0001

CI = confidence interval; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NA = not applicable; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test

Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 59. NPS and change from baseline in patients with comorbid asthma in SINUS-24 and SINUS-52 ITT population according to the response criteria of SNOT-22 total score (≥8.9-point improvement) and NPS (≥1-point improvement)

	ECM (N=170)	Dupilumab Q2W (N=258)
Baseline		
<i>Responders at Week 24</i>		
Number	18	148
Mean (SD)	5.972 (0.899)	6.189 (1.152)
<i>Non-responders at Week 24</i>		
Number	150	110
Mean (SD)	5.800 (1.362)	5.909 (1.294)
Week 24		
<i>Responders at Week 24</i>		
Number	18	148
Mean (SD)	4.278 (1.574)	3.230 (1.720)
Change from baseline		
Number	18	148
Mean (SD)	-1.694 (1.226)	-2.959 (1.332)
LS mean (SE)	-1.655 (0.051)	-2.974 (0.023)
LS mean diff (95% CI)	NA	-1.319 (-1.422, -1.216)
p value vs. ECM	NA	<0.0001
<i>Non-responders at Week 24</i>		
Number	144	101
Mean (SD)	6.132 (1.160)	5.381 (1.668)
Change from baseline		
Number	144	101
Mean (SD)	0.354 (1.014)	-0.520 (1.284)
LS mean (SE)	0.455 (0.118)	-0.515 (0.135)
LS mean diff (95% CI)	NA	-0.970 (-1.261, -0.679)
p value vs. ECM	NA	<0.0001
Week 52		
<i>Responders at Week 24 AND Week 52</i>		
Number	0	39
Mean (SD)	NA	2.526 (1.732)
Change from baseline		
Number	0	39
Mean (SD)	NA	-3.731 (1.477)
LS mean (SE)	NE	-3.618 (0.279)
LS mean diff (95% CI)	NA	NE
p value vs. ECM	NA	NE
<i>Non-responders at Week 24 OR Week 52</i>		
Number	84	41
Mean (SD)	6.089 (1.562)	4.793 (2.275)
Change from baseline		
Number	84	41

	ECM (N=170)	Dupilumab Q2W (N=258)
Mean (SD)	0.214 (1.283)	-1.207 (1.732)
LS mean (SE)	0.286 (0.181)	-1.287 (0.239)
LS mean diff (95% CI)	NA	-1.573 (-2.121, -1.025)
p value vs. ECM	NA	<0.0001

CI = confidence interval; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NPS = nasal polyp score; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test

Source: Sanofi. Data on File, Post-hoc analyses.¹

Mapped SNOT-22 to EQ-5D-3L health state utilities (Crump Models 1-3)

Table 60. Mapped SNOT-22 to EQ-5D-3L health state utilities (Crump Models 1-3) in patients with comorbid asthma in SINUS-24 and SINUS-52 ITT pooled population according to the response criteria of NPS (≥1-point improvement)

	ECM (N=170)			Dupilumab Q2W (N=258)			All (N=428)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Baseline									
<i>All</i>									
Number	168	168	168	252	252	252	420	420	420
Mean (SD)	0.489 (0.140)	0.604 (0.190)	0.603 (0.190)	0.520 (0.134)	0.635 (0.174)	0.635 (0.177)	0.508 (0.137)	0.623 (0.181)	0.623 (0.183)
<i>Responders at Week 24</i>									
Number	23	23	23	166	166	166	189	189	189
Mean (SD)	0.533 (0.115)	0.663 (0.176)	0.661 (0.169)	0.513 (0.131)	0.628 (0.172)	0.630 (0.176)	0.516 (0.129)	0.632 (0.172)	0.634 (0.175)
<i>Non-responders at Week 24</i>									
Number	145	145	145	86	86	86	231	231	231
Mean (SD)	0.482 (0.143)	0.595 (0.192)	0.594 (0.192)	0.534 (0.140)	0.648 (0.179)	0.646 (0.181)	0.501 (0.144)	0.615 (0.188)	0.613 (0.189)
Week 24									
<i>All</i>									
Number	160	160	160	247	247	247	407	407	407
Mean (SD)	0.583 (0.156)	0.670 (0.181)	0.669 (0.181)	0.722 (0.119)	0.748 (0.125)	0.749 (0.130)	0.668 (0.151)	0.717 (0.154)	0.718 (0.157)
Change from baseline									
Number	160	160	160	247	247	247	407	407	407
Mean (SD)	0.090 (0.128)	0.058 (0.160)	0.059 (0.160)	0.204 (0.144)	0.115 (0.158)	0.116 (0.158)	0.159 (0.149)	0.093 (0.161)	0.093 (0.161)
LS mean (SE)	0.076 (0.011)	0.048 (0.012)	0.047 (0.012)	0.208 (0.010)	0.117 (0.010)	0.116 (0.010)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.131 (0.108, 0.155)	0.069 (0.044, 0.094)	0.069 (0.044, 0.095)	NA	NA	NA
p value vs. ECM	NA	NA	NA	<0.0001	<0.0001	<0.0001	NA	NA	NA
<i>Responders at Week 24</i>									
Number	23	23	23	164	164	164	187	187	187
Mean (SD)	0.664 (0.146)	0.737 (0.161)	0.736 (0.158)	0.748 (0.095)	0.762 (0.107)	0.764 (0.113)	0.738 (0.106)	0.759 (0.115)	0.761 (0.119)
Change from baseline									
Number	23	23	23	164	164	164	187	187	187
Mean (SD)	0.131 (0.100)	0.075 (0.117)	0.076 (0.115)	0.236 (0.139)	0.134 (0.161)	0.135 (0.161)	0.223 (0.139)	0.127 (0.158)	0.128 (0.157)

	ECM (N=170)			Dupilumab Q2W (N=258)			All (N=428)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
LS mean (SE)	0.148 (0.021)	0.095 (0.022)	0.091 (0.023)	0.243 (0.010)	0.137 (0.011)	0.137 (0.011)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.095 (0.052, 0.138)	0.042 (-0.003, 0.088)	0.046 (-0.001, 0.092)	NA	NA	NA
p value vs. ECM	NA	NA	NA	<0.0001	0.0688	0.0557	NA	NA	NA
Non-responders at Week 24									
Number	137	137	137	83	83	83	220	220	220
Mean (SD)	0.569 (0.155)	0.658 (0.182)	0.658 (0.183)	0.672 (0.145)	0.721 (0.151)	0.719 (0.155)	0.608 (0.159)	0.682 (0.174)	0.681 (0.175)
Change from baseline									
Number	137	137	137	83	83	83	220	220	220
Mean (SD)	0.083 (0.131)	0.055 (0.167)	0.056 (0.166)	0.140 (0.134)	0.076 (0.144)	0.078 (0.145)	0.105 (0.135)	0.063 (0.158)	0.064 (0.158)
LS mean (SE)	0.064 (0.013)	0.041 (0.015)	0.042 (0.015)	0.143 (0.016)	0.080 (0.018)	0.081 (0.018)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.079 (0.046, 0.113)	0.039 (0.002, 0.077)	0.039 (0.001, 0.076)	NA	NA	NA
p value vs. ECM	NA	NA	NA	<0.0001	0.0415	0.0446	NA	NA	NA
Week 52									
Responders at Week 24 AND Week 52									
Number	1	1	1	45	45	45	104	104	104
Mean (SD)	0.698 (NC)	0.829 (NC)	0.817 (NC)	0.768 (0.100)	0.772 (0.122)	0.775 (0.124)	0.760 (0.093)	0.763 (0.116)	0.766 (0.120)
Change from baseline									
Number	1	1	1	45	45	45	104	104	104
Mean (SD)	0.054 (NC)	-0.077 (NC)	-0.073 (NC)	0.233 (0.136)	0.113 (0.176)	0.113 (0.175)	0.237 (0.137)	0.113 (0.172)	0.114 (0.171)
LS mean (SE)	0.165 (0.097)	0.123 (0.115)	0.113 (0.118)	0.242 (0.016)	0.112 (0.019)	0.109 (0.020)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.077 (-0.124, 0.278)	-0.012 (NE, NE)	-0.004 (-0.248, 0.240)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.4328	0.9203	0.9731	NA	NA	NA
Non-responders at Week 24 AND Week 52									
Number	67	67	67	22	22	22	107	107	107
Mean (SD)	0.575 (0.140)	0.682 (0.178)	0.682 (0.181)	0.643 (0.156)	0.686 (0.163)	0.673 (0.163)	0.602 (0.151)	0.684 (0.172)	0.682 (0.173)
Change from baseline									
Number	67	67	67	22	22	22	107	107	107
Mean (SD)	0.104 (0.123)	0.095 (0.152)	0.095 (0.153)	0.147 (0.119)	0.077 (0.163)	0.078 (0.165)	0.121 (0.134)	0.090 (0.160)	0.090 (0.161)

	ECM (N=170)			Dupilumab Q2W (N=258)			All (N=428)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
LS mean (SE)	0.093 (0.017)	0.092 (0.019)	0.093 (0.019)	0.150 (0.028)	0.084 (0.031)	0.079 (0.031)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.057 (-0.001, 0.116)	-0.009 (-0.074, 0.056)	-0.013 (-0.079, 0.052)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.0530	0.7931	0.6888	NA	NA	NA
<i>Non-responders at Week 24 OR Week 52</i>									
Number	83	83	83	36	36	36	150	150	150
Mean (SD)	0.596 (0.150)	0.696 (0.178)	0.697 (0.179)	0.684 (0.149)	0.709 (0.150)	0.703 (0.153)	0.636 (0.156)	0.706 (0.165)	0.704 (0.166)
<i>Change from baseline</i>									
Number	83	83	83	36	36	36	150	150	150
Mean (SD)	0.111 (0.129)	0.094 (0.161)	0.095 (0.160)	0.170 (0.133)	0.081 (0.175)	0.083 (0.176)	0.142 (0.146)	0.097 (0.169)	0.098 (0.169)
LS mean (SE)	0.097 (0.015)	0.087 (0.017)	0.088 (0.017)	0.179 (0.022)	0.093 (0.024)	0.091 (0.024)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.083 (0.033, 0.132)	0.006 (-0.048, 0.059)	0.003 (-0.051, 0.057)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.0010	0.8383	0.9105	NA	NA	NA

CI = confidence interval; EQ-5D-3L = EuroQol 5-Dimension 3-Level; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NA = not applicable; NP = nasal polyp; NPS = nasal polyp score; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every two weeks; SD = standard deviation; SE = standard error
Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 61. Mapped SNOT-22 to EQ-5D-3L health state utilities (Crump Models 1-3) in patients with comorbid asthma in SINUS-24 and SINUS-52 ITT pooled population according to the response criteria of SNOT-22 total score (≥8.9-point improvement)

	ECM (N=170)			Dupilumab Q2W (N=258)			All (N=428)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Baseline									
<i>Responders at Week 24</i>									
Number	68	68	68	194	194	194	262	262	262
Mean (SD)	0.492 (0.133)	0.606 (0.188)	0.603 (0.186)	0.500 (0.127)	0.618 (0.174)	0.619 (0.176)	0.498 (0.128)	0.615 (0.177)	0.615 (0.179)
<i>Non-responders at Week 24</i>									

	ECM (N=170)			Dupilumab Q2W (N=258)			All (N=428)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Number	100	100	100	58	58	58	158	158	158
Mean (SD)	0.487 (0.145)	0.603 (0.193)	0.604 (0.194)	0.587 (0.139)	0.692 (0.164)	0.691 (0.171)	0.524 (0.150)	0.636 (0.188)	0.636 (0.190)
Week 24									
<i>Responders at Week 24</i>									
Number	68	68	68	194	194	194	262	262	262
Mean (SD)	0.666 (0.123)	0.742 (0.136)	0.739 (0.136)	0.750 (0.095)	0.765 (0.107)	0.767 (0.111)	0.728 (0.109)	0.759 (0.115)	0.759 (0.118)
Change from baseline									
Number	68	68	68	194	194	194	262	262	262
Mean (SD)	0.175 (0.099)	0.136 (0.141)	0.136 (0.141)	0.250 (0.122)	0.147 (0.154)	0.148 (0.154)	0.230 (0.121)	0.144 (0.151)	0.145 (0.151)
LS mean (SE)	0.169 (0.002)	0.128 (0.002)	0.125 (0.002)	0.254 (0.001)	0.151 (0.001)	0.151 (0.001)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.085 (0.081, 0.089)	0.023 (0.019, 0.027)	0.026 (0.022, 0.030)	NA	NA	NA
p value vs. ECM	NA	NA	NA	<0.0001	<0.0001	<.0001	NA	NA	NA
<i>Non-responders at Week 24</i>									
Number	92	92	92	53	53	53	145	145	145
Mean (SD)	0.521 (0.150)	0.616 (0.193)	0.618 (0.193)	0.621 (0.142)	0.688 (0.163)	0.685 (0.170)	0.558 (0.154)	0.642 (0.185)	0.643 (0.187)
Change from baseline									
Number	92	92	92	53	53	53	145	145	145
Mean (SD)	0.027 (0.109)	0.001 (0.150)	0.001 (0.148)	0.034 (0.080)	-0.002 (0.108)	-0.001 (0.108)	0.030 (0.099)	-0.000 (0.136)	0.000 (0.135)
LS mean (SE)	0.015 (0.014)	-0.009 (0.017)	-0.009 (0.017)	0.047 (0.018)	0.003 (0.022)	0.001 (0.022)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.032 (-0.005, 0.069)	0.012 (-0.033, 0.057)	0.010 (-0.035, 0.055)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.0898	0.6015	0.6608	NA	NA	NA
Week 52									
<i>Responders at Week 24 AND Week 52</i>									
Number	15	15	15	57	57	57	140	140	140
Mean (SD)	0.620 (0.154)	0.689 (0.190)	0.683 (0.192)	0.767 (0.101)	0.772 (0.112)	0.772 (0.116)	0.748 (0.109)	0.759 (0.120)	0.760 (0.125)
Change from baseline									
Number	15	15	15	57	57	57	140	140	140

	ECM (N=170)			Dupilumab Q2W (N=258)			All (N=428)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Mean (SD)	0.194 (0.081)	0.172 (0.111)	0.173 (0.110)	0.256 (0.111)	0.139 (0.166)	0.139 (0.167)	0.261 (0.120)	0.153 (0.162)	0.153 (0.163)
LS mean (SE)	0.152 (0.024)	0.110 (0.028)	0.108 (0.029)	0.260 (0.013)	0.150 (0.015)	0.149 (0.016)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.108 (0.051, 0.166)	0.040 (-0.027, 0.108)	0.040 (-0.029, 0.110)	NA	NA	NA
p value vs. ECM	NA	NA	NA	<0.0001	0.2001	0.2085	NA	NA	NA
<i>Non-responders at Week 24 AND Week 52</i>									
Number	47	47	47	17	17	17	78	78	78
Mean (SD)	0.557 (0.149)	0.670 (0.189)	0.672 (0.189)	0.594 (0.148)	0.636 (0.181)	0.634 (0.184)	0.573 (0.152)	0.659 (0.182)	0.659 (0.182)
Change from baseline									
Number	47	47	47	17	17	17	78	78	78
Mean (SD)	0.055 (0.120)	0.040 (0.154)	0.040 (0.152)	0.054 (0.118)	-0.016 (0.170)	-0.014 (0.168)	0.048 (0.109)	0.018 (0.147)	0.019 (0.145)
LS mean (SE)	0.047 (0.017)	0.041 (0.022)	0.041 (0.021)	0.064 (0.029)	-0.007 (0.036)	-0.007 (0.036)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.017 (-0.045, 0.080)	-0.048 (-0.125, 0.028)	-0.048 (-0.124, 0.027)	NA	NA	NA
p value vs. ECM	NA	NA	NA		0.2158	0.2101	NA	NA	NA
<i>Non-responders at Week 24 OR Week 52</i>									
Number	69	69	69	24	24	24	114	114	114
Mean (SD)	0.593 (0.149)	0.700 (0.176)	0.701 (0.177)	0.644 (0.152)	0.678 (0.170)	0.676 (0.174)	0.611 (0.152)	0.692 (0.173)	0.692 (0.174)
Change from baseline									
Number	69	69	69	24	24	24	114	114	114
Mean (SD)	0.093 (0.130)	0.075 (0.166)	0.075 (0.165)	0.084 (0.120)	0.004 (0.160)	0.005 (0.159)	0.083 (0.122)	0.043 (0.160)	0.044 (0.159)
LS mean (SE)	0.073 (0.016)	0.061 (0.019)	0.062 (0.019)	0.093 (0.027)	0.013 (0.031)	0.014 (0.031)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.019 (-0.037, 0.076)	-0.048 (-0.114, 0.017)	-0.048 (-0.114, 0.017)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.4986	0.1503	0.1484	NA	NA	NA

CI = confidence interval; EQ-5D-3L = EuroQol 5-Dimension 3-Level; ITT = intention-to-treat; LS = least squares; NA = not applicable; NP = nasal polyp; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test
Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 62. Mapped SNOT-22 to EQ-5D-3L health state utilities (Crump Models 1-3) in patients with comorbid asthma in SINUS-24 and SINUS-52 ITT pooled population according to the response criteria of SNOT-22 total score (≥ 8.9 -point improvement) and NPS (≥ 1 -point improvement)

	ECM (N=82)			Dupilumab Q2W (N=102)			All (N=204)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Baseline									
<i>Responders at Week 24</i>									
Number	18	18	18	148	148	148	166	166	166
Mean (SD)	0.516 (0.112)	0.640 (0.184)	0.638 (0.175)	0.495 (0.122)	0.612 (0.167)	0.614 (0.170)	0.497 (0.120)	0.615 (0.168)	0.616 (0.171)
<i>Non-responders at Week 24</i>									
Number	150	150	150	104	104	104	254	254	254
Mean (SD)	0.486 (0.143)	0.600 (0.191)	0.599 (0.192)	0.556 (0.144)	0.668 (0.180)	0.667 (0.183)	0.515 (0.147)	0.628 (0.189)	0.627 (0.191)
Week 24									
<i>Responders at Week 24</i>									
Number	18	18	18	148	148	148	166	166	166
Mean (SD)	0.685 (0.148)	0.740 (0.161)	0.740 (0.153)	0.754 (0.092)	0.767 (0.102)	0.769 (0.107)	0.747 (0.102)	0.764 (0.109)	0.765 (0.113)
<i>Change from baseline</i>									
Number	18	18	18	148	148	148	166	166	166
Mean (SD)	0.169 (0.074)	0.101 (0.105)	0.102 (0.101)	0.259 (0.125)	0.155 (0.154)	0.155 (0.154)	0.249 (0.123)	0.149 (0.150)	0.149 (0.150)
LS mean (SE)	0.184 (0.004)	0.115 (0.004)	0.112 (0.004)	0.265 (0.002)	0.158 (0.002)	0.158 (0.002)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.080 (0.073, 0.088)	0.043 (0.035, 0.050)	0.045 (0.038, 0.053)	NA	NA	NA
p value vs. ECM	NA	NA	NA	<0.0001	<0.0001	<0.0001	NA	NA	NA
<i>Non-responders at Week 24</i>									
Number	142	142	142	99	99	99	241	241	241
Mean (SD)	0.570 (0.153)	0.661 (0.182)	0.661 (0.183)	0.675 (0.138)	0.721 (0.150)	0.720 (0.154)	0.613 (0.156)	0.685 (0.172)	0.685 (0.174)
<i>Change from baseline</i>									
Number	142	142	142	99	99	99	241	241	241
Mean (SD)	0.080 (0.130)	0.053 (0.166)	0.053 (0.165)	0.120 (0.131)	0.056 (0.145)	0.057 (0.146)	0.096 (0.132)	0.054 (0.157)	0.055 (0.157)
LS mean (SE)	0.059 (0.013)	0.036 (0.014)	0.036 (0.014)	0.133 (0.015)	0.065 (0.016)	0.065 (0.016)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.074 (0.042, 0.105)	0.029 (-0.006, 0.064)	0.029 (-0.006, 0.064)	NA	NA	NA
p value vs. ECM	NA	NA	NA	<0.0001	0.1062	0.1071	NA	NA	NA

	ECM (N=82)			Dupilumab Q2W (N=102)			All (N=204)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Week 52									
<i>Responders at Week 24 AND Week 52</i>									
Number	0	0	0	39	39	39	91	91	91
Mean (SD)	NA	NA	NA	0.776 (0.097)	0.778 (0.116)	0.780 (0.120)	0.769 (0.090)	0.771 (0.110)	0.774 (0.116)
Change from baseline									
Number	0	0	0	39	39	39	91	91	91
Mean (SD)	NA	NA	NA	0.264 (0.113)	0.143 (0.162)	0.142 (0.163)	0.267 (0.116)	0.141 (0.161)	0.141 (0.161)
LS mean (SE)	NE	NE	NE	0.266 (0.017)	0.143 (0.020)	0.140 (0.020)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	NE	NE	NE	NA	NA	NA
p value vs. ECM	NA	NA	NA	NE	NE	NE	NA	NA	NA
<i>Non-responders at Week 24 AND Week 52</i>									
Number	73	73	73	26	26	26	123	123	123
Mean (SD)	0.577 (0.141)	0.682 (0.179)	0.682 (0.182)	0.643 (0.147)	0.671 (0.163)	0.663 (0.161)	0.606 (0.149)	0.679 (0.171)	0.678 (0.172)
Change from baseline									
Number	73	73	73	26	26	26	123	123	123
Mean (SD)	0.093 (0.127)	0.077 (0.161)	0.078 (0.161)	0.116 (0.132)	0.033 (0.184)	0.035 (0.185)	0.102 (0.136)	0.064 (0.169)	0.065 (0.169)
LS mean (SE)	0.082 (0.016)	0.075 (0.018)	0.076 (0.018)	0.131 (0.025)	0.050 (0.029)	0.047 (0.029)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.049 (-0.006, 0.104)	-0.025 (-0.088, 0.038)	-0.028 (-0.091, 0.035)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.0784	0.4344	0.3760	NA	NA	NA
<i>Non-responders at Week 24 OR Week 52</i>									
Number	84	84	84	42	42	42	163	163	163
Mean (SD)	0.598 (0.149)	0.698 (0.177)	0.698 (0.179)	0.688 (0.144)	0.712 (0.150)	0.709 (0.153)	0.641 (0.152)	0.706 (0.163)	0.705 (0.164)
Change from baseline									
Number	84	84	84	42	42	42	163	163	163
Mean (SD)	0.111 (0.129)	0.092 (0.161)	0.093 (0.160)	0.150 (0.137)	0.058 (0.179)	0.060 (0.179)	0.133 (0.145)	0.083 (0.172)	0.084 (0.171)
LS mean (SE)	0.092 (0.015)	0.080 (0.016)	0.081 (0.016)	0.165 (0.020)	0.074 (0.022)	0.074 (0.022)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.073 (0.026, 0.120)	-0.005 (-0.056, 0.046)	-0.006 (-0.058, 0.045)	NA	NA	NA

	ECM (N=82)			Dupilumab Q2W (N=102)			All (N=204)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
p value vs. ECM	NA	NA	NA	0.0022	0.8453	0.8101	NA	NA	NA

CI = confidence interval; EQ-5D-3L = EuroQol 5-Dimension 3-Level; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NPS = nasal polyp score; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test

Source: Sanofi. Data on File, Post-hoc analyses.¹

EQ-5D-5L utilities (Hernandez 2020 crosswalk method, UK tariffs)

Table 63. EQ-5D-5L utilities (Hernandez 2020 crosswalk method, UK tariffs) in patients with comorbid asthma in SINUS-24 and SINUS-52 ITT pooled population according to the response criteria of NPS (≥1-point improvement)

	ECM (N=170)	Dupilumab Q2W (N=258)
Baseline		
<i>All</i>		
Number	166	248
Mean (SD)	0.754 (0.193)	0.769 (0.192)
<i>Responders at Week 24</i>		
Number	23	164
Mean (SD)	0.809 (0.142)	0.779 (0.174)
<i>Non-responders at Week 24</i>		
Number	143	84
Mean (SD)	0.746 (0.199)	0.751 (0.224)
Week 24		
<i>All</i>		
Number	159	243
Mean (SD)	0.787 (0.194)	0.853 (0.166)
Change from baseline		
Number	159	243
Mean (SD)	0.033 (0.130)	0.085 (0.157)
LS mean (SE)	0.031 (0.012)	0.092 (0.010)
LS mean diff (95% CI)	NA	0.061 (0.035, 0.087)
p value vs. ECM	NA	<0.0001
<i>Responders at Week 24</i>		
Number	23	161
Mean (SD)	0.884 (0.109)	0.878 (0.131)
Change from baseline		
Number	23	161
Mean (SD)	0.075 (0.129)	0.099 (0.161)
LS mean (SE)	0.095 (0.025)	0.111 (0.012)
LS mean diff (95% CI)	NA	0.016 (−0.035, 0.067)
p value vs. ECM	NA	0.5415
<i>Non-responders at Week 24</i>		
Number	136	82
Mean (SD)	0.771 (0.201)	0.806 (0.213)
Change from baseline		
Number	136	82
Mean (SD)	0.026 (0.129)	0.058 (0.146)
LS mean (SE)	0.026 (0.014)	0.059 (0.017)
LS mean diff (95% CI)	NA	0.033 (−0.003, 0.068)
p value vs. ECM	NA	0.0717
Week 52		
<i>Responders at Week 24 AND Week 52</i>		
Number	1	44
Mean (SD)	0.790 (NC)	0.894 (0.149)
Change from baseline		
Number	1	44
Mean (SD)	0.052 (NC)	0.101 (0.206)

	ECM (N=170)	Dupilumab Q2W (N=258)
LS mean (SE)	0.067 (0.155)	0.100 (0.026)
LS mean diff (95% CI)	NA	0.033 (-0.274, 0.340)
p value vs. ECM	NA	0.8323
Non-responders at Week 24 AND Week 52		
Number	67	21
Mean (SD)	0.749 (0.219)	0.732 (0.274)
Change from baseline		
Number	67	21
Mean (SD)	0.027 (0.155)	0.053 (0.116)
LS mean (SE)	0.022 (0.021)	0.048 (0.036)
LS mean diff (95% CI)	NA	0.027 (-0.047, 0.100)
p value vs. ECM	NA	0.4749
Non-responders at Week 24 OR Week 52		
Number	83	35
Mean (SD)	0.775 (0.209)	0.807 (0.245)
Change from baseline		
Number	83	35
Mean (SD)	0.038 (0.155)	0.069 (0.123)
LS mean (SE)	0.034 (0.018)	0.071 (0.027)
LS mean diff (95% CI)	NA	0.037 (-0.022, 0.096)
p value vs. ECM	NA	0.2167

CI = confidence interval; EQ-5D-5L = EuroQol 5-Dimension 5-Level; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NPS = nasal polyp score; Q2W = once every two weeks; SD = standard deviation; SE = standard error

Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 64. EQ-5D-5L utilities (Hernandez 2020 crosswalk method, UK tariffs) in patients with comorbid asthma in SINUS-24 and SINUS-52 ITT pooled population according to the response criteria of SNOT-22 total score (≥ 8.9 -point improvement)

	ECM (N=170)	Dupilumab Q2W (N=258)
Baseline		
Responders at Week 24		
Number	68	193
Mean (SD)	0.793 (0.152)	0.767 (0.180)
Non-responders at Week 24		
Number	98	55
Mean (SD)	0.727 (0.214)	0.774 (0.233)
Week 24		
Responders at Week 24		
Number	68	192
Mean (SD)	0.870 (0.119)	0.878 (0.133)
Change from baseline		
Number	68	192
Mean (SD)	0.076 (0.134)	0.109 (0.159)
LS mean (SE)	0.088 (0.015)	0.112 (0.011)
LS mean diff (95% CI)	NA	0.024 (-0.007, 0.055)
p value vs. ECM	NA	0.1356
Non-responders at Week 24		
Number	91	51
Mean (SD)	0.725 (0.216)	0.763 (0.236)
Change from baseline		

	ECM (N=170)	Dupilumab Q2W (N=258)
Number	91	51
Mean (SD)	0.001 (0.117)	-0.006 (0.106)
LS mean (SE)	0.010 (0.015)	0.009 (0.019)
LS mean diff (95% CI)	NA	-0.001 (-0.041, 0.039)
p value vs. ECM	NA	0.9697
Week 52		
<i>Responders at Week 24 AND Week 52</i>		
Number	15	55
Mean (SD)	0.823 (0.202)	0.896 (0.148)
Change from baseline		
Number	15	55
Mean (SD)	0.032 (0.119)	0.112 (0.188)
LS mean (SE)	0.043 (0.034)	0.113 (0.019)
LS mean diff (95% CI)	NA	0.070 (-0.004, 0.144)
p value vs. ECM	NA	0.0626
<i>Non-responders at Week 24 AND Week 52</i>		
Number	47	17
Mean (SD)	0.725 (0.222)	0.692 (0.290)
Change from baseline		
Number	47	17
Mean (SD)	0.004 (0.141)	0.017 (0.118)
LS mean (SE)	0.006 (0.021)	0.024 (0.036)
LS mean diff (95% CI)	NA	0.019 (-0.057, 0.094)
p value vs. ECM	NA	0.6283
<i>Non-responders at Week 24 OR Week 52</i>		
Number	69	24
Mean (SD)	0.765 (0.209)	0.763 (0.269)
Change from baseline		
Number	69	24
Mean (SD)	0.040 (0.161)	0.030 (0.121)
LS mean (SE)	0.029 (0.022)	0.026 (0.036)
LS mean diff (95% CI)	NA	-0.003 (-0.078, 0.073)
p value vs. ECM	NA	0.9454

CI = confidence interval; EQ-5D-5L = EuroQol 5-Dimension 5-Level; ITT = intention-to-treat; LS = least squares; NA = not applicable; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test

Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 65. EQ-5D-5L utilities (Hernandez 2020 crosswalk method, UK tariffs) in patients with comorbid asthma in SINUS-24 and SINUS-52 ITT pooled population according to the response criteria of SNOT-22 total score (≥8.9-point improvement) and NPS (≥1-point improvement)

	ECM (N=82)	Dupilumab Q2W (N=122)
Baseline		
<i>Responders at Week 24</i>		
Number	18	147
Mean (SD)	0.796 (0.150)	0.769 (0.176)
<i>Non-responders at Week 24</i>		
Number	148	101
Mean (SD)	0.749 (0.198)	0.768 (0.215)
Week 24		
<i>Responders at Week 24</i>		

	ECM (N=82)	Dupilumab Q2W (N=122)
Number	18	146
Mean (SD)	0.876 (0.117)	0.879 (0.131)
Change from baseline		
Number	18	146
Mean (SD)	0.081 (0.140)	0.109 (0.161)
LS mean (SE)	0.098 (0.029)	0.120 (0.013)
LS mean diff (95% CI)	NA	0.023 (-0.035, 0.081)
p value vs. ECM	NA	0.4447
<i>Non-responders at Week 24</i>		
Number	141	97
Mean (SD)	0.776 (0.199)	0.815 (0.203)
Change from baseline		
Number	141	97
Mean (SD)	0.027 (0.128)	0.050 (0.144)
LS mean (SE)	0.028 (0.013)	0.056 (0.015)
LS mean diff (95% CI)	NA	0.028 (-0.005, 0.061)
p value vs. ECM	NA	0.0940
Week 52		
<i>Responders at Week 24 AND Week 52</i>		
Number	0	38
Mean (SD)	NA	0.899 (0.151)
Change from baseline		
Number	0	38
Mean (SD)	NA	0.119 (0.213)
LS mean (SE)	NE	0.116 (0.024)
LS mean diff (95% CI)	NA	NE
p value vs. ECM	NA	NE
<i>Non-responders at Week 24 AND Week 52</i>		
Number	73	25
Mean (SD)	0.755 (0.213)	0.745 (0.258)
Change from baseline		
Number	73	25
Mean (SD)	0.022 (0.152)	0.039 (0.114)
LS mean (SE)	0.021 (0.019)	0.044 (0.032)
LS mean diff (95% CI)	NA	0.022 (-0.045, 0.089)
p value vs. ECM	NA	0.5156
<i>Non-responders at Week 24 OR Week 52</i>		
Number	84	41
Mean (SD)	0.775 (0.208)	0.815 (0.233)
Change from baseline		
Number	84	41
Mean (SD)	0.038 (0.154)	0.057 (0.121)
LS mean (SE)	0.030 (0.019)	0.056 (0.026)
LS mean diff (95% CI)	NA	0.026 (-0.033, 0.086)
p value vs. ECM	NA	0.3861

CI = confidence interval; EQ-5D-5L = EuroQol 5-Dimension 5-Level; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NPS = nasal polyp score; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test
Source: Sanofi. Data on File, Post-hoc analyses.¹

Patients with ≥ 1 prior NP surgery

Baseline characteristics

Table 66. Baseline characteristics of patients with ≥ 1 prior NP surgery in SINUS-24 and SINUS-52 pooled ITT population

	ECM	Dupilumab Q2W	All
N	187	187	459
Male, n (%)	103 (55.1)	115 (61.5)	268 (58.4)
Age, mean (SD)	50.97 (13.16)	50.94 (12.36)	51.38 (12.61)
Race, n (%)			
Caucasian/White	170 (90.9)	170 (90.9)	409 (89.1)
Black/African decent	4 (2.1)	1 (0.5)	7 (1.5)
Asian/Oriental	12 (6.4)	12 (6.4)	37 (8.1)
American Indian/Alaska Native	1 (0.5)	4 (2.1)	5 (1.1)
Native Hawaiian/Other Pacific Islander	0	0	0
Multiple	0	0	1 (0.2)
Unknown	0	0	0
Ethnicity			
Hispanic or Latino	14 (7.6)	23 (12.3)	47 (10.3)
Not Hispanic or Latino	171 (92.4)	164 (87.7)	409 (89.7)
Territory			
North America	27 (14.4)	31 (16.6)	8 (17.4)
European Union	82 (43.9)	83 (44.4)	182 (39.7)
Rest of the World	78 (41.7)	73 (39.0)	197 (42.9)
BMI (kg/m ²), mean (SD)	27.70 (5.46)	27.46 (4.95)	27.60 (5.30)
Time since first diagnosis of nasal polyps (years), mean (SD)	13.75 (9.16)	14.61 (10.13)	14.20 (9.62)
≥ 3 previous surgeries for nasal polyps, n (%)	47 (25.1)	55 (29.4)	111 (24.2)
Time since most recent surgery for nasal polyps (years), mean (SD)	7.06 (6.33)	6.69 (6.33)	7.16 (6.44)
SCS use in the past 2 years, n (%)	118 (63.1)	113 (60.4)	292 (63.6)
Bilateral endoscopic NPS* (scale 0-8), mean (SD)	5.74 (1.27)	5.80 (1.27)	5.86 (1.26)
NC score* (scale 0-3), mean (SD)	2.47 (0.53)	2.37 (0.60)	2.44 (0.56)
SNOT-22 total score* (scale 0-110), mean (SD)	53.47 (19.92)	49.09 (20.00)	51.63 (20.19)
Smell test (UPSIT) score** (scale 0-40), mean (SD)	13.01 (7.46)	13.09 (8.20)	12.80 (7.52)
LoS score* (scale 0-3), mean (SD)	2.77 (0.48)	2.78 (0.54)	2.79 (0.52)
LMK-CT total score* (scale 0-24), mean (SD)	19.16 (4.10)	19.14 (4.01)	19.07 (3.97)
Rhinosinusitis disease severity* (VAS 0-10cm), mean (SD)	8.10 (2.00)	7.87 (1.93)	8.00 (2.00)
Baseline NPIF** (L/min), mean (SD)	87.68 (55.43)	89.01 (54.11)	89.32 (57.37)
Baseline blood eosinophils (x10 ⁹ cells/L), mean (SD)	0.46 (0.32)	0.49 (0.41)	0.47 (0.36)
Any comorbid type 2 medical history including asthma and NSAID-ERD, n (%)	154 (82.4)	154 (82.4)	386 (84.1)
Comorbid asthma, n (%)	121 (64.7)	121 (64.7)	304 (66.2)
Comorbid NSAID-ERD, n (%)	65 (34.8)	63 (33.7)	159 (34.6)

	ECM	Dupilumab Q2W	All
Any comorbid type 2 medical history excluding asthma and NSAID-ERD, n (%)	117 (62.6)	115 (61.5)	294 (64.1)
Age of asthma onset in patients with comorbid asthma (years), mean (SD)	32.91 (14.88)	34.55 (14.50)	33.98 (15.28)
Baseline ACQ-6 score* in patients with comorbid asthma, mean (SD)	1.59 (1.06)	1.46 (1.07)	1.53 (1.09)
Baseline GINA 4 or 5 in patients with comorbid asthma, n (%)	57 (30.5)	64 (23.5)	121 (26.4)

ACQ-6 = 6-item Asthma Control Questionnaire; BMI = body mass index; ERD = exacerbated respiratory disease; GINA = Global Initiative for Asthma; ITT = intention-to-treat; LMK-CT = Lund-Mackay computed tomography; LoS = loss-of-smell; NC = nasal congestion/obstruction; NP = nasal polyp; NPIF = peak nasal inspiratory flow; NPS = nasal polyp score; NSAID = non-steroidal anti-inflammatory drug; Q2W = every 2 weeks; SD = standard deviation; SNOT-22 = 22-item Sino-Nasal Outcome Test; UPSIT = University of Pennsylvania Smell Identification Test; VAS = visual analogue scale

*Higher scores indicate greater disease severity.

** Higher scores indicate lower disease severity.

Source: Sanofi. Data on File, Post-hoc analyses.¹

Response rates

Table 67. Response rates for patients with ≥1 prior NP surgery in SINUS-24 and SINUS-52 pooled ITT population according to the different response criteria

	ECM (N=187)	Dupilumab Q2W (N=272)
Overall response at Week 24		
NPS (≥1-point improvement)		
Responders, n (%)	25 (13.4)	173 (63.6)
Non-responders, n (%)	162 (86.6)	99 (36.4)
SNOT-22 total score (≥8.9-point improvement)		
Responders, n (%)	82 (43.9)	205 (75.4)
Non-responders, n (%)	105 (56.1)	67 (24.6)
SNOT-22 total score (≥8.9-point improvement) and NPS (≥1-point improvement)		
Responders, n (%)	20 (10.7)	154 (56.6)
Non-responders, n (%)	167 (89.3)	118 (43.4)
Overall response at Week 52		
All		
NPS (≥1-point improvement)		
Responders, n (%)	11 (12.5)	66 (75.0)
Non-responders, n (%)	77 (87.5)	22 (25.0)
SNOT-22 total score (≥8.9-point improvement)		
Responders, n (%)	23 (26.1)	68 (77.3)
Non-responders, n (%)	65 (73.9)	20 (22.7)
SNOT-22 total score (≥8.9-point improvement) and NPS (≥1-point improvement)		
Responders, n (%)	5 (5.7)	59 (67.0)
Non-responders, n (%)	83 (94.3)	29 (33.0)
Responders at Week 24		
NPS (≥1-point improvement)		
Responders, n (%)	3 (42.9)	53 (98.1)
Non-responders, n (%)	4 (57.1)	1 (1.9)
SNOT-22 total score (≥8.9-point improvement)		
Responders, n (%)	19 (54.3)	58 (96.7)
Non-responders, n (%)	16 (45.7)	2 (3.3)

	ECM (N=187)	Dupilumab Q2W (N=272)
SNOT-22 total score (≥8.9-point improvement) and NPS (≥1-point improvement)	ECM (N=5)	Dupilumab Q2W (N=46)
Responders, n (%)	2 (40.0)	44 (95.7)
Non-responders, n (%)	3 (60.0)	2 (4.3)
Non-responders at Week 24		
NPS (≥1-point improvement)	ECM (N=81)	Dupilumab Q2W (N=34)
Responders, n (%)	8 (9.9)	13 (38.2)
Non-responders, n (%)	73 (90.1)	21 (61.8)
SNOT-22 total score (≥8.9-point improvement)	ECM (N=53)	Dupilumab Q2W (N=28)
Responders, n (%)	4 (7.5)	10 (35.7)
Non-responders, n (%)	49 (92.5)	18 (64.3)
SNOT-22 total score (≥8.9-point improvement) and NPS (≥1-point improvement)	ECM (N=83)	Dupilumab Q2W (N=42)
Responders, n (%)	3 (3.6)	15 (35.7)
Non-responders, n (%)	80 (96.4)	27 (64.3)

ITT = intention-to-treat; NP = nasal polyp; NPS = nasal polyp score; Q2W = once every two weeks; SNOT-22: 22-item Sino Nasal Outcome Test

Source: Sanofi. Data on File, Post-hoc analyses.¹

SNOT-22 total score

Table 68. SNOT-22 total score and change from baseline in patients with ≥1 prior NP surgery in SINUS-24 and SINUS-52 ITT population according to the response criteria of NPS (≥1-point improvement)

	ECM (N=187)	Dupilumab Q2W (N=272)
Baseline		
<i>All</i>		
Number	186	266
Mean (SD)	53.468 (19.921)	50.350 (20.316)
<i>Responders at Week 24</i>		
Number	25	169
Mean (SD)	47.240 (11.766)	52.325 (20.434)
<i>Non-responders at Week 24</i>		
Number	161	97
Mean (SD)	54.435 (20.763)	46.907 (19.744)
Week 24		
<i>All</i>		
Number	177	258
Mean (SD)	43.011 (21.818)	21.574 (16.758)
Change from baseline		
Number	177	258
Mean (SD)	-9.932 (19.013)	-28.888 (21.847)
LS mean (SE)	-9.226 (1.567)	-30.117 (1.413)
LS mean diff (95% CI)	NA	-20.891 (-24.183, -17.600)
p value vs. ECM	NA	<0.0001
<i>Responders at Week 24</i>		
Number	25	167
Mean (SD)	28.640 (19.659)	18.515 (14.755)
Change from baseline		
Number	25	167
Mean (SD)	-18.600 (15.403)	-33.910 (21.116)

	ECM (N=187)	Dupilumab Q2W (N=272)
LS mean (SE)	-22.642 (3.288)	-34.848 (1.674)
LS mean diff (95% CI)	NA	-12.206 (-18.607, -5.805)
p value vs. ECM	NA	0.0002
Non-responders at Week 24		
Number	152	91
Mean (SD)	45.375 (21.298)	27.187 (18.739)
Change from baseline		
Number	152	91
Mean (SD)	-8.507 (19.213)	-19.670 (20.196)
LS mean (SE)	-7.719 (1.880)	-22.972 (2.207)
LS mean diff (95% CI)	NA	-15.253 (-19.823, -10.683)
p value vs. ECM	NA	<0.0001
Week 52		
Responders at Week 24 AND Week 52		
Number	3	51
Mean (SD)	22.333 (12.897)	15.569 (16.364)
Change from baseline		
Number	3	51
Mean (SD)	-20.333 (11.590)	-35.608 (22.276)
LS mean (SE)	-29.953 (8.750)	-38.285 (2.505)
LS mean diff (95% CI)	NA	-8.332 (-27.220, 10.556)
p value vs. ECM	NA	0.3556
Non-responders at Week 24 OR Week 52		
Number	79	32
Mean (SD)	48.367 (21.233)	28.156 (21.890)
Change from baseline		
Number	79	32
Mean (SD)	-7.266 (18.457)	-20.813 (17.868)
LS mean (SE)	-6.073 (2.341)	-22.827 (3.289)
LS mean diff (95% CI)	NA	-16.754 (-23.979, -9.529)
p value vs. ECM	NA	<0.0001

CI = confidence interval; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NP = nasal polyp; NPS = nasal polyp score; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test
Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 69. SNOT-22 total score and change from baseline in patients with ≥1 prior NP surgery in SINUS-24 and SINUS-52 ITT population according to the response criteria of SNOT-22 total score (≥8.9-point improvement)

	ECM (N=187)	Dupilumab Q2W (N=272)
Baseline		
Responders at Week 24		
Number	82	205
Mean (SD)	55.720 (19.978)	53.039 (19.846)
Non-responders at Week 24		
Number	104	61
Mean (SD)	51.692 (19.792)	41.311 (19.395)
Week 24		
Responders at Week 24		
Number	82	205
Mean (SD)	31.646 (18.125)	17.512 (13.435)

	ECM (N=187)	Dupilumab Q2W (N=272)
Change from baseline		
Number	82	205
Mean (SD)	-24.073 (13.447)	-35.527 (18.992)
LS mean (SE)	-22.011 (0.258)	-35.635 (0.194)
LS mean diff (95% CI)	NA	-13.625 (-14.146, -13.103)
p value vs. ECM	NA	<0.0001
Non-responders at Week 24		
Number	95	53
Mean (SD)	52.821 (19.957)	37.283 (19.058)
Change from baseline		
Number	95	53
Mean (SD)	2.274 (14.000)	-3.208 (9.902)
LS mean (SE)	0.396 (2.070)	-9.634 (2.537)
LS mean diff (95% CI)	NA	-10.030 (-15.252, -4.809)
p value vs. ECM	NA	0.0002
Week 52		
Responders at Week 24 AND Week 52		
Number	19	58
Mean (SD)	40.421 (24.049)	14.672 (15.332)
Change from baseline		
Number	19	58
Mean (SD)	-25.316 (13.772)	-38.259 (19.066)
LS mean (SE)	-19.915 (3.413)	-40.092 (2.178)
LS mean diff (95% CI)	NA	-20.178 (-28.697, -11.658)
p value vs. ECM	NA	<0.0001
Non-responders at Week 24 OR Week 52		
Number	63	25
Mean (SD)	49.524 (20.413)	33.760 (21.980)
Change from baseline		
Number	63	25
Mean (SD)	-2.444 (16.206)	-10.520 (14.216)
LS mean (SE)	-1.574 (2.449)	-11.495 (3.373)
LS mean diff (95% CI)	NA	-9.921 (-17.338, -2.504)
p value vs. ECM	NA	0.0088

CI = confidence interval; ITT = intention-to-treat; LS = least squares; NA = not applicable; NP = nasal polyp; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test
Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 70. SNOT-22 total score and change from baseline in patients with ≥ 1 prior NP surgery in SINUS-24 and SINUS-52 ITT population according to the response criteria of SNOT-22 total score (≥ 8.9 -point improvement) and NPS (≥ 1 -point improvement)

	ECM (N=187)	Dupilumab Q2W (N=272)
Baseline		
Responders at Week 24		
Number	20	154
Mean (SD)	47.350 (11.641)	54.195 (19.862)
Non-responders at Week 24		
Number	166	112
Mean (SD)	54.205 (20.598)	45.063 (19.823)
Week 24		
Responders at Week 24		

	ECM (N=187)	Dupilumab Q2W (N=272)
Number	20	154
Mean (SD)	22.800 (16.536)	17.545 (14.368)
Change from baseline		
Number	20	154
Mean (SD)	-24.550 (9.859)	-36.649 (19.608)
LS mean (SE)	-28.886 (0.523)	-36.712 (0.247)
LS mean diff (95% CI)	NA	-7.826 (-8.843, -6.809)
p value vs. ECM	NA	<0.0001
<i>Non-responders at Week 24</i>		
Number	157	104
Mean (SD)	45.586 (21.088)	27.538 (18.271)
Change from baseline		
Number	157	104
Mean (SD)	-8.070 (19.108)	-17.394 (19.910)
LS mean (SE)	-7.047 (1.809)	-21.721 (2.088)
LS mean diff (95% CI)	NA	-14.673 (-19.025, -10.321)
p value vs. ECM	NA	<0.0001
Week 52		
<i>Responders at Week 24 AND Week 52</i>		
Number	2	44
Mean (SD)	20.500 (17.678)	13.795 (15.740)
Change from baseline		
Number	2	44
Mean (SD)	-26.500 (6.364)	-40.273 (19.776)
LS mean (SE)	-32.997 (10.263)	-42.375 (2.531)
LS mean diff (95% CI)	NA	-9.378 (-31.296, 12.541)
p value vs. ECM	NA	0.3732
<i>Non-responders at Week 24 OR Week 52</i>		
Number	80	39
Mean (SD)	48.088 (21.246)	27.897 (20.897)
Change from baseline		
Number	80	39
Mean (SD)	-7.275 (18.340)	-18.205 (17.864)
LS mean (SE)	-5.730 (2.274)	-21.132 (2.985)
LS mean diff (95% CI)	NA	-15.403 (-22.134, -8.671)
p value vs. ECM	NA	<0.0001

CI = confidence interval; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NP = nasal polyp; NPS = nasal polyp score; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test

Source: Sanofi. Data on File, Post-hoc analyses.¹

NPS

Table 71. NPS and change from baseline in patients with ≥ 1 prior NP surgery in SINUS-24 and SINUS-52 ITT population according to the response criteria of NPS (≥ 1 -point improvement)

	ECM (N=187)	Dupilumab Q2W (N=272)
Baseline		
<i>All</i>		
Number	186	271
Mean (SD)	5.739 (1.266)	5.945 (1.259)
<i>Responders at Week 24</i>		

	ECM (N=187)	Dupilumab Q2W (N=272)
Number	25	173
Mean (SD)	6.160 (0.997)	6.118 (1.187)
<i>Non-responders at Week 24</i>		
Number	161	98
Mean (SD)	5.674 (1.293)	5.638 (1.329)
Week 24		
<i>All</i>		
Number	177	257
Mean (SD)	5.853 (1.330)	4.045 (2.000)
Change from baseline		
Number	177	257
Mean (SD)	0.133 (1.226)	-1.893 (1.881)
LS mean (SE)	0.161 (0.145)	-1.825 (0.129)
LS mean diff (95% CI)	NA	-1.986 (-2.289, -1.683)
p value vs. ECM	NA	<0.0001
<i>Responders at Week 24</i>		
Number	25	173
Mean (SD)	4.400 (1.521)	3.223 (1.773)
Change from baseline		
Number	25	173
Mean (SD)	-1.760 (1.062)	-2.896 (1.324)
LS mean (SE)	-1.775 (0.045)	-2.916 (0.023)
LS mean diff (95% CI)	NA	-1.141 (-1.230, -1.053)
p value vs. ECM	NA	<0.0001
<i>Non-responders at Week 24</i>		
Number	152	84
Mean (SD)	6.092 (1.134)	5.738 (1.228)
Change from baseline		
Number	152	84
Mean (SD)	0.444 (0.939)	0.173 (0.930)
LS mean (SE)	0.458 (0.116)	-0.160 (0.136)
LS mean diff (95% CI)	NA	-0.619 (-0.905, -0.333)
p value vs. ECM	NA	<0.0001
Week 52		
<i>Responders at Week 24 AND Week 52</i>		
Number	3	53
Mean (SD)	4.167 (0.289)	2.519 (1.770)
Change from baseline		
Number	3	53
Mean (SD)	-2.000 (0.500)	-3.717 (1.479)
LS mean (SE)	-1.832 (0.861)	-3.630 (0.244)
LS mean diff (95% CI)	NA	-1.798 (-3.659, 0.063)
p value vs. ECM	NA	0.0447
<i>Non-responders at Week 24 OR Week 52</i>		
Number	79	30
Mean (SD)	6.000 (1.553)	4.700 (2.369)
Change from baseline		
Number	79	30
Mean (SD)	0.165 (1.184)	-1.000 (1.722)
LS mean (SE)	0.335 (0.197)	-1.024 (0.278)

	ECM (N=187)	Dupilumab Q2W (N=272)
LS mean diff (95% CI)	NA	-1.359 (-1.963, -0.755)
p value vs. ECM	NA	<0.0001

CI = confidence interval; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NP = nasal polyp; NPS = nasal polyp score; Q2W = once every two weeks; SD = standard deviation; SE = standard error
Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 72. NPS and change from baseline in patients with ≥ 1 prior NP surgery in SINUS-24 and SINUS-52 ITT population according to the response criteria of SNOT-22 total score (≥ 8.9 -point improvement)

	ECM (N=187)	Dupilumab Q2W (N=272)
Baseline		
<i>Responders at Week 24</i>		
Number	81	205
Mean (SD)	5.864 (1.165)	5.929 (1.288)
<i>Non-responders at Week 24</i>		
Number	105	66
Mean (SD)	5.643 (1.337)	5.992 (1.175)
Week 24		
<i>Responders at Week 24</i>		
Number	78	198
Mean (SD)	5.532 (1.534)	3.667 (1.916)
Change from baseline		
Number	78	198
Mean (SD)	-0.295 (1.247)	-2.250 (1.843)
LS mean (SE)	-0.307 (0.212)	-2.262 (0.159)
LS mean diff (95% CI)	NA	-1.955 (-2.381, -1.528)
p value vs. ECM	NA	<0.0001
<i>Non-responders at Week 24</i>		
Number	99	59
Mean (SD)	6.106 (1.086)	5.314 (1.747)
Change from baseline		
Number	99	59
Mean (SD)	0.470 (1.104)	-0.695 (1.480)
LS mean (SE)	0.554 (0.167)	-0.597 (0.196)
LS mean diff (95% CI)	NA	-1.151 (-1.553, -0.749)
p value vs. ECM	NA	<0.0001
Week 52		
<i>Responders at Week 24 AND Week 52</i>		
Number	19	56
Mean (SD)	5.842 (2.055)	2.625 (1.845)
Change from baseline		
Number	19	56
Mean (SD)	-0.474 (1.296)	-3.330 (1.802)
LS mean (SE)	-0.316 (0.398)	-3.141 (0.257)
LS mean diff (95% CI)	NA	-2.824 (-3.714, -1.935)
p value vs. ECM	NA	<0.0001
<i>Non-responders at Week 24 OR Week 52</i>		
Number	63	27
Mean (SD)	5.960 (1.401)	4.722 (2.399)
Change from baseline		
Number	63	27

	ECM (N=187)	Dupilumab Q2W (N=272)
Mean (SD)	0.254 (1.174)	-1.500 (1.976)
LS mean (SE)	0.355 (0.243)	-1.363 (0.328)
LS mean diff (95% CI)	NA	-1.718 (-2.423, -1.014)
p value vs. ECM	NA	<0.0001

CI = confidence interval; ITT = intention-to-treat; LS = least squares; NA = not applicable; NP = nasal polyp; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test

Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 73. NPS and change from baseline in patients with ≥ 1 prior NP surgery in SINUS-24 and SINUS-52 ITT population according to the response criteria of SNOT-22 total score (≥ 8.9 -point improvement) and NPS (≥ 1 -point improvement)

	ECM (N=187)	Dupilumab Q2W (N=272)
Baseline		
<i>Responders at Week 24</i>		
Number	20	154
Mean (SD)	6.050 (0.972)	6.123 (1.205)
<i>Non-responders at Week 24</i>		
Number	166	117
Mean (SD)	5.702 (1.294)	5.709 (1.295)
Week 24		
<i>Responders at Week 24</i>		
Number	20	154
Mean (SD)	4.225 (1.593)	3.162 (1.800)
<i>Change from baseline</i>		
Number	20	154
Mean (SD)	-1.825 (1.173)	-2.961 (1.349)
LS mean (SE)	-1.828 (0.052)	-2.969 (0.024)
LS mean diff (95% CI)	NA	-1.141 (-1.242, -1.041)
p value vs. ECM	NA	<0.0001
<i>Non-responders at Week 24</i>		
Number	157	103
Mean (SD)	6.061 (1.141)	5.364 (1.497)
<i>Change from baseline</i>		
Number	157	103
Mean (SD)	0.382 (0.987)	-0.296 (1.362)
LS mean (SE)	0.465 (0.122)	-0.436 (0.139)
LS mean diff (95% CI)	NA	-0.901 (-1.192, -0.610)
p value vs. ECM	NA	<0.0001
Week 52		
<i>Responders at Week 24 AND Week 52</i>		
Number	2	44
Mean (SD)	4.000 (0.000)	2.386 (1.775)
<i>Change from baseline</i>		
Number	2	44
Mean (SD)	-1.750 (0.354)	-3.841 (1.516)
LS mean (SE)	-1.868 (1.113)	-3.775 (0.274)
LS mean diff (95% CI)	NA	-1.907 (-4.284, 0.471)
p value vs. ECM	NA	0.0969
<i>Non-responders at Week 24 OR Week 52</i>		
Number	80	39
Mean (SD)	5.981 (1.552)	4.346 (2.306)

	ECM (N=187)	Dupilumab Q2W (N=272)
Change from baseline		
Number	80	39
Mean (SD)	0.131 (1.214)	-1.487 (1.833)
LS mean (SE)	0.307 (0.199)	-1.409 (0.258)
LS mean diff (95% CI)	NA	-1.716 (-2.287, -1.144)
p value vs. ECM	NA	<0.0001

CI = confidence interval; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NPS = nasal polyp score; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test

Source: Sanofi. Data on File, Post-hoc analyses.¹

Mapped SNOT-22 to EQ-5D-3L health state utilities (Crump Models 1-3)

Table 74. Mapped SNOT-22 to EQ-5D-3L health state utilities (Crump Models 1-3) in patients with ≥1 prior NP surgery in SINUS-24 and SINUS-52 ITT pooled population according to the response criteria of NPS (≥1-point improvement)

	ECM (N=187)			Dupilumab Q2W (N=272)			All (N=459)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Baseline									
<i>All</i>									
Number	186	186	186	266	266	266	452	452	452
Mean (SD)	0.511 (0.135)	0.636 (0.182)	0.638 (0.184)	0.532 (0.138)	0.656 (0.175)	0.659 (0.178)	0.524 (0.137)	0.648 (0.178)	0.651 (0.181)
<i>Responders at Week 24</i>									
Number	25	25	25	169	169	169	194	194	194
Mean (SD)	0.554 (0.080)	0.690 (0.138)	0.689 (0.133)	0.519 (0.139)	0.642 (0.183)	0.646 (0.186)	0.523 (0.133)	0.648 (0.178)	0.651 (0.181)
<i>Non-responders at Week 24</i>									
Number	161	161	161	97	97	97	258	258	258
Mean (SD)	0.505 (0.141)	0.628 (0.187)	0.631 (0.190)	0.556 (0.134)	0.680 (0.159)	0.683 (0.161)	0.524 (0.141)	0.647 (0.179)	0.650 (0.181)
Week 24									
<i>All</i>									
Number	177	177	177	258	258	258	435	435	435
Mean (SD)	0.594 (0.146)	0.689 (0.174)	0.692 (0.175)	0.730 (0.112)	0.766 (0.111)	0.770 (0.116)	0.675 (0.143)	0.735 (0.145)	0.738 (0.148)
<i>Change from baseline</i>									
Number	177	177	177	258	258	258	435	435	435
Mean (SD)	0.080 (0.127)	0.046 (0.154)	0.046 (0.154)	0.198 (0.148)	0.112 (0.158)	0.113 (0.158)	0.150 (0.151)	0.085 (0.160)	0.086 (0.160)
LS mean (SE)	0.072 (0.010)	0.044 (0.011)	0.044 (0.011)	0.203 (0.009)	0.117 (0.010)	0.118 (0.010)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.131 (0.109, 0.153)	0.073 (0.050, 0.096)	0.074 (0.051, 0.097)	NA	NA	NA
p value vs. ECM	NA	NA	NA	<0.0001	<0.0001	<0.0001	NA	NA	NA
<i>Responders at Week 24</i>									
Number	25	25	25	167	167	167	192	192	192
Mean (SD)	0.680 (0.134)	0.749 (0.127)	0.749 (0.128)	0.749 (0.100)	0.771 (0.105)	0.776 (0.110)	0.740 (0.107)	0.768 (0.108)	0.772 (0.112)
<i>Change from baseline</i>									
Number	25	25	25	167	167	167	192	192	192

	ECM (N=187)			Dupilumab Q2W (N=272)			All (N=459)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Mean (SD)	0.126 (0.105)	0.058 (0.123)	0.060 (0.125)	0.231 (0.144)	0.131 (0.166)	0.131 (0.166)	0.217 (0.143)	0.121 (0.162)	0.122 (0.162)
LS mean (SE)	0.154 (0.022)	0.097 (0.022)	0.093 (0.022)	0.237 (0.011)	0.135 (0.011)	0.135 (0.011)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.083 (0.040, 0.127)	0.038 (-0.005, 0.080)	0.042 (-0.001, 0.086)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.0002	0.0826	0.0570	NA	NA	NA
<i>Non-responders at Week 24</i>									
Number	152	152	152	91	91	91	243	243	243
Mean (SD)	0.580 (0.144)	0.680 (0.179)	0.683 (0.181)	0.694 (0.123)	0.757 (0.122)	0.760 (0.127)	0.623 (0.147)	0.709 (0.164)	0.712 (0.166)
Change from baseline									
Number	152	152	152	91	91	91	243	243	243
Mean (SD)	0.072 (0.129)	0.044 (0.159)	0.044 (0.159)	0.138 (0.136)	0.078 (0.137)	0.078 (0.138)	0.097 (0.135)	0.057 (0.152)	0.057 (0.152)
LS mean (SE)	0.061 (0.013)	0.039 (0.014)	0.040 (0.014)	0.154 (0.015)	0.094 (0.016)	0.095 (0.016)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.093 (0.063, 0.124)	0.055 (0.021, 0.088)	0.054 (0.021, 0.088)	NA	NA	NA
p value vs. ECM	NA	NA	NA	<0.0001	0.0014	0.0016	NA	NA	NA
Week 52									
<i>Responders at Week 24 AND Week 52</i>									
Number	3	3	3	51	51	51	103	103	103
Mean (SD)	0.723 (0.088)	0.790 (0.034)	0.803 (0.012)	0.769 (0.111)	0.777 (0.123)	0.784 (0.122)	0.761 (0.103)	0.772 (0.110)	0.776 (0.110)
Change from baseline									
Number	3	3	3	51	51	51	103	103	103
Mean (SD)	0.138 (0.079)	0.104 (0.157)	0.110 (0.159)	0.242 (0.151)	0.124 (0.186)	0.125 (0.186)	0.244 (0.145)	0.130 (0.183)	0.130 (0.182)
LS mean (SE)	0.204 (0.060)	0.166 (0.061)	0.170 (0.061)	0.260 (0.017)	0.152 (0.018)	0.151 (0.017)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.057 (-0.072, 0.185)	-0.014 (-0.146, 0.118)	-0.019 (-0.151, 0.113)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.3556	0.8210	0.7616	NA	NA	NA
<i>Non-responders at Week 24 AND Week 52</i>									
Number	67	67	67	19	19	19	101	101	101
Mean (SD)	0.574 (0.145)	0.682 (0.187)	0.684 (0.189)	0.677 (0.160)	0.728 (0.146)	0.725 (0.151)	0.614 (0.155)	0.701 (0.173)	0.702 (0.176)
Change from baseline									
Number	67	67	67	19	19	19	101	101	101

	ECM (N=187)			Dupilumab Q2W (N=272)			All (N=459)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Mean (SD)	0.093 (0.139)	0.088 (0.166)	0.087 (0.167)	0.137 (0.096)	0.051 (0.129)	0.052 (0.130)	0.113 (0.139)	0.078 (0.156)	0.078 (0.157)
LS mean (SE)	0.076 (0.018)	0.073 (0.019)	0.075 (0.020)	0.143 (0.031)	0.067 (0.034)	0.066 (0.034)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.067 (0.003, 0.130)	-0.006 (-0.076, 0.064)	-0.008 (-0.079, 0.062)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.0399	0.8669	0.8144	NA	NA	NA
Non-responders at Week 24 OR Week 52									
Number	79	79	79	32	32	32	142	142	142
Mean (SD)	0.590 (0.151)	0.694 (0.188)	0.696 (0.190)	0.705 (0.142)	0.745 (0.132)	0.749 (0.141)	0.646 (0.154)	0.719 (0.165)	0.721 (0.168)
Change from baseline									
Number	79	79	79	32	32	32	142	142	142
Mean (SD)	0.094 (0.141)	0.079 (0.168)	0.079 (0.168)	0.163 (0.109)	0.067 (0.141)	0.069 (0.141)	0.136 (0.148)	0.083 (0.161)	0.084 (0.161)
LS mean (SE)	0.072 (0.016)	0.062 (0.018)	0.064 (0.018)	0.166 (0.023)	0.080 (0.025)	0.082 (0.025)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.094 (0.044, 0.143)	0.017 (-0.037, 0.071)	0.018 (-0.037, 0.073)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.0002	0.5319	0.5229	NA	NA	NA

CI = confidence interval; EQ-5D-3L = EuroQol 5-Dimension 3-Level; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NA = not applicable; NP = nasal polyp; NPS = nasal polyp score; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every two weeks; SD = standard deviation; SE = standard error
Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 75. Mapped SNOT-22 to EQ-5D-3L health state utilities (Crump Models 1-3) in patients with ≥1 prior NP surgery in SINUS-24 and SINUS-52 ITT pooled population according to the response criteria of SNOT-22 total score (≥8.9-point improvement)

	ECM (N=187)			Dupilumab Q2W (N=272)			All (N=459)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Baseline									
Responders at Week 24									
Number	82	82	82	205	205	205	287	287	287
Mean (SD)	0.496 (0.136)	0.617 (0.189)	0.617 (0.190)	0.514 (0.135)	0.638 (0.179)	0.641 (0.180)	0.509 (0.135)	0.632 (0.182)	0.634 (0.183)
Non-responders at Week 24									

	ECM (N=187)			Dupilumab Q2W (N=272)			All (N=459)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Number	104	104	104	61	61	61	165	165	165
Mean (SD)	0.523 (0.135)	0.651 (0.176)	0.655 (0.178)	0.594 (0.132)	0.716 (0.150)	0.720 (0.157)	0.549 (0.138)	0.675 (0.170)	0.679 (0.173)
Week 24									
<i>Responders at Week 24</i>									
Number	82	82	82	205	205	205	287	287	287
Mean (SD)	0.660 (0.123)	0.739 (0.138)	0.740 (0.140)	0.756 (0.091)	0.779 (0.101)	0.783 (0.105)	0.728 (0.110)	0.768 (0.114)	0.771 (0.117)
Change from baseline									
Number	82	82	82	205	205	205	287	287	287
Mean (SD)	0.164 (0.091)	0.122 (0.127)	0.122 (0.128)	0.242 (0.129)	0.141 (0.158)	0.142 (0.158)	0.219 (0.125)	0.136 (0.150)	0.136 (0.150)
LS mean (SE)	0.150 (0.002)	0.108 (0.002)	0.108 (0.002)	0.242 (0.001)	0.145 (0.001)	0.147 (0.001)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.093 (0.089, 0.096)	0.038 (0.034, 0.042)	0.040 (0.036, 0.044)	NA	NA	NA
p value vs. ECM	NA	NA	NA	<0.0001	<0.0001	<0.0001	NA	NA	NA
<i>Non-responders at Week 24</i>									
Number	95	95	95	53	53	53	148	148	148
Mean (SD)	0.538 (0.142)	0.647 (0.191)	0.651 (0.192)	0.629 (0.126)	0.716 (0.136)	0.719 (0.142)	0.570 (0.142)	0.672 (0.176)	0.675 (0.179)
Change from baseline									
Number	95	95	95	53	53	53	148	148	148
Mean (SD)	0.007 (0.108)	-0.019 (0.146)	-0.020 (0.145)	0.029 (0.075)	-0.001 (0.093)	-0.001 (0.094)	0.015 (0.097)	-0.013 (0.129)	-0.013 (0.129)
LS mean (SE)	0.010 (0.015)	-0.013 (0.018)	-0.013 (0.018)	0.063 (0.018)	0.018 (0.022)	0.016 (0.022)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.053 (0.016, 0.089)	0.031 (-0.013, 0.074)	0.029 (-0.014, 0.073)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.0048	0.1705	0.1877	NA	NA	NA
Week 52									
<i>Responders at Week 24 AND Week 52</i>									
Number	19	19	19	58	58	58	143	143	143
Mean (SD)	0.600 (0.164)	0.659 (0.184)	0.659 (0.186)	0.775 (0.104)	0.782 (0.114)	0.786 (0.116)	0.743 (0.123)	0.758 (0.126)	0.761 (0.128)
Change from baseline									
Number	19	19	19	58	58	58	143	143	143
Mean (SD)	0.172 (0.094)	0.163 (0.108)	0.164 (0.109)	0.260 (0.130)	0.143 (0.175)	0.143 (0.175)	0.255 (0.130)	0.150 (0.166)	0.151 (0.166)

	ECM (N=187)			Dupilumab Q2W (N=272)			All (N=459)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
LS mean (SE)	0.135 (0.023)	0.090 (0.025)	0.090 (0.025)	0.273 (0.015)	0.166 (0.016)	0.167 (0.016)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.137 (0.079, 0.195)	0.076 (0.014, 0.138)	0.077 (0.014, 0.140)	NA	NA	NA
p value vs. ECM	NA	NA	NA	<0.0001	0.0088	0.0087	NA	NA	NA
<i>Non-responders at Week 24 AND Week 52</i>									
Number	43	43	43	13	13	13	65	65	65
Mean (SD)	0.556 (0.154)	0.668 (0.198)	0.672 (0.199)	0.610 (0.161)	0.683 (0.178)	0.689 (0.187)	0.581 (0.155)	0.677 (0.185)	0.681 (0.187)
Change from baseline									
Number	43	43	43	13	13	13	65	65	65
Mean (SD)	0.034 (0.138)	0.016 (0.162)	0.016 (0.162)	0.071 (0.113)	0.003 (0.130)	0.006 (0.129)	0.040 (0.124)	0.010 (0.145)	0.011 (0.145)
LS mean (SE)	0.028 (0.021)	0.022 (0.025)	0.023 (0.025)	0.070 (0.035)	0.009 (0.041)	0.010 (0.041)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.042 (-0.033, 0.117)	-0.013 (-0.101, 0.074)	0.010 (0.041)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.2711	0.7693		NA	NA	NA
<i>Non-responders at Week 24 OR Week 52</i>									
Number	63	63	63	25	25	25	102	102	102
Mean (SD)	0.593 (0.148)	0.710 (0.186)	0.713 (0.188)	0.673 (0.148)	0.726 (0.147)	0.733 (0.155)	0.626 (0.149)	0.718 (0.169)	0.721 (0.172)
Change from baseline									
Number	63	63	63	25	25	25	102	102	102
Mean (SD)	0.072 (0.142)	0.055 (0.174)	0.055 (0.174)	0.099 (0.098)	0.009 (0.122)	0.010 (0.121)	0.077 (0.128)	0.037 (0.157)	0.037 (0.156)
LS mean (SE)	0.048 (0.018)	0.043 (0.022)	0.044 (0.022)	0.096 (0.026)	0.018 (0.030)	0.021 (0.030)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.048 (-0.008, 0.104)	-0.025 (-0.091, 0.041)	-0.023 (-0.089, 0.043)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.0940	0.4508	0.4945	NA	NA	NA

CI = confidence interval; EQ-5D-3L = EuroQol 5-Dimension 3-Level; ITT = intention-to-treat; LS = least squares; NA = not applicable; NP = nasal polyp; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test
Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 76. Mapped SNOT-22 to EQ-5D-3L health state utilities (Crump Models 1-3) in patients with ≥ 1 prior NP surgery in SINUS-24 and SINUS-52 ITT pooled population according to the response criteria of SNOT-22 total score (≥ 8.9 -point improvement) and NPS (≥ 1 -point improvement)

	ECM (N=187)			Dupilumab Q2W (N=272)			All (N=459)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Baseline									
<i>Responders at Week 24</i>									
Number	20	20	20	154	154	154	174	174	174
Mean (SD)	0.553 (0.079)	0.680 (0.143)	0.679 (0.136)	0.506 (0.135)	0.630 (0.183)	0.634 (0.186)	0.512 (0.131)	0.636 (0.179)	0.639 (0.181)
<i>Non-responders at Week 24</i>									
Number	166	166	166	112	112	112	278	278	278
Mean (SD)	0.506 (0.140)	0.631 (0.186)	0.634 (0.189)	0.568 (0.135)	0.691 (0.159)	0.694 (0.161)	0.531 (0.141)	0.655 (0.178)	0.658 (0.180)
Week 24									
<i>Responders at Week 24</i>									
Number	20	20	20	154	154	154	174	174	174
Mean (SD)	0.720 (0.112)	0.772 (0.108)	0.774 (0.105)	0.755 (0.098)	0.775 (0.106)	0.779 (0.111)	0.751 (0.100)	0.775 (0.106)	0.778 (0.110)
<i>Change from baseline</i>									
Number	20	20	20	154	154	154	174	174	174
Mean (SD)	0.167 (0.067)	0.093 (0.097)	0.096 (0.096)	0.249 (0.133)	0.145 (0.163)	0.145 (0.163)	0.240 (0.130)	0.139 (0.157)	0.140 (0.157)
LS mean (SE)	0.196 (0.004)	0.128 (0.004)	0.127 (0.004)	0.250 (0.002)	0.148 (0.002)	0.149 (0.002)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.053 (0.046, 0.060)	0.020 (0.013, 0.027)	0.022 (0.015, 0.029)	NA	NA	NA
p value vs. ECM	NA	NA	NA	<0.0001	<0.0001	<0.0001	NA	NA	NA
<i>Non-responders at Week 24</i>									
Number	157	157	157	104	104	104	261	261	261
Mean (SD)	0.578 (0.143)	0.679 (0.178)	0.682 (0.180)	0.691 (0.120)	0.753 (0.119)	0.757 (0.123)	0.623 (0.145)	0.708 (0.161)	0.712 (0.164)
<i>Change from baseline</i>									
Number	157	157	157	104	104	104	261	261	261
Mean (SD)	0.068 (0.129)	0.040 (0.159)	0.040 (0.159)	0.122 (0.135)	0.063 (0.137)	0.064 (0.137)	0.090 (0.134)	0.049 (0.151)	0.050 (0.151)
LS mean (SE)	0.056 (0.012)	0.034 (0.013)	0.034 (0.013)	0.146 (0.014)	0.083 (0.015)	0.084 (0.016)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.089 (0.060, 0.118)	0.049 (0.017, 0.081)	0.050 (0.017, 0.082)	NA	NA	NA
p value vs. ECM	NA	NA	NA	<0.0001	0.0026	0.0025	NA	NA	NA

	ECM (N=187)			Dupilumab Q2W (N=272)			All (N=459)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Week 52									
<i>Responders at Week 24 AND Week 52</i>									
Number	2	2	2	44	44	44	91	91	91
Mean (SD)	0.735 (0.120)	0.770 (0.001)	0.796 (0.001)	0.781 (0.107)	0.784 (0.118)	0.790 (0.118)	0.770 (0.101)	0.779 (0.104)	0.783 (0.106)
Change from baseline									
Number	2	2	2	44	44	44	91	91	91
Mean (SD)	0.180 (0.043)	0.195 (0.002)	0.201 (0.002)	0.274 (0.134)	0.154 (0.180)	0.154 (0.180)	0.271 (0.129)	0.156 (0.174)	0.156 (0.174)
LS mean (SE)	0.224 (0.070)	0.168 (0.072)	0.180 (0.072)	0.288 (0.017)	0.177 (0.018)	0.175 (0.018)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.064 (-0.085, 0.213)	0.009 (-0.145, 0.163)	-0.005 (-0.160, 0.150)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.3732	0.9059	0.9481	NA	NA	NA
<i>Non-responders at Week 24 AND Week 52</i>									
Number	74	74	74	22	22	22	114	114	114
Mean (SD)	0.579 (0.146)	0.687 (0.189)	0.690 (0.192)	0.675 (0.151)	0.722 (0.149)	0.721 (0.153)	0.619 (0.153)	0.702 (0.174)	0.704 (0.176)
Change from baseline									
Number	74	74	74	22	22	22	114	114	114
Mean (SD)	0.083 (0.139)	0.071 (0.170)	0.071 (0.171)	0.115 (0.107)	0.024 (0.138)	0.026 (0.138)	0.098 (0.139)	0.060 (0.160)	0.060 (0.160)
LS mean (SE)	0.068 (0.017)	0.062 (0.019)	0.063 (0.019)	0.128 (0.028)	0.046 (0.032)	0.046 (0.032)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.060 (0.001, 0.119)	-0.016 (-0.082, 0.050)	-0.018 (-0.084, 0.049)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.0446	0.6414	0.6036	NA	NA	NA
<i>Non-responders at Week 24 OR Week 52</i>									
Number	80	80	80	39	39	39	154	154	154
Mean (SD)	0.591 (0.150)	0.696 (0.188)	0.698 (0.189)	0.703 (0.136)	0.743 (0.134)	0.748 (0.141)	0.650 (0.151)	0.719 (0.163)	0.722 (0.165)
Change from baseline									
Number	80	80	80	39	39	39	154	154	154
Mean (SD)	0.093 (0.140)	0.077 (0.168)	0.077 (0.168)	0.141 (0.115)	0.044 (0.143)	0.046 (0.142)	0.128 (0.146)	0.071 (0.162)	0.073 (0.162)
LS mean (SE)	0.070 (0.016)	0.058 (0.017)	0.060 (0.017)	0.152 (0.021)	0.063 (0.023)	0.066 (0.023)	NA	NA	NA

	ECM (N=187)			Dupilumab Q2W (N=272)			All (N=459)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
LS mean diff (95% CI)	NA	NA	NA	0.082 (0.036, 0.129)	0.005 (-0.046, 0.056)	0.006 (-0.045, 0.057)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.0005	0.8505	0.8128	NA	NA	NA

CI = confidence interval; EQ-5D-3L = EuroQol 5-Dimension 3-Level; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NP = nasal polyp; NPS = nasal polyp score; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test

Source: Sanofi. Data on File, Post-hoc analyses.¹

EQ-5D-5L utilities (Hernandez 2020 crosswalk method, UK tariffs)

Table 77. EQ-5D-5L utilities (Hernandez 2020 crosswalk method, UK tariffs) in patients with ≥ 1 prior NP surgery in SINUS-24 and SINUS-52 ITT pooled population according to the response criteria of NPS (≥ 1 -point improvement)

	ECM (N=187)	Dupilumab Q2W (N=272)
Baseline		
<i>All</i>		
Number	184	446
Mean (SD)	0.776 (0.176)	0.782 (0.184)
<i>Responders at Week 24</i>		
Number	25	167
Mean (SD)	0.826 (0.110)	0.779 (0.180)
<i>Non-responders at Week 24</i>		
Number	159	95
Mean (SD)	0.768 (0.184)	0.797 (0.205)
Week 24		
<i>All</i>		
Number	176	254
Mean (SD)	0.815 (0.168)	0.872 (0.153)
Change from baseline		
Number	176	254
Mean (SD)	0.040 (0.147)	0.088 (0.176)
LS mean (SE)	0.045 (0.012)	0.101 (0.011)
LS mean diff (95% CI)	NA	0.056 (0.031, 0.082)
p value vs. ECM	NA	<0.0001
<i>Responders at Week 24</i>		
Number	25	165
Mean (SD)	0.900 (0.107)	0.883 (0.137)
Change from baseline		
Number	25	165
Mean (SD)	0.074 (0.138)	0.104 (0.179)
LS mean (SE)	0.102 (0.028)	0.110 (0.014)
LS mean diff (95% CI)	NA	0.008 (-0.046, 0.062)
p value vs. ECM	NA	0.7712
<i>Non-responders at Week 24</i>		
Number	151	89
Mean (SD)	0.801 (0.172)	0.851 (0.178)
Change from baseline		
Number	151	89
Mean (SD)	0.035 (0.148)	0.057 (0.166)
LS mean (SE)	0.046 (0.014)	0.081 (0.017)
LS mean diff (95% CI)	NA	0.036 (0.001, 0.070)
p value vs. ECM	NA	0.0411
Week 52		
<i>Responders at Week 24 AND Week 52</i>		
Number	3	50
Mean (SD)	0.851 (0.054)	0.900 (0.150)
Change from baseline		
Number	3	50
Mean (SD)	0.074 (0.023)	0.117 (0.202)

	ECM (N=187)	Dupilumab Q2W (N=272)
LS mean (SE)	0.080 (0.085)	0.135 (0.025)
LS mean diff (95% CI)	NA	0.055 (-0.116, 0.227)
p value vs. ECM	NA	0.5288
Non-responders at Week 24 AND Week 52		
Number	67	19
Mean (SD)	0.773 (0.232)	0.795 (0.279)
Change from baseline		
Number	67	19
Mean (SD)	0.032 (0.197)	0.017 (0.108)
LS mean (SE)	0.016 (0.023)	0.002 (0.041)
LS mean diff (95% CI)	NA	-0.014 (-0.097, 0.070)
p value vs. ECM	NA	0.7511
Non-responders at Week 24 OR Week 52		
Number	79	31
Mean (SD)	0.791 (0.223)	0.838 (0.240)
Change from baseline		
Number	79	31
Mean (SD)	0.033 (0.188)	0.057 (0.177)
LS mean (SE)	0.021 (0.021)	0.056 (0.031)
LS mean diff (95% CI)	NA	0.034 (-0.032, 0.101)
p value vs. ECM	NA	0.3067

CI = confidence interval; EQ-5D-5L = EuroQol 5-Dimension 5-Level; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NP = nasal polyp; NPS = nasal polyp score; Q2W = once every two weeks; SD = standard deviation; SE = standard error
Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 78. EQ-5D-5L utilities (Hernandez 2020 crosswalk method, UK tariffs) in patients with ≥1 prior NP surgery in SINUS-24 and SINUS-52 ITT pooled population according to the response criteria of SNOT-22 total score (≥8.9-point improvement)

	ECM (N=187)	Dupilumab Q2W (N=272)
Baseline		
Responders at Week 24		
Number	82	204
Mean (SD)	0.802 (0.155)	0.780 (0.183)
Non-responders at Week 24		
Number	102	58
Mean (SD)	0.755 (0.190)	0.805 (0.210)
Week 24		
Responders at Week 24		
Number	82	203
Mean (SD)	0.878 (0.112)	0.888 (0.134)
Change from baseline		
Number	82	203
Mean (SD)	0.076 (0.139)	0.108 (0.175)
LS mean (SE)	0.084 (0.015)	0.105 (0.011)
LS mean diff (95% CI)	NA	0.021 (-0.009, 0.051)
p value vs. ECM	NA	0.1697
Non-responders at Week 24		
Number	94	51
Mean (SD)	0.760 (0.188)	0.808 (0.202)
Change from baseline		

	ECM (N=187)	Dupilumab Q2W (N=272)
Number	94	51
Mean (SD)	0.009 (0.148)	0.006 (0.157)
LS mean (SE)	0.035 (0.019)	0.056 (0.022)
LS mean diff (95% CI)	NA	0.022 (-0.024, 0.068)
p value vs. ECM	NA	0.3490
Week 52		
<i>Responders at Week 24 AND Week 52</i>		
Number	19	56
Mean (SD)	0.828 (0.200)	0.901 (0.150)
Change from baseline		
Number	19	56
Mean (SD)	0.059 (0.146)	0.117 (0.194)
LS mean (SE)	0.054 (0.030)	0.126 (0.020)
LS mean diff (95% CI)	NA	0.072 (0.004, 0.139)
p value vs. ECM	NA	0.0377
<i>Non-responders at Week 24 AND Week 52</i>		
Number	43	13
Mean (SD)	0.726 (0.243)	0.723 (0.321)
Change from baseline		
Number	43	13
Mean (SD)	-0.006 (0.197)	-0.015 (0.102)
LS mean (SE)	-0.004 (0.029)	-0.015 (0.049)
LS mean diff (95% CI)	NA	-0.011 (-0.117, 0.095)
p value vs. ECM	NA	0.8373
<i>Non-responders at Week 24 OR Week 52</i>		
Number	63	25
Mean (SD)	0.783 (0.226)	0.820 (0.254)
Change from baseline		
Number	63	25
Mean (SD)	0.027 (0.195)	0.042 (0.187)
LS mean (SE)	0.017 (0.028)	0.031 (0.039)
LS mean diff (95% CI)	NA	0.014 (-0.072, 0.100)
p value vs. ECM	NA	0.7514

CI = confidence interval; EQ-5D-5L = EuroQol 5-Dimension 5-Level; ITT = intention-to-treat; LS = least squares; NA = not applicable; NP = nasal polyp; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test

Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 79. EQ-5D-5L utilities (Hernandez 2020 crosswalk method, UK tariffs) in patients with ≥ 1 prior NP surgery in SINUS-24 and SINUS-52 ITT pooled population according to the response criteria of SNOT-22 total score (≥ 8.9 -point improvement) and NPS (≥ 1 -point improvement)

	ECM (N=187)	Dupilumab Q2W (N=272)
Baseline		
<i>Responders at Week 24</i>		
Number	20	153
Mean (SD)	0.820 (0.113)	0.775 (0.183)
<i>Non-responders at Week 24</i>		
Number	164	109
Mean (SD)	0.771 (0.182)	0.801 (0.198)
Week 24		
<i>Responders at Week 24</i>		

	ECM (N=187)	Dupilumab Q2W (N=272)
Number	20	153
Mean (SD)	0.912 (0.104)	0.888 (0.134)
Change from baseline		
Number	20	153
Mean (SD)	0.092 (0.139)	0.113 (0.179)
LS mean (SE)	0.121 (0.005)	0.120 (0.002)
LS mean diff (95% CI)	NA	-0.001 (-0.010, 0.008)
p value vs. ECM	NA	0.8479
Non-responders at Week 24		
Number	156	101
Mean (SD)	0.803 (0.170)	0.847 (0.176)
Change from baseline		
Number	156	101
Mean (SD)	0.034 (0.147)	0.048 (0.165)
LS mean (SE)	0.042 (0.014)	0.074 (0.016)
LS mean diff (95% CI)	NA	0.032 (-0.001, 0.064)
p value vs. ECM	NA	0.0589
Week 52		
Responders at Week 24 AND Week 52		
Number	2	43
Mean (SD)	0.882 (0.013)	0.904 (0.153)
Change from baseline		
Number	2	43
Mean (SD)	0.085 (0.019)	0.132 (0.212)
LS mean (SE)	0.091 (0.087)	0.145 (0.022)
LS mean diff (95% CI)	NA	0.054 (-0.121, 0.229)
p value vs. ECM	NA	0.5432
Non-responders at Week 24 AND Week 52		
Number	74	22
Mean (SD)	0.781 (0.226)	0.797 (0.265)
Change from baseline		
Number	74	22
Mean (SD)	0.026 (0.190)	0.014 (0.103)
LS mean (SE)	0.017 (0.022)	0.007 (0.037)
LS mean diff (95% CI)	NA	-0.009 (-0.086, 0.067)
p value vs. ECM	NA	0.8091
Non-responders at Week 24 OR Week 52		
Number	80	38
Mean (SD)	0.791 (0.222)	0.845 (0.224)
Change from baseline		
Number	80	38
Mean (SD)	0.033 (0.187)	0.051 (0.163)
LS mean (SE)	0.021 (0.022)	0.051 (0.029)
LS mean diff (95% CI)	NA	0.031 (-0.034, 0.096)
p value vs. ECM	NA	0.3569

CI = confidence interval; EQ-5D-5L = EuroQol 5-Dimension 5-Level; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NP = nasal polyp; NPS = nasal polyp score; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test
Source: Sanofi. Data on File, Post-hoc analyses.¹

Patients with ≥ 1 prior NP surgery and comorbid NSAID-ERD

Baseline characteristics

Table 80. Baseline characteristics of patients with ≥ 1 prior NP surgery and comorbid NSAID-ERD in SINUS-24 and SINUS-52 pooled ITT population

	ECM	Dupilumab Q2W	All
N	65	63	159
Male, n (%)	25 (38.5)	31 (49.2)	72 (45.3)
Age, mean (SD)	49.69 (14.61)	50.10 (12.82)	50.54 (12.98)
Race, n (%)			
Caucasian/White	57 (87.7)	58 (92.1)	141 (88.7)
Black/African decent	2 (3.1)	0	2 (1.3)
Asian/Oriental	5 (7.7)	4 (6.3)	13 (8.2)
American Indian/Alaska Native	1 (1.5)	1 (1.6)	2 (1.3)
Native Hawaiian/Other Pacific Islander	0	0	0
Multiple	0	0	1 (0.6)
Unknown	0	0	0
Ethnicity			
Hispanic or Latino	8 (12.5)	5 (7.9)	17 (10.8)
Not Hispanic or Latino	56 (87.5)	58 (92.1)	141 (89.2)
Territory			
North America	11 (16.9)	10 (15.9)	30 (18.9)
European Union	22 (33.8)	27 (42.9)	56 (35.2)
Rest of the World	32 (49.2)	26 (41.3)	73 (45.9)
BMI (kg/m ²), mean (SD)	27.78 (5.89)	27.28 (4.52)	27.33 (5.09)
Time since first diagnosis of nasal polyps (years), mean (SD)	13.63 (8.46)	16.37 (9.19)	14.74 (8.95)
≥ 3 previous surgery for nasal polyps, n (%)	18 (27.7)	25 (39.7)	48 (30.2)
Time since most recent surgery for nasal polyps (years), mean (SD)	6.06 (4.26)	6.42 (4.69)	6.34 (4.70)
SCS use in the past 2 years, n (%)	47 (72.3)	36 (57.1)	104 (65.4)
Bilateral endoscopic NPS* (scale 0-8), mean (SD)	5.66 (1.23)	5.61 (1.45)	5.76 (1.32)
NC score* (scale 0-3), mean (SD)	2.54 (0.47)	2.30 (0.63)	2.45 (0.57)
SNOT-22 total score* (scale 0-110), mean (SD)	56.20 (18.87)	47.88 (18.19)	53.18 (18.78)
Smell test (UPSIT) score** (scale 0-40), mean (SD)	11.62 (6.51)	12.27 (7.40)	11.67 (6.51)
LoS score* (scale 0-3), mean (SD)	2.86 (0.32)	2.86 (0.40)	2.86 (0.40)
LMK-CT total score* (scale 0-24), mean (SD)	19.77 (3.67)	19.15 (4.19)	19.34 (3.83)
Rhinosinusitis disease severity* (VAS 0-10cm), mean (SD)	8.14 (2.15)	7.94 (1.64)	8.05 (2.03)
Baseline NPIF** (L/min), mean (SD)	91.05 (57.16)	91.03 (53.49)	89.10 (55.20)
Baseline blood eosinophils ($\times 10^9$ cells/L), mean (SD)	0.44 (0.26)	0.55 (0.46)	0.48 (0.36)
Comorbid asthma, n (%)	57 (87.7)	55 (87.3)	141 (88.7)
Any comorbid type 2 medical history excluding asthma and NSAID-ERD, n (%)	48 (73.8)	46 (73.0)	118 (74.2)
Age of asthma onset in patients with comorbid asthma (years), mean (SD)	31.73 (14.85)	34.22 (12.09)	33.39 (13.92)

	ECM	Dupilumab Q2W	All
Baseline ACQ-6 score* in patients with comorbid asthma, mean (SD)	1.57 (0.99)	1.31 (0.98)	1.49 (1.06)

ACQ-6 = 6-item Asthma Control Questionnaire; BMI = body mass index; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LMK-CT = Lund-Mackay computed tomography; LoS = loss-of-smell; NC = nasal congestion/obstruction; NPIF = peak nasal inspiratory flow; NPS = nasal polyp score; NSAID = non-steroidal anti-inflammatory drug; Q2W = every 2 weeks; SD = standard deviation; SNOT-22 = 22-item Sino-Nasal Outcome Test; UPSIT = University of Pennsylvania Smell Identification Test; VAS = visual analogue scale

*Higher scores indicate greater disease severity.

** Higher scores indicate lower disease severity.

Source: Sanofi. Data on File, Post-hoc analyses.¹

Response rates

Table 81. Response rates for patients with ≥1 prior NP surgery and comorbid NSAID-ERD in SINUS-24 and SINUS-52 pooled ITT population according to the different response criteria

		ECM (N=65)	Dupilumab Q2W (N=94)
Overall response at Week 24			
NPS (≥1-point improvement)			
Responders, n (%)	8 (12.3)	63 (67.0)	
Non-responders, n (%)	57 (87.7)	31 (33.0)	
SNOT-22 total score (≥8.9-point improvement)			
Responders, n (%)	25 (38.5)	70 (74.5)	
Non-responders, n (%)	40 (61.5)	24 (25.5)	
SNOT-22 total score (≥8.9-point improvement) and NPS (≥1-point improvement)			
Responders, n (%)	7 (10.8)	55 (58.5)	
Non-responders, n (%)	58 (89.2)	39 (41.5)	
Overall response at Week 52			
All			
NPS (≥1-point improvement)			
Responders, n (%)	6 (17.1)	23 (92.0)	
Non-responders, n (%)	29 (82.9)	2 (8.0)	
SNOT-22 total score (≥8.9-point improvement)			
Responders, n (%)	8 (22.9)	20 (80.0)	
Non-responders, n (%)	27 (77.1)	5 (20.0)	
SNOT-22 total score (≥8.9-point improvement) and NPS (≥1-point improvement)			
Responders, n (%)	2 (5.7)	20 (80.0)	
Non-responders, n (%)	33 (94.3)	5 (20.0)	
Responders at Week 24			
NPS (≥1-point improvement)	ECM (N=1)	Dupilumab Q2W (N=16)	
Responders, n (%)	0	16 (100)	
Non-responders, n (%)	1 (100)	0	
SNOT-22 total score (≥8.9-point improvement)	ECM (N=11)	Dupilumab Q2W (N=17)	
Responders, n (%)	6 (54.5)	16 (94.1)	
Non-responders, n (%)	5 (45.5)	1 (5.9)	
SNOT-22 total score (≥8.9-point improvement) and NPS (≥1-point improvement)	ECM (N=1)	Dupilumab Q2W (N=12)	
Responders, n (%)	0	11 (91.7)	
Non-responders, n (%)	1 (100)	1 (8.3)	
Non-responders at Week 24			
NPS (≥1-point improvement)	ECM (N=8)	Dupilumab Q2W (N=9)	

	ECM (N=65)	Dupilumab Q2W (N=94)
Responders, n (%)	6 (17.6)	7 (77.8)
Non-responders, n (%)	28 (82.4)	2 (22.2)
SNOT-22 total score (≥ 8.9-point improvement)	ECM (N=4)	Dupilumab Q2W (N=8)
Responders, n (%)	2 (8.3)	4 (50.0)
Non-responders, n (%)	22 (91.7)	4 (50.0)
SNOT-22 total score (≥ 8.9-point improvement) and NPS (≥ 1-point improvement)	ECM (N=8)	Dupilumab Q2W (N=13)
Responders, n (%)	2 (5.9)	9 (69.2)
Non-responders, n (%)	32 (94.1)	4 (30.8)

ITT = intention-to-treat; NPS = nasal polyp score; Q2W = once every two weeks; SNOT-22: 22-item Sino Nasal Outcome Test
Source: Sanofi. Data on File, Post-hoc analyses.¹

SNOT-22 total score

Table 82. SNOT-22 total score and change from baseline in patients with ≥ 1 prior NP surgery and comorbid NSAID-ERD in SINUS-24 and SINUS-52 ITT population according to the response criteria of NPS (≥ 1 -point improvement)

	ECM (N=65)	Dupilumab Q2W (N=94)
Baseline		
<i>All</i>		
Number	65	90
Mean (SD)	56.200 (18.867)	51.000 (18.522)
<i>Responders at Week 24</i>		
Number	8	60
Mean (SD)	50.000 (11.263)	52.217 (17.423)
<i>Non-responders at Week 24</i>		
Number	57	30
Mean (SD)	57.070 (19.614)	48.567 (20.641)
Week 24		
<i>All</i>		
Number	64	88
Mean (SD)	47.766 (22.110)	21.966 (16.484)
Change from baseline		
Number	64	88
Mean (SD)	-8.344 (20.416)	-28.955 (21.544)
LS mean (SE)	-6.586 (2.678)	-31.170 (2.391)
LS mean diff (95% CI)	NA	-24.584 (-30.394, -18.773)
p value vs. ECM	NA	<0.0001
<i>Responders at Week 24</i>		
Number	8	59
Mean (SD)	28.500 (21.334)	18.407 (11.347)
Change from baseline		
Number	8	59
Mean (SD)	-21.500 (17.525)	-34.203 (19.688)
LS mean (SE)	-23.492 (5.057)	-35.088 (2.283)
LS mean diff (95% CI)	NA	-11.596 (-21.789, -1.404)
p value vs. ECM	NA	0.0257
<i>Non-responders at Week 24</i>		
Number	56	29
Mean (SD)	50.518 (20.984)	29.207 (22.283)

	ECM (N=65)	Dupilumab Q2W (N=94)
Change from baseline		
Number	56	29
Mean (SD)	-6.464 (20.238)	-18.276 (21.519)
LS mean (SE)	-4.063 (3.337)	-21.990 (4.205)
LS mean diff (95% CI)	NA	-17.927 (-26.643, -9.211)
p value vs. ECM	NA	<0.0001
Week 52		
<i>Responders at Week 24 AND Week 52</i>		
Number	0	15
Mean (SD)	NA	15.933 (14.325)
Change from baseline		
Number	0	15
Mean (SD)	NA	-28.733 (20.603)
LS mean (SE)	NE	-35.866 (3.760)
LS mean diff (95% CI)	NA	NE
p value vs. ECM	NA	NE
<i>Non-responders at Week 24 OR Week 52</i>		
Number	34	9
Mean (SD)	48.765 (22.285)	29.000 (32.113)
Change from baseline		
Number	34	9
Mean (SD)	-8.971 (18.338)	-26.444 (26.283)
LS mean (SE)	-7.925 (3.838)	-25.906 (7.042)
LS mean diff (95% CI)	NA	-17.981 (-33.219, -2.744)
p value vs. ECM	NA	0.0207

CI = confidence interval; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NP = nasal polyp; NPS = nasal polyp score; NSAID = non-steroidal anti-inflammatory disease; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 83. SNOT-22 total score and change from baseline in patients with ≥ 1 prior NP surgery and comorbid NSAID-ERD in SINUS-24 and SINUS-52 ITT population according to the response criteria of SNOT-22 total score (≥ 8.9 -point improvement)

	ECM (N=82)	Dupilumab Q2W (N=122)
Baseline		
<i>Responders at Week 24</i>		
Number	25	70
Mean (SD)	60.080 (17.776)	53.014 (17.080)
<i>Non-responders at Week 24</i>		
Number	40	20
Mean (SD)	53.775 (19.340)	43.950 (21.915)
Week 24		
<i>Responders at Week 24</i>		
Number	25	70
Mean (SD)	35.200 (20.185)	17.057 (10.642)
Change from baseline		
Number	25	70
Mean (SD)	-24.880 (13.547)	-35.957 (17.787)
LS mean (SE)	-20.509 (0.438)	-37.416 (0.297)
LS mean diff (95% CI)	NA	-16.908 (-17.806, -16.009)
p value vs. ECM	NA	<0.0001

	ECM (N=82)	Dupilumab Q2W (N=122)
Non-responders at Week 24		
Number	39	18
Mean (SD)	55.821 (19.562)	41.056 (21.114)
Change from baseline		
Number	39	18
Mean (SD)	2.256 (16.730)	-1.722 (10.203)
LS mean (SE)	2.611 (3.469)	-8.768 (4.625)
LS mean diff (95% CI)	NA	-11.380 (-20.936, -1.823)
p value vs. ECM	NA	0.0196
Week 52		
Responders at Week 24 AND Week 52		
Number	6	16
Mean (SD)	44.667 (28.395)	14.125 (11.575)
Change from baseline		
Number	6	16
Mean (SD)	-27.333 (11.928)	-38.813 (17.494)
LS mean (SE)	-16.273 (5.719)	-42.496 (3.541)
LS mean diff (95% CI)	NA	-26.223 (-41.598, -10.847)
p value vs. ECM	NA	0.0005
Non-responders at Week 24 OR Week 52		
Number	28	8
Mean (SD)	49.643 (21.287)	34.250 (33.623)
Change from baseline		
Number	28	8
Mean (SD)	-5.036 (17.137)	-6.000 (12.906)
LS mean (SE)	-2.311 (3.532)	-6.824 (6.218)
LS mean diff (95% CI)	NA	-4.513 (-17.853, 8.827)
p value vs. ECM	NA	0.5073

CI = confidence interval; ITT = intention-to-treat; LS = least squares; NA = not applicable; NP = nasal polyp; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test

Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 84. SNOT-22 total score and change from baseline in patients with ≥ 1 prior NP surgery and comorbid NSAID-ERD in SINUS-24 and SINUS-52 ITT population according to the response criteria of SNOT-22 total score (≥ 8.9 -point improvement) and NPS (≥ 1 -point improvement)

	ECM (N=82)	Dupilumab Q2W (N=122)
Baseline		
Responders at Week 24		
Number	7	55
Mean (SD)	51.714 (10.981)	53.782 (17.247)
Non-responders at Week 24		
Number	58	35
Mean (SD)	56.741 (19.602)	46.629 (19.833)
Week 24		
Responders at Week 24		
Number	7	55
Mean (SD)	25.857 (21.583)	17.345 (10.904)
Change from baseline		
Number	7	55

	ECM (N=82)	Dupilumab Q2W (N=122)
Mean (SD)	-25.857 (13.459)	-36.436 (18.460)
LS mean (SE)	-26.860 (0.750)	-37.497 (0.327)
LS mean diff (95% CI)	NA	-10.637 (-12.158, -9.117)
p value vs. ECM	NA	<0.0001
Non-responders at Week 24		
Number	57	33
Mean (SD)	50.456 (20.801)	29.667 (20.982)
Change from baseline		
Number	57	33
Mean (SD)	-6.193 (20.160)	-16.485 (20.743)
LS mean (SE)	-3.229 (3.235)	-20.431 (3.961)
LS mean diff (95% CI)	NA	-17.203 (-25.401, -9.004)
p value vs. ECM	NA	<0.0001
Week 52		
Responders at Week 24 AND Week 52		
Number	0	11
Mean (SD)	NA	12.909 (10.728)
Change from baseline		
Number	0	11
Mean (SD)	NA	-36.545 (16.281)
LS mean (SE)	NE	
LS mean diff (95% CI)	NA	NE
p value vs. ECM	NA	NE
Non-responders at Week 24 OR Week 52		
Number	34	13
Mean (SD)	48.765 (22.285)	27.538 (28.368)
Change from baseline		
Number	34	13
Mean (SD)	-8.971 (18.338)	-20.538 (24.700)
LS mean (SE)	-7.187 (3.775)	-23.353 (5.954)
LS mean diff (95% CI)	NA	-16.166 (-29.426, -2.906)
p value vs. ECM	NA	0.0169

CI = confidence interval; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NP = nasal polyp; NPS = nasal polyp score; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test Source: Sanofi. Data on File, Post-hoc analyses.¹

NPS

Table 85. NPS and change from baseline in patients with ≥1 prior NP surgery and comorbid NSAID-ERD in SINUS-24 and SINUS-52 ITT population according to the response criteria of NPS (≥1-point improvement)

	ECM (N=65)	Dupilumab Q2W (N=94)
Baseline		
<i>All</i>		
Number	64	94
Mean (SD)	5.656 (1.231)	5.830 (1.383)
Responders at Week 24		
Number	8	63
Mean (SD)	6.000 (0.845)	6.103 (1.154)
Non-responders at Week 24		

	ECM (N=65)	Dupilumab Q2W (N=94)
Number	56	31
Mean (SD)	5.607 (1.275)	5.274 (1.642)
Week 24		
<i>All</i>		
Number	64	88
Mean (SD)	5.781 (1.330)	3.926 (1.756)
Change from baseline		
Number	64	88
Mean (SD)	0.125 (1.218)	-1.881 (1.897)
LS mean (SE)	-0.123 (0.228)	-2.098 (0.201)
LS mean diff (95% CI)	NA	-1.975 (-2.462, -1.487)
p value vs. ECM	NA	<0.0001
<i>Responders at Week 24</i>		
Number	8	63
Mean (SD)	4.188 (1.413)	3.349 (1.593)
Change from baseline		
Number	8	63
Mean (SD)	-1.813 (1.335)	-2.754 (1.301)
LS mean (SE)	-1.937 (0.076)	-2.915 (0.033)
LS mean diff (95% CI)	NA	-0.978 (-1.130, -0.826)
p value vs. ECM	NA	<0.0001
<i>Non-responders at Week 24</i>		
Number	56	25
Mean (SD)	6.009 (1.162)	5.380 (1.244)
Change from baseline		
Number	56	25
Mean (SD)	0.402 (0.922)	0.320 (1.274)
LS mean (SE)	0.302 (0.212)	-0.621 (0.288)
LS mean diff (95% CI)	NA	-0.924 (-1.501, -0.346)
p value vs. ECM	NA	0.0017
Week 52		
<i>Responders at Week 24 AND Week 52</i>		
Number	0	16
Mean (SD)	NA	2.719 (1.414)
Change from baseline		
Number	0	16
Mean (SD)	NA	-3.281 (1.095)
LS mean (SE)	NE	-3.393 (0.327)
LS mean diff (95% CI)	NA	NE
p value vs. ECM	NA	NE
<i>Non-responders at Week 24 OR Week 52</i>		
Number	34	9
Mean (SD)	5.662 (1.778)	3.111 (2.781)
Change from baseline		
Number	34	9
Mean (SD)	-0.147 (1.294)	-2.056 (2.098)
LS mean (SE)	-0.211 (0.309)	-2.153 (0.576)
LS mean diff (95% CI)	NA	-1.943 (-3.188, -0.698)
p value vs. ECM	NA	0.0022

CI = confidence interval; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NP = nasal polyp; NPS = nasal polyp score; NSAID = non-steroidal anti-inflammatory disease; Q2W = once every two weeks; SD = standard deviation; SE = standard error
Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 86. NPS and change from baseline in patients with ≥ 1 prior NP surgery and comorbid NSAID-ERD in SINUS-24 and SINUS-52 ITT population according to the response criteria of SNOT-22 total score (≥ 8.9 -point improvement)

	ECM (N=65)	Dupilumab Q2W (N=94)
Baseline		
<i>Responders at Week 24</i>		
Number	24	70
Mean (SD)	5.438 (0.913)	5.829 (1.380)
<i>Non-responders at Week 24</i>		
Number	40	24
Mean (SD)	5.788 (1.382)	5.833 (1.419)
Week 24		
<i>Responders at Week 24</i>		
Number	24	67
Mean (SD)	4.958 (1.259)	3.567 (1.660)
Change from baseline		
Number	24	67
Mean (SD)	-0.479 (1.298)	-2.239 (1.900)
LS mean (SE)	-0.832 (0.355)	-2.372 (0.242)
LS mean diff (95% CI)	NA	-1.540 (-2.263, -0.816)
p value vs. ECM	NA	<0.0001
<i>Non-responders at Week 24</i>		
Number	40	21
Mean (SD)	6.275 (1.121)	5.071 (1.583)
Change from baseline		
Number	40	21
Mean (SD)	0.488 (1.022)	-0.738 (1.393)
LS mean (SE)	0.282 (0.253)	-1.241 (0.321)
LS mean diff (95% CI)	NA	-1.523 (-2.171, -0.875)
p value vs. ECM	NA	<0.0001
Week 52		
<i>Responders at Week 24 AND Week 52</i>		
Number	6	16
Mean (SD)	4.917 (2.558)	2.375 (1.500)
Change from baseline		
Number	6	16
Mean (SD)	-0.667 (1.835)	-3.250 (1.354)
LS mean (SE)	-1.003 (0.646)	-3.415 (0.403)
LS mean diff (95% CI)	NA	-2.412 (-3.887, -0.937)
p value vs. ECM	NA	0.0014
<i>Non-responders at Week 24 OR Week 52</i>		
Number	28	9
Mean (SD)	5.821 (1.582)	3.722 (2.464)
Change from baseline		
Number	28	9
Mean (SD)	-0.036 (1.162)	-2.111 (1.833)
LS mean (SE)	-0.186 (0.351)	-2.275 (0.555)

	ECM (N=65)	Dupilumab Q2W (N=94)
LS mean diff (95% CI)	NA	-2.090 (-3.281, -0.898)
p value vs. ECM	NA	0.0006

CI = confidence interval; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NA = not applicable; NP = nasal polyp; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test
Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 87. NPS and change from baseline in patients with ≥1 prior NP surgery and comorbid NSAID-ERD in SINUS-24 and SINUS-52 ITT population according to the response criteria of SNOT-22 total score (≥8.9-point improvement) and NPS (≥1-point improvement)

	ECM (N=65)	Dupilumab Q2W (N=94)
Baseline		
<i>Responders at Week 24</i>		
Number	7	55
Mean (SD)	5.929 (0.886)	6.100 (1.172)
<i>Non-responders at Week 24</i>		
Number	57	39
Mean (SD)	5.623 (1.269)	5.449 (1.572)
Week 24		
<i>Responders at Week 24</i>		
Number	7	55
Mean (SD)	4.071 (1.484)	3.245 (1.598)
Change from baseline		
Number	7	55
Mean (SD)	-1.857 (1.435)	-2.855 (1.304)
LS mean (SE)	-1.935 (0.081)	-2.997 (0.035)
LS mean diff (95% CI)	NA	-1.062 (-1.227, -0.898)
p value vs. ECM	NA	<0.0001
<i>Non-responders at Week 24</i>		
Number	57	33
Mean (SD)	5.991 (1.159)	5.061 (1.396)
Change from baseline		
Number	57	33
Mean (SD)	0.368 (0.947)	-0.258 (1.601)
LS mean (SE)	0.252 (0.217)	-0.911 (0.268)
LS mean diff (95% CI)	NA	-1.163 (-1.705, -0.620)
p value vs. ECM	NA	<0.0001
Week 52		
<i>Responders at Week 24 AND Week 52</i>		
Number	0	11
Mean (SD)	NA	2.500 (1.285)
Change from baseline		
Number	0	11
Mean (SD)	NA	-3.545 (1.011)
LS mean (SE)	NE	-3.534 (0.382)
LS mean diff (95% CI)	NA	NE
p value vs. ECM	NA	NE
<i>Non-responders at Week 24 OR Week 52</i>		
Number	34	14
Mean (SD)	5.662 (1.778)	3.143 (2.381)
Change from baseline		

	ECM (N=65)	Dupilumab Q2W (N=94)
Number	34	14
Mean (SD)	-0.147 (1.294)	-2.286 (1.794)
LS mean (SE)	-0.223 (0.301)	-2.427 (0.455)
LS mean diff (95% CI)	NA	-2.204 (-3.223, -1.185)
p value vs. ECM	NA	<0.0001

CI = confidence interval; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NP = nasal polyp; NPS = nasal polyp score; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test
Source: Sanofi. Data on File, Post-hoc analyses.¹

Mapped SNOT-22 to EQ-5D-3L health state utilities (Crump Models 1-3)

Table 88. Mapped SNOT-22 to EQ-5D-3L health state utilities (Crump Models 1-3) in patients with ≥ 1 prior NP surgery and comorbid NSAID-ERD in SINUS-24 and SINUS-52 ITT pooled population according to the response criteria of NPS (≥ 1 -point improvement)

	ECM (N=65)			Dupilumab Q2W (N=94)			All (N=159)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Baseline									
<i>All</i>									
Number	65	65	65	90	90	90	155	155	155
Mean (SD)	0.493 (0.128)	0.612 (0.175)	0.612 (0.172)	0.528 (0.126)	0.659 (0.163)	0.661 (0.166)	0.513 (0.128)	0.639 (0.169)	0.640 (0.170)
<i>Responders at Week 24</i>									
Number	8	8	8	60	60	60	68	68	68
Mean (SD)	0.535 (0.077)	0.661 (0.097)	0.652 (0.085)	0.520 (0.118)	0.648 (0.157)	0.650 (0.161)	0.522 (0.114)	0.650 (0.151)	0.650 (0.153)
<i>Non-responders at Week 24</i>									
Number	57	57	57	30	30	30	87	87	87
Mean (SD)	0.487 (0.133)	0.605 (0.182)	0.606 (0.181)	0.545 (0.140)	0.682 (0.175)	0.682 (0.178)	0.507 (0.138)	0.632 (0.182)	0.632 (0.183)
Week 24									
<i>All</i>									
Number	64	64	64	88	88	88	152	152	152
Mean (SD)	0.559 (0.154)	0.641 (0.177)	0.640 (0.177)	0.727 (0.108)	0.769 (0.124)	0.771 (0.131)	0.657 (0.153)	0.715 (0.161)	0.716 (0.165)
<i>Change from baseline</i>									
Number	64	64	64	88	88	88	152	152	152
Mean (SD)	0.066 (0.142)	0.029 (0.170)	0.028 (0.168)	0.199 (0.144)	0.110 (0.149)	0.111 (0.148)	0.143 (0.157)	0.076 (0.162)	0.076 (0.162)
LS mean (SE)	0.055 (0.018)	0.022 (0.019)	0.020 (0.020)	0.214 (0.016)	0.128 (0.017)	0.128 (0.018)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.159 (0.119, 0.198)	0.106 (0.064, 0.148)	0.107 (0.065, 0.150)	NA	NA	NA
p value vs. ECM	NA	NA	NA	<0.0001	<0.0001	<0.0001	NA	NA	NA
<i>Responders at Week 24</i>									
Number	8	8	8	59	59	59	67	67	67
Mean (SD)	0.681 (0.145)	0.728 (0.140)	0.719 (0.134)	0.750 (0.077)	0.774 (0.099)	0.777 (0.103)	0.741 (0.089)	0.769 (0.104)	0.770 (0.108)
<i>Change from baseline</i>									
Number	8	8	8	59	59	59	67	67	67
Mean (SD)	0.146 (0.119)	0.067 (0.143)	0.067 (0.141)	0.233 (0.134)	0.130 (0.153)	0.131 (0.153)	0.222 (0.134)	0.123 (0.152)	0.124 (0.152)

	ECM (N=65)			Dupilumab Q2W (N=94)			All (N=159)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
LS mean (SE)	0.160 (0.035)	0.091 (0.038)	0.080 (0.039)	0.239 (0.016)	0.147 (0.017)	0.147 (0.018)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.079 (0.009, 0.149)	0.056 (-0.021, 0.133)	0.067 (-0.011, 0.146)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.0260	0.1544	0.0924	NA	NA	NA
Non-responders at Week 24									
Number	56	56	56	29	29	29	85	85	85
Mean (SD)	0.542 (0.148)	0.629 (0.180)	0.629 (0.181)	0.682 (0.144)	0.757 (0.165)	0.757 (0.175)	0.590 (0.160)	0.673 (0.184)	0.673 (0.188)
Change from baseline									
Number	56	56	56	29	29	29	85	85	85
Mean (SD)	0.055 (0.142)	0.023 (0.174)	0.023 (0.172)	0.130 (0.141)	0.068 (0.131)	0.069 (0.132)	0.081 (0.145)	0.039 (0.161)	0.039 (0.160)
LS mean (SE)	0.040 (0.023)	0.008 (0.025)	0.009 (0.025)	0.155 (0.029)	0.094 (0.032)	0.093 (0.032)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.115 (0.055, 0.175)	0.085 (0.019, 0.151)	0.084 (0.018, 0.151)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.0002	0.0112	0.0131	NA	NA	NA
Week 52									
Responders at Week 24 AND Week 52									
Number	0	0	0	15	15	15	34	34	34
Mean (SD)	NA	NA	NA	0.766 (0.097)	0.787 (0.117)	0.793 (0.119)	0.767 (0.085)	0.780 (0.104)	0.783 (0.105)
Change from baseline									
Number	0	0	0	15	15	15	34	34	34
Mean (SD)	NA	NA	NA	0.195 (0.140)	0.082 (0.142)	0.081 (0.142)	0.244 (0.144)	0.121 (0.172)	0.121 (0.172)
LS mean (SE)	NE	NE	NE	0.244 (0.026)	0.124 (0.030)	0.122 (0.030)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	NE	NE	NA	NA	NA	NA
p value vs. ECM	NA	NA	NA	NE	NE	NA	NA	NA	NA
Non-responders at Week 24 AND Week 52									
Number	27	27	27	2	2	2	33	33	33
Mean (SD)	0.556 (0.157)	0.641 (0.195)	0.641 (0.201)	0.365 (0.202)	0.436 (0.289)	0.416 (0.277)	0.563 (0.167)	0.647 (0.199)	0.645 (0.204)
Change from baseline									
Number	27	27	27	2	2	2	33	33	33
Mean (SD)	0.100 (0.141)	0.077 (0.158)	0.077 (0.157)	0.010 (0.014)	0.001 (0.001)	-0.002 (0.003)	0.098 (0.134)	0.066 (0.145)	0.065 (0.143)
LS mean (SE)	0.082 (0.029)	0.051 (0.030)	0.049 (0.030)	-0.045 (0.099)	-0.072 (0.103)	-0.078 (0.104)	NA	NA	NA

	ECM (N=65)			Dupilumab Q2W (N=94)			All (N=159)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
LS mean diff (95% CI)	NA	NA	NA	-0.127 (-0.322, 0.068)	-0.123 (-0.325, 0.079)	-0.128 (-0.332, 0.077)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.2016	0.2331	0.2205	NA	NA	NA
<i>Non-responders at Week 24 OR Week 52</i>									
Number	34	34	34	9	9	9	54	54	54
Mean (SD)	0.576 (0.165)	0.657 (0.200)	0.657 (0.204)	0.686 (0.209)	0.704 (0.207)	0.711 (0.225)	0.629 (0.173)	0.695 (0.191)	0.695 (0.196)
<i>Change from baseline</i>									
Number	34	34	34	9	9	9	54	54	54
Mean (SD)	0.093 (0.144)	0.063 (0.168)	0.063 (0.164)	0.188 (0.168)	0.067 (0.189)	0.072 (0.190)	0.143 (0.170)	0.084 (0.173)	0.086 (0.171)
LS mean (SE)	0.083 (0.027)	0.046 (0.029)	0.046 (0.029)	0.181 (0.050)	0.069 (0.052)	0.073 (0.053)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.099 (-0.009, 0.207)	0.023 (-0.090, 0.136)	0.027 (-0.088, 0.142)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.0728	0.6929	0.6477	NA	NA	NA

CI = confidence interval; EQ-5D-3L = EuroQol 5-Dimension 3-Level; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NA = not applicable; NP = nasal polyp; NPS = nasal polyp score; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every two weeks; SD = standard deviation; SE = standard error
Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 89. Mapped SNOT-22 to EQ-5D-3L health state utilities (Crump Models 1-3) in patients with comorbid asthma in SINUS-24 and SINUS-52 ITT pooled population according to the response criteria of SNOT-22 total score (≥8.9-point improvement)

	ECM (N=65)			Dupilumab Q2W (N=94)			All (N=159)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Baseline									
<i>Responders at Week 24</i>									
Number	25	25	25	70	70	70	95	95	95
Mean (SD)	0.466 (0.121)	0.575 (0.171)	0.572 (0.171)	0.514 (0.116)	0.655 (0.158)	0.656 (0.160)	0.502 (0.119)	0.634 (0.165)	0.634 (0.166)
<i>Non-responders at Week 24</i>									
Number	40	40	40	20	20	20	60	60	60
Mean (SD)	0.509 (0.132)	0.635 (0.175)	0.636 (0.171)	0.576 (0.149)	0.676 (0.182)	0.679 (0.192)	0.531 (0.140)	0.649 (0.177)	0.650 (0.178)
Week 24									
<i>Responders at Week 24</i>									

	ECM (N=65)			Dupilumab Q2W (N=94)			All (N=159)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Number	25	25	25	70	70	70	95	95	95
Mean (SD)	0.635 (0.137)	0.715 (0.149)	0.711 (0.151)	0.759 (0.072)	0.792 (0.095)	0.794 (0.100)	0.726 (0.108)	0.772 (0.116)	0.772 (0.120)
Change from baseline									
Number	25	25	25	70	70	70	95	95	95
Mean (SD)	0.169 (0.092)	0.139 (0.107)	0.139 (0.105)	0.245 (0.121)	0.137 (0.150)	0.138 (0.150)	0.225 (0.118)	0.138 (0.140)	0.139 (0.139)
LS mean (SE)	0.139 (0.003)	0.106 (0.003)	0.104 (0.003)	0.254 (0.002)	0.159 (0.002)	0.159 (0.002)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.115 (0.109, 0.121)	0.052 (0.045, 0.059)	0.055 (0.048, 0.063)	NA	NA	NA
p value vs. ECM	NA	NA	NA	<0.0001	<0.0001	<0.0001	NA	NA	NA
Non-responders at Week 24									
Number	39	39	39	18	18	18	57	57	57
Mean (SD)	0.511 (0.145)	0.594 (0.180)	0.595 (0.180)	0.605 (0.136)	0.679 (0.178)	0.679 (0.189)	0.541 (0.148)	0.621 (0.182)	0.622 (0.185)
Change from baseline									
Number	39	39	39	18	18	18	57	57	57
Mean (SD)	0.000 (0.129)	-0.042 (0.165)	-0.042 (0.164)	0.022 (0.067)	0.003 (0.077)	0.003 (0.077)	0.007 (0.113)	-0.028 (0.144)	-0.028 (0.143)
LS mean (SE)	-0.002 (0.025)	-0.040 (0.029)	-0.042 (0.029)	0.067 (0.033)	0.025 (0.038)	0.023 (0.038)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.069 (-0.000, 0.138)	0.065 (-0.012, 0.142)	0.064 (-0.014, 0.142)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.0511	0.0978	0.1060	NA	NA	NA
Week 52									
Responders at Week 24 AND Week 52									
Number	6	6	6	16	16	16	47	47	47
Mean (SD)	0.571 (0.193)	0.620 (0.253)	0.609 (0.253)	0.779 (0.079)	0.788 (0.098)	0.796 (0.109)	0.748 (0.115)	0.764 (0.133)	0.766 (0.138)
Change from baseline									
Number	6	6	6	16	16	16	47	47	47
Mean (SD)	0.186 (0.081)	0.179 (0.040)	0.177 (0.044)	0.264 (0.119)	0.131 (0.159)	0.132 (0.160)	0.275 (0.133)	0.158 (0.166)	0.158 (0.166)
LS mean (SE)	0.111 (0.039)	0.052 (0.051)	0.047 (0.051)	0.289 (0.024)	0.160 (0.031)	0.163 (0.031)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.178 (0.074, 0.283)	0.108 (-0.028, 0.243)	0.116 (-0.021, 0.254)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.0005	0.0838	0.0665	NA	NA	NA

	ECM (N=65)			Dupilumab Q2W (N=94)			All (N=159)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
<i>Non-responders at Week 24 AND Week 52</i>									
Number	21	21	21	3	3	3	27	27	27
Mean (SD)	0.545 (0.168)	0.636 (0.202)	0.637 (0.206)	0.426 (0.178)	0.444 (0.205)	0.434 (0.199)	0.543 (0.165)	0.627 (0.202)	0.627 (0.206)
Change from baseline									
Number	21	21	21	3	3	3	27	27	27
Mean (SD)	0.047 (0.156)	0.014 (0.180)	0.015 (0.178)	-0.016 (0.046)	-0.061 (0.107)	-0.060 (0.101)	0.036 (0.139)	0.009 (0.163)	0.010 (0.161)
LS mean (SE)	0.038 (0.034)	0.014 (0.039)	0.013 (0.039)	-0.053 (0.087)	-0.106 (0.102)	-0.108 (0.103)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	-0.091 (-0.262, 0.081)	-0.120 (-0.321, 0.081)	-0.121 (-0.324, 0.082)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.2992	0.2429	0.2425	NA	NA	NA
<i>Non-responders at Week 24 OR Week 52</i>									
Number	28	28	28	8	8	8	41	41	41
Mean (SD)	0.577 (0.162)	0.665 (0.192)	0.667 (0.195)	0.651 (0.220)	0.691 (0.233)	0.695 (0.242)	0.607 (0.172)	0.686 (0.193)	0.687 (0.197)
Change from baseline									
Number	28	28	28	8	8	8	41	41	41
Mean (SD)	0.074 (0.148)	0.038 (0.174)	0.039 (0.171)	0.050 (0.080)	-0.031 (0.084)	-0.030 (0.080)	0.075 (0.137)	0.031 (0.156)	0.032 (0.153)
LS mean (SE)	0.053 (0.030)	0.017 (0.033)	0.016 (0.033)	0.062 (0.053)	-0.017 (0.057)	-0.021 (0.056)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.009 (-0.104, 0.122)	-0.034 (-0.155, 0.087)	-0.037 (-0.157, 0.084)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.8741	0.5823	0.5489	NA	NA	NA

CI = confidence interval; EQ-5D-3L = EuroQol 5-Dimension 3-Level; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NA = not applicable; NP = nasal polyp; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test
Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 90. Mapped SNOT-22 to EQ-5D-3L health state utilities (Crump Models 1-3) in patients with ≥ 1 prior NP surgery and comorbid NSAID-ERD in SINUS-24 and SINUS-52 ITT pooled population according to the response criteria of SNOT-22 total score (≥ 8.9 -point improvement) and NPS (≥ 1 -point improvement)

	ECM (N=65)			Dupilumab Q2W (N=94)			All (N=159)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Baseline									
<i>Responders at Week 24</i>									
Number	7	7	7	55	55	55	62	62	62
Mean (SD)	0.523 (0.075)	0.653 (0.101)	0.646 (0.090)	0.509 (0.117)	0.641 (0.159)	0.643 (0.163)	0.511 (0.113)	0.643 (0.153)	0.643 (0.156)
<i>Non-responders at Week 24</i>									
Number	58	58	58	35	35	35	93	93	93
Mean (SD)	0.489 (0.133)	0.607 (0.181)	0.607 (0.180)	0.558 (0.135)	0.688 (0.167)	0.689 (0.171)	0.515 (0.137)	0.637 (0.180)	0.638 (0.180)
Week 24									
<i>Responders at Week 24</i>									
Number	7	7	7	55	55	55	62	62	62
Mean (SD)	0.699 (0.147)	0.757 (0.122)	0.751 (0.108)	0.757 (0.074)	0.783 (0.095)	0.786 (0.100)	0.750 (0.086)	0.780 (0.098)	0.782 (0.101)
<i>Change from baseline</i>									
Number	7	7	7	55	55	55	62	62	62
Mean (SD)	0.176 (0.092)	0.104 (0.103)	0.105 (0.099)	0.248 (0.126)	0.142 (0.151)	0.143 (0.150)	0.240 (0.124)	0.138 (0.146)	0.139 (0.145)
LS mean (SE)	0.183 (0.005)	0.120 (0.006)	0.110 (0.006)	0.255 (0.002)	0.161 (0.002)	0.161 (0.002)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.072 (0.062, 0.083)	0.042 (0.030, 0.053)	0.051 (0.039, 0.062)	NA	NA	NA
p value vs. ECM	NA	NA	NA	<0.0001	<0.0001	<0.0001	NA	NA	NA
<i>Non-responders at Week 24</i>									
Number	57	57	57	33	33	33	90	90	90
Mean (SD)	0.542 (0.147)	0.627 (0.179)	0.627 (0.180)	0.678 (0.136)	0.744 (0.160)	0.745 (0.168)	0.592 (0.157)	0.670 (0.180)	0.670 (0.184)
<i>Change from baseline</i>									
Number	57	57	57	33	33	33	90	90	90
Mean (SD)	0.053 (0.142)	0.019 (0.175)	0.019 (0.173)	0.117 (0.136)	0.056 (0.130)	0.057 (0.131)	0.076 (0.143)	0.033 (0.160)	0.033 (0.159)
LS mean (SE)	0.034 (0.022)	0.005 (0.025)	0.005 (0.025)	0.144 (0.027)	0.080 (0.030)	0.080 (0.030)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.110 (0.054, 0.167)	0.076 (0.014, 0.138)	0.075 (0.013, 0.138)	NA	NA	NA

	ECM (N=65)			Dupilumab Q2W (N=94)			All (N=159)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
p value vs. ECM	NA	NA	NA	0.0001	0.0170	0.0187	NA	NA	NA
Week 52									
<i>Responders at Week 24 AND Week 52</i>									
Number	0	0	0	11	11	11	30	30	30
Mean (SD)	NA	NA	NA	0.787 (0.073)	0.803 (0.085)	0.810 (0.089)	0.775 (0.075)	0.785 (0.091)	0.788 (0.093)
Change from baseline									
Number	0	0	0	11	11	11	30	30	30
Mean (SD)	NA	NA	NA	0.249 (0.111)	0.120 (0.134)	0.119 (0.137)	0.270 (0.128)	0.140 (0.171)	0.140 (0.171)
LS mean (SE)	NE	NE	NE	0.279 (0.024)	0.155 (0.030)	0.154 (0.030)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	NE	NE	NE	NA	NA	NA
p value vs. ECM	NA	NA	NA	NE	NE	NE	NA	NA	NA
<i>Non-responders at Week 24 AND Week 52</i>									
Number	31	31	31	3	3	3	39	39	39
Mean (SD)	0.564 (0.162)	0.647 (0.202)	0.648 (0.206)	0.426 (0.178)	0.444 (0.205)	0.434 (0.199)	0.572 (0.167)	0.649 (0.202)	0.649 (0.206)
Change from baseline									
Number	31	31	31	3	3	3	39	39	39
Mean (SD)	0.082 (0.144)	0.053 (0.172)	0.053 (0.169)	-0.016 (0.046)	-0.061 (0.107)	-0.060 (0.101)	0.077 (0.138)	0.042 (0.158)	0.042 (0.155)
LS mean (SE)	0.071 (0.027)	0.038 (0.030)	0.038 (0.030)	-0.045 (0.081)	-0.112 (0.092)	-0.115 (0.092)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	-0.116 (-0.275, 0.044)	-0.151 (-0.331, 0.029)	-0.152 (-0.332, 0.028)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.1549	0.1009	0.0980	NA	NA	NA
<i>Non-responders at Week 24 OR Week 52</i>									
Number	34	34	34	13	13	13	58	58	58
Mean (SD)	0.576 (0.165)	0.657 (0.200)	0.657 (0.204)	0.693 (0.186)	0.716 (0.195)	0.722 (0.208)	0.635 (0.172)	0.698 (0.189)	0.699 (0.194)
Change from baseline									
Number	34	34	34	13	13	13	58	58	58
Mean (SD)	0.093 (0.144)	0.063 (0.168)	0.063 (0.164)	0.145 (0.162)	0.040 (0.171)	0.043 (0.170)	0.136 (0.168)	0.077 (0.171)	0.079 (0.169)
LS mean (SE)	0.078 (0.027)	0.045 (0.028)	0.045 (0.029)	0.161 (0.042)	0.056 (0.044)	0.058 (0.045)	NA	NA	NA

	ECM (N=65)			Dupilumab Q2W (N=94)			All (N=159)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
LS mean diff (95% CI)	NA	NA	NA	0.083 (-0.011, 0.177)	0.011 (-0.087, 0.110)	0.013 (-0.087, 0.113)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.0836	0.8218	0.7965	NA	NA	NA

CI = confidence interval; EQ-5D-3L = EuroQol 5-Dimension 3-Level; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NP = nasal polyp; NPS = nasal polyp score; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test

Source: Sanofi. Data on File, Post-hoc analyses.¹

EQ-5D-5L utilities (Hernandez 2020 crosswalk method, UK tariffs)

Table 91. EQ-5D-5L utilities (Hernandez 2020 crosswalk method, UK tariffs) in patients with ≥ 1 prior NP surgery and comorbid NSAID-ERD in SINUS-24 and SINUS-52 ITT pooled population according to the response criteria of NPS (≥ 1 -point improvement)

	ECM (N=65)	Dupilumab Q2W (N=94)
Baseline		
<i>All</i>		
Number	65	87
Mean (SD)	0.748 (0.148)	0.782 (0.186)
<i>Responders at Week 24</i>		
Number	8	58
Mean (SD)	0.790 (0.118)	0.798 (0.158)
<i>Non-responders at Week 24</i>		
Number	57	29
Mean (SD)	0.742 (0.152)	0.750 (0.231)
Week 24		
<i>All</i>		
Number	63	85
Mean (SD)	0.780 (0.180)	0.854 (0.195)
Change from baseline		
Number	63	85
Mean (SD)	0.033 (0.144)	0.072 (0.156)
LS mean (SE)	0.028 (0.021)	0.080 (0.019)
LS mean diff (95% CI)	NA	0.052 (0.007, 0.097)
p value vs. ECM	NA	0.0243
<i>Responders at Week 24</i>		
Number	8	57
Mean (SD)	0.889 (0.119)	0.873 (0.156)
Change from baseline		
Number	8	57
Mean (SD)	0.099 (0.190)	0.078 (0.154)
LS mean (SE)	0.087 (0.052)	0.087 (0.024)
LS mean diff (95% CI)	NA	0.000 (-0.105, 0.106)
p value vs. ECM	NA	0.9936
<i>Non-responders at Week 24</i>		
Number	55	28
Mean (SD)	0.764 (0.182)	0.815 (0.256)
Change from baseline		
Number	55	28
Mean (SD)	0.024 (0.136)	0.061 (0.164)
LS mean (SE)	0.025 (0.025)	0.064 (0.031)
LS mean diff (95% CI)	NA	0.039 (-0.025, 0.103)
p value vs. ECM	NA	0.2339
Week 52		
<i>Responders at Week 24 AND Week 52</i>		
Number	0	14
Mean (SD)	NA	0.903 (0.124)
Change from baseline		
Number	0	14
Mean (SD)	NA	0.063 (0.098)

	ECM (N=65)	Dupilumab Q2W (N=94)
LS mean (SE)	NE	0.081 (0.025)
LS mean diff (95% CI)	NA	NE
p value vs. ECM	NA	NE
Non-responders at Week 24 AND Week 52		
Number	27	2
Mean (SD)	0.739 (0.271)	0.206 (0.621)
Change from baseline		
Number	27	2
Mean (SD)	0.013 (0.215)	0.000 (0.000)
LS mean (SE)	-0.013 (0.045)	-0.031 (0.183)
LS mean diff (95% CI)	NA	-0.018 (-0.381, 0.346)
p value vs. ECM	NA	0.9228
Non-responders at Week 24 OR Week 52		
Number	34	9
Mean (SD)	0.769 (0.256)	0.745 (0.397)
Change from baseline		
Number	34	9
Mean (SD)	0.023 (0.202)	0.065 (0.122)
LS mean (SE)	0.013 (0.036)	0.064 (0.066)
LS mean diff (95% CI)	NA	0.050 (-0.092, 0.193)
p value vs. ECM	NA	0.4896

CI = confidence interval; EQ-5D-5L = EuroQol 5-Dimension 5-Level; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NP = nasal polyp; NPS = nasal polyp score; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every two weeks; SD = standard deviation; SE = standard error
Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 92. EQ-5D-5L utilities (Hernandez 2020 crosswalk method, UK tariffs) in patients with ≥1 prior NP surgery and comorbid NSAID-ERD in SINUS-24 and SINUS-52 ITT pooled population according to the response criteria of SNOT-22 total score (≥8.9-point improvement)

	ECM (N=65)	Dupilumab Q2W (N=94)
Baseline		
Responders at Week 24		
Number	25	69
Mean (SD)	0.761 (0.147)	0.793 (0.154)
Non-responders at Week 24		
Number	40	18
Mean (SD)	0.740 (0.151)	0.743 (0.278)
Week 24		
Responders at Week 24		
Number	25	69
Mean (SD)	0.852 (0.131)	0.882 (0.155)
Change from baseline		
Number	Number	25
Mean (SD)	Mean (SD)	0.091 (0.143)
LS mean (SE)	0.064 (0.004)	0.092 (0.003)
LS mean diff (95% CI)	NA	0.028 (0.019, 0.037)
p value vs. ECM	NA	<0.0001
Non-responders at Week 24		
Number	38	16
Mean (SD)	0.732 (0.193)	0.735 (0.294)
Change from baseline		

	ECM (N=65)	Dupilumab Q2W (N=94)
Number	38	16
Mean (SD)	-0.005 (0.134)	0.001 (0.097)
LS mean (SE)	0.015 (0.028)	0.027 (0.037)
LS mean diff (95% CI)	NA	0.012 (-0.064, 0.088)
p value vs. ECM	NA	0.7618
Week 52		
<i>Responders at Week 24 AND Week 52</i>		
Number	6	15
Mean (SD)	0.724 (0.292)	0.904 (0.123)
Change from baseline		
Number	6	15
Mean (SD)	0.032 (0.159)	0.094 (0.100)
LS mean (SE)	-0.009 (0.055)	0.091 (0.035)
LS mean diff (95% CI)	NA	0.100 (-0.046, 0.247)
p value vs. ECM	NA	0.1318
<i>Non-responders at Week 24 AND Week 52</i>		
Number	21	3
Mean (SD)	0.726 (0.271)	0.338 (0.495)
Change from baseline		
Number	21	3
Mean (SD)	0.001 (0.237)	-0.028 (0.048)
LS mean (SE)	-0.013 (0.053)	-0.120 (0.153)
LS mean diff (95% CI)	NA	-0.107 (-0.415, 0.202)
p value vs. ECM	NA	0.4976
<i>Non-responders at Week 24 OR Week 52</i>		
Number	28	8
Mean (SD)	0.779 (0.253)	0.724 (0.416)
Change from baseline		
Number	28	8
Mean (SD)	0.021 (0.213)	0.007 (0.096)
LS mean (SE)	0.014 (0.041)	-0.003 (0.069)
LS mean diff (95% CI)	NA	-0.017 (-0.164, 0.130)
p value vs. ECM	NA	0.8178

CI = confidence interval; EQ-5D-5L = EuroQol 5-Dimension 5-Level; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NA = not applicable; NP = nasal polyp; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test
Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 93. EQ-5D-5L utilities (Hernandez 2020 crosswalk method, UK tariffs) in patients with ≥1 prior NP surgery and comorbid NSAID-ERD in SINUS-24 and SINUS-52 ITT pooled population according to the response criteria of SNOT-22 total score (≥8.9-point improvement) and NPS (≥1-point improvement)

	ECM (N=65)	Dupilumab Q2W (N=94)
Baseline		
<i>Responders at Week 24</i>		
Number	7	54
Mean (SD)	0.795 (0.126)	0.795 (0.159)
<i>Non-responders at Week 24</i>		

	ECM (N=65)	Dupilumab Q2W (N=94)
Number	58	33
Mean (SD)	0.742 (0.151)	0.762 (0.224)
Week 24		
<i>Responders at Week 24</i>		
Number	7	54
Mean (SD)	0.886 (0.128)	0.875 (0.157)
Change from baseline		
Number	7	54
Mean (SD)	0.091 (0.203)	0.081 (0.155)
LS mean (SE)	0.084 (0.008)	0.093 (0.004)
LS mean diff (95% CI)	NA	0.009 (-0.007, 0.026)
p value vs. ECM	NA	0.2708
<i>Non-responders at Week 24</i>		
Number	56	31
Mean (SD)	0.767 (0.182)	0.816 (0.247)
Change from baseline		
Number	56	31
Mean (SD)	0.026 (0.136)	0.058 (0.160)
LS mean (SE)	0.025 (0.024)	0.059 (0.030)
LS mean diff (95% CI)	NA	0.034 (-0.028, 0.095)
p value vs. ECM	NA	0.2816
Week 52		
<i>Responders at Week 24 AND Week 52</i>		
Number	0	10
Mean (SD)	NA	0.915 (0.102)
Change from baseline		
Number	0	10
Mean (SD)	NA	0.090 (0.090)
LS mean (SE)	NE	0.104 (0.027)
LS mean diff (95% CI)	NA	NE
p value vs. ECM	NA	NE
<i>Non-responders at Week 24 AND Week 52</i>		
Number	31	3
Mean (SD)	0.756 (0.262)	0.338 (0.495)
Change from baseline		
Number	31	3
Mean (SD)	0.007 (0.205)	-0.028 (0.048)
LS mean (SE)	-0.009 (0.039)	-0.071 (0.135)
LS mean diff (95% CI)	NA	-0.062 (-0.329, 0.204)
p value vs. ECM	NA	0.6461
<i>Non-responders at Week 24 OR Week 52</i>		
Number	34	13
Mean (SD)	0.769 (0.256)	0.785 (0.342)
Change from baseline		
Number	34	13
Mean (SD)	0.023 (0.202)	0.044 (0.115)
LS mean (SE)	0.015 (0.035)	0.044 (0.054)
LS mean diff (95% CI)	NA	0.029 (-0.090, 0.148)
p value vs. ECM	NA	0.6343

CI = confidence interval; EQ-5D-5L = EuroQol 5-Dimension 5-Level; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NP = nasal polyp; NPS = nasal polyp score; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test

Source: Sanofi. Data on File, Post-hoc analyses.¹

Patients with ≥ 1 prior NP surgery and comorbid asthma

Baseline characteristics

Table 94. Baseline characteristics of patients with ≥ 1 prior NP surgery and comorbid asthma in SINUS-24 and SINUS-52 pooled ITT population

	ECM	Dupilumab Q2W	All
N	121	121	304
Male, n (%)	54 (44.6)	63 (52.1)	151 (49.7)
Age, mean (SD)	50.54 (13.19)	51.60 (12.36)	51.58 (12.60)
Race, n (%)			
Caucasian/White	108 (89.3)	112 (92.6)	270 (88.8)
Black/African decent	3 (2.5)	1 (0.8)	5 (1.6)
Asian/Oriental	9 (7.4)	5 (4.1)	24 (7.9)
American Indian/Alaska Native	1 (0.8)	3 (2.5)	4 (1.3)
Native Hawaiian/Other Pacific Islander	0	0	0
Multiple	0	0	1 (0.3)
Unknown	0	0	0
Ethnicity			
Hispanic or Latino	10 (8.4)	16 (13.2)	31 (10.3)
Not Hispanic or Latino	109 (91.6)	105 (86.8)	271 (89.7)
Territory			
North America	18 (14.9)	20 (16.5)	53 (17.4)
European Union	50 (41.3)	53 (43.8)	116 (38.2)
Rest of the World	53 (43.8)	48 (39.7)	135 (44.4)
BMI (kg/m ²), mean (SD)	27.60 (5.95)	27.36 (4.46)	27.47 (5.23)
Time since first diagnosis of nasal polyps (years), mean (SD)	14.50 (9.39)	15.51 (10.37)	14.61 (9.60)
≥ 3 previous surgery for nasal polyps, n (%)	33 (27.3)	40 (33.1)	81 (26.6)
Time since most recent surgery for nasal polyps (years), mean (SD)	7.23 (6.43)	6.61 (5.37)	6.91 (5.74)
SCS use in the past 2 years, n (%)	81 (66.9)	79 (65.3)	204 (67.1)
Bilateral endoscopic NPS* (scale 0-8), mean (SD)	5.65 (1.28)	5.73 (1.26)	5.83 (1.25)
NC score* (scale 0-3), mean (SD)	2.47 (0.51)	2.39 (0.63)	2.45 (0.57)
SNOT-22 total score* (scale 0-110), mean (SD)	57.36 (19.00)	50.44 (19.27)	53.98 (19.43)
Smell test (UPSIT) score** (scale 0-40), mean (SD)	12.76 (7.24)	11.70 (6.78)	11.93 (6.57)
LoS score* (scale 0-3), mean (SD)	2.79 (0.48)	2.87 (0.39)	2.83 (0.47)
LMK-CT total score* (scale 0-24), mean (SD)	19.26 (3.93)	19.48 (3.91)	19.39 (3.78)
Rhinosinusitis disease severity* (VAS 0-10cm), mean (SD)	8.10 (2.17)	7.92 (1.85)	8.01 (2.07)
Baseline NPIF** (L/min), mean (SD)	90.82 (57.59)	91.68 (55.97)	91.90 (59.26)
Baseline blood eosinophils (x10 ⁹ cells/L), mean (SD)	0.52 (0.34)	0.59 (0.47)	0.54 (0.40)

	ECM	Dupilumab Q2W	All
Comorbid NSAID-ERD, n (%)	57 (47.1)	55 (45.5)	141 (46.4)
Any comorbid type 2 medical history excluding asthma and NSAID-ERD, n (%)	89 (73.6)	83 (68.6)	219 (72.0)
Age of asthma onset in patients with comorbid asthma (years), mean (SD)	32.91 (14.88)	34.55 (14.50)	33.98 (15.28)
Baseline ACQ-6 score*, mean (SD)	1.59 (1.06)	1.46 (1.07)	1.53 (1.09)
Baseline GINA 4 or 5, n (%)	57 (47.1)	64 (35.0)	121 (39.8)

ACQ-6 = 6-item Asthma Control Questionnaire; BMI = body mass index; ITT = intention-to-treat; LMK-CT = Lund-Mackay computed tomography; LoS = loss-of-smell; NC = nasal congestion/obstruction; NP = nasal polyp; NPIF = peak nasal inspiratory flow; NPS = nasal polyp score; Q2W = every 2 weeks; SD = standard deviation; SNOT-22 = 22-item Sino-Nasal Outcome Test; UPSIT = University of Pennsylvania Smell Identification Test; VAS = visual analogue scale

*Higher scores indicate greater disease severity.

** Higher scores indicate lower disease severity.

Source: Sanofi. Data on File, Post-hoc analyses.¹

Response rates

Table 95. Response rates for patients with ≥ 1 prior NP surgery and comorbid asthma in SINUS-24 and SINUS-52 pooled ITT population according to the different response criteria

	ECM (N=121)	Dupilumab Q2W (N=183)
Overall response at Week 24		
NPS (≥ 1-point improvement)		
Responders, n (%)	18 (14.9)	123 (67.2)
Non-responders, n (%)	103 (85.1)	60 (32.8)
SNOT-22 total score (≥ 8.9-point improvement)		
Responders, n (%)	51 (42.1)	137 (74.9)
Non-responders, n (%)	70 (57.9)	46 (25.1)
SNOT-22 total score (≥ 8.9-point improvement) and NPS (≥ 1-point improvement)		
Responders, n (%)	14 (11.6)	108 (59.0)
Non-responders, n (%)	107 (88.4)	75 (41.0)
Overall response at Week 52		
All		
NPS (≥ 1-point improvement)		
Responders, n (%)	7 (11.5)	43 (75.4)
Non-responders, n (%)	54 (88.5)	14 (24.6)
SNOT-22 total score (≥ 8.9-point improvement)		
Responders, n (%)	13 (21.3)	43 (75.4)
Non-responders, n (%)	48 (78.7)	14 (24.6)
SNOT-22 total score (≥ 8.9-point improvement) and NPS (≥ 1-point improvement)		
Responders, n (%)	3 (4.9)	38 (66.7)
Non-responders, n (%)	58 (95.1)	19 (33.3)
Responders at Week 24		
NPS (≥ 1-point improvement)		
Responders, n (%)	1 (20.0)	36 (97.3)
Non-responders, n (%)	4 (80.0)	1 (2.7)
SNOT-22 total score (≥ 8.9-point improvement)		
Responders, n (%)	11 (45.8)	39 (95.1)
Non-responders, n (%)	13 (54.2)	2 (4.9)
SNOT-22 total score (≥ 8.9-point improvement) and NPS (≥ 1-point improvement)		
	ECM (N=3)	Dupilumab Q2W (N=32)

	ECM (N=121)	Dupilumab Q2W (N=183)
Responders, n (%)	0	30 (93.8)
Non-responders, n (%)	3 (100)	2 (6.3)
Non-responders at Week 24		
NPS (≥1-point improvement)	ECM (N=56)	Dupilumab Q2W (N=20)
Responders, n (%)	6 (10.7)	7 (35.0)
Non-responders, n (%)	50 (89.3)	13 (65.0)
SNOT-22 total score (≥8.9-point improvement)	ECM (N=37)	Dupilumab Q2W (N=16)
Responders, n (%)	2 (5.4)	4 (25.0)
Non-responders, n (%)	35 (94.6)	12 (75.0)
SNOT-22 total score (≥8.9-point improvement) and NPS (≥1-point improvement)	ECM (N=58)	Dupilumab Q2W (N=25)
Responders, n (%)	3 (5.2)	8 (32.0)
Non-responders, n (%)	55 (94.8)	17 (68.0)

ITT = intention-to-treat; NP = nasal polyp; NPS = nasal polyp score; Q2W = once every two weeks; SNOT-22: 22-item Sino Nasal Outcome Test

Source: Sanofi. Data on File, Post-hoc analyses.¹

SNOT-22 total score

Table 96. SNOT-22 total score and change from baseline in patients with ≥1 prior NP surgery and comorbid asthma in SINUS-24 and SINUS-52 ITT population according to the response criteria of NPS (≥1-point improvement)

	ECM (N=121)	Dupilumab Q2W (N=183)
Baseline		
<i>All</i>		
Number	120	178
Mean (SD)	57.358 (18.998)	51.697 (19.443)
<i>Responders at Week 24</i>		
Number	18	120
Mean (SD)	48.556 (12.757)	53.817 (19.018)
<i>Non-responders at Week 24</i>		
Number	102	58
Mean (SD)	58.912 (19.535)	47.310 (19.743)
Week 24		
<i>All</i>		
Number	112	173
Mean (SD)	45.661 (22.316)	21.775 (16.485)
Change from baseline		
Number	112	173
Mean (SD)	-10.902 (19.787)	-30.185 (21.805)
LS mean (SE)	-8.484 (1.907)	-30.905 (1.706)
LS mean diff (95% CI)	NA	-22.420 (-26.601, -18.240)
p value vs. ECM	NA	<0.0001
<i>Responders at Week 24</i>		
Number	18	118
Mean (SD)	30.111 (19.393)	19.356 (13.896)
Change from baseline		
Number	18	118
Mean (SD)	-18.444 (14.983)	-34.627 (20.532)
LS mean (SE)	-22.481 (3.671)	-35.343 (1.883)

	ECM (N=121)	Dupilumab Q2W (N=183)
LS mean diff (95% CI)	NA	-12.862 (-20.266, -5.458)
p value vs. ECM	NA	0.0007
<i>Non-responders at Week 24</i>		
Number	94	55
Mean (SD)	48.638 (21.676)	26.964 (20.173)
Change from baseline		
Number	94	55
Mean (SD)	-9.457 (20.326)	-20.655 (21.573)
LS mean (SE)	-6.212 (2.372)	-22.886 (2.869)
LS mean diff (95% CI)	NA	-16.674 (-22.965, -10.382)
p value vs. ECM	NA	<0.0001
Week 52		
<i>Responders at Week 24 AND Week 52</i>		
Number	1	35
Mean (SD)	26.000 (NC)	16.286 (16.233)
Change from baseline		
Number	1	35
Mean (SD)	-8.000 (NC)	-34.200 (20.116)
LS mean (SE)	-26.413 (15.359)	-35.517 (2.810)
LS mean diff (95% CI)	NA	-9.105 (-41.924, 23.714)
p value vs. ECM	NA	0.5659
<i>Non-responders at Week 24 OR Week 52</i>		
Number	55	18
Mean (SD)	50.455 (21.424)	29.722 (25.139)
Change from baseline		
Number	55	18
Mean (SD)	-8.309 (16.982)	-24.667 (21.332)
LS mean (SE)	-7.302 (2.715)	-26.153 (4.406)
LS mean diff (95% CI)	NA	-18.851 (-28.560, -9.142)
p value vs. ECM	NA	0.0001

CI = confidence interval; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NP = nasal polyp; NPS = nasal polyp score; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test

Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 97. SNOT-22 total score and change from baseline in patients with ≥ 1 prior NP surgery and comorbid asthma in SINUS-24 and SINUS-52 ITT population according to the response criteria of SNOT-22 total score (≥ 8.9 -point improvement)

	ECM (N=121)	Dupilumab Q2W (N=183)
Baseline		
<i>Responders at Week 24</i>		
Number	51	137
Mean (SD)	56.647 (19.549)	55.117 (18.059)
<i>Non-responders at Week 24</i>		
Number	69	41
Mean (SD)	57.884 (18.707)	40.268 (19.751)
Week 24		
<i>Responders at Week 24</i>		
Number	51	137
Mean (SD)	31.157 (17.597)	18.080 (13.104)
Change from baseline		

	ECM (N=121)	Dupilumab Q2W (N=183)
Number	51	137
Mean (SD)	-25.490 (15.052)	-37.036 (18.433)
LS mean (SE)	-23.770 (0.323)	-36.890 (0.232)
LS mean diff (95% CI)	NA	-13.120 (-13.775, -12.464)
p value vs. ECM	NA	<0.0001
Non-responders at Week 24		
Number	61	36
Mean (SD)	57.787 (18.301)	35.833 (20.284)
Change from baseline		
Number	61	36
Mean (SD)	1.295 (14.260)	-4.111 (11.538)
LS mean (SE)	0.895 (2.381)	-10.517 (3.074)
LS mean diff (95% CI)	NA	-11.412 (-18.270, -4.555)
p value vs. ECM	NA	0.0011
Week 52		
Responders at Week 24 AND Week 52		
Number	11	39
Mean (SD)	40.000 (24.384)	15.436 (15.639)
Change from baseline		
Number	11	39
Mean (SD)	-27.727 (11.628)	-38.436 (16.626)
LS mean (SE)	-21.449 (4.320)	-39.599 (2.423)
LS mean diff (95% CI)	NA	-18.149 (-28.895, -7.404)
p value vs. ECM	NA	0.0004
Non-responders at Week 24 OR Week 52		
Number	45	14
Mean (SD)	52.467 (20.256)	35.929 (25.159)
Change from baseline		
Number	45	14
Mean (SD)	-3.556 (14.347)	-10.143 (17.150)
LS mean (SE)	-3.262 (2.577)	-13.064 (4.489)
LS mean diff (95% CI)	NA	-9.802 (-19.509, -0.094)
p value vs. ECM	NA	0.0478

CI = confidence interval; ITT = intention-to-treat; LS = least squares; NA = not applicable; NP = nasal polyp; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test
Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 98. SNOT-22 total score and change from baseline in patients with ≥ 1 prior NP surgery and comorbid asthma in SINUS-24 and SINUS-52 ITT population according to the response criteria of SNOT-22 total score (≥ 8.9 -point improvement) and NPS (≥ 1 -point improvement)

	ECM (N=121)	Dupilumab Q2W (N=183)
Baseline		
Responders at Week 24		
Number	14	108
Mean (SD)	49.214 (12.398)	56.343 (17.687)
Non-responders at Week 24		
Number	106	70
Mean (SD)	58.434 (19.494)	44.529 (19.969)
Week 24		
Responders at Week 24		
Number	14	108

	ECM (N=121)	Dupilumab Q2W (N=183)
Mean (SD)	24.857 (18.038)	18.713 (13.902)
Change from baseline		
Number	14	108
Mean (SD)	-24.357 (10.674)	-37.630 (18.733)
LS mean (SE)	-28.533 (0.627)	-37.451 (0.288)
LS mean diff (95% CI)	NA	-8.917 (-10.168, -7.667)
p value vs. ECM	NA	<0.0001
<i>Non-responders at Week 24</i>		
Number	98	65
Mean (SD)	48.633 (21.328)	26.862 (19.107)
Change from baseline		
Number	98	65
Mean (SD)	-8.980 (20.072)	-17.815 (21.027)
LS mean (SE)	-5.438 (2.271)	-21.776 (2.673)
LS mean diff (95% CI)	NA	-16.337 (-22.227, -10.448)
p value vs. ECM	NA	<0.0001
Week 52		
<i>Responders at Week 24 AND Week 52</i>		
Number	0	30
Mean (SD)	NA	14.867 (15.741)
Change from baseline		
Number	0	30
Mean (SD)	NA	-39.067 (16.513)
LS mean (SE)	NE	-39.620 (2.766)
LS mean diff (95% CI)	NA	NE
p value vs. ECM	NA	NE
<i>Non-responders at Week 24 OR Week 52</i>		
Number	56	23
Mean (SD)	50.018 (21.479)	28.652 (23.538)
Change from baseline		
Number	56	23
Mean (SD)	-8.304 (16.827)	-20.391 (21.453)
LS mean (SE)	-6.503 (2.627)	-23.528 (3.942)
LS mean diff (95% CI)	NA	-17.025 (-25.975, -8.075)
p value vs. ECM	NA	0.0002

CI = confidence interval; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NP = nasal polyp; NPS = nasal polyp score; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test

Source: Sanofi. Data on File, Post-hoc analyses.¹

NPS

Table 99. NPS and change from baseline in patients with ≥ 1 prior NP surgery and comorbid asthma in SINUS-24 and SINUS-52 ITT population according to the response criteria of NPS (≥ 1 -point improvement)

	ECM (N=121)	Dupilumab Q2W (N=183)
Baseline		
<i>All</i>		
Number	120	183
Mean (SD)	5.654 (1.283)	5.943 (1.218)
<i>Responders at Week 24</i>		

	ECM (N=121)	Dupilumab Q2W (N=183)
Number	18	123
Mean (SD)	6.000 (0.939)	6.057 (1.151)
<i>Non-responders at Week 24</i>		
Number	102	60
Mean (SD)	5.593 (1.329)	5.708 (1.325)
Week 24		
<i>All</i>		
Number	114	174
Mean (SD)	5.706 (1.338)	3.853 (2.007)
Change from baseline		
Number	114	174
Mean (SD)	0.088 (1.312)	-2.086 (1.862)
LS mean (SE)	0.027 (0.174)	-2.054 (0.156)
LS mean diff (95% CI)	NA	-2.081 (-2.461, -1.700)
p value vs. ECM	NA	<0.0001
<i>Responders at Week 24</i>		
Number	18	123
Mean (SD)	4.250 (1.593)	3.085 (1.738)
Change from baseline		
Number	18	123
Mean (SD)	-1.750 (1.204)	-2.972 (1.381)
LS mean (SE)	-1.931 (0.054)	-3.168 (0.028)
LS mean diff (95% CI)	NA	-1.237 (-1.346, -1.128)
p value vs. ECM	NA	<0.0001
<i>Non-responders at Week 24</i>		
Number	96	51
Mean (SD)	5.979 (1.095)	5.706 (1.270)
Change from baseline		
Number	96	51
Mean (SD)	0.432 (1.015)	0.049 (0.873)
LS mean (SE)	0.462 (0.131)	-0.177 (0.165)
LS mean diff (95% CI)	NA	-0.639 (-0.998, -0.280)
p value vs. ECM	NA	0.0005
Week 52		
<i>Responders at Week 24 AND Week 52</i>		
Number	1	36
Mean (SD)	4.500 (NC)	2.333 (1.604)
Change from baseline		
Number	1	36
Mean (SD)	-2.500 (NC)	-3.736 (1.514)
LS mean (SE)	-1.598 (1.558)	-3.871 (0.282)
LS mean diff (95% CI)	NA	-2.273 (-5.609, 1.063)
p value vs. ECM	NA	0.1611
<i>Non-responders at Week 24 OR Week 52</i>		
Number	55	17
Mean (SD)	5.936 (1.639)	5.029 (2.440)
Change from baseline		
Number	55	17
Mean (SD)	0.191 (1.267)	-1.029 (1.866)
LS mean (SE)	0.212 (0.229)	-0.161 (0.368)

	ECM (N=121)	Dupilumab Q2W (N=183)
LS mean diff (95% CI)	NA	-1.373 (-2.178, -0.568)
p value vs. ECM	NA	0.0008

CI = confidence interval; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NP = nasal polyp; NPS = nasal polyp score; Q2W = once every two weeks; SD = standard deviation; SE = standard error
Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 100. NPS and change from baseline in patients with ≥ 1 prior NP surgery and comorbid asthma in SINUS-24 and SINUS-52 ITT population according to the response criteria of SNOT-22 total score (≥ 8.9 -point improvement)

	ECM (N=121)	Dupilumab Q2W (N=183)
Baseline		
<i>Responders at Week 24</i>		
Number	50	137
Mean (SD)	5.740 (1.117)	5.960 (1.235)
<i>Non-responders at Week 24</i>		
Number	70	46
Mean (SD)	5.593 (1.394)	5.891 (1.178)
Week 24		
<i>Responders at Week 24</i>		
Number	49	132
Mean (SD)	5.276 (1.507)	3.470 (1.903)
Change from baseline		
Number	49	132
Mean (SD)	-0.439 (1.302)	-2.485 (1.793)
LS mean (SE)	-0.657 (0.265)	-2.620 (0.190)
LS mean diff (95% CI)	NA	-1.963 (-2.502, -1.424)
p value vs. ECM	NA	<0.0001
<i>Non-responders at Week 24</i>		
Number	65	42
Mean (SD)	6.031 (1.100)	5.060 (1.858)
Change from baseline		
Number	65	42
Mean (SD)	0.485 (1.182)	-0.833 (1.497)
LS mean (SE)	0.594 (0.183)	-0.662 (0.223)
LS mean diff (95% CI)	NA	-1.256 (-1.731, -0.781)
p value vs. ECM	NA	<0.0001
Week 52		
<i>Responders at Week 24 AND Week 52</i>		
Number	11	37
Mean (SD)	5.455 (2.185)	2.527 (1.795)
Change from baseline		
Number	11	37
Mean (SD)	-0.682 (1.454)	-3.473 (1.779)
LS mean (SE)	-0.680 (0.525)	-3.490 (0.300)
LS mean diff (95% CI)	NA	-2.810 (-3.970, -1.650)
p value vs. ECM	NA	<0.0001
<i>Non-responders at Week 24 OR Week 52</i>		
Number	45	16
Mean (SD)	6.022 (1.481)	4.750 (2.556)
Change from baseline		
Number	45	16

	ECM (N=121)	Dupilumab Q2W (N=183)
Mean (SD)	0.344 (1.200)	-1.469 (2.029)
LS mean (SE)	0.317 (0.263)	-1.421 (0.429)
LS mean diff (95% CI)	NA	-1.737 (-2.648, -0.826)
p value vs. ECM	NA	0.0002

CI = confidence interval; ITT = intention-to-treat; LS = least squares; NA = not applicable; NP = nasal polyp; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test

Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 101. NPS and change from baseline in patients with ≥ 1 prior NP surgery and comorbid asthma in SINUS-24 and SINUS-52 ITT population according to the response criteria of SNOT-22 total score (≥ 8.9 -point improvement) and NPS (≥ 1 -point improvement)

	ECM (N=121)	Dupilumab Q2W (N=183)
Baseline		
<i>Responders at Week 24</i>		
Number	14	108
Mean (SD)	5.929 (0.978)	6.106 (1.186)
<i>Non-responders at Week 24</i>		
Number	106	75
Mean (SD)	5.618 (1.318)	5.707 (1.233)
Week 24		
<i>Responders at Week 24</i>		
Number	14	108
Mean (SD)	4.071 (1.708)	3.046 (1.783)
Change from baseline		
Number	14	108
Mean (SD)	-1.857 (1.351)	-3.060 (1.400)
LS mean (SE)	-2.073 (0.064)	-3.245 (0.030)
LS mean diff (95% CI)	NA	-1.173 (-1.300, -1.046)
p value vs. ECM	NA	<0.0001
<i>Non-responders at Week 24</i>		
Number	100	66
Mean (SD)	5.935 (1.109)	5.174 (1.621)
Change from baseline		
Number	100	66
Mean (SD)	0.360 (1.057)	-0.492 (1.357)
LS mean (SE)	0.444 (0.144)	-0.546 (0.172)
LS mean diff (95% CI)	NA	-0.991 (-1.359, -0.623)
p value vs. ECM	NA	<0.0001
Week 52		
<i>Responders at Week 24 AND Week 52</i>		
Number	0	30
Mean (SD)	NA	2.333 (1.739)
Change from baseline		
Number	0	30
Mean (SD)	NA	-3.833 (1.577)
LS mean (SE)	NE	-3.920 (0.319)
LS mean diff (95% CI)	NA	NE
p value vs. ECM	NA	NE
<i>Non-responders at Week 24 OR Week 52</i>		
Number	56	23
Mean (SD)	5.911 (1.635)	4.326 (2.429)

	ECM (N=121)	Dupilumab Q2W (N=183)
Change from baseline		
Number	56	23
Mean (SD)	0.143 (1.306)	-1.609 (1.954)
LS mean (SE)	0.124 (0.231)	-1.673 (0.339)
LS mean diff (95% CI)	NA	-1.798 (-2.554, -1.041)
p value vs. ECM	NA	<0.0001

CI = confidence interval; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NPS = nasal polyp score; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test

Source: Sanofi. Data on File, Post-hoc analyses.¹

Mapped SNOT-22 to EQ-5D-3L health state utilities (Crump Models 1-3)

Table 102. Mapped SNOT-22 to EQ-5D-3L health state utilities (Crump Models 1-3) in patients with ≥ 1 prior NP surgery and comorbid asthma in SINUS-24 and SINUS-52 ITT pooled population according to the response criteria of NPS (≥ 1 -point improvement)

	ECM (N=121)			Dupilumab Q2W (N=183)			All (N=304)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Baseline									
<i>All</i>									
Number	120	120	120	178	178	178	298	298	298
Mean (SD)	0.485 (0.129)	0.607 (0.180)	0.606 (0.180)	0.523 (0.132)	0.643 (0.171)	0.644 (0.174)	0.508 (0.132)	0.629 (0.175)	0.629 (0.177)
<i>Responders at Week 24</i>									
Number	18	18	18	120	120	120	138	138	138
Mean (SD)	0.545 (0.087)	0.691 (0.151)	0.685 (0.144)	0.509 (0.129)	0.628 (0.172)	0.630 (0.175)	0.514 (0.125)	0.637 (0.170)	0.638 (0.172)
<i>Non-responders at Week 24</i>									
Number	102	102	102	58	58	58	160	160	160
Mean (SD)	0.474 (0.133)	0.592 (0.181)	0.592 (0.182)	0.553 (0.134)	0.674 (0.167)	0.673 (0.168)	0.503 (0.138)	0.622 (0.180)	0.621 (0.181)
Week 24									
<i>All</i>									
Number	112	112	112	173	173	173	285	285	285
Mean (SD)	0.581 (0.150)	0.672 (0.173)	0.671 (0.173)	0.729 (0.110)	0.763 (0.114)	0.764 (0.119)	0.671 (0.146)	0.727 (0.147)	0.728 (0.149)
<i>Change from baseline</i>									
Number	112	112	112	173	173	173	285	285	285
Mean (SD)	0.091 (0.130)	0.054 (0.160)	0.055 (0.160)	0.207 (0.147)	0.122 (0.157)	0.123 (0.157)	0.162 (0.151)	0.095 (0.161)	0.096 (0.161)
LS mean (SE)	0.072 (0.013)	0.046 (0.013)	0.045 (0.013)	0.209 (0.011)	0.126 (0.012)	0.126 (0.012)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.137 (0.109, 0.165)	0.080 (0.051, 0.109)	0.081 (0.051, 0.110)	NA	NA	NA
p value vs. ECM	NA	NA	NA	<0.0001	<0.0001	<0.0001	NA	NA	NA
<i>Responders at Week 24</i>									
Number	18	18	18	118	118	118	136	136	136
Mean (SD)	0.670 (0.132)	0.740 (0.135)	0.735 (0.132)	0.743 (0.094)	0.768 (0.101)	0.771 (0.106)	0.734 (0.103)	0.764 (0.106)	0.766 (0.110)
<i>Change from baseline</i>									
Number	18	18	18	118	118	118	136	136	136
Mean (SD)	0.125 (0.102)	0.049 (0.114)	0.050 (0.111)	0.235 (0.140)	0.141 (0.161)	0.142 (0.161)	0.221 (0.140)	0.129 (0.158)	0.130 (0.158)

	ECM (N=121)			Dupilumab Q2W (N=183)			All (N=304)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
LS mean (SE)	0.153 (0.025)	0.100 (0.025)	0.091 (0.025)	0.240 (0.013)	0.147 (0.013)	0.146 (0.013)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.088 (0.037, 0.138)	0.047 (-0.003, 0.097)	0.055 (0.004, 0.106)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.0007	0.0651	0.0353	NA	NA	NA
Non-responders at Week 24									
Number	94	94	94	55	55	55	149	149	149
Mean (SD)	0.564 (0.148)	0.659 (0.177)	0.659 (0.178)	0.697 (0.132)	0.753 (0.138)	0.751 (0.142)	0.613 (0.156)	0.694 (0.169)	0.693 (0.171)
Change from baseline									
Number	94	94	94	55	55	55	149	149	149
Mean (SD)	0.085 (0.134)	0.055 (0.168)	0.056 (0.168)	0.146 (0.145)	0.082 (0.140)	0.083 (0.141)	0.107 (0.141)	0.065 (0.159)	0.066 (0.159)
LS mean (SE)	0.058 (0.016)	0.037 (0.017)	0.039 (0.018)	0.155 (0.019)	0.094 (0.021)	0.094 (0.021)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.097 (0.056, 0.139)	0.056 (0.011, 0.102)	0.055 (0.010, 0.101)	NA	NA	NA
p value vs. ECM	NA	NA	NA	<0.0001	0.0149	0.0178	NA	NA	NA
Week 52									
Responders at Week 24 AND Week 52									
Number	1	1	1	35	35	35	76	76	76
Mean (SD)	0.698 (NC)	0.829 (NC)	0.817 (NC)	0.764 (0.110)	0.777 (0.126)	0.780 (0.126)	0.758 (0.101)	0.770 (0.112)	0.773 (0.113)
Change from baseline									
Number	1	1	1	35	35	35	76	76	76
Mean (SD)	0.054 (NC)	-0.077 (NC)	-0.073 (NC)	0.233 (0.137)	0.124 (0.174)	0.124 (0.173)	0.241 (0.141)	0.126 (0.178)	0.126 (0.176)
LS mean (SE)	0.180 (0.104)	0.171 (0.110)	0.161 (0.110)	0.242 (0.019)	0.133 (0.020)	0.130 (0.020)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.062 (-0.161, 0.285)	-0.038 (-0.274, 0.198)	-0.031 (-0.266, 0.204)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.5659	0.7380	0.7844	NA	NA	NA
Non-responders at Week 24 AND Week 52									
Number	45	45	45	11	11	11	66	66	66
Mean (SD)	0.570 (0.143)	0.680 (0.188)	0.679 (0.191)	0.671 (0.181)	0.705 (0.179)	0.692 (0.181)	0.605 (0.155)	0.694 (0.178)	0.691 (0.180)
Change from baseline									
Number	45	45	45	11	11	11	66	66	66
Mean (SD)	0.114 (0.122)	0.097 (0.153)	0.096 (0.155)	0.161 (0.103)	0.044 (0.161)	0.046 (0.163)	0.124 (0.128)	0.084 (0.156)	0.084 (0.157)

	ECM (N=121)			Dupilumab Q2W (N=183)			All (N=304)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
LS mean (SE)	0.099 (0.019)	0.083 (0.022)	0.083 (0.022)	0.169 (0.038)	0.058 (0.043)	0.056 (0.044)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.070 (−0.007, 0.147)	−0.024 (−0.112, 0.064)	−0.027 (−0.117, 0.062)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.0758	0.5885	0.5456	NA	NA	NA
<i>Non-responders at Week 24 OR Week 52</i>									
Number	55	55	55	18	18	18	93	93	93
Mean (SD)	0.589 (0.152)	0.691 (0.190)	0.689 (0.191)	0.703 (0.162)	0.730 (0.158)	0.726 (0.167)	0.641 (0.158)	0.716 (0.171)	0.713 (0.173)
<i>Change from baseline</i>									
Number	55	55	55	18	18	18	93	93	93
Mean (SD)	0.113 (0.130)	0.086 (0.162)	0.087 (0.162)	0.198 (0.123)	0.091 (0.173)	0.093 (0.174)	0.150 (0.149)	0.097 (0.165)	0.098 (0.165)
LS mean (SE)	0.097 (0.018)	0.076 (0.020)	0.077 (0.020)	0.197 (0.030)	0.094 (0.033)	0.095 (0.033)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.100 (0.035, 0.166)	0.018 (−0.054, 0.091)	0.018 (−0.056, 0.091)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.0027	0.6203	0.6353	NA	NA	NA

CI = confidence interval; EQ-5D-3L = EuroQol 5-Dimension 3-Level; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LS = least squares; NA = not applicable; NP = nasal polyp; NPS = nasal polyp score; NSAID = non-steroidal anti-inflammatory drug; Q2W = once every two weeks; SD = standard deviation; SE = standard error
Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 103. Mapped SNOT-22 to EQ-5D-3L health state utilities (Crump Models 1-3) in patients with ≥1 prior NP surgery and comorbid asthma in SINUS-24 and SINUS-52 ITT pooled population according to the response criteria of SNOT-22 total score (≥8.9-point improvement)

	ECM (N=121)			Dupilumab Q2W (N=183)			All (N=304)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Baseline									
<i>Responders at Week 24</i>									
Number	51	51	51	137	137	137	188	188	188
Mean (SD)	0.490 (0.133)	0.613 (0.192)	0.609 (0.191)	0.500 (0.123)	0.623 (0.170)	0.624 (0.171)	0.497 (0.125)	0.621 (0.176)	0.620 (0.176)
<i>Non-responders at Week 24</i>									

	ECM (N=121)			Dupilumab Q2W (N=183)			All (N=304)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Number	69	69	69	41	41	41	110	110	110
Mean (SD)	0.481 (0.127)	0.603 (0.171)	0.604 (0.172)	0.601 (0.134)	0.710 (0.160)	0.712 (0.168)	0.526 (0.142)	0.643 (0.175)	0.644 (0.178)
Week 24									
<i>Responders at Week 24</i>									
Number	51	51	51	137	137	137	188	188	188
Mean (SD)	0.663 (0.120)	0.739 (0.133)	0.735 (0.136)	0.752 (0.089)	0.775 (0.101)	0.777 (0.105)	0.728 (0.106)	0.765 (0.111)	0.765 (0.115)
Change from baseline									
Number	51	51	51	137	137	137	188	188	188
Mean (SD)	0.173 (0.102)	0.126 (0.144)	0.126 (0.145)	0.252 (0.125)	0.152 (0.157)	0.153 (0.157)	0.231 (0.124)	0.145 (0.153)	0.145 (0.154)
LS mean (SE)	0.162 (0.002)	0.121 (0.002)	0.119 (0.002)	0.251 (0.002)	0.156 (0.002)	0.158 (0.002)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.089 (0.085, 0.094)	0.035 (0.031, 0.040)	0.039 (0.034, 0.044)	NA	NA	NA
p value vs. ECM	NA	NA	NA	<0.0001	<0.0001	<0.0001	NA	NA	NA
<i>Non-responders at Week 24</i>									
Number	61	61	61	36	36	36	97	97	97
Mean (SD)	0.513 (0.139)	0.616 (0.183)	0.618 (0.184)	0.640 (0.134)	0.718 (0.146)	0.718 (0.154)	0.560 (0.150)	0.654 (0.177)	0.655 (0.179)
Change from baseline									
Number	61	61	61	36	36	36	97	97	97
Mean (SD)	0.023 (0.109)	-0.005 (0.149)	-0.005 (0.148)	0.036 (0.085)	0.010 (0.095)	0.011 (0.095)	0.028 (0.101)	0.000 (0.131)	0.001 (0.131)
LS mean (SE)	0.016 (0.017)	-0.007 (0.020)	-0.006 (0.020)	0.067 (0.022)	0.029 (0.025)	0.028 (0.025)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.051 (0.003, 0.100)	0.036 (-0.019, 0.091)	0.034 (-0.020, 0.089)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.0368	0.1986	0.2196	NA	NA	NA
Week 52									
<i>Responders at Week 24 AND Week 52</i>									
Number	11	11	11	39	39	39	96	96	96
Mean (SD)	0.603 (0.166)	0.666 (0.207)	0.658 (0.205)	0.770 (0.106)	0.782 (0.117)	0.783 (0.120)	0.748 (0.117)	0.764 (0.123)	0.765 (0.126)
Change from baseline									
Number	11	11	11	39	39	39	96	96	96
Mean (SD)	0.189 (0.079)	0.155 (0.119)	0.157 (0.117)	0.261 (0.113)	0.148 (0.170)	0.149 (0.170)	0.268 (0.123)	0.160 (0.166)	0.161 (0.165)

	ECM (N=121)			Dupilumab Q2W (N=183)			All (N=304)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
LS mean (SE)	0.146 (0.029)	0.092 (0.033)	0.088 (0.033)	0.269 (0.016)	0.163 (0.018)	0.162 (0.018)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.123 (0.050, 0.196)	0.070 (-0.010, 0.151)	0.074 (-0.008, 0.155)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.0004	0.0595	0.0516	NA	NA	NA
<i>Non-responders at Week 24 AND Week 52</i>									
Number	30	30	30	8	8	8	47	47	47
Mean (SD)	0.549 (0.157)	0.659 (0.200)	0.660 (0.200)	0.594 (0.182)	0.647 (0.209)	0.647 (0.217)	0.578 (0.159)	0.667 (0.188)	0.668 (0.189)
Change from baseline									
Number	30	30	30	8	8	8	47	47	47
Mean (SD)	0.063 (0.125)	0.037 (0.155)	0.038 (0.155)	0.082 (0.134)	-0.002 (0.152)	0.002 (0.149)	0.058 (0.115)	0.023 (0.141)	0.024 (0.140)
LS mean (SE)	0.062 (0.022)	0.046 (0.026)	0.046 (0.026)	0.090 (0.044)	0.009 (0.052)	0.009 (0.052)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.028 (-0.065, 0.121)	-0.037 (-0.146, 0.072)	-0.038 (-0.146, 0.071)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.5515	0.5009	0.4979	NA	NA	NA
<i>Non-responders at Week 24 OR Week 52</i>									
Number	45	45	45	14	14	14	73	73	73
Mean (SD)	0.588 (0.149)	0.700 (0.186)	0.700 (0.187)	0.669 (0.169)	0.704 (0.177)	0.704 (0.184)	0.623 (0.153)	0.709 (0.174)	0.708 (0.175)
Change from baseline									
Number	45	45	45	14	14	14	73	73	73
Mean (SD)	0.094 (0.133)	0.066 (0.167)	0.066 (0.167)	0.108 (0.117)	0.014 (0.142)	0.015 (0.142)	0.090 (0.124)	0.044 (0.156)	0.045 (0.155)
LS mean (SE)	0.077 (0.020)	0.056 (0.023)	0.056 (0.023)	0.118 (0.034)	0.022 (0.040)	0.023 (0.040)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.041 (-0.033, 0.115)	-0.033 (-0.119, 0.052)	-0.032 (-0.119, 0.054)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.2745	0.4440	0.4603	NA	NA	NA

CI = confidence interval; EQ-5D-3L = EuroQol 5-Dimension 3-Level; ITT = intention-to-treat; LS = least squares; NA = not applicable; NP = nasal polyp; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test
Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 104. Mapped SNOT-22 to EQ-5D-3L health state utilities (Crump Models 1-3) in patients with ≥1 prior NP surgery and comorbid asthma in SINUS-24 and SINUS-52 ITT pooled population according to the response criteria of SNOT-22 total score (≥8.9-point improvement) and NPS (≥1-point improvement)

	ECM (N=121)			Dupilumab Q2W (N=183)			All (N=304)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Baseline									
<i>Responders at Week 24</i>									
Number	14	14	14	108	108	108	122	122	122
Mean (SD)	0.540 (0.084)	0.680 (0.157)	0.674 (0.148)	0.492 (0.120)	0.614 (0.169)	0.615 (0.172)	0.497 (0.117)	0.622 (0.169)	0.622 (0.170)
<i>Non-responders at Week 24</i>									
Number	106	106	106	70	70	70	176	176	176
Mean (SD)	0.477 (0.133)	0.597 (0.181)	0.597 (0.182)	0.572 (0.136)	0.689 (0.166)	0.689 (0.168)	0.515 (0.141)	0.634 (0.180)	0.634 (0.182)
Week 24									
<i>Responders at Week 24</i>									
Number	14	14	14	108	108	108	122	122	122
Mean (SD)	0.706 (0.123)	0.756 (0.125)	0.752 (0.116)	0.748 (0.095)	0.770 (0.102)	0.772 (0.108)	0.743 (0.098)	0.768 (0.105)	0.769 (0.109)
<i>Change from baseline</i>									
Number	14	14	14	108	108	108	122	122	122
Mean (SD)	0.166 (0.073)	0.076 (0.099)	0.078 (0.095)	0.256 (0.127)	0.156 (0.158)	0.156 (0.158)	0.246 (0.125)	0.147 (0.154)	0.147 (0.154)
LS mean (SE)	0.194 (0.004)	0.123 (0.004)	0.116 (0.004)	0.255 (0.002)	0.161 (0.002)	0.161 (0.002)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.061 (0.052, 0.069)	0.038 (0.029, 0.046)	0.044 (0.035, 0.053)	NA	NA	NA
p value vs. ECM	NA	NA	NA	<0.0001	<0.0001	<0.0001	NA	NA	NA
<i>Non-responders at Week 24</i>									
Number	98	98	98	65	65	65	163	163	163
Mean (SD)	0.564 (0.145)	0.660 (0.176)	0.660 (0.177)	0.697 (0.126)	0.752 (0.130)	0.752 (0.135)	0.617 (0.152)	0.697 (0.165)	0.697 (0.167)
<i>Change from baseline</i>									
Number	98	98	98	65	65	65	163	163	163
Mean (SD)	0.081 (0.133)	0.051 (0.167)	0.051 (0.167)	0.126 (0.142)	0.066 (0.138)	0.068 (0.138)	0.099 (0.138)	0.057 (0.156)	0.058 (0.156)
LS mean (SE)	0.052 (0.015)	0.032 (0.016)	0.033 (0.017)	0.147 (0.018)	0.083 (0.019)	0.084 (0.019)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.095 (0.056, 0.134)	0.052 (0.010, 0.093)	0.052 (0.010, 0.094)	NA	NA	NA

	ECM (N=121)			Dupilumab Q2W (N=183)			All (N=304)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
p value vs. ECM	NA	NA	NA	<0.0001	0.0160	0.0162	NA	NA	NA
Week 52									
<i>Responders at Week 24 AND Week 52</i>									
Number	0	0	0	30	30	30	66	66	66
Mean (SD)	NA	NA	NA	0.774 (0.107)	0.781 (0.121)	0.783 (0.122)	0.768 (0.098)	0.777 (0.106)	0.780 (0.108)
Change from baseline									
Number	0	0	0	30	30	30	66	66	66
Mean (SD)	NA	NA	NA	0.266 (0.112)	0.152 (0.168)	0.151 (0.168)	0.273 (0.118)	0.154 (0.169)	0.153 (0.169)
LS mean (SE)	NE	NE	NE	0.269 (0.019)	0.157 (0.020)	0.154 (0.020)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	NE	NE	NE	NA	NA	NA
p value vs. ECM	NA	NA	NA	NE	NE	NE	NA	NA	NA
<i>Non-responders at Week 24 AND Week 52</i>									
Number	50	50	50	13	13	13	76	76	76
Mean (SD)	0.572 (0.145)	0.680 (0.191)	0.679 (0.193)	0.663 (0.168)	0.693 (0.180)	0.685 (0.181)	0.609 (0.153)	0.691 (0.179)	0.689 (0.180)
Change from baseline									
Number	50	50	50	13	13	13	76	76	76
Mean (SD)	0.099 (0.128)	0.075 (0.166)	0.075 (0.166)	0.129 (0.123)	0.014 (0.164)	0.017 (0.165)	0.105 (0.132)	0.061 (0.163)	0.062 (0.163)
LS mean (SE)	0.086 (0.018)	0.068 (0.021)	0.068 (0.021)	0.146 (0.036)	0.038 (0.042)	0.036 (0.042)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.060 (-0.014, 0.135)	-0.030 (-0.116, 0.057)	-0.032 (-0.119, 0.055)	NA	NA	NA
p value vs. ECM	NA	NA	NA	0.1137	0.4993	0.4741	NA	NA	NA
<i>Non-responders at Week 24 OR Week 52</i>									
Number	56	56	56	23	23	23	103	103	103
Mean (SD)	0.591 (0.151)	0.693 (0.189)	0.692 (0.190)	0.704 (0.152)	0.735 (0.157)	0.734 (0.164)	0.647 (0.154)	0.717 (0.168)	0.715 (0.169)
Change from baseline									
Number	56	56	56	23	23	23	103	103	103
Mean (SD)	0.112 (0.129)	0.083 (0.162)	0.084 (0.162)	0.162 (0.135)	0.063 (0.168)	0.064 (0.169)	0.139 (0.148)	0.082 (0.167)	0.083 (0.167)
LS mean (SE)	0.091 (0.018)	0.070 (0.020)	0.071 (0.020)	0.175 (0.027)	0.076 (0.030)	0.078 (0.030)	NA	NA	NA
LS mean diff (95% CI)	NA	NA	NA	0.085 (0.024, 0.145)	0.006 (-0.061, 0.073)	0.007 (-0.061, 0.075)	NA	NA	NA

	ECM (N=121)			Dupilumab Q2W (N=183)			All (N=304)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
p value vs. ECM	NA	NA	NA	0.0064	0.8581	0.8402	NA	NA	NA

CI = confidence interval; EQ-5D-3L = EuroQol 5-Dimension 3-Level; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NP = nasal polyp; NPS = nasal polyp score; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test

Source: Sanofi. Data on File, Post-hoc analyses.¹

EQ-5D-5L utilities (Hernandez 2020 crosswalk method, UK tariffs)

Table 105. EQ-5D-5L utilities (Hernandez 2020 crosswalk method, UK tariffs) in patients with ≥ 1 prior NP surgery and comorbid asthma in SINUS-24 and SINUS-52 ITT pooled population according to the response criteria of NPS (≥ 1 -point improvement)

	ECM (N=121)	Dupilumab Q2W (N=183)
Baseline		
<i>All</i>		
Number	118	174
Mean (SD)	0.759 (0.176)	0.781 (0.173)
<i>Responders at Week 24</i>		
Number	18	118
Mean (SD)	0.832 (0.121)	0.776 (0.160)
<i>Non-responders at Week 24</i>		
Number	100	56
Mean (SD)	0.746 (0.182)	0.791 (0.200)
Week 24		
<i>All</i>		
Number	111	170
Mean (SD)	0.793 (0.176)	0.862 (0.161)
Change from baseline		
Number	111	170
Mean (SD)	0.035 (0.135)	0.083 (0.150)
LS mean (SE)	0.027 (0.014)	0.086 (0.012)
LS mean diff (95% CI)	NA	0.059 (0.029, 0.090)
p value vs. ECM	NA	0.0001
<i>Responders at Week 24</i>		
Number	18	116
Mean (SD)	0.895 (0.107)	0.874 (0.138)
Change from baseline		
Number	18	116
Mean (SD)	0.063 (0.137)	0.099 (0.155)
LS mean (SE)	0.084 (0.031)	0.103 (0.016)
LS mean diff (95% CI)	NA	0.019 (-0.044, 0.082)
p value vs. ECM	NA	0.5487
<i>Non-responders at Week 24</i>		
Number	93	54
Mean (SD)	0.773 (0.181)	0.836 (0.202)
Change from baseline		
Number	93	54
Mean (SD)	0.029 (0.135)	0.049 (0.135)
LS mean (SE)	0.023 (0.016)	0.054 (0.019)
LS mean diff (95% CI)	NA	0.030 (-0.012, 0.072)
p value vs. ECM	NA	0.1589
Week 52		
<i>Responders at Week 24 AND Week 52</i>		
Number	1	34
Mean (SD)	0.790 (NC)	0.883 (0.163)
Change from baseline		
Number	1	34
Mean (SD)	0.052 (NC)	0.100 (0.164)

	ECM (N=121)	Dupilumab Q2W (N=183)
LS mean (SE)	0.102 (0.163)	0.078 (0.030)
LS mean diff (95% CI)	NA	-0.024 (-0.352, 0.304)
p value vs. ECM	NA	0.8855
Non-responders at Week 24 AND Week 52		
Number	45	11
Mean (SD)	0.764 (0.201)	0.720 (0.341)
Change from baseline		
Number	45	11
Mean (SD)	0.040 (0.162)	0.049 (0.104)
LS mean (SE)	0.040 (0.024)	0.052 (0.049)
LS mean diff (95% CI)	NA	0.012 (-0.085, 0.109)
p value vs. ECM	NA	0.8142
Non-responders at Week 24 OR Week 52		
Number	55	18
Mean (SD)	0.784 (0.194)	0.782 (0.295)
Change from baseline		
Number	55	18
Mean (SD)	0.041 (0.158)	0.061 (0.105)
LS mean (SE)	0.038 (0.021)	0.059 (0.035)
LS mean diff (95% CI)	NA	0.021 (-0.055, 0.097)
p value vs. ECM	NA	0.5864

CI = confidence interval; EQ-5D-5L = EuroQol 5-Dimension 5-Level; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NP = nasal polyp; NPS = nasal polyp score; Q2W = once every two weeks; SD = standard deviation; SE = standard error
Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 106. EQ-5D-5L utilities (Hernandez 2020 crosswalk method, UK tariffs) in patients with ≥1 prior NP surgery and comorbid asthma in SINUS-24 and SINUS-52 ITT pooled population according to the response criteria of SNOT-22 total score (≥8.9-point improvement)

	ECM (N=121)	Dupilumab Q2W (N=183)
Baseline		
Responders at Week 24		
Number	51	136
Mean (SD)	0.790 (0.156)	0.775 (0.157)
Non-responders at Week 24		
Number	67	38
Mean (SD)	0.735 (0.188)	0.804 (0.222)
Week 24		
Responders at Week 24		
Number	51	136
Mean (SD)	0.870 (0.123)	0.880 (0.136)
Change from baseline		
Number	51	136
Mean (SD)	0.080 (0.141)	0.105 (0.153)
LS mean (SE)	0.081 (0.003)	0.102 (0.002)
LS mean diff (95% CI)	NA	0.022 (0.016, 0.028)
p value vs. ECM	NA	<0.0001
Non-responders at Week 24		
Number	60	34
Mean (SD)	0.728 (0.189)	0.794 (0.227)
Change from baseline		

	ECM (N=121)	Dupilumab Q2W (N=183)
Number	60	34
Mean (SD)	-0.004 (0.119)	-0.005 (0.099)
LS mean (SE)	0.004 (0.018)	0.020 (0.022)
LS mean diff (95% CI)	NA	0.016 (-0.032, 0.063)
p value vs. ECM	NA	0.5219
Week 52		
<i>Responders at Week 24 AND Week 52</i>		
Number	11	38
Mean (SD)	0.802 (0.232)	0.883 (0.166)
Change from baseline		
Number	11	38
Mean (SD)	0.034 (0.126)	0.114 (0.155)
LS mean (SE)	0.024 (0.040)	0.099 (0.023)
LS mean diff (95% CI)	NA	0.075 (-0.013, 0.163)
p value vs. ECM	NA	0.0949
<i>Non-responders at Week 24 AND Week 52</i>		
Number	30	8
Mean (SD)	0.729 (0.189)	0.621 (0.366)
Change from baseline		
Number	30	8
Mean (SD)	0.016 (0.141)	0.006 (0.100)
LS mean (SE)	0.028 (0.026)	0.038 (0.054)
LS mean diff (95% CI)	NA	0.010 (-0.099, 0.119)
p value vs. ECM	NA	0.8565
<i>Non-responders at Week 24 OR Week 52</i>		
Number	45	14
Mean (SD)	0.780 (0.184)	0.753 (0.315)
Change from baseline		
Number	45	14
Mean (SD)	0.044 (0.165)	0.012 (0.086)
LS mean (SE)	0.039 (0.028)	0.020 (0.048)
LS mean diff (95% CI)	NA	-0.020 (-0.121, 0.082)
p value vs. ECM	NA	0.7054

CI = confidence interval; EQ-5D-5L = EuroQol 5-Dimension 5-Level; ITT = intention-to-treat; LS = least squares; NA = not applicable; NP = nasal polyp; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test

Source: Sanofi. Data on File, Post-hoc analyses.¹

Table 107. EQ-5D-5L utilities (Hernandez 2020 crosswalk method, UK tariffs) in patients with ≥ 1 prior NP surgery and comorbid asthma in SINUS-24 and SINUS-52 ITT pooled population according to the response criteria of SNOT-22 total score (≥ 8.9 -point improvement) and NPS (≥ 1 -point improvement)

	ECM (N=121)	Dupilumab Q2W (N=183)
Baseline		
<i>Responders at Week 24</i>		
Number	14	107
Mean (SD)	0.826 (0.124)	0.770 (0.160)
<i>Non-responders at Week 24</i>		

	ECM (N=121)	Dupilumab Q2W (N=183)
Number	104	67
Mean (SD)	0.750 (0.181)	0.798 (0.192)
Week 24		
<i>Responders at Week 24</i>		
Number	14	107
Mean (SD)	0.895 (0.117)	0.876 (0.138)
Change from baseline		
Number	14	107
Mean (SD)	0.069 (0.149)	0.105 (0.154)
LS mean (SE)	0.088 (0.006)	0.107 (0.003)
LS mean diff (95% CI)	NA	0.019 (0.008, 0.030)
p value vs. ECM	NA	0.0008
<i>Non-responders at Week 24</i>		
Number	97	63
Mean (SD)	0.778 (0.179)	0.839 (0.194)
Change from baseline		
Number	97	63
Mean (SD)	0.030 (0.133)	0.045 (0.137)
LS mean (SE)	0.025 (0.016)	0.054 (0.018)
LS mean diff (95% CI)	NA	0.029 (-0.010, 0.069)
p value vs. ECM	NA	0.1435
Week 52		
<i>Responders at Week 24 AND Week 52</i>		
Number	0	29
Mean (SD)	NA	0.886 (0.166)
Change from baseline		
Number	0	29
Mean (SD)	NA	0.116 (0.169)
LS mean (SE)	NE	0.102 (0.025)
LS mean diff (95% CI)	NA	NE
p value vs. ECM	NA	NE
<i>Non-responders at Week 24 AND Week 52</i>		
Number	50	13
Mean (SD)	0.770 (0.195)	0.720 (0.315)
Change from baseline		
Number	50	13
Mean (SD)	0.032 (0.160)	0.040 (0.102)
LS mean (SE)	0.036 (0.022)	0.050 (0.045)
LS mean diff (95% CI)	NA	0.014 (-0.076, 0.104)
p value vs. ECM	NA	0.7601
<i>Non-responders at Week 24 OR Week 52</i>		
Number	56	23
Mean (SD)	0.785 (0.192)	0.801 (0.270)
Change from baseline		
Number	56	23
Mean (SD)	0.042 (0.157)	0.050 (0.102)
LS mean (SE)	0.033 (0.023)	0.043 (0.035)
LS mean diff (95% CI)	NA	0.010 (-0.067, 0.088)
p value vs. ECM	NA	0.7912

CI = confidence interval; EQ-5D-5L = EuroQol 5-Dimension 5-Level; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NP = nasal polyp; NPS = nasal polyp score; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test
Source: Sanofi. Data on File, Post-hoc analyses.¹

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Single Technology Appraisal

Dupilumab for treating severe chronic rhinosinusitis with nasal polyposis [ID6480]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	
2. Name of organisation	Fifth Sense
3. Job title or position	
4a. Brief description of the organisation (including who funds it). How many members does it have?	Fifth Sense is the charity for people affected by smell and taste disorders (SATDs). Established in 2012, we are the only UK charity focused on smell and taste and the leading patient organisation globally. Fifth Sense provides direct support and information to people affected by SATDs and their families, delivers education to public and professionals, campaigns for better access to specialist services and treatment and supports research to develop a better understanding and find new treatments. The charity is funded primarily through grants, including from the National Lottery Community Fund, and to a lesser extent donations and receives some funding from corporates, including, but not limited, to pharmaceutical companies.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months?	Fifth Sense has very recently signed an agreement with Sanofi to support patient recruitment to clinical trials for new molecules to treat CRSwNP. Sanofi are providing a fee to Fifth Sense as part of this service agreement.

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We gathered information using a combination of surveys, focus groups, and case studies. Focus Groups We conducted two focus groups at the end of 2024 to provide space and time for people with CRSwNP to share their experiences and insights. Each session was attended by approximately 20 individuals living with the condition. The focus groups were promoted through our campaign group, newsletter and social media. Participants engaged in both small group discussions and larger who group discussions covering key topics such as: • The most significant ways CRSwNP impacts their lives, including symptoms like loss of smell and taste and breathing difficulties • Whether existing assessment tools adequately capture the true impact of CRSwNP • The availability of information and support for those living with the condition • The role of GPs and ENT specialists in their care Online Survey Following on from the focus groups, we developed an online survey that was shared through our newsletter and social media. We wanted to ensure that patients with severe CRSwNP were well represented in the responses, so we asked questions that enabled

	us to characterise respondents based on having had at least one operation and meet at least one of the following criteria, based on the 2023 European Position Paper on Rhinosinusitis and Nasal Polyps criteria: • Currently on a waiting list for surgery for CRSwNP • Had at least two courses of systemic corticosteroids (SCS) in the last 12 months • Been told by a clinician that they cannot have further surgery • Cannot be prescribed systemic corticosteroids due to potential harm • Diagnosed with asthma and regularly using a steroid inhaler In total, we received 184 responses to the survey, of which 97 met the criteria for severe CRSwNP. As part of our survey we provided an information sheet we developed which consisted of a brief overview of Dupilumab and how it works, how it is administered, results of some clinical trials and a list of some of the side-effects, with a link to the Sanofi Regeneron Dupilumab patient information sheet which provides a full list. Case Studies A number of individuals provided us with personal accounts of how CRSwNP affects their daily lives. These case studies provide powerful, first-hand testimony. We spoke with one individual who is currently taking Dupilumab for CRSwNP who provided a case study. These are included in full in the appendices. The combination of the survey, focus groups and individual case studies has helped to ensure that our submission is informed by a diverse range of experiences, highlighting the challenges faced by both patients and their families and reinforcing the need for better access to effective treatments.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	CRSwNP has a significant and sometimes devastating impact on nearly every aspect of daily life for those affected, including physical and mental health, social lives, relationships, employment and sleep quality. Many of those living with the condition describe a constant struggle with symptoms including loss of smell, severe nasal congestion, breathing difficulties, debilitating facial pain and sleep disturbances. These in turn lead to depression, anxiety, social isolation and chronic fatigue. In the results of our survey, 80% of respondents said they felt that CRSwNP has a significant impact on their life overall, with 20% saying it has a moderate impact. For those with uncontrolled CRSwNP with the most severe symptoms, it feels like a never-ending cycle. <i>“It affects everything! I can’t think of any aspect of life this does not affect. I’m a pretty strong-minded guy but struggle not to let this condition get me, which ultimately leads to times of depression.”</i> <i>“CRSwNP has taken over my life, I cannot breathe properly and I am in constant pain. At times it feels like I am being smothered by my polyps. My mood is so low because of it, I am being treated for depression and anxiety alongside it.”</i> Loss of smell – a significant, unrecognised impact on every facet of someone’s life Chronic Rhinosinusitis, with or without nasal polyps, is the biggest cause of smell loss (anosmia). It is perhaps the symptom of CRSwNP that has the most significant and wide-ranging impact on people’s lives. Amongst our survey participants, ‘decreased sense of smell/taste’ was rated as the most impactful symptom of all, which mirrors the findings of previously published research¹. This was true for respondents who met the criteria of having severe CRSwNP as well as the overall group. (We deliberately included ‘taste’ in our question as this is often how patients perceive the impact of smell loss, such is the contribution that the sense of smell makes to flavour perception). Loss of smell has a significant but often unrecognised impact on quality of life. People are unable to smell their favourite fragrances, partners and children, homes, gardens, form memories of the places they visit through smell, or enjoy the flavours of their food and drink. Safety at home is put at risk due to the inability to detect dangerous odours such as gas, smoke or spoiled food. Those affected have concerns about personal hygiene too, due to being unable to smell their clothes or body odours. Altogether, these wide-ranging impacts take a significant toll on people’s mental health and wellbeing. In previous research undertaken by Fifth Sense and the University of East Anglia² to capture the impact of smell disorders on people’s quality of life, 61% of participants said they experience depression and/or anxiety, with many saying relationships with family and friends are affected. Many people talk about feelings of isolation and some describe their loss of smell as being akin to a bereavement, such is the emotional impact.

	<i>"CRSwNP has significantly impacted my life. It's like losing a loved one; one minute you can smell, and the next you can't."</i> Physical health can also suffer as people's diet changes, which subsequently impacts nutrition. Some people eat less due to the loss of enjoyment of food and drink, whilst some turn to more sugary or salty foods as they are still able to detect the basic tastes of sweet and salt. The loss of enjoyment of eating and drinking affects social lives too, with those affected saying they eat out, or with family/friends, less, or stop altogether. This in turn has another negative impact on people's quality of life and mental health. <i>"Daily life is depressing and lacking colour in so many ways. I am always conscious about personal hygiene - do I or my clothes smell? What is the point in wearing perfume? Does my house smell of dogs? I don't enjoy cooking any more, as I'm unable to taste what I cook, which definitely affects the quality of food I cook for my family. I'm constantly having to ask my partner "does this towel smell? Is this milk off?"</i> <i>"I love food, and it is troubling to me that I can't taste or smell. I miss so many smells and use my memory to imagine them. I feel it is dangerous not to be able to taste or smell – I don't protect myself from pollution; I don't know when food is burning; when food is off."</i> <i>"I no longer enjoy meals out with family and friends, this has caused issues with loved ones and their lack of understanding of why this is. Cooking for myself is hit & miss, diet and weight affected."</i> <i>"We had a gas leak in the house which was detected by visitors, and required us to be cut off suddenly for a week in a very cold spell. It turned out there had been a small gas leak for several years which I hadn't identified."</i> Bunged up, in pain, can't breathe, can't sleep The inflammation in the nose and sinuses caused by CRSwNP causes breathing difficulties and facial pain, which leads to sleeping difficulties and ongoing fatigue as a result. Congestion can also occur in the ears, causing hearing difficulties. <i>"...I wake up every hour. I'm in constant pain and discomfort. I went through depression because I could no longer taste and smell. I get dizzy spells. I have to blow my nose 24/7. My hearing has reduced and I get ear pain."</i> <i>"...when I have flare up and the steroids have become ineffective, it effects my hearing, which is by far the worst bit. I have diplacusis and this makes it almost unbearable to be around people and sounds. Even more unbearable when a sound is high pitched, coming from my young children."</i>

The mental health impact of CRSwNP

For those with severe and uncontrolled CRSwNP the quality of life impact is immense. Congestion and breathing difficulties result in poorer sleep and ongoing fatigue, loss of smell removes pleasure from many aspects of life whilst creating safety and hygiene worries, and for those for whom current treatments do not provide lasting relief from symptoms there is little hope for a return to normality. It's perhaps not surprising, therefore, that many patients tell us the mental health impact of the disease is significant.

"I spent 10 years using SSRIs. I have been suicidal, depressed and emotionally and sexually limited. I've found I'm better off not socialising as the lack of any enjoyment has a dispiriting effect on me."

"I am tired all the time as struggle to sleep, feel like I am suffocating worse at night. Don't enjoy food as can't breathe when eating. Have no sense of taste or smell. My mental health is suffering. I've had enough of feeling like this. I can't exercise as my asthma is exacerbated by the polyps."

The impact on work and careers

Patients tell us that the condition significantly affects their careers, with some forced to leave jobs in food-related industries or unable to function effectively in roles that require clear communication or physical activity.

"I miss my job as a chef. I rely on memories of tastes and smells to create dishes – I no longer work because I have less sense of taste and no sense of smell."

"I find it very hard at work as I have to concentrate and I find this very difficult due to fatigue and constant blowing of nose...I regularly have sinus pain and often have to take time off"

The impact on loved ones

It's not only patients themselves whose quality of life is affected, but those around them too. Our survey results and conversations with patients have highlighted the knock-on impact on their partners and family members.

"It has an enormous effect on family and my husband in particular. We have taken to sleeping in separate rooms due to the volume of my snoring. This affects our relationship on lots of levels."

"My partner has to deal with me being miserable and tired all the time. As a father, my child is growing up seeing the worst side of me."

We also heard from someone who is a carer for her sick husband who talked about how much more difficult this was made by her CRSwNP:

I had to look after my daughter who had a terminal illness to a few years ago. Regardless what this condition has done to me I had to take care of her and now my husband. I'm currently signed off sick from work to do this as I couldn't manage work with my condition as well as look after my husband. Something had to give. It's hard though as when my nose is on a really bad day and it's caused a migraine I just want to lay in bed but I can't. Being a carer is hard enough without dealing with this condition on top of.

The comments provided here provide a snapshot of a condition that has a significant, deep and chronic impact on every aspect of people's lives: family, work, social, pleasure, physical activity, mental health, safety. Sleep deprivation, coupled with the relentless cycle of surgeries, medications, and symptom relapses, leaves sufferers feeling hopeless and exhausted. Many express frustration with the lack of effective treatments and the dismissive attitude of healthcare providers, leading to a sense of abandonment and despair.

Another challenge for patients is that the impact of their condition is not well-captured by NICE's preferred tool for assessing health-related quality of life, the EQ-5D.

In our survey and focus group meetings we showed patients the EQ-5D and asked them whether they felt the EQ-5D adequately captures the impact that CRSwNP has on their quality of life. Of those who answered the question:

61% said no

39% said yes

The views provided by our survey respondents suggest that the EQ-5D does not adequately capture the reality of living with Chronic Rhinosinusitis with Nasal Polyps (CRSwNP). Many respondents express frustration that the questions are too general, focusing primarily on mobility and self-care, which are not the primary challenges faced by those with CRSwNP.

Key issues raised include:

Lack of focus on smell and taste loss: The form completely ignores smell loss and its profound impact on eating, drinking, safety and emotional well-being.

Failure to address mental health and emotional toll: While anxiety and depression are mentioned, patients feel the grief, frustration, and social isolation caused by CRSwNP are not properly acknowledged.

Not enough consideration for daily challenges: The impact on sleep, breathing difficulties, chronic congestion, personal hygiene concerns, and exhaustion is not covered in the assessment.

Too rigid and inflexible: The tick-box format doesn't allow for nuance, leaving patients unable to fully explain their struggles.

Not designed for CRSwNP: Many feel the EQ-5D is more suited for mobility-related conditions and completely overlooks the myriad burdens of living with CRSwNP.

	Yet there are other Patient Reported Outcome Measures in use that do capture more of the nuances of CRSwNP. The SNOT-22 was developed in 2006 and is now widely used as a robust means of capturing health-related quality of life of CRS (with and without nasal polyps). It covers symptom severity, the social and emotional impact, productivity, and sleep consequences of the disease. Considering patients' views of the EQ-5D, as per our survey, the widespread use of the SNOT-22 in clinical trials (including in many of the trials for Dupixent/Dupilumab) and its ability to capture a much more nuanced picture of the quality of life impact of CRSwNP, we request that NICE considers using data captured by SNOT-22 as a more detailed and accurate measure for assessing health-related quality of life in addition to the EQ-5D in health technology assessments of drugs to treat CRSwNP. As a final point in relation to the impact of CRSwNP, it is worth noting that just because mortality isn't a factor in a disease doesn't mean the quality of life impact of it is any less severe, especially if no relief can be found. More than one respondent to our survey made reference to suicidal thoughts: <i>"I have seriously thought about suicide more than once, as I never get a day off from this illness."</i> References: 1. Erskine SE, Verkerk MM, Notley C, Williamson IG, Philpott CM. Chronic rhinosinusitis: patient experiences of primary and secondary care - a qualitative study. Clin Otolaryngol. 2016 Feb;41(1):8-14. doi: 10.1111/coa.12462. PMID: 25974166. 2. Philpott CM, Boak D. The impact of olfactory disorders in the United kingdom. Chem Senses. 2014 Oct;39(8):711-8. doi: 10.1093/chemse/bju043. Epub 2014 Sep 8. PMID: 25201900.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Firstly, it's important to consider what patients with CRSwNP want from NHS care. From the data we have gathered from our survey and conversations with patients, this can be summarised into three main areas: • Recognition of the impact that symptoms have on their life from GP and ENT Consultants: Many tell us that they feel their condition is not taken seriously by the health system, and treated as insignificant, despite the wide-ranging and severe impact they say it has on their lives. • Fast access to specialist care: People tell us that they want to be referred quickly to a specialist who is knowledgeable on CRSwNP and not be prescribed treatments like nasal sprays and antibiotics that often fail to effectively treat the symptoms, let alone solve the underlying problem. • Effective lasting treatment: Patients with CRSwNP tell us that they want treatment that will alleviate the symptoms of the disease and make significant improvements to their quality of life. Restoration of the sense of smell, and associated improvements in flavour perception ability, is a key desire for many. Current treatments for CRSwNP Many patients with CRS use medication to control their symptoms and do not need surgery. CRSwNP is harder to control with medication, and many patients will be recommended for an operation to remove nasal polyps. As professional body ENT UK state, the main aim of surgery is to <i>...improve the long-term control of symptoms when treatment with medication has not been completely effective.</i> There are an estimated 40,000 sinus surgeries every year in England and Wales. Surgery, with an appropriate follow-up treatment/management plan, will provide adequate relief from symptoms for many patients. But there is a cohort of CRSwNP patients for whom surgery does not provide lasting relief from symptoms. These are covered in more detail under section 8 <i>Is there an unmet need for patients with this condition?</i> What do patients tell us about their experience of NHS care for CRSwNP? Patients tell us about a range of issues, including lack of recognition and support from doctors, variability and inconsistencies in care, including struggles to be referred to a knowledgeable specialist and/or long waiting times, ineffective treatments and the emotional burden of all this. Some people have told us that they have given up on the NHS and are paying for private care. A common theme in our survey responses is a lack of interest and/or understanding from healthcare providers. Respondents frequently report being dismissed by GPs and even ENT consultants, with anosmia often disregarded as insignificant.

"My GP was not very understanding of my condition. And was not very sympathetic. My first ENT surgeon was also not very sympathetic and was very blunt in telling me I would never regain my sense of smell. I don't feel there is much empathy from the medical profession towards sufferers of this condition. I didn't have better treatment with my second Consultant and I felt the second operation went well however I do feel that after care was not great. Advice on how to manage my condition and knowledge about Samters Triad was almost non-existent."

People also talked about long wait times and lack of follow-up. Several respondents describe waiting years for an ENT appointment or surgery, with little to no follow-up care afterward.

"GP has referred me urgently to consultant but there is a 52 week waiting list. Previous operation was awful but helped for about 2 years. There seems to be nothing else I can do."

"The surgery has always been effective for a matter of weeks but then I lose my smell and taste again. Consultants never really follow up for any length of time."

Many people talked about being prescribed ineffective treatments (sometimes repeatedly) by GPs, or occasional prescriptions of oral steroids which do have a positive effect as long as they are taken, with symptoms returning once they are stopped.

"The sinus surgery is only effective to get rid of polyps it does not stop them growing back it does not stop the nasal drip or asthma you still get. There is no support once surgery done. Steroids and nasal sprays are prescribed but do not stop the polyps coming back."

"The only thing that has ever given me relief is prednisolone, but my GP refuses to prescribe it. I have to beg for a short course, even when I am desperate."

Many respondents experience significant side effects from some CRSwNP treatments, particularly long-term steroid use and repeated surgeries. Oral corticosteroids (e.g. Prednisolone) provide temporary relief but come with serious health risks such as osteoporosis, weight gain, diabetes, mood swings, and digestive issues. Some feel trapped in a cycle of steroid dependency, as symptoms return once medication is stopped. Nasal sprays and rinses offer only partial relief, and some worry about their long-term effects on nasal health. Surgery can remove polyps, but they often regrow within months or years, leading to multiple procedures and complications like scar tissue, breathing difficulties, and hearing issues.

	<i>I have had several different nasal sprays all with side effects that I can't tolerate. The latest being really bad headaches when using dymista spray.</i> Some turn to private healthcare out of desperation, spending large amounts on consultations, prescriptions, and surgery because NHS options are too limited or slow. But this doesn't necessarily provide a lasting solution for those with the more severe cases of the disease, where polyps regularly reoccur. <i>"I paid to go private to have my polyps surgically removed as it was a 2 year wait with the NHS just to see an ENT consultant. Unfortunately, they're already coming back."</i> <i>"In order to expedite treatment and have choice of an appropriately qualified specialist, I have largely gone private. At first through insurance, later when insurance premiums became unaffordable, by self-funding. Apart from temporary periods when ALL symptoms completely disappeared by use of oral steroids, treatments have not been successful."</i> The difficulties in getting effective, lasting treatment further adds to the mental and emotional toll of the disease. The constant cycle of ineffective treatments contributes to depression, anxiety, and social isolation, with some even taking antidepressants due to feelings of hopelessness. <i>"My GP says it's something you'll have to learn to live with it. I take an anti-depressant daily which has helped with feeling of abandonment by health professionals and general despair at the situation."</i> <i>"I have been tossed around from doctor to doctor. Every time I see a new one, they want to 'try' the same treatments that have already failed. I feel like my condition isn't taken seriously, and my quality of life has suffered because of it."</i> Looking at this from a different perspective, some patients told us they occasionally get a glimpse of what life could be like were they to be given an effective lasting treatment: <i>"Occasionally, maybe once a year for a couple of hours, I can smell things and it makes it worse in a way, because I know the ability must be there and it just reinforces what I'm missing the rest of the time."</i>

8. Is there an unmet need for patients with this condition?	There is an unmet need for those patients with more severe cases of CRSwNP for whom sinus surgery does not provide lasting relief from symptoms or is not an option. The 97 responses to our survey from patients with severe CRSwNP demonstrate a significant unmet need within the NHS for a treatment that will provide lasting benefit and an escape from the status quo: a frustrating cycle of temporary relief via surgeries or steroids, only for symptoms to return, leaving them exhausted, hopeless, and feeling abandoned by the healthcare system. As one of the Consultant Rhinologists with whom Fifth Sense works explains: <i>"We all have a group of patients who have this more aggressive form of CRSwNP and despite multiple surgical treatments the disease recurs. There is a significant impact on patients' quality of life and also the continued cost of multiple operations on the NHS."</i> The clinicians we work with tell us that, based on data on sinus surgeries undertaken in England, between 3-12% of all patients who have had sinus surgery are in this group. In our survey we asked people how many sinus surgeries they'd had. On average respondents have had 3, whilst 8 people told us they have had over 10 surgeries. Many respondents told us that the operations provide no lasting relief, but are told there are no alternative treatments available and they'll have to have another operation once polyps have regrown. Some, however, have been told they can't have any more operations due to scar tissue or high surgical risks, leaving them with no viable treatment options, as other medications do nothing to stop the growth of the polyps. This has led to deep frustration and despair, as they are forced to endure worsening symptoms without access to alternative treatments. <i>"I have had this condition for the past 30+ years. Over the years I have had to have FESS surgery every 3 years on average, so you can see how many surgeries that has entailed to clear the nasal polyps as I am now 61 and started this cycle in my late twenties. They would just recur."</i> <i>"I have had 10 operations for nasal polyps over the years, which only give short-term relief. My polyps grow back within weeks of surgery. My local ENT has said there is nothing more they can do for me."</i> <i>"The first 9 were done at my local hospital in the North West. They then refused to do any more due to extensive scar tissue, and I'm now high risk for complications"</i> <i>"Repeated surgeries have also left me fearing for the structural integrity of my nose. I have spoken to another patient whose nose collapsed after multiple operations, and I worry I could be next. It feels like I'm playing a game of Jenga with my own face."</i> <i>"Over 20 years living with CRSwNP and 4 surgeries down. Surgery only gives you some relief for a short period of time. I honestly believe my body no longer responds to antihistamines and nasal sprays because of how long I've had to take them. Sinus flushes only do so much."</i>

9. What do patients or carers think are the advantages of the technology?	We spoke with one person who has been taking Dupilumab for CRSwNP for around 12 months. Prior to this they had been living with CRSwNP for several years, experiencing loss of smell, facial pain and headaches. The medication they were given – including steroids and nasal sprays – didn't work for any length of time. A sinus operation initially improved their symptoms, but within a couple of months they had lost the sense of smell again and all other symptoms then returned. This patient was then able to be given Dupilumab as the result of taking part in a clinical trial and described the difference that taking the drug has made: <i>"Since starting with Dupilumab, my symptoms have improved to such an extent that they are no longer present. My sinuses are completely clear, I can breathe through my nostrils normally, I no longer suffer from mental health issues, socialising is no longer a problem, and life is as good as it can be. I cannot stress just how much taking Dupilumab has changed my life in every aspect because CRSwNP is a debilitating condition. In this day and age, with such advancements in medicine, there really shouldn't be any reason why people suffer from CRSwNP like they do. Dupilumab should be made available for sufferers. The symptoms that come with this condition are life-changing for many people, including myself. If Dupilumab helps people like it has helped me, then it really does need to be made available on the NHS."</i> Whilst we were unable to speak with any other people who are taking Dupilumab for CRSwNP, in our survey we asked people what they felt the advantages of the drug would be, based on the information sheet we put together (consisting of a brief overview of the drug and how it works, how it is administered, results of some clinical trials and a list of some of the side-effects, with a link to the Sanofi Regeneron Dupilumab patient information sheet which provides a full list). The message that came through strongly from responses is simple: Lasting relief from symptoms without the need for repeated surgeries or courses of oral steroids, or the side-effects associated with them. Many talked about the improvement in quality of life that the alleviation of symptoms would bring about, often referencing the opportunity to regain their sense of smell. The terms 'life saving' or 'life changing' were used by a number of people. <i>"This would be a lifesaving advantage to me and the quality of my life. I could breathe again through nose, smell taste. No more nasal drips. Better sleep. Everything would be better."</i> <i>"Significantly less daily medication with the risk of side effects and inconvenience/problems with taking these consistently. I believe Dupilumab may be a monthly injection, that's far easier to manage and less intrusive on life and travel. It would be great to know the polyps are far less likely to return, that was an unpleasant operation and took time for the medical team and me and cost a lot! I'd hate to have to have that procedure again. It seems that Dupilumab would be likely to be even more effective at controlling/managing my symptoms, that would be fantastic!"</i>

	<i>"It would be a life changing treatment for people with this condition. Currently we have nowhere to go but ongoing surgeries and steroid use."</i> The removal of the negative impact on long-term health associated with regular steroid use was an important factor for many of our survey participants: <i>"I think that using it could be a better/safer alternative to long term steroid use."</i> <i>"At the moment, I am taking antihistamines, sprays for the sinuses, an inhaler, and decongestant drops when my sinuses are really blocked, which can't be good for me. But you just have to try and find something that helps alleviate the symptoms. It would be amazing to have an injection and not worry about all these pills and hopefully get some smell and taste back, even if it's only a little."</i> An important point to mention that was raised with us by clinicians and the patient who is taking Dupilumab for CRSwNP is that not all patients need to be given the dosage as per the licence in order to have respite from symptoms. <i>"Under the guidance of the consultant, I now do the injections every four weeks, and I'm hoping to increase it to every six weeks."</i> Finally, one participant in our survey neatly summarised the potential benefit of Dupilumab in the context of the myriad quality of life impacts of CRSwNP: <i>"To let me get on with my life like a normal person."</i>

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The person we spoke with who is taking Dupilumab for CRSwNP was unequivocal: <i>"There are no disadvantages to taking this medication—only advantages."</i> Amongst our survey respondents, the main perceived disadvantages of Dupilumab are the potential side-effects, with some people mentioning that they would not like having to inject themselves with the drug. <i>"I am a bit worried about side effects including eye problems and self-injection sights/infection. I would not want to lose my eyesight on top of everything else!!"</i> <i>"Due to the asthma, I would be slightly more concerned about allergic reactions, plus I'm not keen on injections. Infrequent injections would be fine though."</i> Whilst these are a concern for some, many seem to feel that the benefits outweigh the risks, particularly for those whose current symptoms have such a wide-ranging and severe impact on their daily lives. <i>"The side effects seem small compared to the benefits of the people in the trial."</i> <i>"After reading the Dupilumab information sheet. I feel the medication would be less risk than taking prednisolone on a long term basis. The risks seem less severe than prednisolone. To have a quality of life with less risk to health."</i> <i>"All meds will have potential side effects, the common ones mentioned by the information sheet are like having this disease, so what new! Obviously nobody wants the serious side effects but I'd be willing to try dupilumab because I think it would be worth the risk."</i>

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The patients who might benefit more from the technology are those for whom current treatments do not provide lasting relief from symptoms, as outlined in our response to Question 8.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Patients with severe, uncontrolled CRSwNP face an inequality that we wish to raise as part of this appraisal. Dupilumab was approved to treat people with severe asthma with type 2 inflammation by NICE in December 2021. Moderate to severe asthma is a co-morbidity of CRSwNP. At present, those patients with CRSwNP who have severe asthma with type 2 inflammation and meet the criteria set out by NICE are able to be prescribed Dupilumab, which should then treat both conditions. But patients with severe uncontrolled CRSwNP alone, or who have co-current mild to moderate asthma that don't meet the criteria, are unable to be prescribed the drug. In our survey we asked patients living with both conditions how the quality of life impact of severe asthma compares to CRSwNP. 41% of respondents say they have severe asthma with type 2 inflammation in addition to CRSwNP. Of those: 9% said that the symptoms of CRSwNP have less of an impact on their quality of life compared to the symptoms of asthma 43% said that the symptoms of CRSwNP have an equal impact on their quality of life compared to the symptoms of asthma 48% said that the symptoms of CRSwNP have a greater impact on their quality of life compared to the symptoms of asthma To summarise this in the context of the rest of the responses to our survey: • Patients say that CRSwNP affects every aspect of their life • The majority say that the EQ-5D doesn't adequately capture the impact on their life. • The majority of those living with both severe CRSwNP and severe asthma with type 2 inflammation feel that the former has an equal or greater impact on their life than the latter, for which Dupilumab is approved

Other issues

13. Are there any other issues that you would like the committee to consider?	Dupixent/Dupilumab is already being used to treat patients with CRSwNP in over 30 countries around the world. Some of the patients who responded to our survey expressed frustrations that Dupilumab – and indeed other biologic drugs that are being used to treat patients with CRSwNP elsewhere in the world – are not currently available to UK patients. <i>“It works for loss of smell and taste, my son takes it in the USA”</i> <i>“I’ve read of amazing results from forums with members in the USA already using this.”</i> <i>“I have had to live with this disease for over 20 years. People don’t understand the impact that this has on your day to day life, mental health and general wellbeing. Being on a Facebook page for people like me across the world I’ve heard lots of positive things about Dupixent and I pray that one day those like me who suffer with CRSwNP will be lucky to live a life with this medication and have our lives changed for the better. We can live in hope anyway.”</i>

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• CRSwNP can have a significant long-term impact on almost every facet of someone's life, but this often goes unrecognised by care providers. • The majority of patients we engaged with feel that the EQ-5D does not adequately capture the wide-ranging and nuanced impact of severe CRSwNP. We request that NICE considers using data captured by SNOT-22 as a more detailed and accurate measure for assessing health-related quality of life in addition to the EQ-5D in health technology assessments of drugs to treat CRSwNP. • There is a clear unmet need amongst patients with more severe cases of CRSwNP (especially those for whom sinus surgery does not provide long-term relief from symptoms or is not an option) for an effective, lasting treatment that alleviates symptoms, restores quality of life and breaks the ongoing cycle of ineffective treatments, removing the mental and physical health impact associated with these. • We believe there is a health inequality in relation to Dupilumab, where patients with severe CRSwNP who also have severe asthma with type 2 inflammation are able to be prescribed the drug on the basis of their asthma, but patients with severe CRSwNP alone, or less severe asthma, are currently unable to be prescribed it. • We would like to see Dupilumab to be available for NHS patients with more severe cases of CRSwNP for whom current treatments don't provide effective, lasting relief from symptoms.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES

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Appendix to Fifth Sense evidence submission for Dupilumab for treating severe chronic rhinosinusitis with nasal polyposis [ID6480]

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Survey responses

Responses to: Survey to capture views of people with chronic rhinosinusitis with nasal polyps for NICE appraisal for Dupilumab responses.

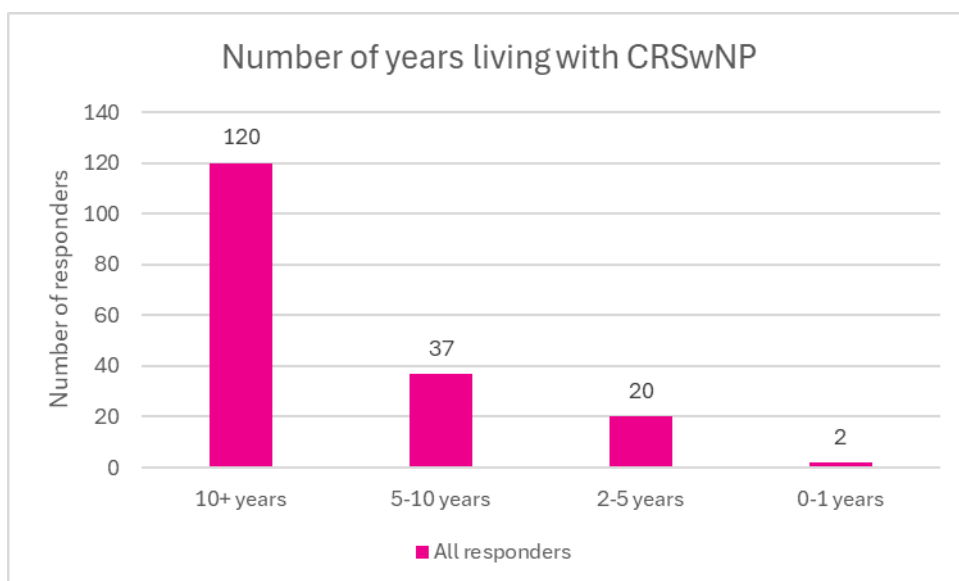
- Survey opened to responders: 14 February – 24 February 2025
- 184 responses

Survey Questions

1. This survey is for people who have chronic rhinosinusitis with nasal polyps (CRSwNP). Please confirm this applies to you.

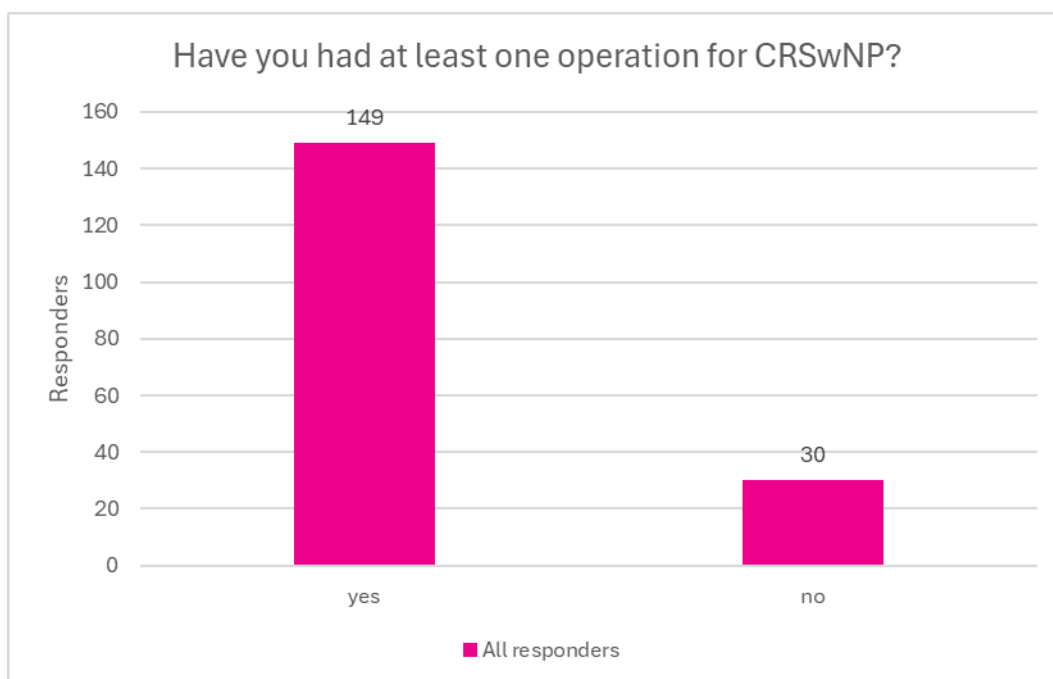
RESPONSE: 100% YES

2. How long have you had CRSwNP?



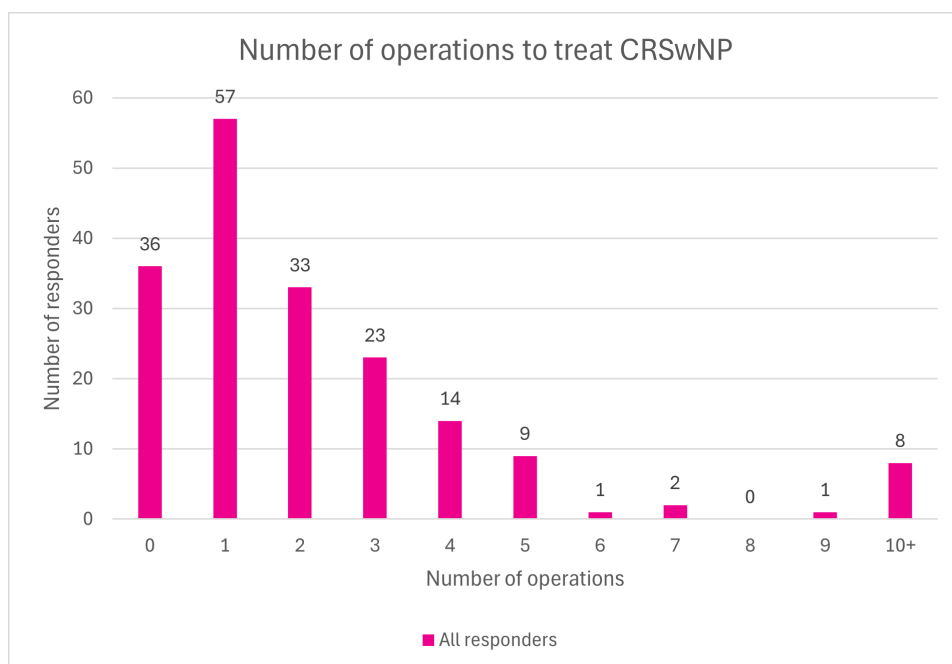
(5 people skipped this question)

3. Have you had at least one operation to treat CRSwNP?



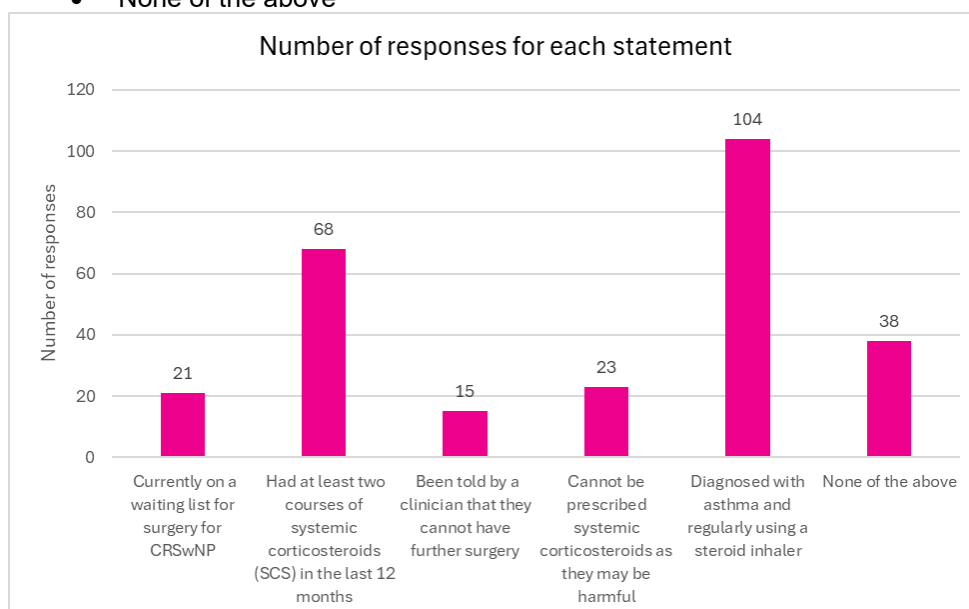
(5 people skipped this question)

4. Please tell us how many operations you have had to treat your CRSwNP



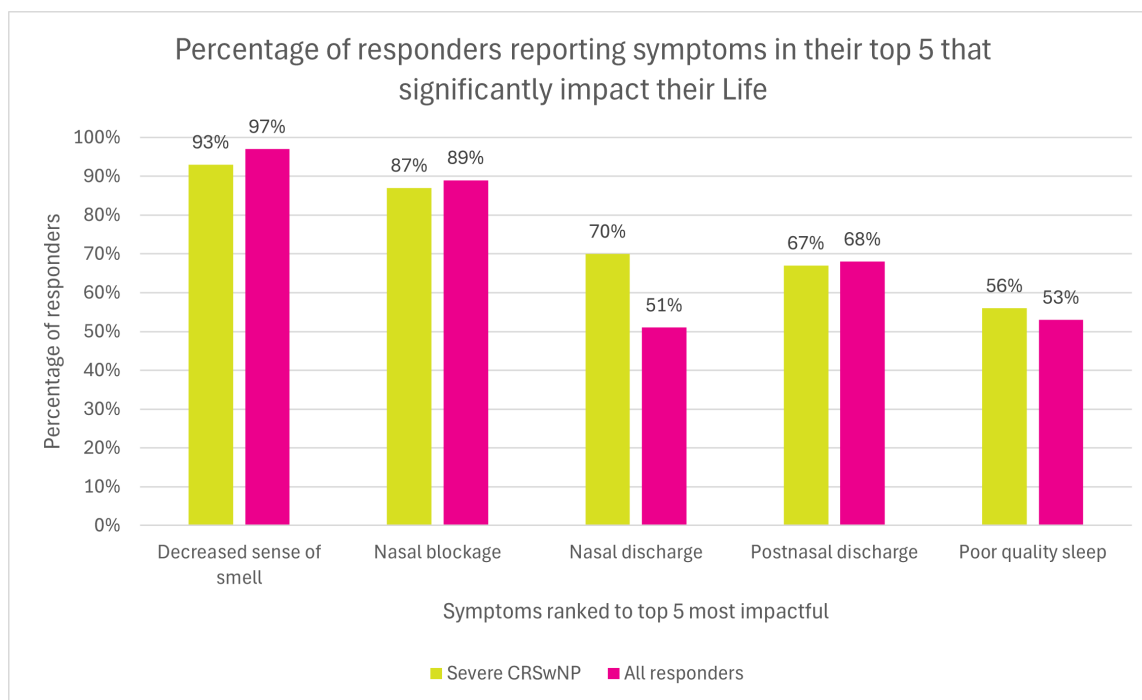
5. Please check all of the following statements that apply to you:

- Currently on a waiting list for surgery for CRSwNP
- Had at least two courses of systemic corticosteroids (SCS) in the last 12 months
- Been told by a clinician that they cannot have further surgery
- Cannot be prescribed systemic corticosteroids as they may be harmful
- Diagnosed with asthma and regularly using a steroid inhaler
- None of the above



(please note that the numbers above represent the number of responses to each statement, not the number of respondents overall)

6. We want to understand which symptoms of CRSwNP have the greatest impact on you. Please rank only your top 5 most impactful symptoms



7. Please tell us in your own words how CRSwNP impacts your life overall. Here are some things you might want to consider: Mood & mental health:

- How does it affect your emotions and well-being?
- Social life: Has it changed how often you go out or take part in activities?
- Work life: Does it impact your job or daily responsibilities
- Keeping active: Has it affected your ability to exercise or take part in sports?
- Relationships: How has it influenced your connections with family, friends, or a partner?
- Pain or discomfort: Do you experience physical symptoms that affect daily life?
- Food & drink: Has your loss of smell or taste affected your enjoyment of meals?
- Safety:
 - Do you worry about your ability to detect dangers like gas, smoke or spoiled food?
- Sleep quality:
 - Does CRSwNP affect how well you sleep?

I am completely depressed and at a loss with this condition. It affects EVERY part of my life.

I have no sense of smell and I live alone... A fire started in my kitchen which I was totally unaware of and sat reading a book until a neighbour smelled burning and alerted me.

I am constantly tired, I can't concentrate at work, I struggle to engage with my family. My mood is terrible, I can't enjoy food. It makes me feel so low.

I miss my job as a chef. I rely on memories of tastes and smells to create dishes – I no longer work because I have less sense of taste and no sense of smell.

I spent 10 years using SSRIs. I have been suicidal, depressed and emotionally and sexually limited. I've found I'm better off not socialising as the lack of any enjoyment has a dispiriting effect on me.

I have had this condition for over 30 years. It has badly affected my opportunities to work, my sleep, my mental health, my confidence, my ability to cook, my relationships with my family, and my overall quality of life.

I sometimes go months without being able to close my mouth because my nose is blocked. This affects my tongue and my voice as well as my sleep and my breathing.

CRSwNP has taken over my life, I cannot breathe properly and I am in constant pain. At times it feels like I am being smothered by my polyps. My mood is so low because of it, I am being treated for depression and anxiety alongside it.

I love food, and it is troubling to me that I can't taste or smell. I miss so many smells and use my memory to imagine them. I feel it is dangerous not to be able to taste or smell – I don't protect myself from pollution; I don't know when food is burning; when food is off.

I no longer sleep beside my wife as the symptoms keep her awake. I wake up every hour. I'm in constant pain and discomfort. I went through depression because I could no longer taste and smell. I get dizzy spells. I struggle financially due to not being able to work the way I need to.

Having no sense of smell impacts on my mental wellbeing. There are significant safety implications of not being able to smell.

The last few years I've started having trouble with my hearing. On a bad day or week I struggle to hear work colleagues or patients, and it's embarrassing having to ask people to speak up and repeat themselves.

Not having a sense of smell significantly reduces my quality of life and poses a risk to my health. I regularly get ear issues which impact my work as I'm unable to function when symptoms are bad.

It affects everything! I can't think of any aspect of life this does not affect. I'm a pretty strong-minded guy but struggle not to let this condition get me, which ultimately leads to times of depression.

I regularly have sinus pain and often have to take time off. I have some strategies to ensure my safety, but it is always on my mind. My personal relationship with my husband is also greatly affected by my condition. Life is no longer enjoyable. I feel I just survive. Very little pleasure.

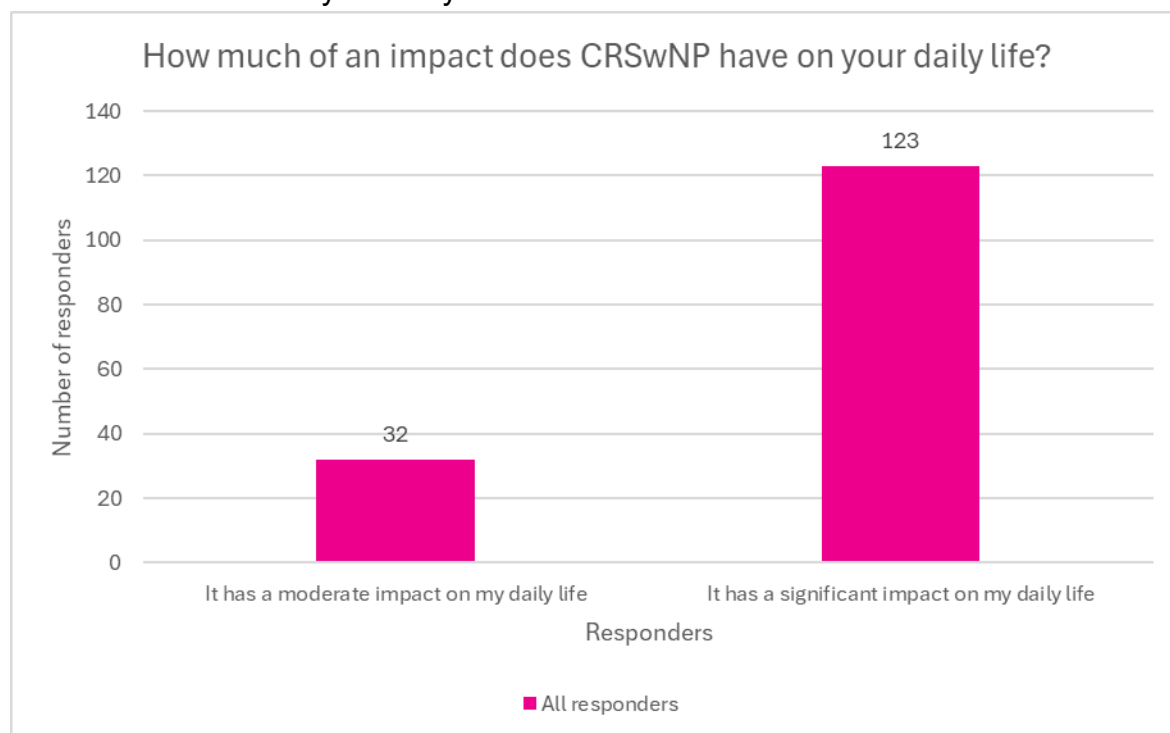
I have had this condition for the past 30+ years. Over the years I have had to have FESS surgery every 3 years on average, so you can see how many surgeries that has entailed to clear the nasal polyps as I am now 61 and started this cycle in my late twenties. They would just recur.

I've had 10 operations over the many years of suffering with this disease. Started with polyps aged 16, first operation aged 23. I'm now 52. Number 11 and upwards WILL happen in my future if no alternative treatment is offered for my condition.

The first 9 were done at my local hospital in the north west. They then refused to do any more due to extensive scar tissue, and I'm now high risk for complications. Number 10 was done in London by a professor experienced in this condition.

My last surgery in November 2023 hasn't worked, and I have spent the last 15 months with constant green mucus, several sinus infections, and generally feeling like crap because of it. Surgery only brings a short relief before the polyps start growing back.

8. Thinking about your statement above, how much of an impact would you say that CRSwNP has on your daily life overall?



(29 people skipped this question)

9. Please tell us about how you think your CRSwNP impacts on your partner, family and friends. Here are some things you might want to consider:

- Emotional impact: Does it cause worry, frustration, or stress for loved ones?
- Social life: Has it changed how often you go out or take part in activities?
- Communication: Do symptoms like congestion make conversations harder?
- Mood: Have changes in your mood had an impact on your relationships?
- Support needs: Do you rely on others for help, and how does this impact them? Sleep quality:
- Does poor sleep affect both you and those around you?
- Daily activities: Have those around you had to stop or change hobbies, work, or household tasks?
- Food & drink: Has your loss of smell/taste affected shared meals with your loved ones? Safety:
- Do others worry about your ability to detect dangers like smoke, gas, or spoiled food?

"It has an enormous effect on family and my husband in particular. We have taken to sleeping in separate rooms due to the volume of my snoring. This affects our relationship on lots of levels."

"My partner does ALL the cooking. She has tried numerous ways to improve my enjoyment and constantly has to deal with the dissatisfaction I feel at mealtimes. We gave up kissing and intimacy

many years ago as the discomfort for me was too much. This, plus the medications I was taking, almost split us up."

"I live alone, so my previous answer covers some of the points, but my family worries about me not being able to smell gas or burning, and my friends and family are always asking me if I can 'smell that,' which is frustrating."

"My husband checks any food such as meat to make sure nothing has gone off before we eat it. He told me my lack of smell worries him for when he won't be here anymore. He's afraid I won't notice a gas leak or spoiled food."

"My wife gets very frustrated when I have difficulty breathing and start coughing and sneezing. My broken sleep affects her, and she ends up suffering as well."

"I know my husband worries whenever I have another operation due to the increased risks. He says each one is taking me longer to recover from. Maybe that's because I'm getting older or I'm just more physically and mentally battered by each operation, I don't know?"

"I'm obsessed with showering because I don't know if my body smells, and it affects my sex life for the same reason. I can't smell my family, and that breaks my heart—I cry sometimes because I would give anything to be able to smell them."

"My partner sometimes gets irritated by my constant sneezing and coughing. A blocked nose makes conversation more difficult for people to understand me, and when polyps are bad, I have to sleep alone."

"My wife has to check my food sometimes as I've eaten things in the past that she has advised me to stop eating due to its taste or smell. It makes me tired, which makes me snappy, which causes arguments."

"Because of this handicap, I find myself OVER EATING. When I try to explain this, every single person says if it happened to them, they would lose weight because they wouldn't eat. This makes me so depressed."

"I don't enjoy cooking anymore as everything I cook doesn't taste as it should, although I don't get any complaints. But we had a fire in the house, and I didn't know because I couldn't smell the smoke. Luckily, we had smoke detectors, but I still felt guilty."

"We recently moved house, and I don't know what it smells like. My husband always buys me the same perfume because I wouldn't know whether I'd like a different one. There's a general feeling of depression that affects the whole family."

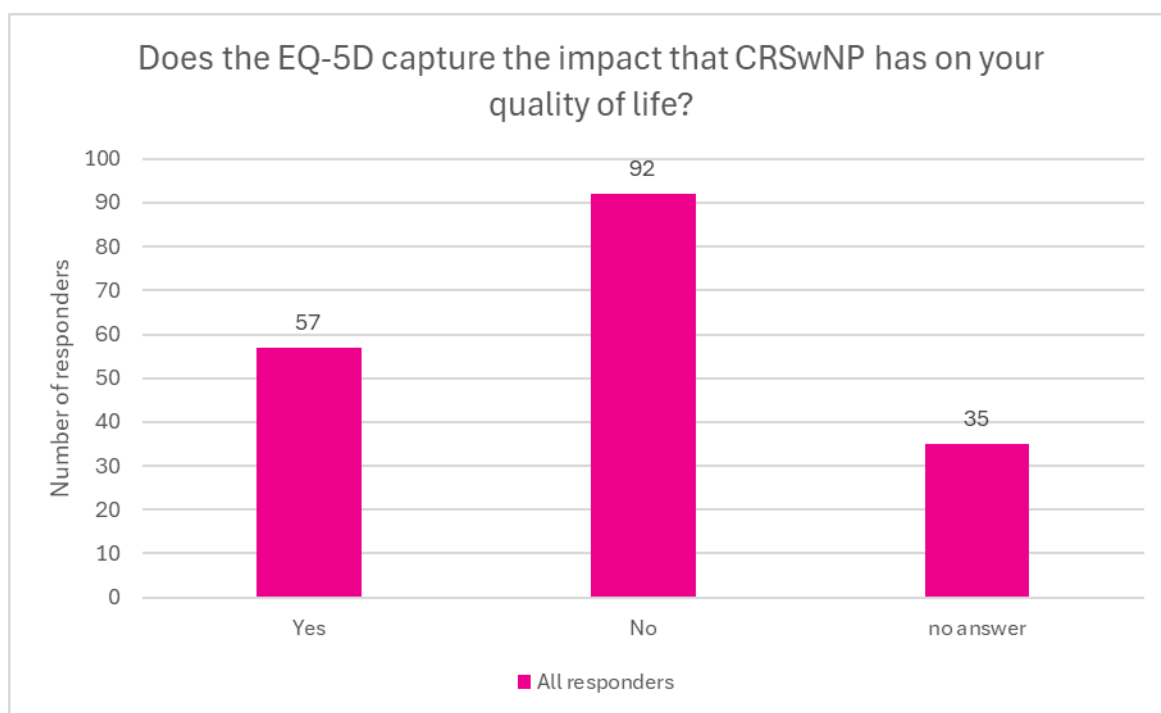
"My partner has to deal with me being miserable and tired all the time. As a father, my child is growing up seeing the worst side of me. My employer can't understand why I'm tired all the time."

"My social life has decreased considerably. I can't consume a lot of foods as they make my symptoms worse, I can't drink alcohol, and I'm either totally blocked up or streaming. It's affecting my life a lot. I have never smelled my children, who are now 24 and 20."

10. Please read the information in this image. This is a questionnaire called the EQ-5D. It is widely used to provide a standardised measure of health-related quality of life in clinical trials, economic evaluations and population health surveys. NICE use it as part of their technology appraisals of new medicines. It asks you how your health affects your daily life in five key areas:

- Mobility (walking around)
- Self-care (washing and dressing)
- Usual activities (work, hobbies)
- Pain/discomfort
- Anxiety/depression

Imagine that you have been asked to complete the EQ-5D specifically for your CRSwNP. Do you think that the EQ-5D adequately captures the impact that CRSwNP has on your quality of life? EQ5D



I do not have mobility problems and I can complete my household chores. The only section I can say is that I have suffered with anxiety and this is due to circumstantial issues, and I have learnt to deal with my anxiety with counselling support.

it doesn't address the issues of lack of desire to prepare / eat food nor does it address the concerns re personal hygiene and the fact that this can become an obsession

The questions are too closed. It does not give you the options to explain what areas you do struggle with, they don't fit into these categories! There are aspects of difficulty in all those areas but they don't fit into the tick boxes.

It completely ignores the impact of anosmia - eating, drinking, safety aspects, social aspects

Needs to be a bit more holistic - feeling confident over risk - have a network of support

"Self-care" is not just about being able to wash or dress yourself, this is a very narrow way of measuring quality of life. It ignores the huge range of symptoms that are affected by CRSwNP on a daily basis.

It doesn't ask any questions about how it affects day to day life. Eating, drinking. Safety issues such as being able to smell burning /gas/spoiled food. I don't feel it really covers many issues repeated to CRSwNP.

It does not ask about quality of sleep, no section on how exercise is impacted

Obviously those question relate to disability in some form or other. Loss of sense of smell is massively impactful on daily living and in my view should be included. This disease and its co-morbidities are disabling to varying degrees and affect my quality of leading a normal life

Nothing of number of operations for an ongoing condition, nothing on current medications and if they improve or not improve quality of life, nothing on sense of smell/taste and the impact on my life, nothing on sleep issues due to lack of breathing etc

Not enough questions about consequences of the illness

I would answer No to all sections, this appears healthy, but CRSwNP does impact my life daily

It doesn't mention any sensory affects at all!

There is nothing here about the ability to enjoy normal interaction with family, friends or others. Having no sense of smell puts you outside of the normal appreciation or enjoyment of many everyday activities, eg sharing a meal, walking in the countryside, shopping, eating out, visiting gardens.

11. Please tell us about your experience and views on the current treatments and care available on the NHS for CRSwNP. Some things to think about are: How effective sinus surgery has been in giving you long-term relief from symptoms Any complications you have had following sinus surgery Details of any other treatments that have helped alleviate your symptoms The quality of care you have had from your GP The quality of care you have had from your ENT consultant(s)

I have had 10 operations for nasal polyps over the years, which only give short-term relief. My polyps grow back within weeks of surgery. My local ENT has said there is nothing more they can do for me.

My GP referred me to ENT years ago, where I was told there was nothing that could be done. I later insisted on another referral and a scan revealed polyps and a deviated septum, which they had completely missed before. I can't help but wonder how much better my condition would be if they had done their job properly 10 years ago.

I have been tossed around from doctor to doctor. Every time I see a new one, they want to 'try' the same treatments that have already failed. I feel like my condition isn't taken seriously, and my quality of life has suffered because of it.

I waited four years to get a referral from my GP to ENT, by which time I couldn't breathe at all through my nose. Even sleeping and basic exercise were difficult.

I was told by my ENT consultant that surgery had probably damaged my smell receptors and that I should 'get used to never being able to smell again.' I was then discharged without any support.

The waiting times are ridiculous. It has been over two years since I was put on the list for my next surgery, and these last two years have been miserable.

The only thing that has ever given me relief is prednisolone, but my GP refuses to prescribe it. I have to beg for a short course, even when I am desperate.

I was told by an ENT consultant that my loss of smell was 'just part of aging'—I was 62 at the time. I had to go private to get the medication I needed, which has made a huge difference.

My polyps begin to grow back almost immediately after surgery. My GP says I just have to 'live with it.' But living like this is unbearable.

ENT consultants have told me Dupilumab isn't available because of cost, even though it could change my life. It is infuriating knowing there's a treatment that could help, but I'm being denied access.

The only thing that helps is a course of strong steroids, but because of the side effects, I'm not allowed more than a short course a couple of times a year. Meanwhile, I'm left struggling daily with no real treatment plan.

I've been on a waiting list for over a year for an ENT appointment. My sinuses are now completely blocked again, and I wake every morning being sick with the mucus that has gone down my throat in the night. My GP just tells me to wait or go private, which I can't afford.

I have been on waiting lists for both the Smell & Taste Clinic and my local ENT for over five months. My GP considers my condition 'non-urgent,' even though it has destroyed my quality of life.

I tried to get referred to Dr. Philpott, an expert in the field, but was told I couldn't because I don't live in his area. Why should where I live determine whether I can access proper care?

I've had three surgeries, each bringing shorter relief than the last. My ENT now says further surgery won't be possible due to scarring, and yet I'm still not eligible for alternative treatments.

I now snore, I struggle to breathe, I've lost my sense of smell, and my GP doesn't know what to do. There is no support, no follow-up, just a life of suffering.

My NHS GP surgery has been receptive and caring but ultimately ineffective. I eventually self-funded treatment at a clinic on the other side of the country, spending a fortune because I was desperate for help.

12. Do you have any concerns or worries about any of the treatments you have been prescribed? Please provide details here

I am currently using steroid drops. I believe they can cause ocular pressure so I do get my eyes checked regularly. I worry about the long term use of these and the affects they might have.

I'm just frustrated and angry that everything I've tried from the steroid nasal sprays to the antibiotics and prednisolone there's just nothing left to try while I wait out this operation and I'm so frustrated and depressed

Yes! Having read about mometasone, I'm aware that long term use causes sense of smell to diminish. If I stop using it, the congestion, discharge & facial pain is unbearable. I feel like in a useless situation. I've been using it for 20+ years, it was first prescribed by an ENT consultant, & my gp just issues repeat prescriptions, without any meaningful reassessment.

I'm not sure if I should remain long term on budesonide to rinse my nasal cavities each day but dr discharged me saying nothing else he could do. Also they are expensive to the NHS and I could potentially be on something cheaper and more effective

Prednisone also can cause weaker bones which I now have and I am taking calcium tablets for that.

My main worry is the long terms effects of using the steroid nasal sprays. In recent years my ENT specialist suggested I had an ear operation (involving drilling into my skull) which I declined. I now have two hearing aids and work hard to clear my sinuses if they start affecting my hearing further. I would be concerned to take any drugs internally as I am already on medication for my heart, including aspirin, one of which has caused a stomach ulcer. I am no longer on the one that caused it but am another one to try and protect my stomach. It seems a vicious circle.

I do worry about the long term affects of taking the nasal spray - does it affect my eyes - mt throat and because I still get a very swollen nasal lining even when I use it

Yes. The steroid nasal drops only work if you administer them every day, twice a day for a few weeks. It is awkward to administer them as it involves lying on the bed with your head hanging off the bed, then dripping the drops in and waiting for them to be soaked up. Otherwise, as soon as you sit up, you swallow the steroids. I find this a very frustrating and inconvenient treatment. After a few weeks of doing this, I might get 1 or 2 weeks of being able to smell and not having a blocked nose, then it fades again. This is not a long-term solution so I have basically given up on the treatment. I am so despondent that there seems to be no way of treating this condition effectively.

I do worry about the long term effect of steroids on my immune system. I worry what I have stored up for my old age.

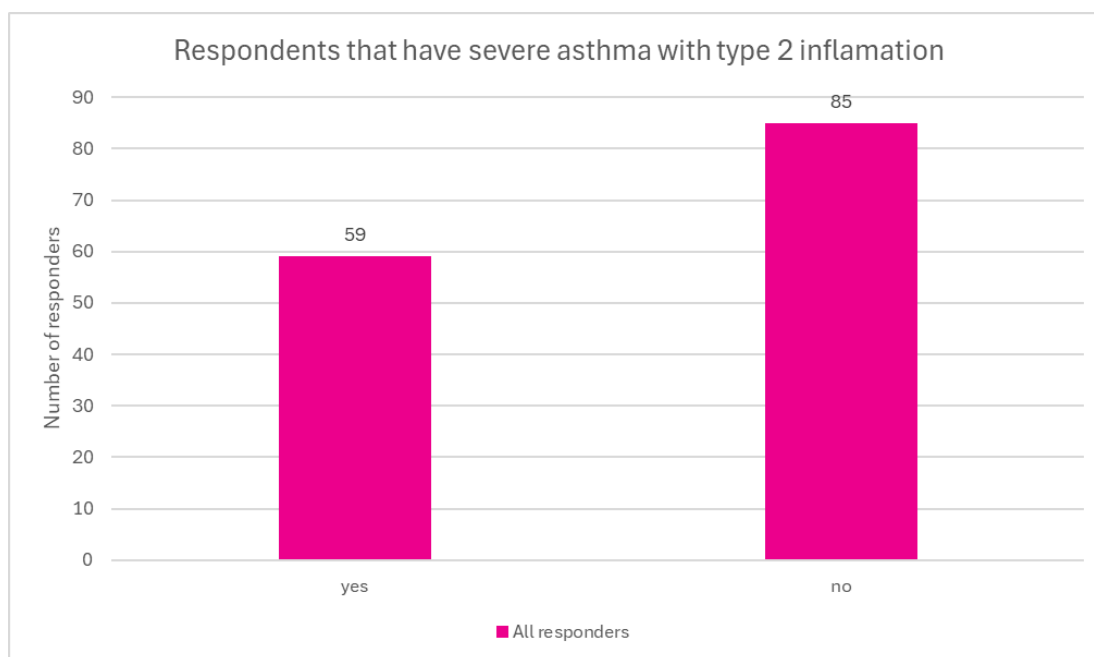
Yes, a treatment prescribed 2 months post op was pulmicort 1mg in a neilmed saline wash. Each time I used it a thick grey sludge came down my nose. I had to stop using it. I would be very reluctant to use an immunomodulator such is a ' nab' as the immune system has a vital role in detecting things like rouge cancer cells. For me I am more likely to put up with the poor quality of life than use it to get a sense of smell back

13. Do you have severe asthma with type 2 inflammation? Symptoms of severe asthma with Type 2 inflammation are similar to those of regular asthma, but they are more severe and persistent. These symptoms may include:

- Frequent coughing, especially at night
- Shortness of breath, even during mild activity or at rest
- Wheezing that persists even with medication
- Difficulty sleeping or sleep disturbances due to asthma symptoms

- Increased use of quick-relief inhalers

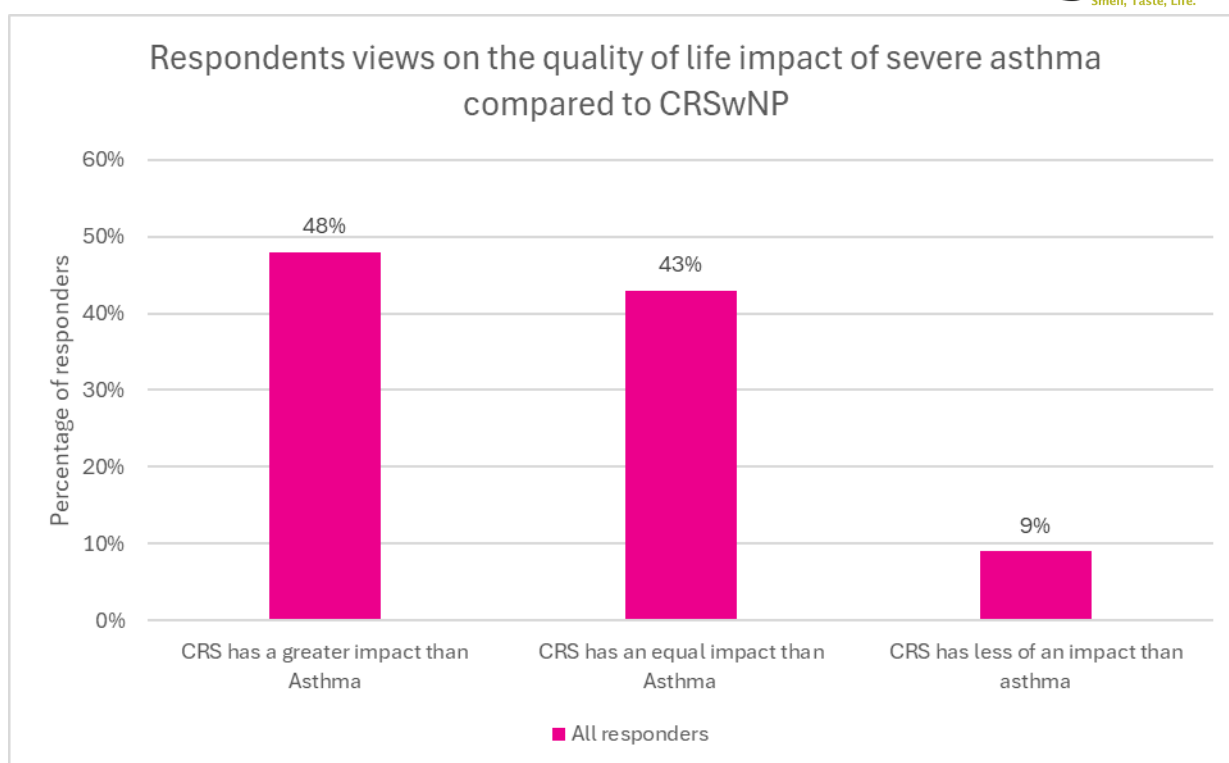
Asthma patients with excessive Type 2 inflammation may have one or more Type 2 inflammatory diseases of varying levels of severity, including Chronic rhinosinusitis with nasal polyps (CRSwNP) and Aspirin-exacerbated respiratory disease (AERD), a chronic inflammatory condition that causes asthma, nasal polyps, and a reaction to aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs). If you're unsure whether you have severe asthma with type 2 inflammation, but you have the symptoms as outlined above, then please select 'yes'.



(40 people skipped this question)

14. Dupilumab is approved on the NHS for treating patients with severe asthma caused by type 2 inflammation that is inadequately controlled. However, it is not currently approved for people with uncontrolled CRSwNP. We are keen to hear from individuals who have both this type of asthma and CRSwNP. We would like to get your views on how the quality of life impact of severe asthma compares to CRSwNP as it could be valuable for our evidence submission. Please select one of the following options.

- The symptoms of CRS have a greater impact on my quality of life compared to the symptoms of asthma
- The symptoms of CRS have an equal impact on my quality of life compared to the symptoms of asthma
- The symptoms of CRS have less of an impact on my quality of life compared to the symptoms of asthma



15. Having read the information sheet on Dupilumab, what do you see as the potential advantages of being prescribed this treatment for your condition?

The advantages are that my sense of smell and taste could return and I wouldn't have to take daily medications and my quality of life would hugely improve. It would also reduce operations being undertaken by the NHS to remove nasal polyps.

It would be a life changing treatment for people with this condition. Currently we have nowhere to go but ongoing surgeries and steroid use.

A better quality of life and sleep. Possibility of smell returning. Less frequent surgery.

Reduction of polyp size and return of sense of smell. My son uses dupilumab for his severe eczema and his quality of life has increased so much. He now doesn't even need to use emollients and steroid creams and doesn't get bullied at school. It has transformed his life so I am excited that in the future I may be able to use it too for my nasal polyps.

Removal of all or most of my disabilities.

Seems it could help with all my inflammatory issues inc skin rash . I would try anything as I have been waiting 10 months to see NHS specialist and Prednisolone only gives me short term relief . A weeks course brings my taste back , within 3 weeks it's gone again .

Regaining my sense of smell and taste and also treating my mild asthma. Not taking the risks of using steroid nose drops in the long term.

Potential to reduce nasal polyps that haven't reacted to steroids, and are too deep for surgery to be successful

A return of sense of smell is wonderful. It makes life 3 dimensional again rather than the feeling you are watching it through a tv screen. People with chronic sinus disease can feel their situation is hopeless so anything that gives hope of a sense of smell again, taken for granted by many, is wonderful

I would hope that treatment with Dupilumab who significantly decrease the growth of the polyps, reducing infections and in particular how long they last and their treatment. I would hope it would make a major improvement to my sense of smell. I was recommended this as a treatment by my ENT consultant but the cost puts it out of my reach

To let me get in with my life like a normal person

Eliminates potentially dangerous steroid treatment thereby removing anxiety etc, and provides good quality of life.

After reading the Dupilumab information sheet. I feel the medication would be less risk than taking prednisone on a long term basis. The risks seem less severe than prednisone. To have a quality of life with less risk to health.

Significantly less daily medication with the risk of side effects and inconvenience/problems with taking these consistently. I believe Dupilumab may be a monthly injection, that's far easier to manage and less intrusive on life and travel. It would be great to know the polyps are far less likely to return, that was an unpleasant operation and took time for the medical team and me and cost a lot! I'd hate to have to have that procedure again. It seems that Dupilumab would be likely to be even more effective at controlling/managing my symptoms, that would be fantastic!

This would be a lifesaving advantage to me and the quality of my life. I could breathe again through nose, smell taste. No more nasal drips. Better sleep. Everything would be better

Hopefully to shrink and stop polyps in their tracks once and for all. This inturn would stop my migraine/ headache, facial pain, mucus build up, hearing issues, and general fatigue from above symptoms causing lack of sleep. A bonus would be regaining smell and taste, even just a little is better than nothing. I've read of amazing results from forums with members in the USA already using this.

16. Having read the information sheet on Dupilumab, what do you see as the potential disadvantages of being prescribed this treatment for your condition?

Eye inflammation is a concern. also undiscovered side effects.

As I also have AERD I would be slightly concerned re potential side effects

Frequency of injections.

The side effects seem small compared to the benefits of the people in the trial

I am a bit worried about side effects including eye problems and self injection sights/infection. I would not want to lose my eyesight on top of everything else!!

I don't see any disadvantages. I already inject myself four times a day for my T1 diabetes, which is well controlled. Having further injections would not be an issue for me.

Due to the asthma, I would be slightly more concerned about allergic reactions, plus I'm not keen on injections. Infrequent injections would be fine though.

I can be sensitive to the drugs I take. The chance of having a reaction is there. But I'm now of an age where to get some fulfilment in an otherwise mostly joyless life is a risk worth taking.

There are side effects but ones that would risk compared to long term use of steroid drops or the resulting depression that comes with no sense of smell or taste.

None, other than possible side effects which are, in my opinion, worth the risk

At this point I'm happy to risk the side effects I don't care anymore

all meds will have potential side effects, the common ones mentioned by the information sheet are like having this disease, so what new! Obviously nobody wants the serious side effects but I'd be willing to try dupilumab because I think it would be worth the risk.

Case studies

Case study 1

Background

At 52 years old, I have endured over three decades of living with chronic rhinosinusitis with nasal polyps (CRSwNP). My symptoms began at 16, and my first surgery was at 23. Since then, I have undergone 10 operations, yet my polyps always grow back within weeks. Despite everything, I have been told that surgery number 11 is inevitable unless I can access an alternative treatment.

For years, my procedures were performed at my local hospital in the North West, but after my ninth surgery, they refused to operate again due to extensive scar tissue and high surgical risks. I had to travel to London for my tenth surgery, performed by a specialist. This came at a huge financial burden—I had to pay for train travel and two nights in a hotel because the surgery was scheduled early in the morning, and I needed to rest before returning home. The thought of enduring this financial and physical strain for every future surgery is exhausting.

Repeated surgeries have also left me fearing for the structural integrity of my nose. I have spoken to another patient whose nose collapsed after multiple operations, and I worry I could be next. It feels like I'm playing a game of Jenga with my own face.

Surgery only ever provides brief relief, and my current medications do little to control my symptoms. Nasal sprays and sinus treatments are ineffective, and even prednisolone—once my lifeline—has lost its effect. I still suffer from chronic migraines, facial pain, sinus pressure, and persistent mucus buildup.

Despite my long medical history, I still have to beg my GP for prednisolone when my symptoms spiral out of control. Many doctors refuse to prescribe it due to concerns about long-term steroid use, yet they offer no alternative solutions. Instead, I am trapped in a merry-go-round of surgeries, antibiotics, and failed treatments, with no way forward.

I have asked about biologic treatments like Dupilumab, but I am always told that it's too expensive and reserved for patients with severe asthma or eczema. Meanwhile, patients in the USA and parts of Europe are already benefitting from it. I know biologics come with potential side effects, but the long-term effects of repeated steroid use and endless surgeries could be just as damaging—if not worse. I won't know unless I am given the chance to try it.

The impact on my daily life and relationships

My condition has profoundly affected my work, relationships, and quality of life:

At work, my colleagues have learned to recognise that I always sound like I have a cold. I recently missed a fire alarm triggered by the smell of smoke—a stark reminder of how unsafe this condition can be.

Hearing loss has become a growing problem. After my ninth surgery, I had grommets fitted in both ears, but my hearing still fluctuates unpredictably. Some days, I wake up unable to hear my colleagues or patients clearly, forcing me to repeatedly ask people to speak up, which is frustrating and embarrassing.

Socially, my condition isolates me. I rarely go out for meals, even with family, because:

- I constantly need tissues to clear my nose, which is embarrassing.
- Food is tasteless, making eating feel like a chore.
- I can't smell anything, so I miss out on the simple pleasures of coffee, fresh bread, or even my own perfume.

Even basic safety concerns add stress to my life. My husband checks all our food to ensure it hasn't spoiled, because I wouldn't be able to tell. He worries about what will happen when he isn't here anymore—how will I know if there's a gas leak, a fire, or if I've eaten something bad?

Balancing my condition with being a full-time carer

My condition would be overwhelming enough on its own, but I am also a full-time carer. A few years ago, I looked after my terminally ill daughter, and now I care for my husband, who has stage 4 prostate cancer.

Even on my worst days, when my sinus pain triggers a migraine, I can't afford to rest—I have to push through. I was recently signed off work because I could no longer balance my condition with my caring responsibilities. Something had to give, and I had no choice but to prioritise my husband's needs over my own health.

Being a carer is already incredibly demanding, but dealing with CRSwNP on top of it is unbearable. The constant exhaustion, hearing loss, and sinus pain make every day a struggle.

A desperate need for change

I urgently need access to alternative treatments like Dupilumab. The current system is failing patients like me, leaving us trapped in a cycle of ineffective surgeries and medications. Biologic treatments could finally stop my polyps from recurring, allowing me to:

- Break free from the endless cycle of surgeries, steroids, and infections
- Reduce my daily pain, fatigue, and hearing issues
- Sleep better and function more easily as a carer
- Possibly regain even a small amount of smell and taste—which would be life-changing

I know that biologic treatments aren't perfect, but I am desperate to at least be given the chance to try. Until then, I am forced to endure a condition that takes more from me every year, with no real solutions in sight.

Case study 2

Background

For more than 30 years, chronic rhinosinusitis with nasal polyps (CRSwNP) has affected every aspect of my life. Getting a diagnosis and treatment was a battle—GPs did not take my symptoms seriously until my asthma became severe enough to warrant referrals to an immunologist, ENT, and asthma specialists.

Since my late twenties, I have undergone functional endoscopic sinus surgery (FESS) every three years on average—that's over 10 surgeries, yet my polyps always return. On bad days, I could go through an entire box of tissues in a single day. The constant congestion, sleep disruption, and difficulty breathing have left me exhausted, affecting my ability to work and my mental health, leading to depression and hopelessness.

Social and Emotional Impact

CRSwNP has made everyday life and socialising incredibly difficult. Going out for meals felt pointless and embarrassing—I couldn't taste or smell anything and had to constantly blow my nose. I also couldn't tolerate alcohol, which further limited my ability to join in social activities.

One of the hardest losses was missing out on the joys of family life. I never got to experience the smell of my babies, and I constantly worried about not being able to detect spoiled food, gas leaks, or smoke—a real safety concern. I lost confidence in my appearance and hygiene, never knowing if I had body odour or bad breath, which forced me to rely on others to tell me—an embarrassing and humiliating experience.

I was once a keen musician, but congestion made it impossible to play woodwind instruments or sing in a choir. Even something as simple as speaking on the phone became difficult because my voice sounded perpetually congested, and people struggled to understand me.

It has an enormous effect on my family, particularly my husband. We have taken to sleeping in separate rooms due to my snoring, which even mouldable earplugs couldn't block. We tried sleeping top to toe, but eventually, we had to sleep separately, which has affected our relationship in many ways. Socialising has always been difficult—it's tiring and frustrating constantly explaining why I can't eat, drink, or enjoy food like everyone else. I also see how sad my family are, which upsets me deeply.

My children have adapted and are thoughtful when choosing gifts, but wider family members often forget or don't fully understand my limitations. I frequently have to ask others to check things for me, such as whether food is spoiled, which frustrates both them and me.

I worry about the long-term effects of steroid use on my immune system and overall health. What am I storing up for my old age?

The reality of NHS treatment for CRSwNP

My experience with functional endoscopic sinus surgery (FESS) has evolved over the years. When I first started, the procedures were archaic—nasal packing felt like having tampons shoved up my nostrils, and removal was excruciating, feeling as if my brain was being pulled out. It often resulted in severe nosebleeds.

Over time, the procedure has improved. Robotic surgery is now used as I have no sinus landmarks left due to repeated operations. Dissolvable gel packing is an improvement, though at first, it was uncomfortable as it ran down the back of my throat. I'm often sick after surgery due to swallowed blood, making the idea of day surgery unrealistic for me. Having undergone 13 surgeries, it is clear that this is not a long-term solution.

Only prednisolone provides relief, though my GPs are reluctant to prescribe it due to the risks of long-term steroid use. Montelukast tablets, Budesonide nasal rinses, and Symbicort inhalers help manage day-to-day symptoms, but once the polyps start to worsen, I inevitably develop rhinosinusitis, which can last weeks or months. GPs do not always understand the impact of this condition, and sometimes I even develop a bad rash as a reaction.

My current ENT consultant is excellent, and I was fortunate to be referred to a multidisciplinary team at hospital in the midlands. However, it has taken me years of battling to get this level of care. Their hands are tied when it comes to Dupilumab (Dupixent) due to NICE restrictions. We have discussed it many times, yet I have

been told it is cheaper to keep performing surgeries than to prescribe Dupilumab on the NHS.

Why Dupilumab would help me

Every time I ask about Dupixent (Dupilumab), I receive the same response: it's too expensive and only available for asthma and eczema patients. However, my CRSwNP symptoms impact my quality of life more than my asthma does. The NHS has determined that repeated surgeries are cheaper than providing Dupilumab, yet this approach only prolongs my suffering. It could shrink and stop polyps from returning, breaking the cycle of surgery and steroids. It could relieve my migraines, facial pain, mucus buildup, hearing issues, and lack of sleep. It might even allow me to regain some smell and taste, even if only partially—which would be life-changing.

I've read incredible success stories from patients in the USA and Europe who are already using Dupilumab. Yes, I understand that there are potential side effects, such as joint pain. However, the long-term damage from steroid use and repeated surgeries is likely far worse. I also know that injecting myself twice monthly won't be pleasant, and I wish there were a tablet form. But at this point, I am desperate for anything that might offer lasting relief.

Currently, there is nowhere to go but ongoing surgeries and steroid use. Dupilumab could be a life-changing treatment for people like me, yet access remains restricted. I, and so many others, deserve the chance to try it—before this disease takes any more away from us.

Case study 3

Background

Over 60 years ago at the age of 17, I lost my sense of smell due to persistent sinus problems and nasal polyps. This condition had a profound impact on my early life and career. By 18, I had undergone multiple surgeries, including two Pattersons' Ethmoidectomies, leaving me with lasting scars and continued nasal issues. Frequent infections, blocked sinuses, and earaches disrupted my ability to work and socialise. My probation period in the Civil Service was extended due to repeated absences for treatments and recovery.

I was born and brought up in Dudley in the West Midlands. At 17, when my problems were diagnosed, my ENT specialist advised me to go and live in Switzerland or Austria, alternatively to Torquay or Bournemouth. This was quite a dramatic change to contemplate. However, eventually, after much treatment outlined in my survey form, at 30 my husband got a job in Torquay and we moved. I had to take three years of unpaid leave from the Civil Service and couldn't get a transfer for nearly

three years, and when I did, I had to accept one at a lower grade to stay on their books. Six months after we moved, my father decided to take early retirement, and my parents moved as well.

Unfortunately, it didn't work out very successfully. My husband didn't like his job, and my mother hated Torquay and made herself ill. My parents returned to Dudley, and we ended up both living and working in Gloucestershire, where I still reside. There is a potentially longer, quite unhappy story that followed this move, which I won't go into, but to summarise—my sinus problems had a monumental impact on my life and the life of my family, socially, emotionally, and financially.

Challenges and impact

For over a decade, I had no sense of smell, though I was fortunate not to lose my sense of taste completely. During this period, I underwent multiple polyp removals and experimented with various treatments. The physical symptoms were debilitating, but the social and emotional toll was just as significant. I had to cancel plans frequently, struggled with hearing in professional training settings, and felt self-conscious in personal relationships. The fear of being unaware of dangers like gas leaks or fire added to the daily challenges of living with anosmia.

In my mid-20s, my husband gave up smoking, and it was some time after (around the time we moved to Torquay) that I realised my general health and sinuses had improved. I attribute some of my better health over the last few decades to not living with or working with anyone who smoked. Some of the worst sinus periods and subsequent polyp removals occurred when I worked in an enclosed office with one or more smokers. I celebrated when smoking was finally banned from public places.

Management and treatment

My condition improved in my 30s when I was prescribed a steroid nasal spray, Syntaris. Though it helped maintain my sense of smell, any attempt to stop treatment resulted in a rapid return of symptoms. Over the years, I have undergone further procedures, including Endoscopic Sinus Surgery at 60, but the effectiveness of surgical interventions has been inconsistent. Finding the right medication has been a struggle, with availability issues forcing me to source Syntaris from Italy at significant personal expense. More recently, I have found Nasacourt to be a suitable alternative.

Despite these treatments, I still experience setbacks, particularly when I catch a cold, which can result in months-long periods of smell loss. Long-term concerns about the effects of steroid use, the need for ongoing sinus care, and hearing difficulties remain an ongoing struggle.

My reflections

Looking back, I feel that some of the surgeries I underwent may have caused more harm than good. The lack of understanding from medical professionals has often left me feeling unsupported, and even now, few doctors take my concerns seriously. My experience has shown me that treatment for smell loss and sinus conditions requires persistence, trial and error, and often personal advocacy. I worry about the long-term effects of continued medication use, but after six decades of managing this condition, I have learned to adapt and seek solutions wherever possible.

I had just got on with my life and not thought in depth about any of this until the Fifth Sense meeting last year. I could see that most of us have been suffering for years, often decades, with little understanding from the medical profession. It isn't serious in the same way cancer and many other conditions are, so it doesn't attract the attention and funding. Although I feel that not a lot can ever be done because of the structure of our sinuses and individuals' own allergies or sensitivities that we are born with, it is good that an organisation like Fifth Sense has at last come to the fore, raising the profile of the condition and looking at the treatments available.

Case study 4

Background

I have had CRSwNP for around 15 years -chronic rhinosinusitis and grade 4 polyps. I have been taking steroids for the same amount of time, nasally and occasionally orally. Due to the steroids allowing me to (or the most part) breathe through my nose, I am not having the operation. ENT have said when the drug becomes ineffective, I can have the operation.

Social, emotional and physical impact

It is controlling my life and also heavily impacts the life and environment of my close family and friends. This is not a death sentence, but it is negatively life-changing. It not only has stolen any enjoyment of food and smells from me intermittently but when I have a flare up and the steroids have become ineffective, it affects my hearing, which is by far the worst bit. I have diplacusis and this makes it almost unbearable to be around people and sounds. Even more unbearable when a sound is high pitched, coming from my young children (4 & 6). If I am having a flare and diplacusis occurs (voices sound like aliens/daleks and everything is out of tune), my life stops. I can't live like this. Even though I wouldn't commit suicide, nor feel that way inclined, the thought of it being easier to be dead has crossed my mind. I am a musician for pleasure and the hearing issues ruin any chance of that. All music sounds off key and it just feels like being in a horror film with all the sounds clanging and clashing together. To deal with the diplacusis I put ear plugs in, which then stops a lot of sound, making it dangerous for my children while I am the main carer for them.

When I have no smell at all, I fear that I wouldn't be able to smell gas in our home or check for smells that would alert me to an issue. I also have vertigo from the polyps from time to time and this adds extra fear to looking after my children and living a normal life. All my symptoms create anxiety and stress which then spreads out into my relationship. It is impossible to live normally with this condition. I live in fear of having my steroids becoming ineffective.

Problems with my current treatment

I do not want to take the steroids forever. I have just been given an emergency card by the NHS to signal that I am dependant on steroids in case of an emergency. Why is this ok? We all know the side effects of steroids on the body and how the drops and sprays could affect our eyesight. We are potentially going to lose more of our senses using these drugs. This is not ok.

What it would mean to be prescribed Dupilumab

It would change my life if this medicine was effective and available. I would be able to not live in fear and enjoy the life pleasures that we all have a right to enjoy. My family would benefit and it would stop the need for potentially multiple surgeries in the future.

Case study 5 (Dupilumab Patient)

My sinus journey

I'm not exactly sure of time frames, but in my early 20s, I suffered terribly with hay fever to the point where I couldn't go to work as the symptoms were horrendous and debilitating.

The doctor decided to give me a yearly hay fever injection, and it was like a miracle cure. However, quite a few years later, I started suffering from blocked sinuses (completely different symptoms to hay fever). I lost my taste and smell, started getting headaches, and felt pain in my face. I spent a lot of time over a few years going back and forth to the doctors, which would result in a different nasal spray or a course of steroids. Eventually, I was referred to ENT, and after being seen by the consultant, I was given some more medication.

I went away only to return a short time later as the medications hadn't worked for any length of time. At this point, they decided to operate. I waited for an appointment, which was a few months later, and within six weeks of having the operation, I had lost all smell and taste again. A few weeks later, it started again with a blocked nose and all other symptoms returning. Apparently, I had been signed off at the hospital despite telling them my symptoms had returned. So it was back to the doctors again, where more medication was given. This went on for two to three years until I was eventually referred back to the ENT department at the hospital, where I saw a

different consultant and nurse. I had several endoscopies, and the polyps I originally had removed had grown back but seemed much bigger this time. The consultant and research nurse were working on a trial at that time, and they asked me if I'd like to be part of it.

This was one of several trials I took part in. One of the trials I was on cleared my symptoms. I didn't know at the time, but during the other trials, I was part of the placebo process. After I had completed the trials and been off the medication for a little while, my symptoms returned, and I saw the consultant again. He performed another endoscopy and then decided to operate. This was done within a matter of weeks, and the experience compared to the first operation I had was completely different and much better. My smell and taste returned for a good while before my symptoms started again. It was then that the consultant informed me that because I'd taken part in this particular trial, I was eligible for a medication called Dupilumab, which required a fortnightly injection that I could do at home.

I've been on this for roughly 12 months now (could be longer). I then had another endoscopy in December 2024, and my sinuses were completely clear with no sign of any polyps. Under the guidance of the consultant, I now do the injections every four weeks, and I'm hoping to increase it to every six weeks.

The impact of having no smell or taste

Having no smell or taste had a huge impact on my life. If I was going out to eat with friends or family, it didn't matter what I chose off the menu as I knew I wouldn't be able to taste it.

For me, the biggest impact was not having any smell, as there are so many wonderful scents in the world, and I felt I was missing out on them all. In addition to this, I found that I couldn't consume any alcohol as this made my symptoms even worse than they already were, and it then took days for it to calm down.

It felt like my symptoms took over my life. I couldn't enjoy socialising and found myself withdrawing from doing this. On the surface, I tried to stay positive, but I was suffering mentally with it all as I couldn't see any end to it. On one occasion, I had been poorly, and being sick caused me real anxiety as I couldn't breathe through my nose, which in turn caused me to panic. This was very scary, and after this event, I was paranoid about being sick again. This played on my mind constantly, especially as my husband worked away, which left me at home on my own.

The transformative effects of dupilumab

Since starting with Dupilumab, my symptoms have improved to such an extent that they are no longer present. My sinuses are completely clear, I can breathe through my nostrils normally, I no longer suffer from mental health issues, socialising is no longer a problem, and life is as good as it can be.

I cannot stress just how much taking Dupilumab has changed my life in every aspect because CRSwNP is a debilitating condition. In this day and age, with such advancements in medicine, there really shouldn't be any reason why people suffer from CRSwNP like they do. Dupilumab should be made available for sufferers. The symptoms that come with this condition are life-changing for many people, including myself. If Dupilumab helps people like it has helped me, then it really does need to be made available on the NHS.

My Experience

My personal experience of chronic sinus problems has been one I wouldn't wish on anyone—it affects every part of your life. My sinuses were completely blocked, and even blowing my nose didn't really help, as the mucus would return as quickly as I could blow it out. Sometimes, even though I was so blocked up, I couldn't blow anything out, and there was a constant nasal drip down the back of my throat, which made me cough all the time to the point of retching and sometimes being sick.

I had no smell or taste at all, and when my sinuses were badly blocked, they used to make a whistling noise that colleagues in the office would comment on, which in turn caused me a lot of embarrassment. I had lots of different nasal sprays, but being so blocked up, as soon as I sprayed them, it would just run out as it couldn't go anywhere else due to the amount of mucus that was there, and I couldn't get rid of it. Sleeping wasn't good, as I would wake with a start, not being able to breathe and having to sleep with my mouth open, which wasn't pleasant. This had a knock-on effect on my husband, as my snoring kept him awake.

All of this had a huge impact on my life, as at the time, I had a physical job and struggled with the day-to-day tasks that were expected. I also felt that I didn't want to socialise, partly due to constant tiredness and pain but also due to the symptoms I had that caused embarrassment.

Now, after being on Dupilumab, I can honestly say it has been the best thing for my sinuses. I can breathe clearly, I have my smell and taste, my hearing isn't impaired, and I have no facial pain or headaches. There are no disadvantages to taking this medication—only advantages. I have experienced and am still experiencing 100% improvement in all aspects of my life. I fully attribute these improvements to the medication I am taking.

Focus group notes

Summary of conversations from CRSwNP focus groups

Fifth Sense held two focus groups at the end of 2024 to provide time and space for people with Chronic rhinosinusitis with nasal polyps.

Focus group 1: 26 November 2024 7pm – 8pm

Discussion questions:

- What are the most significant ways that your CRSwNP impacts on your life? Think about: What symptoms affect you the most (i.e. loss of smell and taste, breathing difficulties etc)?
- Do you feel the form adequately captures the impact that CRSwNP has on your lives?
- Are there any other things you think it should be asking?
- Do you think there is enough information and support available to help people living with CRSwNP?
- What more would you like to see?
- Has your GP been helpful?

Summary of discussions:

Challenges of smell and taste disorders

- Lack of pleasure from food
- Smell memories and the emotional connection with friends and loved ones
- Concerns about personal hygiene
- Significant effects on mental health and overall well-being
- More impactful than other health conditions for some individuals, leading to emotional exhaustion
- Social anxiety due to noticeable symptoms (e.g., sniffing)
- Disrupted sleep patterns and associated consequences
- Waking up with a dry mouth
- Difficulty engaging in physical exercise
- Challenges with treatment adherence (e.g., requiring specific positions for administration)
- Variability in treatment effectiveness

- Inability to detect dangers (e.g., gas leaks, spoiled food, or signs of illness)
- Common co-occurrence with asthma
- Perception that ENT specialists show limited interest
- Side effects of steroids, such as eye issues detected by opticians
- Multiple surgeries often with limited long-term success

Personal experiences

- One participant has had no sense of smell for nearly two decades, leading to social withdrawal, lack of interest in food, and feelings of isolation. Regular steroid use has resulted in asthma and skin conditions, while hearing has also been affected. Symptoms are currently managed but persist.
- Another participant has undergone multiple surgeries with no lasting improvement and experiences severe congestion, hearing difficulties, and sleep disturbances. Steroid side effects include an itchy rash, and mobility is also impacted.
- A different participant experiences temporary recovery of smell with steroid use, but the effect fades after a few weeks. Due to breathing difficulties, hearing issues, and the lack of long-term solutions, they have discontinued treatment.
- Another individual experiences intermittent taste and smell function but suffers from chronic congestion, sore throats, headaches, and facial pain. Long-term steroid use has led to weight gain.
- A participant shared experiences of undergoing a clinical trial, completing regular assessments, and suspecting involvement in a placebo-controlled study.

Key themes from group discussion

- Smell and taste loss is mentally challenging and affects all aspects of life.
- Social interactions, especially meals, become sources of anxiety.
- Frustration with frequent comments about appearing to have a cold.
- Embarrassment about the condition leads to reluctance in discussing it.
- Persistent anxiety and depression directly linked to the disorder.
- Prolonged use of steroid sprays raises concerns about glaucoma.
- Hearing issues, including distortion (diplacusis), muffled sounds, and blocked ear tubes, are common.

- Safety concerns regarding gas, fire, wounds, and food spoilage.
- Heightened focus on personal hygiene due to an inability to detect body odor.
- Feeling isolated and left out of social activities.
- Avoidance of activities like singing or choir participation due to nasal tone and hearing difficulties.
- Career limitations in fields such as food preparation and fragrance-related work.

Poll results

- All participants reported regular steroid use.
- Some noted inconsistencies in asthma treatment due to unclear prescribing guidelines.

Macro patient discussion

- The need for a clear care pathway was emphasised.
- Long waiting lists (up to three years) for specialist consultations were highlighted.

Focus group 2: 10th December 7pm – 8pm

Discussion questions:

- What support & info have you had from your GP?
- What support and info have you had from ENT?

Summary of discussions

Support from GP and ENT

- Participants had mixed experiences with support from healthcare professionals.
- Some reported receiving helpful guidance and referrals, while others felt their concerns were not fully understood or taken seriously.
- There were mentions of delays in diagnosis and treatment, with some expressing a desire for clearer pathways to specialist care.
- A common suggestion was for improved training and awareness among GPs and ENTs regarding [condition or issue discussed].

Single Technology Appraisal

Dupilumab for Treating Severe Chronic Rhinosinusitis with Nasal Polyposis [ID6480]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	[REDACTED]
2. Name of organisation	Sinus UK – Patient Organisation CIC
3. Job title or position	[REDACTED]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Sinus UK is a patient organisation representing the interests of people with sinus diseases, which aims to: • ensure more information is available for patients; and • support greater recognition and understanding of the impact of sinus related diseases. Sinus UK does not currently receive any regular funding. Sinus UK has previously received two small grants to fund specific work and payments have been made to Sinus UK's Chief Executive for patient advocacy work (in addition to the funding outlined in response to 4b below). Largely the work that has been undertaken to date, in particular in setting up our patient group, raising awareness through social media and liaising with NICE (e.g. drafting this submission), has been done on a voluntary basis.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months?	Sanofi UK engaged Sinus UK in a paid consultancy of £14,070 to organise patient roundtables to gain a better understanding of the impact of living with nasal polyps. This amount was invoiced between October 2024 and January 2025. This included honoraria for the patients involved.
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.
5. How did you gather information about the experiences of patients and carers to include in your submission?	This submission comprises information and patient experiences gathered from: an online survey of patients; insights workshops with patients; 1:1 discussions with patients; the Sinus UK Patient Group; desk research; and 1:1 discussions with healthcare professionals. The two main sources of information were:

	1. <u>Qualitative Insights</u>: In December 2024, Sinus UK carried out two online insights workshops and one 1:1 interview with patients to gain a better understanding of the impact of living with severe CRSwNP. Sinus UK was engaged by Sanofi UK in a paid consultancy for this work. • Sinus UK engaged with 7 NHS ENT consultants to support the recruitment of patients, as well as using its own existing patient contacts. • 11 patients were recruited who had a confirmed diagnosis of CRSwNP by a healthcare professional, had undergone at least one sinus surgery and whose CRSwNP was 'uncontrolled'. • A mixed methodology was used to gather data consisting of one, semi-structured, 1:1 phone interview and two semi-structured qualitative insights workshops between 20 November and 17 December 2024. • The phone interview lasted 1 hour. The 2 workshops were both online, 3 hours in length, with 5 patients at each. The same experienced facilitator conducted all 3 sessions. • The data was analysed by one author using inductive thematic analysis. An AI transcript, with 90% accuracy, was produced for each session, the transcript and audio recording were analysed to establish key themes. • A report was compiled based on these interviews and workshops and submitted to Sanofi UK as well as being used to inform this submission. 2. <u>Quantitative Insights</u>: In February 2025, Sinus UK conducted an online survey of UK based patients with severe CRSwNP, with the aim of better understanding patient experiences. • The survey was open to UK based patients with a confirmed diagnosis of CRSwNP, who had undergone at least one sinus surgery and were still under the care of an ENT consultant (or waiting for an appointment with an ENT consultant). • 51 patients completed the online survey. • The survey questions and summary data are submitted as Appendix 1.

	Effect on Quality of Life Of these symptoms, patients with severe CRSwNP have identified blocked nose, loss of smell or taste and breathing problems as having the most impact on their quality of life. The data from our online survey supports this and also shows that some patients identify fatigue, poor sleep and pain as having an equally large impact on their quality of life (the summary data is submitted at Appendix 1). We briefly explore these symptoms below, focusing on what the symptoms actually mean for patients living with CRSwNP and the impact they have on their quality of life. In some cases the presentation of the symptom (e.g. 'blocked nose') for CRSwNP patients differs from how the symptom may be understood in the wider population. 1. <u>Blocked Nose</u> A 'blocked nose' for a CRSwNP patient can often mean that their nasal passages are completely obstructed, by polyps and thick mucus. It does not simply mean that their nose is a bit 'stuffy', as it would be with a common cold. Although a patient may have periods when they have some airflow through their nose, all patients from our insights workshops and 1:1 discussions have suffered prolonged periods of time when their noses were almost or completely blocked. <i>"I couldn't breathe through my nose for months and months and months. I mean getting on for years probably"</i> (workshop participant) The patients we spoke to attribute this blockage to: (i) <u>Nasal Polyps</u>: Many of the patients had suffered with polyps that were so pervasive they could "see the polyps" in their nose. These polyps then form a barrier blocking the nasal passages. This makes clearing the nasal passages very difficult. One patient described this experience as: <i>"for me it was so blocked by a physical obstruction that you couldn't blow the stuff out anyway, you had to honk it up. It is absolutely horrible."</i> (ii) <u>Thick Mucus</u>: These polyps were often combined with thicker, more solid bits of mucus that builds up in the nose and that is very hard to get past the polyps. This mucus can become thicker and compacted over time.

	CRSwNP patients will have a significant amount of this type of mucus. When the nose is blocked with polyps it makes it almost impossible to clear, leaving a permanent sense of fullness. This blockage has the following effects: (i) <u>Treatment being rendered ineffective</u>: Nasal sprays are a common treatment for managing CRSwNP, as well as daily rinsing of the sinuses with saline solution. However, when your nose is blocked neither can get up the nasal passages and into the sinuses, potentially making them ineffective as a form of treatment. This has potential implications for the efficacy of these treatments and their capacity to manage symptoms effectively. Which is all the more serious given that when a patient has reached this stage in being blocked, they are most likely at the severe end of CRSwNP and therefore in greater need of treatment. <i>“...because I was that blocked and that bunged up I’d squirt the rinse up my nostril and it’d come straight back out again because it couldn’t go any further”</i> (workshop participant) (ii) <u>Panic attacks due to not being able to breathe</u>: 3 patients described in detail how frightening it is to have a blocked nose and the panic it causes them. For 2 of them the panic came at the point at which they were falling asleep. As the body relaxes you instinctively breath through your nose but you are not able to. <i>“I was almost having panic attacks at night because of drifting off to sleep and instinctively trying to breathe through my nose and remembering that I couldn’t”</i> (workshop participant) 2. <u>Runny nose</u> Paradoxically, despite having blocked noses, patients report also having a ‘runny nose’. Everyone in our workshops referred to the fact their noses constantly ran with more liquid-like mucus. <i>“the combination of the blocked and yet runny nose makes no logical sense, how can you be blocked and runny at the same time”</i> (workshop participant) 3. <u>Loss of smell (and taste)</u> Loss of smell, and the resulting diminished sense of taste, is a symptom that impacts quality of life for most patients. When asked to identify the 3 symptoms which most impact their quality of life, from a list of 15

	symptoms, loss of smell or taste had the most impact amongst the survey respondents (33 out of 51 respondents said that this was one of the 3 symptoms most impacting their quality of life). 8 of the 11 patients from our insights workshops and 1:1 discussions had no sense of smell for many years – several for over 10 years and one for more than 20 years. <i>“One of your five senses is gone, isn’t it? Two if your taste is affected as well”</i> (workshop participant) Quality of life for patients is severely restricted, not just because of the loss of enjoyment of smelling and tasting food or the pleasure of the scent of flowers, but also from a practical perspective of not knowing when action is needed. Patients are unaware of the signs that smell gives them in daily life, such as needing to change their baby’s nappy, or possible danger, like the smell of smoke or gas. Some patients are fortunate to get their sense of smell back after a course of steroids or surgery. Although this is often temporary. With the exception of 1 patient from our insights workshops and 1:1 discussions, they all lost their smell again after a few weeks or months. <i>“I remember when I got mine back after the operation, it was amazing. It was like I was a child again”</i> (workshop participant) 4. <u>Poor Sleep & Fatigue</u> The widespread impact of poor sleep on patients living with severe CRSwNP is evident from our research. Factors including a blocked nose and only being able to breathe through the mouth mean that patients struggle to get to sleep and stay asleep. Both poor sleep and fatigue were ranked highly by the survey respondents as impacting their quality of life (15 out of 51 respondents identified poor sleep and 16 out of 51 respondents identified fatigue as one of the 3 symptoms most impacting their quality of life). <i>“I was so exhausted from lack of proper sleep”</i> (workshop participant) Sleep is crucial to being able to function in daily life. It can be influenced by many factors and what is deemed to be a good night’s sleep differs from person to person. However, it was clear that all the patients we spoke to in our insights workshops and 1:1 discussions had suffered from periods of very poor sleep as a result of their CRSwNP. One patient likened it to <i>“the first year after you have a baby”</i>. Another referred to it as <i>“sleep deprivation”</i>. Patients spoke about being <i>“constantly tired”</i>, sleeping separately from their partner and even

	resorting to sleeping upright in a chair. <i>“We all know that if you don't get proper sleep, it has a knock-on effect with everything that you do in your day. You have no energy, no motivation, because you're just tired”</i> (workshop participant) At the severe end, the resulting fatigue can be devastating, limiting a patient's ability to work and enjoy their leisure time. This fatigue leads to reduced productivity or even limits the ability to work for some. One patient had to change to a part time role because they could not cope, due to the poor sleep and fatigue. Another gave up work altogether because they could no longer function in the work setting. <i>“I found that working full time was just impossible because I was waking up just feeling so tired because you can't sleep at night. So now I've gone part-time. That's how it's impacted my life. I work part-time hours”</i> (workshop participant) 5. <u>Anxiety (Social & Work)</u> Many people living with CRSwNP who we spoke to and surveyed listed anxiety as one of their symptoms. This anxiety affects patients in both their social and working lives. Although social anxiety impacted some patients more than others, everyone in our insights workshops and 1:1 discussions spoke about the social anxiety experienced because of their condition. It both diminished their confidence and led to some people avoiding certain social situations. <i>“I lost confidence in social situations. I started to avoid some social situations because I felt like I sounded strange when I spoke”</i> (workshop participant) The main reasons given for this anxiety were: - Embarrassment about blowing their nose in public - Embarrassment about the frequency of which they had to blow their nose - Fear about how they are perceived by others <i>“You just feel a bit, oh, everybody's looking at me again”</i> - Difficulties talking and breathing Similarly, in the work setting, people living with CRSwNP experienced anxiety which affected their performance in their jobs.

	<i>"There were times when I was asked to speak in a meeting or a conference and I declined because I couldn't speak in front of everybody and especially strangers, I couldn't have done it."</i> 6. <u>Depression & Mental Health Issues</u> It is widely understood that many people living with chronic conditions experience mental health problems at some stage. We did not explore this formally in relation to CRSwNP during our insights workshops and 1:1 discussions, yet it was spontaneously mentioned by 2 patients. One patient spoke about how CRSwNP "...can be a bit depressing because it's relentless. There's no escape from it". As a result we included a question about the impact of CRSwNP on patients' mental health within our online survey. 50 out of 51 respondents said that their CRSwNP had an impact on their mental health and for over 75% of respondents this was more than half the time or nearly all of the time. 7. <u>Hearing Loss, Dizziness & Balance Issues</u> As the sinuses are located close to the ear canal, when they become congested it can affect hearing function. This is not an issue which affects all people living with CRSwNP, or at least it is not a symptom which patients highlight as causing the most impact, but hearing issues were mentioned by at least 6 patients during our insights workshops and 1:1 discussions. <i>"My ears are constantly blocked. I work with children. It's hard to hear what they're saying. I'm always saying, pardon"</i> (workshop patient) As well as a loss of hearing, at least 4 patients at our insights workshops and 1:1 discussions spoke about suffering from dizziness and balance issues due to the impact their blocked noses had on their ears: <i>"I had it for six months and felt dizzy all the time"</i> (workshop patient) 8. <u>Pain</u> In our survey, 13 out of 51 respondents listed pain as one of the top three symptoms which had the most impact on their quality of life. Patients describe the pain as facial pain caused by pressure in the sinuses and headaches

	caused by their CRSwNP. <i>“It was just pain in the head all the time” (workshop patient)</i> <i>“The facial pain was my big thing. Just this constant pain around my face, around my eyes, around my teeth or on my jaw” (workshop patient)</i> 9. <u>Recurrent Sinus Infections</u> We did not specifically raise the question of recurrent sinus infections with patients in our workshops, discussions or survey, however it was mentioned by some patients. The regularity with which some patients need to take antibiotics for sinus infections is clearly a concern.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Treatments Although there is a range of pharmacological treatments available, the only way of effectively reducing symptoms for severe CRSwNP are: 1. Corticosteroids 2. Nasal Surgery Unfortunately, from our research, the majority of patients find the options available to them do not provide long-term benefits. Patients reference having many courses of corticosteroids that, although effective at the time, do not provide relief for more than a few weeks or months. The removal of nasal polyps through surgery provides some longer term relief and an improvement in symptoms but, for the majority of patients, this only lasts around 6 months. The data from our survey shows that symptoms returned within less than 6 months for over 50% of respondents. For these patients this means a return to the worst symptoms we listed in section 6: • Severely blocked nose • No sense of smell or taste

	• Poor sleep • Fatigue • Facial pain These symptoms mean a continuation of poor quality of life and an inability to function anywhere close to their 'normal'. Care Many patients describe a “<i>convoluted process</i>” to getting a diagnosis of CRSwNP, with a long time spent going “<i>backward and forwards</i>” to the GP. In many cases primary care is not very proactive in referring them to secondary care, and nearly half the patients from our insights workshops and 1:1 discussions paid privately to see an ENT consultant as they had “<i>had enough</i>” and needed urgent help. Patients often have a long and difficult journey before they are able to receive more effective treatment from an ENT consultant and can be in a poor state of health by the time they reach the secondary care setting. <u>Postcode Lottery</u>: Owing to the great differences across the UK in the availability and quality of ENT services, we observe that some patients are in a worse position than others simply because of where they live. One patient spoke of how she was without any secondary care support as her local ENT service did not currently have an ENT consultant. <u>Time to Diagnosis</u>: The amount of time people wait from first experiencing symptoms to being diagnosed with CRSwNP varies. From our online survey we can see that a minority waited less than 12 months (21.57%) whilst the majority waited over 12 months (78.43%), with almost a quarter waiting over 4 years (23.53%). The situation was similar for the patients from our insights workshops and 1:1 discussions. Patients feel frustrated at having to wait so long just for a diagnosis, without the correct care or treatment. <u>Time to Surgery</u>: Once patients are diagnosed and under specialist care, they do not appear to encounter such lengthy wait times. The majority of patients do wait over 6 months for their first surgery, but over 45% of survey respondents waited 12 months, and over 30% waited more than 18 months.
8. Is there an unmet need for patients with this condition?	Yes there is an unmet need. Once surgery and steroids prove to be ineffective long-term solutions, patients have nowhere else to go treatment wise, except to enter a recurring cycle of more steroids and more surgery, and simply hope for a different outcome. Whilst enduring very poor quality of life.

	There is clearly the need for an additional treatment within the pathway for these severe CRSwNP patients to provide them with long-term relief from the debilitating symptoms they are living with day to day. Many patients and members of our patient group frequent international online support groups and, as such, are aware of biologics being available in other European countries and in the US. They find it frustrating that such treatments are not available in the UK. <i>"It just becomes frustrating because they've all got biologics"</i>

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	From our research and discussions (both in person and online) with people living with severe CRSwNP, it is clear that patients would like the opportunity to be prescribed the technology (biologics) in the UK. Patients view the advantage of biologics as being a much-needed treatment to fill the gap where current treatments are not, or are no longer, effective. They see this as a long-term solution instead of bouncing between invasive surgery, steroids and multiple courses of antibiotics to achieve even temporary relief. Patients have referred to this technology as <i>"life changing"</i>. Both from a prospective patient point of view and from those currently prescribed biologics. <i>"It can be life changing. Well, I'm hoping that this research that you're doing will expose the need for biologics because the NHS is way behind the times on that. So that I think is life changing."</i> We have spoken to patients who are currently prescribed biologics, both on the NHS and by paying privately. These patients have described them as <i>"life changing"</i>.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	From our research, the only disadvantage raised by people living with severe CRSwNP is the potential side effects. Having read about patient experiences with biologics in Europe and the US, some people voice concerns about the side effects they may experience if prescribed the technology.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Yes, there are two groups of patients who might benefit more from the technology than others: 1. <u>Patients living with severe CRSwNP for whom surgery does not offer any long-term relief from symptoms</u>: As explained in response to Questions 6 and 9 above, there is currently no alternative treatment for patients living with uncontrolled, severe CRSwNP. These patients are most likely to have extremely low quality of life and can not function normally day to day. They are trapped in an endless cycle of invasive surgery, steroids and antibiotics. 2. <u>Patients living with severe CRSwNP who have comorbid conditions, particularly asthma</u>: Many of the patients mentioned in point 1 above also have comorbid conditions. The most common being asthma. In our survey 96% of patients reported having been diagnosed with asthma as well as CRSwNP, and being prescribed steroid inhalers. These patients may not currently be eligible for a biologic on the NHS as their asthma does not meet the necessary treatment threshold. If a biologic was available on the NHS for severe CRSwNP, it may also have a positive benefit for the asthma symptoms of this type of patient as well.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	It is important to ensure that patients receive equal access to care and treatment across the country.

Other issues

13. Are there any other issues that you would like the committee to consider?	No.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Living with severe CRSwNP is not like having a common cold. But unfortunately this is how many patients feel their condition is perceived. CRSwNP is a long-term inflammatory condition which, at its worst, leaves patients in a “<i>desperate state</i>” and feeling like they “<i>can’t carry on this way</i>”. • Although there is a range of pharmacological treatments available, the only ways of effectively reducing symptoms for severe CRSwNP are corticosteroids and nasal surgery. • For severe CRSwNP patients, steroids may only provide a few weeks of relief and surgery a few months. Once steroids and surgery prove to be ineffective long-term solutions, patients have nowhere else to go treatment wise except to enter a recurring cycle of more steroids and more surgery, and simply hope for a different outcome. Whilst enduring very poor quality of life.

	• There is clearly the need for an additional treatment within the pathway for these severe CRSwNP patients to provide them with long-term relief from the debilitating symptoms they are living with day to day. • Patients welcome the prospect of a new treatment option. They view the advantage of biologics as being a much-needed treatment to fill the gap where current treatments are not, or are no longer, effective. They see this as a long-term solution instead of bouncing between invasive surgery, steroids and multiple courses of antibiotics to achieve even temporary relief.

Thank you for your time.

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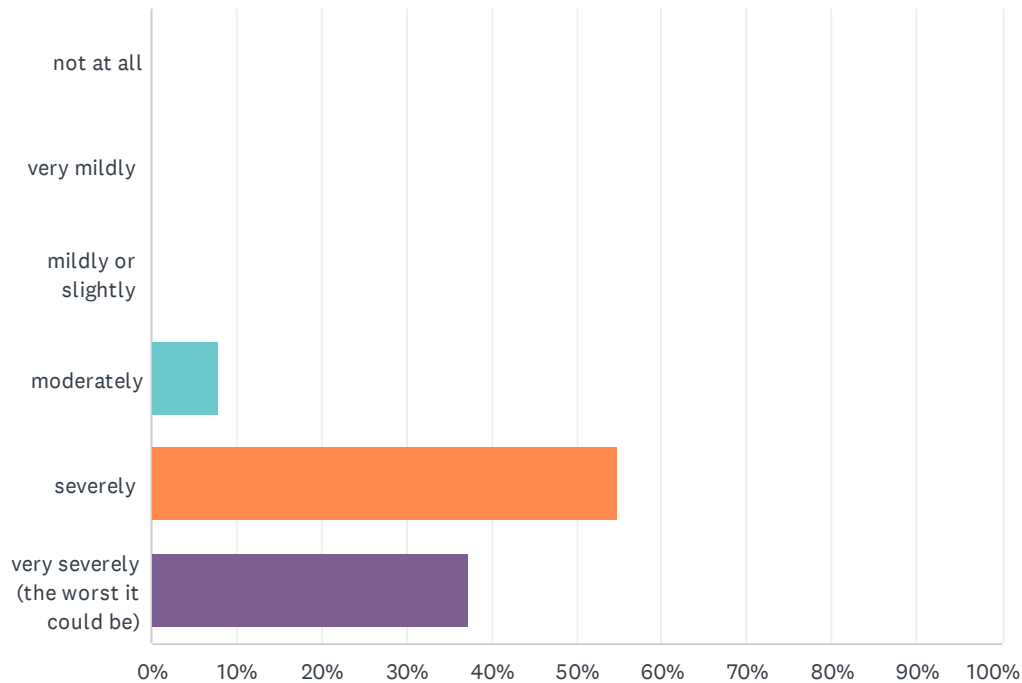
The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

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Q1 Impact of CRSwNP pre-surgery: Please use the scale below to rate how much your CRSwNP impacted your life whilst you were waiting for your first surgery.

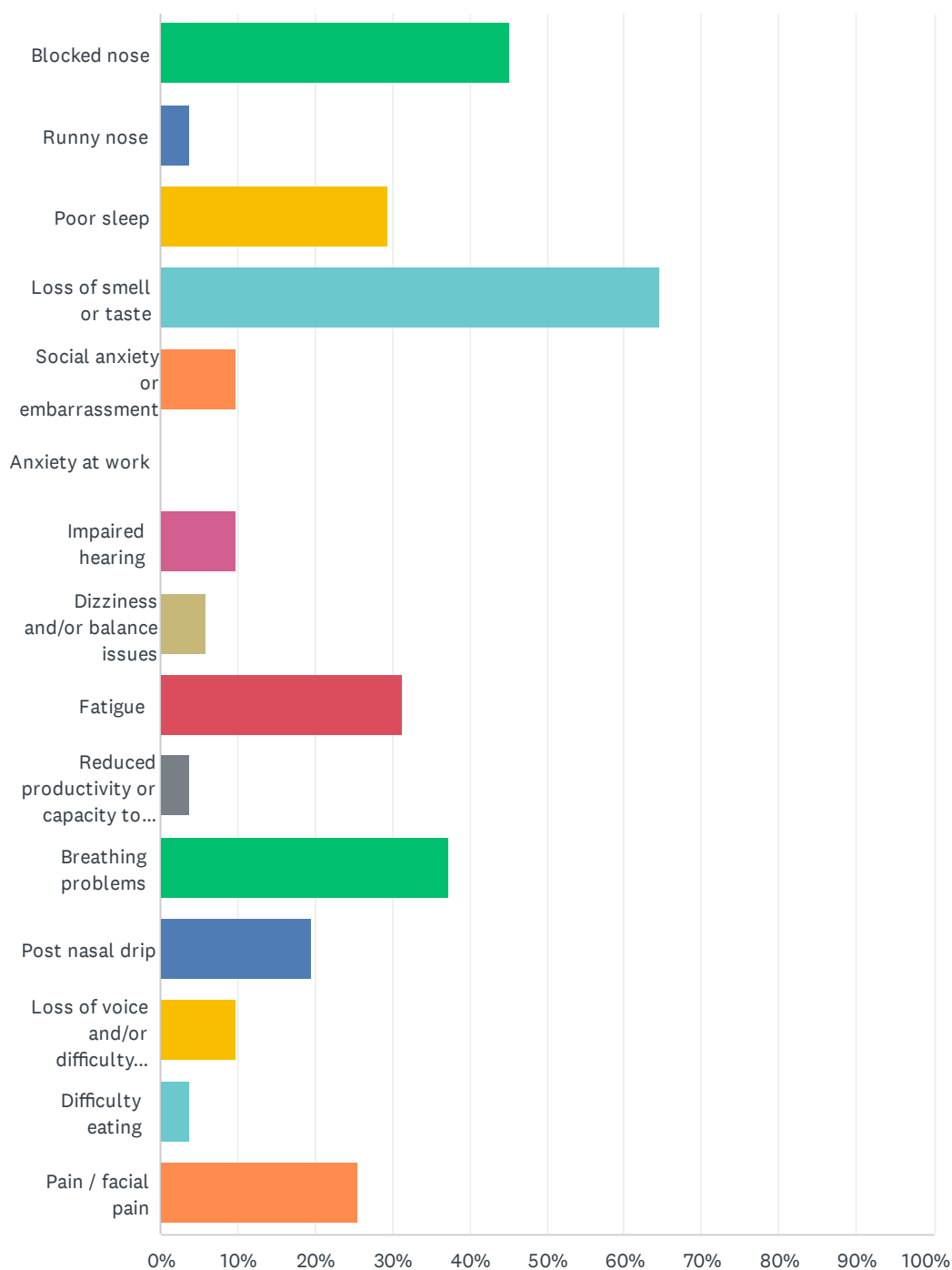
Answered: 51 Skipped: 0



ANSWER CHOICES	RESPONSES	
not at all	0.00%	0
very mildly	0.00%	0
mildly or slightly	0.00%	0
moderately	7.84%	4
severely	54.90%	28
very severely (the worst it could be)	37.25%	19
TOTAL		51

Q2 Quality of life: Which of your CRSwNP symptoms have the most impact on your quality of life? Please choose THREE (3).

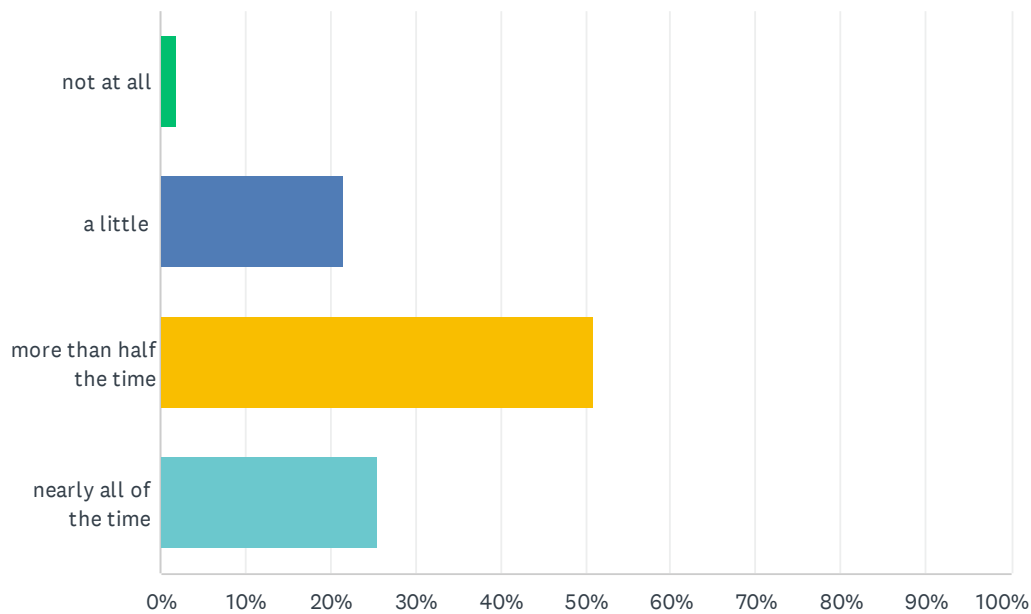
Answered: 51 Skipped: 0



ANSWER CHOICES	RESPONSES	
Blocked nose	45.10%	23
Runny nose	3.92%	2
Poor sleep	29.41%	15
Loss of smell or taste	64.71%	33
Social anxiety or embarrassment	9.80%	5
Anxiety at work	0.00%	0
Impaired hearing	9.80%	5
Dizziness and/or balance issues	5.88%	3
Fatigue	31.37%	16
Reduced productivity or capacity to work	3.92%	2
Breathing problems	37.25%	19
Post nasal drip	19.61%	10
Loss of voice and/or difficulty speaking	9.80%	5
Difficulty eating	3.92%	2
Pain / facial pain	25.49%	13
Total Respondents: 51		

Q3 Mental Health: Please use the scale below to rate how much your CRSwNP affects your mental health (this may include, changes in your mood, thoughts or behaviours - for example, low mood, feeling depressed or hopeless, excessive fears, withdrawing from activities or work).

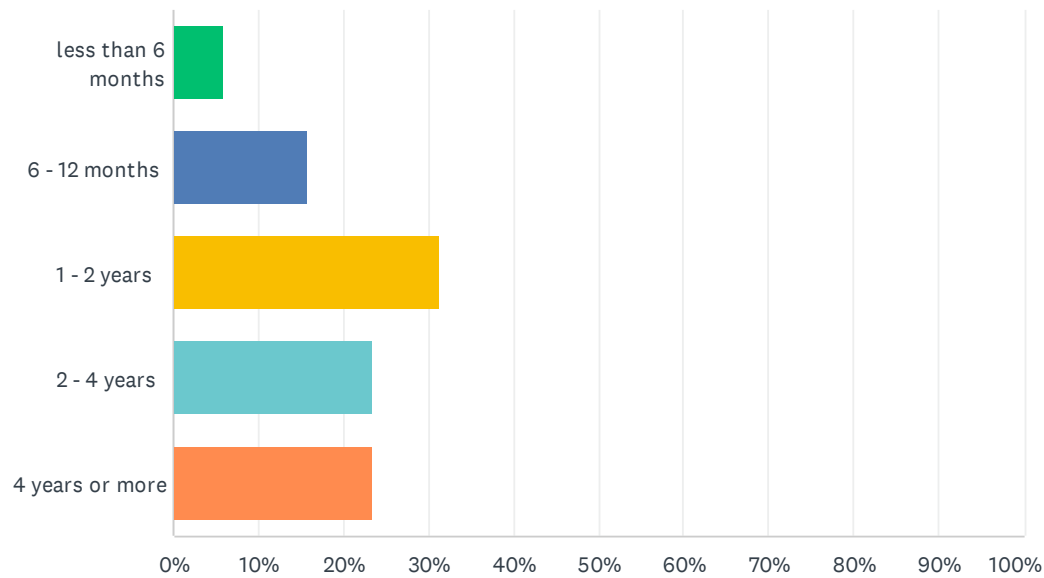
Answered: 51 Skipped: 0



ANSWER CHOICES	RESPONSES	
not at all	1.96%	1
a little	21.57%	11
more than half the time	50.98%	26
nearly all of the time	25.49%	13
TOTAL		51

Q4 Time to diagnosis: How long did you wait from first experiencing symptoms to being diagnosed with CRSwNP?

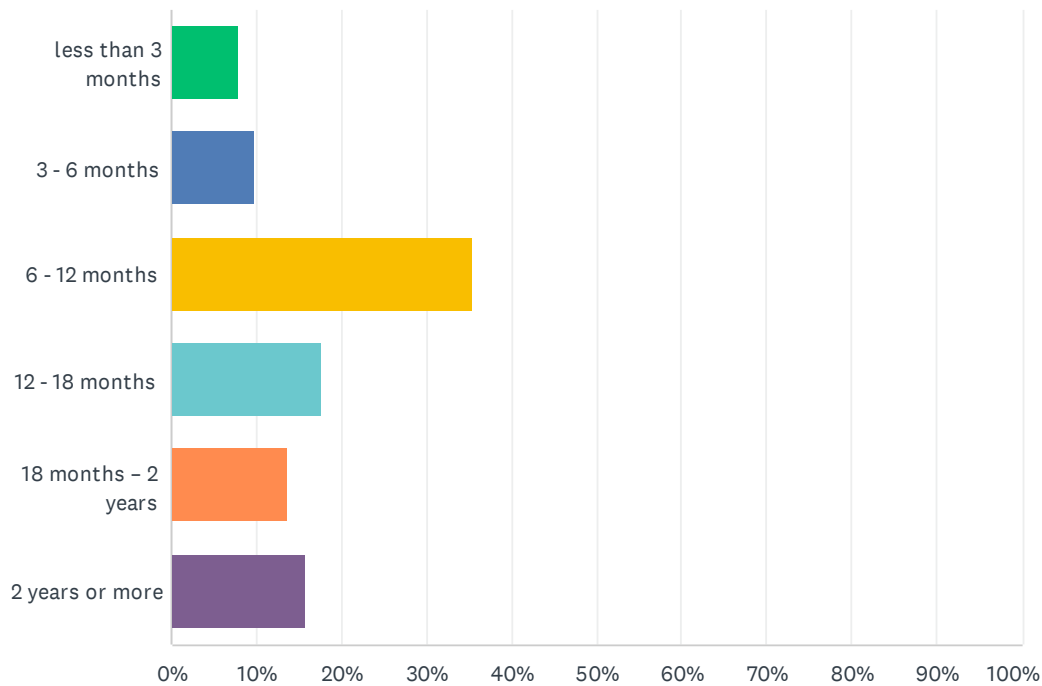
Answered: 51 Skipped: 0



ANSWER CHOICES	RESPONSES	
less than 6 months	5.88%	3
6 - 12 months	15.69%	8
1 - 2 years	31.37%	16
2 - 4 years	23.53%	12
4 years or more	23.53%	12
TOTAL		51

Q5 Time to surgery: How long did you wait between diagnosis by ENT and your first surgery?

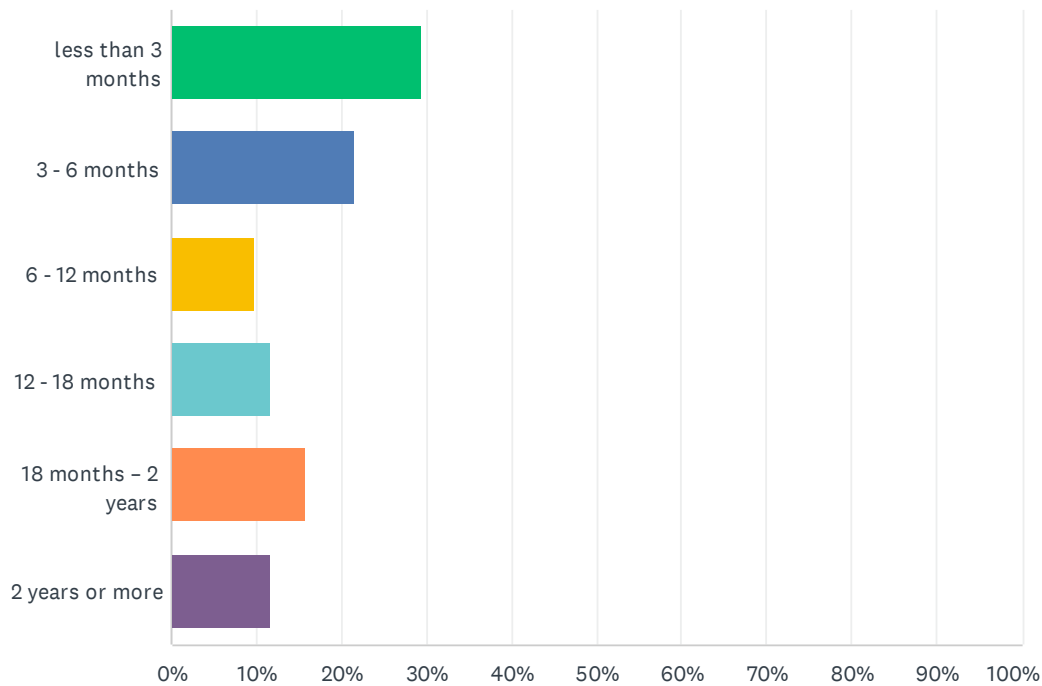
Answered: 51 Skipped: 0



ANSWER CHOICES	RESPONSES	
less than 3 months	7.84%	4
3 - 6 months	9.80%	5
6 - 12 months	35.29%	18
12 - 18 months	17.65%	9
18 months – 2 years	13.73%	7
2 years or more	15.69%	8
TOTAL		51

Q6 Return of symptoms: Did your symptoms return after surgery? If yes, please indicate the length of time before your symptoms returned.

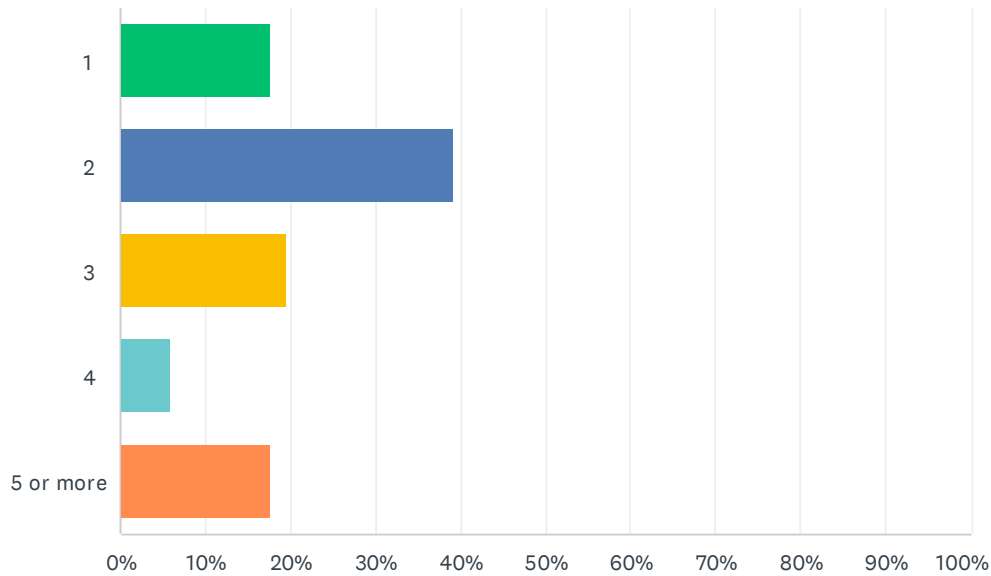
Answered: 51 Skipped: 0



ANSWER CHOICES	RESPONSES	
less than 3 months	29.41%	15
3 - 6 months	21.57%	11
6 - 12 months	9.80%	5
12 - 18 months	11.76%	6
18 months – 2 years	15.69%	8
2 years or more	11.76%	6
TOTAL		51

Q7 Surgery: How many times have you undergone surgery for your CRSwNP?

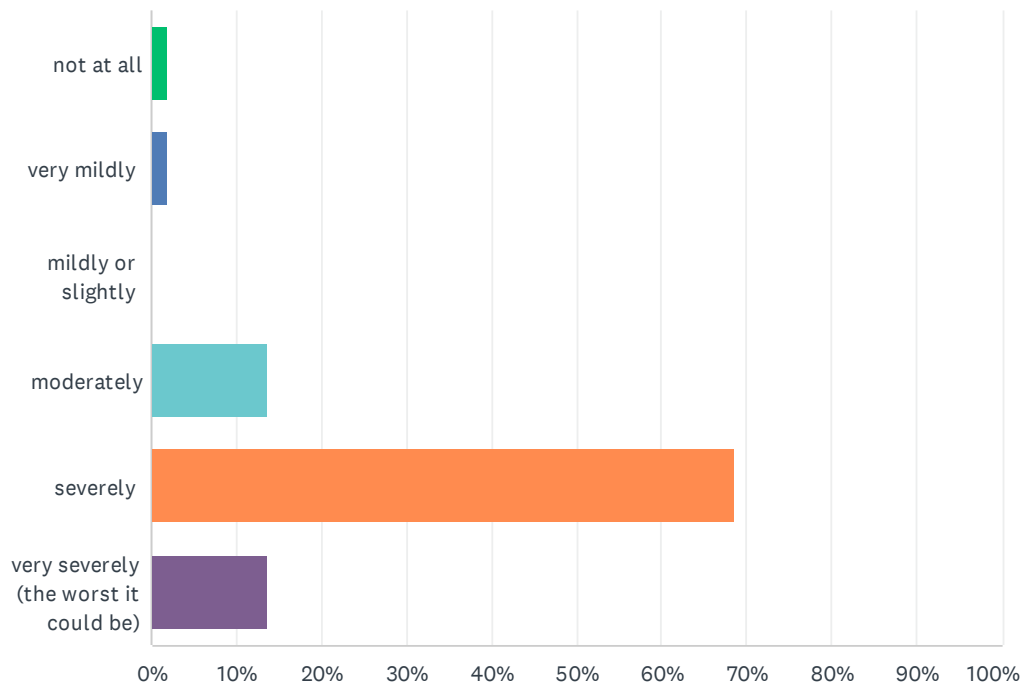
Answered: 51 Skipped: 0



ANSWER CHOICES	RESPONSES	
1	17.65%	9
2	39.22%	20
3	19.61%	10
4	5.88%	3
5 or more	17.65%	9
TOTAL		51

Q8 Impact of CRSwNP post-surgery: If you have had more than 1 surgery, please use the scale below to rate how much your CRSwNP impacted your life whilst you were waiting for your second (or third or more) surgery.

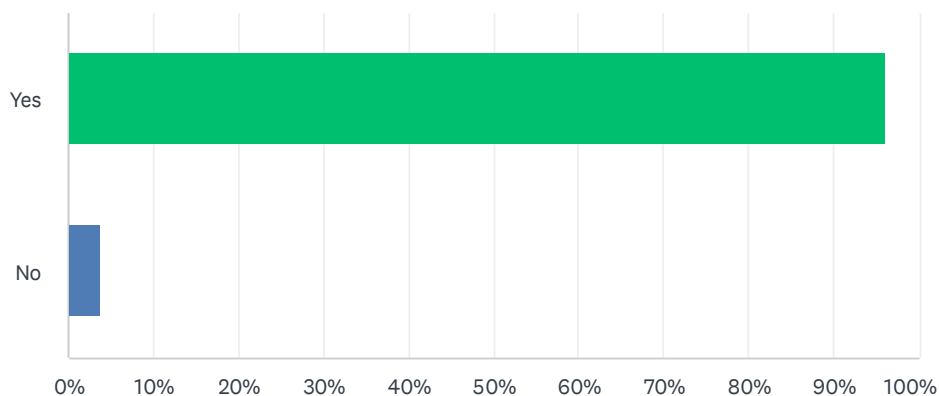
Answered: 51 Skipped: 0



ANSWER CHOICES	RESPONSES	
not at all	1.96%	1
very mildly	1.96%	1
mildly or slightly	0.00%	0
moderately	13.73%	7
severely	68.63%	35
very severely (the worst it could be)	13.73%	7
TOTAL		51

Q9 Asthma diagnosis: Have you been diagnosed with asthma?

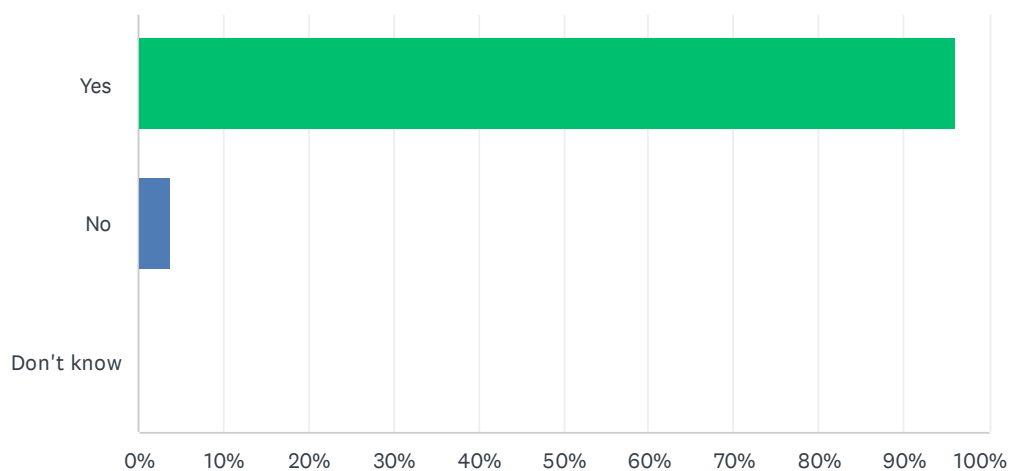
Answered: 51 Skipped: 0



ANSWER CHOICES	RESPONSES	
Yes	96.08%	49
No	3.92%	2
TOTAL		51

Q10 Asthma treatment: If you answered yes to Q9, are you currently prescribed steroid inhalers for your asthma?

Answered: 51 Skipped: 0



ANSWER CHOICES		RESPONSES	
Yes		96.08%	49
No		3.92%	2
Don't know		0.00%	0
TOTAL			51

Single Technology Appraisal
Dupilumab for treating severe chronic rhinosinusitis with nasal polyposis [ID6480]
Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	
2. Name of organisation	Association of Respiratory Nurses (ARNS)
3. Job title or position	
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians. Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	ARNS is a non-profit organisation run by committee member nurses.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	NO
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	NO

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	It is recommended as a add on therapy as a treatment in patients with chronic rhinosinusitis and nasal polyposis. It aims to control inflammation and reduce the size or even eliminate polyps in the nose.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction in exacerbations, reduction in emergency visits and reduction in symptom burden and unnecessary additional medications such as oral corticosteroids.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There are various biologics on the market and some others that also can help with nasal problems which patient who have for a diagnosis of severe asthma and alongside they can help with symptoms. There are other standard options such as nasal corticosteroids, oral corticosteroids, ENT (surgical removal of polys) as a option already.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Nasal washes, nasal steroidal sprays, antihistamines, those with severe asthma maybe already on dupilumab or another biologic which also helps with these symptoms via the NHS.
9a. Are any clinical guidelines used in the	NICE asthma guidelines NICE prescribing guidance

treatment of the condition, and if so, which?	
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There are difference of opinions depending on geographic area and can depend on the speciality patients are under. For example, ENT my chose to medicate and remove polyps, Severe asthma service may escalate medication only.
9c. What impact would the technology have on the current pathway of care?	It would be a add on at the end of the current pathway if patients are still very symptomatic and uncontrolled.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It is used to treat severe asthma, but some evidence suggests it helps improve patients' nasal symptoms also and reduce polyps.
10a. How does healthcare resource use differ between the technology and current care?	It is currently licenced for severe asthma and not just for treating rhinosinusitis and polyps.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	I would recommend specialist clinics. With possible licence to be given under homecare once established.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Staff, NHS funding and approval, training.

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
11a. Do you expect the technology to increase length of life more than current care?	No
11b. Do you expect the technology to increase health-related quality of life more than current care?	I cannot confidently say so.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients at the severe end of disease who are uncontrolled, and it is affecting their quality of life and have a significant symptom burden it would be more effective for than the general population. It would be extremely expensive to give to the general population also.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	More so as I presume the injections are 2 weekly, will need funding, clinics space, staff, monitoring of treatment, requiring time and additional resources and measurement tools to evaluate benefits of treatment. Patients may not be able to self-administer the medication.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes, I would expect a treatment time to response is need of how long to continue and when to discontinue treatment.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	I think more evidence is needed, there is some limited data in severe asthma patients who have co-existing polyps and nasal issues who have seen benefit from this treatment.
16a. Is the technology a 'step-change' in the management of the condition?	Yes a step up at the very top, but more as a add on treatment.

16b. Does the use of the technology address any particular unmet need of the patient population?	No
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Minimal side effects noted will not affect quality of life, although if they have to attend a hospital every 2 weeks for injections this may have a negative effect on their quality of life or be an inconvenience.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	I think some is outdated data, the first reference used is from 2013. The data on population also is outdated from 2018 and personally I think the percentage would be lower.
18a. If not, how could the results be extrapolated to the UK setting?	They need newer data.
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Symptom improvements, and exacerbation reductions – yes
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	I am unable to comment on this.
18d. Are there any adverse effects that were not apparent in clinical	NO

trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	Similar

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	NO
21b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• Already available for some patients with severe asthma and have been found to have benefit on reducing nasal symptoms and polyps. • Used as a add on treatment • Requires monitoring of response to treatment • clarity is needed on terms of use • Need to identify how response to treatment is measured accurately

Thank you for your time.

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Single Technology Appraisal

Dupilumab for treating severe chronic rhinosinusitis with nasal polyposis [ID6480]

Clinical expert statement

Information on completing this form

In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as '**confidential [CON]**' in turquoise, and all information submitted as '**depersonalised data [DPD]**' in pink. If confidential information is submitted, please also

Clinical expert statement

Dupilumab for treating severe chronic rhinosinusitis with nasal polyposis [ID6480]

1 of 12

send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

The deadline for your response is **5pm on Friday 30 May 2025**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating severe chronic rhinosinusitis with nasal polyposis and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Prof Claire Hopkins
2. Name of organisation	
3. Job title or position	Professor of Rhinology, Guy's and St Thomas' Hospitals NHS Trust
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with severe chronic rhinosinusitis with nasal polyposis? ☒ A specialist in the clinical evidence base for severe chronic rhinosinusitis with nasal polyposis or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes

Clinical expert statement

Dupilumab for treating severe chronic rhinosinusitis with nasal polyposis [ID6480]

3 of 12

7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	
8. What is the main aim of treatment for severe chronic rhinosinusitis with nasal polyposis? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To achieve disease control and remission – that is to reduce the impact of symptoms (such as nasal obstruction, loss of sense of smell, rhinorrhoea, sleep disturbance) on quality of life and ability to perform work and leisure activities, while minimising need for treatment associated with a risk of harm (ie repeat courses of oral corticosteroids or repeated surgery)
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A meaningful clinical response equating to ‘controlled disease’ would usually be determined by a reduction in SNOT-22 (validated patient rated outcome score) down to mild levels and no need for OCS or surgery. Partially controlled would be some residual symptoms despite OCS or surgery
10. In your view, is there an unmet need for patients and healthcare professionals in severe chronic rhinosinusitis with nasal polyposis?	Yes- while surgery is successful in relieving symptoms in the majority of patients, many patients do not regain their sense of smell and a small proportion of patients derive minimal benefit or have a rapid recurrence of polyps and associated symptoms, and so undergo repeated surgeries at short intervals
11. How is severe chronic rhinosinusitis with nasal polyposis currently treated in the NHS? - Are any clinical guidelines used in the treatment of the condition, and if so, which? - Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Currently treatment follows a stepwise approach as defined in the UK commissioning guidance chrome-extension://efaidnbmninnibpcjpcglclefindmkaj/https://www.rcseng.ac.uk/-/media/files/rcs/standards-and-research/commissioning/rhinosinusitis-commissioning-guide-for-republication.pdf We have shown that approx. 1% of UK adults is being actively treated for nasal polyps at a single time point About 70% will be adequately managed with medical treatment including intranasal topical steroid. About 30% undergo surgery. Of these nearly 20% will require revision surgery within a 5 year period. About 5% of patients with nasal polyps experience repeated recurrence and undergo multiple revision surgeries. Patients with asthma, especially those with aspirin exacerbated respiratory disease (AERD), have a higher risk of recurrence, than those without.

Clinical expert statement

What impact would the technology have on the current pathway of care?	The pathways are fairly standard across the UK although waiting times for surgery vary, access to aspirin desensitisation for patients with AERD for is limited to only a handful of centres and waiting times are very long, and the standard of surgery offered is variable (more complete surgery being associated with a lower risk of revision) It should be noted that the UK now deviates from the European Position Paper 2020 which is considered to define the global standard of care, and recommends biologics for patients who have a recurrence of polyps after previous surgery https://www.rhinologyjournal.com/Documents/Supplements/EPOS2020_executive_summary.pdf Access to biologics for patients who have recurrence despite optimum medical and surgical care would significantly improve quality of life for the most severely affected patients The British Rhinological Society has created recommendations for who we think are in most need of this new treatment – having reflected on current evidence, risks of recurrence and understanding costs of care . https://onlinelibrary.wiley.com/doi/10.1111/coa.13779
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? - How does healthcare resource use differ between the technology and current care? - In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) - What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The cost of treatment is greater, however availability to the most severe patients, who often undergo multiple revision surgeries, will remove patients from surgical waiting lists, Treatment can usually be offered on a homecare basis with annual hospital follow up. I would recommend the treatment be available in a relatively small number of specialist ENT clinics where all treatment options are available- eg comprehensive surgery and aspirin desensitisation. While primary surgery could be performed in any unit with ENT, if patients requiring revision surgery in less than 5 years were referred to specialist centres, subsequent surgery and postop care could be optimised, and if this failed then use of dupilumab could be considered. This will ensure that the most severe patients receive clinically and the most cost-effective care. I would not recommend unrestricted access in all centres as this have been associated with overuse in some European countries.

Clinical expert statement

	Specialist nurses would be required to assist with first injections and monitoring – there are already similar procedures in difficult to treat asthma clinics. As numbers of patients would be relatively small, and as most care is provided remotely, there would not need to be a very large number of centres,
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? - Do you expect the technology to increase length of life more than current care? - Do you expect the technology to increase health-related quality of life more than current care?	Nasal polyps are not associated with an increased mortality (although may be associated with severe reactions to aspirin and non-steroidal, and severe asthma) A proportion of patients with severe nasal polyps remain uncontrolled despite surgery and medical treatment at the current time and have significant impairment of quality of life, Dupilumab is described by these patients as life changing. I have a number of patients who receive dupilumab either for their asthma, or privately on a self pay basis – their responder rate is very high, patients are able to avoid further surgery and often report minimal levels of ongoing symptoms
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with aspirin exacerbated respiratory disease (asthma, nasal polyps and aspirin intolerance) have very high rates of recurrence after surgery, symptoms are uncontrolled and often undergo multiple surgeries, Many simply give up on surgery as polyp recurrence seems inevitable. We are not currently able to achieve control of symptoms for this group of patients despite comprehensive surgery and adjuvant treatment such as aspirin desensitisation (which has a high risk of side effects). While this group of patients receive less benefit from current standard of care they have been shown to achieve relatively greater improvements from treatment with dupilumab Almost all patients with comorbid asthma would also likely achieve improvements in their asthma Patients with loss of sense of smell have a higher risk of mental health issues, and this would likely improve with more effective treatments
15. Will the technology be easier or more difficult to use for patients or	Avoiding the need for surgery will reduce waiting lists, avoid time of work for post-operative recovery and therefore will be easier to deliver. As above, systems are already in place for

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healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	home delivered care and remote monitoring in asthma clinics and this could be replicated for nasal polyps
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	I would recommend that we applied the rules in the guidance https://www.euforea.eu/news/epos-euforea-update-on-indication-and-evaluation-of-biologics-in-crswnp-2023/ Endoscopy is required but this is standard of care in ENT clinics so no new service or equipment would be required for assessment and delivery
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Indirect costs of time of work for surgery Risk of harm and costs of complications of repeated course of oral corticosteroids – obesity, hypertension, cataracts, osteoporosis Risks of complications of surgery Delays in providing surgical care for other ENT conditions due to the burden of providing repeated surgeries to a small group of patients Benefit on comorbid asthma, eczema and allergic rhinitis likely will not be considered The trial demonstrated that intervals between dosing could be increased to 4 weekly at 6 months without loss of efficacy but this is not currently reflected in the MHRA licence – amending this would improve the cost-effectiveness
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	This would be a step change in the treatment of severe nasal polyps in the UK. Dupilumab is available in most European and N American countries we are now outliers in having no reimbursement for nasal polyps

Clinical expert statement

improve the way that current need is met? - Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	However, at the current time I believe that patients with nasal polyps should still have one 'good' surgery and optimal postoperative medical care and biologics be reserved for patients in whom this fails to achieve control of disease. This would address the unmet needs of uncontrolled nasal polyps – which are highlighted in the attached articles https://pmc.ncbi.nlm.nih.gov/articles/PMC8974789/
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Approximately 5% patients taking dupilumab discontinue due to lack of efficacy or side effects – such as joint pain or dry eyes
20. Do the clinical trials on the technology reflect current UK clinical practice? - If not, how could the results be extrapolated to the UK setting? - What, in your view, are the most important outcomes, and were they measured in the trials? - If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? - Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes – the patients recruited to the phase 3 trials for dupilumab are reflective of the cohort of severe nasal polyps patients in the UK The most important outcomes are reduction in symptom scores (SNOT22) reduction in need for surgery and oral corticosteroids and improvement in sense of smell – ie achieving disease control. These were all measured and reported in the trials and there is significant benefit. Real life studies show even greater benefit and higher response rates As benefit can be Transient hyper-eosinophilia may occur in approx. 1 in 200 – this did not appear in the trials. There is guidance in place to monitor and manage this in https://www.euforea.eu/news/epos-euforea-update-on-indication-and-evaluation-of-biologics-in-crswnp-2023/
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	https://www.jacionline.org/article/S0091-6749(21)01393-2/fulltext Important to consider in comparison of other biologics
22. How do data on real-world experience compare with the trial data?	There are now a large number of real world studies – the vast majority show superior outcomes in a RW setting that the outcomes reported in the phase 3 trials. Eg

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	https://onlinelibrary.wiley.com/doi/10.1111/all.15772 In the trials patients were not selected for having type 2 inflammation – application of EPOS guidelines will likely have helped improve the responder rate over the cohort recruited to clinicaltrials
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by	No

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the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Nasal polyps are a common chronic condition affecting about 4% of the UK adult population, and a point prevalence of approx. 1% undergoing active care.

70% may be managed by medical treatment alone; surgery is effective at relieving symptoms but some patients, especially those with asthma and aspirin exacerbated respiratory disease, fail to achieve significant benefit and/or suffer early recurrence requiring multiple revision surgeries

Surgery carries a small but important risk of major complications and waiting lists are lengthy while oral corticosteroids usually only achieve transient improvements and carry a risk of cumulative harm with repeated use.

Dupilumab has been shown to achieve significant, sustained improvements in symptoms scores and obviate the need for surgery or oral corticosteroids, with low rates of adverse events..

This would be lifechanging for the relatively small proportion of patients with severe uncontrolled nasal polyps – while the majority should continue to be treated with medical and surgical treatment. This is an opportunity to refine treatment pathways across all aspects of care of nasal polyps and develop specialist centres to ensure improved clinical and cost-effectiveness of treatments offered.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Clinical expert statement

Dupilumab for treating severe chronic rhinosinusitis with nasal polyposis [ID6480]

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Single Technology Appraisal

Dupilumab for treating severe chronic rhinosinusitis with nasal polyposis [ID6480]

Clinical expert statement

Information on completing this form

In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as '**confidential [CON]**' in turquoise, and all information submitted as '**depersonalised data [DPD]**' in pink. If confidential information is submitted, please also

Clinical expert statement

Dupilumab for treating severe chronic rhinosinusitis with nasal polyposis [ID6480]

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send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

The deadline for your response is **5pm on Friday 30 May 2025**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating severe chronic rhinosinusitis with nasal polyposis and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Professor Carl Philpott
2. Name of organisation	University of East Anglia
3. Job title or position	Professor of Rhinology & Olfactology
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with severe chronic rhinosinusitis with nasal polyposis? ☒ A specialist in the clinical evidence base for severe chronic rhinosinusitis with nasal polyposis or technology? ☒ Other (please specify): Trustee of SmellTaste (UK charity for those with smell and taste disorders)
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☒ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Clinical expert statement

Dupilumab for treating severe chronic rhinosinusitis with nasal polyposis [ID6480]

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8. What is the main aim of treatment for severe chronic rhinosinusitis with nasal polyposis? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To improve disease control and symptom burden.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	An improvement in the SNOT-22 score of 9 points or more (SNOT-22 is the validated HRQoL measure for CRS)
10. In your view, is there an unmet need for patients and healthcare professionals in severe chronic rhinosinusitis with nasal polyposis?	Yes – i see many patients like this in my clinic and through our charity SmellTaste.
11. How is severe chronic rhinosinusitis with nasal polyposis currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	These are the European guidelines: rhinologyjournal.com/Documents/Supplements/supplement_29.pdf Familiarity and uptake is variable: https://bmjopen.bmj.com/content/8/12/e022643 The MACRO Programme is looking to refine the care pathway: https://workstream2.themacroprogramme.org.uk/ For those patients who relapse after surgery, then biologic therapies will be greatly beneficial in reducing disease and symptom burden as is evident from the RCTs to date. See also: manuscript_3049.pdf
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care?	The British Rhinological Society has set out parameters for how these should be used in practice: https://pubmed.ncbi.nlm.nih.gov/33817954/ These should be prescribed by clinicians with a tertiary practice who see the most severely affected CRS patients. The only investment is the cost of drug given that patients will be able to self-care after initiation of therapy. These practitioners will have the suitable existing facilities to see these patients for any follow up monitoring.

Clinical expert statement

• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes. The effect size of the leading biologic therapies show an impressive impact on symptom burden and disease control.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients most likely to benefit include: • Non-steroidal anti-inflammatory exacerbated respiratory disease • CRS patients with concomitant asthma (regardless of severity) • Patients who have undergone complete endoscopic sinus surgery and relapsed despite post-op intranasal corticosteroids • Patients who are dependent on oral corticosteroids for maintenance treatment.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Easier. Once patients are comfortable with self-injecting, they can self-manage.

Clinical expert statement

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	See EPOS and BRS guidelines above for stopping. Real world evidence suggests therapy for 2-2.5 years with decreasing frequency of injections is needed.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Yes. The hidden costs of CRS are ones documented here: https://pubmed.ncbi.nlm.nih.gov/32172284/
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	Yes this will be a major step change in managing patients with repeated surgery and oral corticosteroids. Lower and upper airways will benefit.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Dry eye and arthralgia are main side-effects of dupilumab and would warrant a switch to an alternative biologic.
20. Do the clinical trials on the technology reflect current UK clinical practice? - If not, how could the results be extrapolated to the UK setting? - What, in your view, are the most important outcomes, and were they measured in the trials?	Yes I believe they reflect the CRS population that we would seek to target with the technology.

Clinical expert statement

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	https://pubmed.ncbi.nlm.nih.gov/32172284/ https://pubmed.ncbi.nlm.nih.gov/40202121/
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population	Not aware of any if the access to care is equitable.

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Dupilumab for treating severe chronic rhinosinusitis with nasal polyposis [ID6480]

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- lead to recommendations that have an adverse impact on disabled people.

Please consider whether these issues are different from issues with current care and why.

More information on how NICE deals with equalities issues can be found in the [NICE equality scheme](#).

[Find more general information about the Equality Act and equalities issues here.](#)

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Patients with severe CRS need better treatment

Monoclonal antibodies could help improve patient care and their quality of life

Tertiary clinicians should lead the delivery of these treatments

Adherence to guidelines will support targeting the correct patients

The hidden cost of CRS disease burden will be tackled by the availability of this technology

Thank you for your time.

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Single Technology Appraisal

Dupilumab for treating severe chronic rhinosinusitis with nasal polyposis [ID6480]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In [part 1](#) we are asking you about living with severe chronic rhinosinusitis with nasal polyposis or caring for a patient with severe chronic rhinosinusitis with nasal polyposis. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our [hints and tips for patient experts](#). You can also refer to the [Patient Organisation submission guide](#). **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Patient expert statement

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Your response should not be longer than 15 pages.

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Part 1: Living with this condition or caring for a patient with severe chronic rhinosinusitis with nasal polyposis

Table 1 About you, severe chronic rhinosinusitis with nasal polyposis, current treatments and equality

1. Your name	Sophie Dodworth
2. Are you (please tick all that apply)	☒ A patient with severe chronic rhinosinusitis with nasal polyposis? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with severe chronic rhinosinusitis with nasal polyposis? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Fifth Sense
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and do not wish to complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and do not wish to complete this statement ☒ I agree with it and will be completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement after attending the expert

Patient expert statement

	engagement teleconference ☐ I have completed part 2 of the statement but was not able to attend the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with severe chronic rhinosinusitis with nasal polyposis? If you are a carer (for someone with severe chronic rhinosinusitis with nasal polyposis) please share your experience of caring for them	I have had CRSwNP for around 15 years - chronic rhinosinusitis and grade 4 polyps. I have been taking steroids for the same amount of time, nasally and occasionally orally. Due to the steroids allowing me to (for the most part) breathe through my nose, I am not having the operation. ENT have said when the drug becomes ineffective, I can have the operation. It is controlling my life and also heavily impacts the life and environment of my close family and friends. While this is not a death sentence, it is negatively life changing. It has stolen any enjoyment of food and smells from me intermittently. This is devastating, especially if you see food, taste and smells as part of pleasure time. That pleasure is ripped away from you. The dopamine a person would have from these moments is no more. Sleep is disrupted when the congestion is present which hugely impacts life, work, health and family. When I have a flair up and the steroids have become ineffective, it effects my hearing, which is by far the worst bit. It causes me diplacusis, and this makes it almost unbearable to be around people and sounds. Even more unbearable when a sound is high pitched, coming from my young children (4 & 6). If I am having a flair and diplacusis occurs (voices sound like aliens/daleks and everything is out of tune), my life stops. I can't live like this. Even though I am nowhere near suicidal, the thought of it being easier to be dead has crossed my mind. I am a musician for pleasure and the hearing issues ruin any chance of that. All music sounds off key and it just feels like being in a horror film with all the sounds clanging and clashing together. To deal with the diplacusis I put ear plugs in, which then stops a lot of sound, making it dangerous for my children while I am the main carer for

Patient expert statement

	them. When I have no smell at all, I fear that I wouldn't be able to smell gas in our home or check for smells that would alert me to an issue. I also have vertigo from the polyps from time to time and this adds extra fear to looking after my children and living a normal life. All my symptoms create anxiety and stress which then spreads out into my relationship. It is <i>impossible</i> to live normally with this condition. I live in fear of having my steroids becoming ineffective.
7a. What do you think of the current treatments and care available for severe chronic rhinosinusitis with nasal polyposis on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	Treatments (steroids) are not effective for the majority. For those of us that are on continual steroids, we are at risk with the side effects. Personally, I use nasal steroids every day and these come with a side effect of potential risks to the eyesight, it is not pleasant to live in fear of destroying certain parts of your health to temporarily help others. I am aware that we are only supposed to use prednisolone twice a year but speak to others that are prescribed more than twice a year for this condition. Long term use of oral steroids clearly comes with many awful risks. I am part of a large community of people online that suffer with the same disorder, and we are all aware that other countries have biologics and are living almost normal lives. We are desperate for these drugs here. We are all fed up and crying out for help and some further understanding or research on how difficult it is to live with this. Surgery seems to sadly be a common reoccurrence for many, with multiple surgeries, some having their polyps return only months or even weeks after. How is this effective management? How much are multiple surgeries costing the NHS? How about the costs of mental health drugs and alternative therapies for the anxiety and depression this brings?

Patient expert statement

8. If there are disadvantages for patients of current NHS treatments for severe chronic rhinosinusitis with nasal polyposis (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Risks to vision and breathing problems with long term use of steroid nasal sprays and drops. Long term use of prednisolone can lead to osteoporosis, poorly controlled diabetes, eyesight problems and high blood pressure. Many report that only oral steroids provide some short-lived relief. The majority needing to have multiple surgeries.
9a. If there are advantages of dupilumab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does dupilumab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	a. Dupilumab seems to have worked so well for so many already using it. They seem to be living normal lives, lifted out of depression, able to smell and taste, able to socialise, work without ailment, care for family and dependants, not suffer with vertigo or hearing issues, stop the need for surgery, sleep returns to normal. b. For me, to not have to live in fear of feeling alien or abnormal due to hearing would be at the top, I want to be able to be a healthy mum and enjoy music again freely. Anxiety and depression lifting and not being controlled by the polyps comes a close second. Being able to smell and taste and enjoy socialising again would be wonderful and essential to mental health and enjoying the small pleasures, which are so devastatingly missed when not there. c. Yes, many people find steroids nasally to be ineffective whereas dupilumab seems to work for the majority. It would stop the need for repeat surgeries. There doesn't seem to be any reported eye issues with dupilumab.
10. If there are disadvantages of dupilumab over current treatments on the NHS please describe these. For example, are there any risks with dupilumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	There seems to be some people reporting bad aches and pains, rashes and blistering. These seem to be the more common side effects talked about.
11. Are there any groups of patients who might benefit more from dupilumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility,	The patients I have heard benefit more are the people with severe asthma and skin conditions, like eczema.

Patient expert statement

dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering severe chronic rhinosinusitis with nasal polyposis and dupilumab? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	Not that I am aware of.
13. Are there any other issues that you would like the committee to consider?	I would like to think that the costs of NHS treatment for all the issues that arise with this condition are considered. Including but not limited to: - Vertigo - Mental health issues - Hearing issues - Steroid prescriptions long term - Multiple surgeries for polyp removal - ENT consultations

Patient expert statement

	Time spent with NHS doctors for consultations for headaches, sleep issues, asthma flares, sinus infections etc. Long term steroid use side effects.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- There must be access to more effective drugs, like **dupilumab**.
- This is not a 'mild' condition, it is devastatingly life changing.
- We need your help to be able to live normally.
- You cannot enjoy life with this condition, we need change.
- The effects of life with this condition cost-wise on the NHS must be on a par with providing **dupilumab**.

Thank you for your time.

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Patient expert statement

Single Technology Appraisal

Dupilumab for treating severe chronic rhinosinusitis with nasal polyposis [ID6480]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In [part 1](#) we are asking you about living with severe chronic rhinosinusitis with nasal polyposis or caring for a patient with severe chronic rhinosinusitis with nasal polyposis. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our [hints and tips for patient experts](#). You can also refer to the [Patient Organisation submission guide](#). **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Patient expert statement

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Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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Part 1: Living with this condition or caring for a patient with severe chronic rhinosinusitis with nasal polyposis

Table 1 About you, severe chronic rhinosinusitis with nasal polyposis, current treatments and equality

1. Your name	Andrew Knill
2. Are you (please tick all that apply)	☒ A patient with severe chronic rhinosinusitis with nasal polyposis? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with severe chronic rhinosinusitis with nasal polyposis? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Sinus UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and do not wish to complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and do not wish to complete this statement ☐ I agree with it and will be completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: I have been a patient advocate for CRSwNP since 2018

Patient expert statement

	• I founded Sinus UK in 2021 owing to the fact, to the best of my knowledge, there were no patient organisations anywhere in the world that purely focused on representing patients with sinus diseases. • During my time as a patient advocate for CRSwNP: ○ I sat on a number of European and global patient advisory boards for CRSwNP, meeting other patients; ○ I was the patient representative on the latest guidelines for nasal polyps (European Position Paper on Rhinosinusitis and Nasal Polyps - EPOS 2020) and co-authored the patient section and the condensed patient version of the guidelines; ○ I have co-authored a number of clinical papers in this area; ○ I was part of the EUFOREA working group that looked at inclusion and success criteria for biologics in CRSwNP in 2019. • During my time with Sinus UK I have: ○ Spoken to many patients in the UK who suffer from CRSwNP; ○ Facilitated patient insights workshops with UK CRSwNP patients; ○ Run an online survey of UK patients with CRSwNP to understand their experiences; ○ Helped establish and regularly monitor and engage with a Facebook group for UK patients with Sinus disease, most of whom have CRSwNP. This group now has around 80 members. ☐ I have completed part 2 of the statement after attending the expert engagement teleconference ☐ I have completed part 2 of the statement but was not able to attend the expert engagement teleconference ☐ I have not completed part 2 of the statement

Patient expert statement

6. What is your experience of living with severe chronic rhinosinusitis with nasal polyposis? If you are a carer (for someone with severe chronic rhinosinusitis with nasal polyposis) please share your experience of caring for them	I have had CRSwNP for around 24 years. During this time I have had 4 operations and one minor corrective operation, many courses of prednisolone (an oral corticosteroid – OCS) and have taken a daily cocktail of 5 different medicines to slow the progression of my symptoms. CRSwNP has dominated my life throughout those 24 years. At its lowest points my CRSwNP has left me with a nose that was almost completely blocked, yet one that also ran with liquid mucus all the time. This made sleeping very difficult, concentrating at work very hard and affected my ability to socialise normally (which was particularly hard in my 20s). I've had no sense of smell or taste for many years at a time. Something I really struggled with as food and drink are fundamental to my enjoyment of life (my wife was a food writer and recipe developer in her spare time and cooking and eating together is a big part of how we relax). This lack of smell had other issues as well, for instance when my children were babies and I would often change dirty nappies too late as I couldn't smell them and they would have nasty bouts of nappy rash as a consequence. All this had a detrimental effect on my mental health. This was exacerbated by the long waits to get treatment from the NHS and the fact that any treatment only had a benefit for a limited period of time. I'm fortunate that my fourth operation worked well, I have my smell and taste back and my nasal blockage is down to a very manageable level. Despite this I still live in constant fear that my condition will regress again and there is nothing I can do about it. I had a downturn in symptoms around Christmas and lost my smell and taste for the first 3 months of the year before a long course of steroids brought it back and reduced the nasal blockages I was experiencing.

Patient expert statement

7a. What do you think of the current treatments and care available for severe chronic rhinosinusitis with nasal polyposis on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	a) My Views on Current Treatment CRSwNP has suffered from a severe lack of treatment innovation for a long time. Once the first line treatment option of different nasal sprays hasn't worked for you, you are left with two options – Surgery or oral corticosteroids (OCS). Surgery – I have had mixed experiences with surgery. From having symptom relief for as little as 3 months, to having symptom relief last about a year before my symptoms fully returned, and for my latest operation I had symptom relief for about 2.5 years before they returned. Surgery takes a long time to get booked in, leaving you in a very poor state of health whilst you wait (no one puts themselves forward for surgery when they are in a good state of health, you're normally at a very low point and then have to wait upwards of 12 months to have it). The operation takes a minimum of two weeks to get over before you can return to work and then 3-6 months for your nose to properly calm down and get back to 'normal'. One operation or two you can understand, but having 4 doesn't feel a sensible treatment pathway. OCS – I have taken so many courses of OCS I couldn't begin to recall how many, and to be honest, I don't want to. I know there is lots of evidence of the long-term impact of OCS. But you will take them if you are desperate for some temporary relief from your symptoms. I have probably taken on average 2 courses a year over the 24 years, with a minimum course of 5 days and a maximum of 3 weeks. They are horrible things to take. I feel like I've had too much caffeine all the time, really struggle sleeping and am permanently anxious.

Patient expert statement

	It is a sad situation that the only options available to me at the severe end of CRSwNP are surgery or steroids. Neither could be described as a 'new' innovation in treatment. b) Other People's Views on Current Treatment I've found my experience to be echoed by those of other patients. Surgery – There is a range of experiences here. Some people hated surgery and the facial pain you're left with, whereas others seemed to take it more in their stride. However, of the many patients I have spoken to, two themes come out. Firstly, it can take a long time to wait for an op during which people they are at their lowest ebb symptom wise. Secondly, surgery doesn't work for everyone. Most of the people I spoke to have found surgery only provide up to 6 months of relief, some less. Admittedly the patients I speak to will likely be on the more severe end of the disease and so there could be some bias in there. OCS – These are seen as a necessary evil. Many people don't like taking them but know they will offer temporary relief. For some that relief may only be a week or two but they will clearly take them just for that short relief from symptoms. Many people save up taking them. So, they will consciously be in a poor state of health for a few more months so they can take them in time for a holiday or Christmas. I have done the same myself.
8. If there are disadvantages for patients of current NHS treatments for severe chronic rhinosinusitis with nasal polyposis (for example, how they are given or taken, side effects of treatment, and any others) please describe these	A) Nasal sprays – Generally these are convenient to take, albeit people with limited hand mobility or impaired movement may struggle to use them. The issue with sprays is if your nose is really blocked the spray can't get into your nose and just runs out the nose, making them potentially ineffective for patients with severe CRSwNP.

Patient expert statement

	B) OCS – There is a body of evidence that highlights the long-term risks of taking OCS. In my experience some healthcare professionals are very cautious in prescribing them because of these risks. They are also not very pleasant to take causing sleep loss, anxiety and a general sense of ‘being wired’ which can make working and leading a normal life harder. In my experience, with the patients I speak to, OCS only really offer temporary relief from symptoms, as little as a matter of weeks for some people. This seems like an increased risk for limited benefit. C) Surgery – No surgery is pleasant and one that clears out the cavities in your face (your sinuses) can be really uncomfortable. For most of the people we speak to it requires at least two weeks off work and can take a number of months for the effects to settle down. Although surgery is effective for some people I have spoken to, it isn’t effective for everyone and is a lot of disruption to simply be back to where you were, with a poor quality of life, within as little as 6 months. I was in a poor state in less than 6 months after my first surgery. The main disadvantage of all of the above treatments is that when they don’t provide long term symptom relief for a patient, they have nowhere else to go. I have experienced this myself, spending many miserable years taking course after course of OCS whilst hoping the next surgery might work better than the last, only to find it didn’t and being left with no other options. It is currently a very short treatment pathway and there is a need for more treatment options to be available on it, for those patients for whom current treatments don’t work.

Patient expert statement

9a. If there are advantages of dupilumab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does dupilumab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	Another treatment option: As outlined above, dupilumab could offer a much-needed additional treatment for patients and this is one of its main advantages. The current treatment pathway is limited for severe CRSwNP patients for whom surgery or OCS don't offer long term relief. As far for the advantages of the treatment itself vs current treatment, they are: • Speed of prescribing – Unlike waiting a year or more for surgery, I assume a biologic could be prescribed to those people who need it far more quickly, giving much needed symptom relief earlier. • Convenience – Although there will likely be a need for increased monitoring and maybe more consultant visits, this may be preferable to the disruption caused by surgery. • Longer symptom relief – For those patients for whom surgery isn't providing longer term symptom relief, dupilumab may provide that. • Reducing OCS use – I would assume there will be less need for OSC on a biologic thus reducing the long-term risks caused by OCS
10. If there are disadvantages of dupilumab over current treatments on the NHS please describe these. For example, are there any risks with dupilumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I am not expert in the specifics of the treatment but would assume the disadvantages would be: • Side effects – No treatment is without them • Increased monitoring – I assume there will be a need for more blood tests and hospital visits • Won't work for everyone – There will only be a certain % of patients for whom this will work
11. Are there any groups of patients who might benefit more from dupilumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility,	Those patients for whom current treatment options (nasal sprays, OCS and surgery) are not offering long term symptom relief. Once the effects of a course of OCS or surgery wears off (maybe months or maybe only weeks) and the patient returns to a poor state of health, there is nowhere else for the patient to go other than to repeat the same treatments and hope for a different outcome.

Patient expert statement

dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering severe chronic rhinosinusitis with nasal polyposis and dupilumab? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	The only inequity I can think of is the disparity between ENT services across the UK, which may mean a difference in who receives a biologic and who doesn't. This isn't unique to this treatment though and is an issue across the NHS.
13. Are there any other issues that you would like the committee to consider?	

Patient expert statement

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- CRSwNP has dominated my life for over 24 years. Severely impacting how well I could work, socialise and perform everyday functions. I have suffered periods of very poor sleep, fatigue, facial pain and fullness and have had long stretches without any smell or taste. The impact on my overall mental health as a result of this has been noticeable.
- Although there is a range of pharmacological treatments available, the only ways of effectively reducing my symptoms and those of other people with severe CRSwNP are corticosteroids and nasal surgery.
- For severe CRSwNP patients, steroids may only provide a few weeks of relief and surgery a few months. Once steroids and surgery prove to be ineffective long-term solutions, patients have nowhere else to go treatment wise except to enter a recurring cycle of more steroids and more surgery, and simply hope for a different outcome. Whilst enduring very poor quality of life. I have had firsthand experience of this vicious cycle.
- There is clearly a need for an additional treatment within the pathway for these severe CRSwNP patients to provide them with long-term relief from the debilitating symptoms they are living with day to day.
- I, along with other patients, welcome the prospect of a new treatment option. Biologics have the potential to be a much-needed treatment to fill the gap where current treatments are not, or are no longer, effective. This could be a long-term solution instead of bouncing between invasive surgery, steroids and multiple courses of antibiotics to achieve even temporary relief.

Thank you for your time.

Patient expert statement

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Dupilumab for treating severe chronic rhinosinusitis with nasal polyposis [ID6480]

STA Report

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 174243.

Title:	Dupilumab for treating severe chronic rhinosinusitis with nasal polyposis [ID6480]
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Date completed:	10/04/2025
Source of funding:	This report was commissioned by the NIHR Evidence Synthesis Programme as project number 174243.
Declared competing interests of the authors	No competing interests were declared which affect the impartiality of this report. BMJ Technology Assessment Group (BMJ-TAG) and the editorial team of The BMJ work independently to one another. The views and opinions expressed in this report are those of the BMJ-TAG.
Acknowledgments:	The EAG would like to thank Mr Vikas Acharya (Consultant Rhinologist and ENT Surgeon, The Royal National ENT and Eastman Dental Hospitals, UCLH), Miss Nara Orban (Consultant Paediatric & Adult ENT Surgeon, The Royal London Hospital), Mr Rami Salib (Associate Professor of Rhinology, University Hospital Southampton) and Mr Tony McGilligan (Consultant ENT surgeon, Royal Sussex County Hospital) for providing clinical advice throughout the project, and for providing feedback on the clinical and health economic sections of the report.
Rider on responsibility for report:	The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.
Report reference:	Edwards SJ, Dadswell C, Ennis K, Vasileiou M, and Mackenzie I. Dupilumab for treating severe chronic rhinosinusitis with nasal polyposis: A Single Technology Appraisal. BMJ Technology Assessment Group, 2025.

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Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Clare Dadswell	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary, background and clinical results sections
Melina Vasileiou	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and assisted with drafting the clinical results sections
Kate Ennis	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Isaac Mackenzie	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections

All authors read and commented on draft versions of the EAG report.

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List of Abbreviations

BL	Baseline
CRSwNP	Chronic rhinosinusitis with nasal polyposis
CRSSNP	Chronic rhinosinusitis without nasal polyposis
CS	Company submission
CE	Cost-effectiveness
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CQ	Clarification question
CT	Computed tomography
DSU	Decision support unit
DUP	Dupilumab
EAG	External Assessment Group
ECM	Established clinical management
ENT	Ear, Nose and Throat
EPOS	European Position Paper on Rhinosinusitis and Nasal Polyps
EQ-5D	European Quality of Life 5 Dimensions
EQ-5D-3L	European Quality of Life 5 Dimensions 3 Level Version
ESS	Endoscopic sinus surgery
GP	General Practitioner
HCRU	Health care resource use
HES	Hospital Episodes Statistics
HRQoL	Health-related quality of life
HS	Health state
HSE	Health Survey for England
HTA	Health Technology Appraisal
ICER	Incremental cost-effectiveness ratio
INCS	Inhaled nasal corticosteroids
ITT	Intention to treat
LMK-CT	Lund-Mackay Computed Tomography
LoS	Loss of smell
LS mean	Least squares mean
LY	Life years
MCID	Minimal clinically important difference
MDT	Multidisciplinary care team
MI	Multiple imputation
NC	Nasal congestion
NHS	National Health Service
NHB	Net health benefit

NICE	National Institute of Health and Care Excellence
NP	Nasal polyps
NPS	Nasal polyp score
NSAID-ERD	Nonsteroidal anti-inflammatory drug-exacerbated respiratory disease
OCS	Oral corticosteroids
OWSA	One-way sensitivity analyses
PAS	Patient access scheme
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
Q2W	Once every two weeks
Q4W	Once every four weeks
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RR	Relative risk
SF-6D	Short form six dimension
SCS	Systemic corticosteroids
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SNOT-22	22-item Sinonasal Outcomes Test
STA	Single Technology Appraisal
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TSD	Technical support document
TSS	Total symptom score
UPSIT	University of Pennsylvania Smell Identification Test
WOCF	Worst observation carried forward
WTP	Willingness to pay

1 Executive summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the [main EAG report](#).

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Error! Not a valid bookmark self-reference. presents a summary of the EAG's key issues on the evidence submitted on the clinical and cost effectiveness of dupilumab for treating uncontrolled chronic rhinosinusitis with nasal polypsis (CRSwNP).

Table 1. Summary of key issues

ID	Summary of issue	Report sections
1	Different populations used for the evaluation of clinical and cost-effectiveness	2.3 and 3.3
2	Different outcomes used to assess clinical and cost-effectiveness	2.3.4 and 4.2.4
3	Lack of long-term data	3.3.1 and 3.3.2
4	Uncertainty in transition probability from post-op controlled to uncontrolled health state	4.2.5.1
5	Inappropriate utility values used in the economic model	4.2.7.4

Abbreviations: EAG, External Assessment Group

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- Utility values derived from EQ-5D observed in the SINUS trials.
- Surgery gain utility derived from Remenschneider *et al.* 2015.
- Exclusion of asthma costs and mortality risk.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing the proportion of patients with controlled CRSwNP;
- Reducing the rate of surgery

Overall, the technology is modelled to affect costs by:

- Higher acquisition costs compared to current standard treatment of established clinical management alone;
- Reduction in surgery and post-surgery related costs;
- Lower management costs for CRSwNP.

The modelling assumptions that have the greatest effect on the ICER are:

- Method used to estimate health state utility values.

1.3 The clinical and cost effectiveness evidence: summary of the EAG's key issues

Table 2. Issue 1: Different populations used for the evaluation of clinical and cost-effectiveness

Report section	2.3 and 3.3
Description of issue and why the EAG has identified it as important	The company's proposed positioning of dupilumab is for patients who have had prior surgery for nasal polyps (NP). This population is reflected in the company's base case, which includes only those patients from the SINUS-24 and SINUS-52 trials who had prior NP surgery. However, clinical evidence provided in the CS was based on the full ITT population, including both patients who had, or had not had, prior surgery. This population does not align with the positioning of dupilumab proposed by the company. The use of the full ITT population for the evaluation of clinical effectiveness may mask differences in treatment response between patients who have had prior NP surgery and those who have not. In addition, the EAG does not consider it appropriate to use different populations for the evaluation of clinical and cost-effectiveness.
What alternative approach has the EAG suggested?	The EAG requested the results for all primary and secondary outcomes based on the analysis of the prior NP surgery subgroup. This information was provided by the company for the overall analysis and two of the subgroups outlined in the scope (patients with asthma and patients with NSAID-ERD). Differences between the full ITT population and the prior NP surgery subgroup were small and did not affect the interpretation of the results. The EAG focused its critique on results for the prior NP surgery subgroup, to align with the company's proposed positioning of dupilumab and the economic base case. Where results were not available for the prior NP surgery subgroup, the EAG has included results from the ITT population in its critique and acknowledged the potential limitations of this approach.
What is the expected effect on the cost-effectiveness estimates?	As the population used in the cost-effectiveness model is based on the prior surgery population, the EAG does not consider this issue to affect the cost-effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	As the company provided the results for the prior NP surgery subgroup for the pooled 24-week analysis, much of this issue has been resolved. Further information for this subgroup between weeks 24 and 52 of the SINUS-52 trial would provide a greater understanding of the longer-term effects of dupilumab, specifically for patients who have had prior NP surgery.
Abbreviations: EAG, External Assessment Group; ITT, intention to treat; NSAID-ERD, non-steroidal anti-inflammatory drug-exacerbated respiratory disease; NP, nasal polyps.	

Table 3. Issue 2: Difference between the primary outcomes in the trials and the economic model

Report section	2.3.4 and 4.2.4
Description of issue and why the EAG has identified it as important	A different combination of outcomes was used to assess the effectiveness of dupilumab in the clinical and cost-effectiveness sections of the CS. While clinical effectiveness was assessed using NPS and NC score, the economic model used a response criterion based on a combination of NPS and SNOT-22 scores. This response criterion was based on a <i>post-hoc</i> analysis by the company that was not pre-specified, rather than the primary outcome in the key trials. The use of different outcomes to indicate response to treatment could result in different estimates of the relative effectiveness of dupilumab and ECM between the clinical and economic analyses. If the response measure used in the economic analysis differs to that expected to be applied in clinical practice this will result in differences in the cost-effectiveness of dupilumab. In addition, the use of a combination outcome to assess response in the economic analysis also resulted in fewer patients included in the analysis and therefore increased the uncertainty.
What alternative approach has the EAG suggested?	While the EAG use the same treatment response criteria as the company in the EAG base-case analysis, clinical experts to the EAG suggested that SNOT-22 alone would be commonly used in clinical practice to assess response to treatment. Therefore, the EAG also present results of the EAG preferred base-case analysis using the SNOT-22 only response criteria. The EAG also requested alternative economic analyses based on bilateral NPS alone, to better align the clinical and economic comparisons, and to identify the impact of the alternative measures used in the base case.
What is the expected effect on the cost-effectiveness estimates?	Using the SNOT-22 responder criteria increased the company's post clarification base case deterministic ICER from £23,410 to £28,128. The EAG notes that due to the smaller incremental QALYs in the EAG base-case analysis (see Section 6.3), and the EAG's use of the trial-based responder analysis to inform transition probabilities compared to the company's analysis of AROMA, the change in responder criteria has a much greater impact on the resulting EAG base-case ICER, with the use of SNOT-22 only resulting in an ICER of £76,832 (probabilistic).
What additional evidence or analyses might help to resolve this key issue?	The choice of outcomes for the clinical analysis appears appropriate as this matches the co-primary endpoints in the SINUS-24 and SINUS-52 trials. While the EAG does not consider any further analyses will resolve the issue, committee may wish to obtain further clinical insight into what criteria would be used in clinical practice if dupilumab was recommended.
Abbreviations: CS, company submission; EAG, External Assessment Group; ECM; established clinical management; ICER, incremental cost-effectiveness ratio; NPS, nasal polyp score; NC, nasal congestion; QALY, quality adjusted life year ; SNOT-22, 22-item Sinonasal Outcomes Test.	

Table 4. Issue 3: Lack of long-term data

Report section	3.3.1 and 3.3.2
Description of issue and why the EAG has identified it as important	The pooled analysis of the SINUS-24 and SINUS-52 trials provided evidence of the effectiveness of dupilumab over a 24-week treatment period. SINUS-52 provided additional evidence between weeks 24 and 52, although this was for the ITT population, rather than the prior NP surgery subgroup. The only evidence beyond this time point was from the ongoing AROMA

	study, for which evidence is currently available up to 24 months. However, the single-arm study design used for AROMA prevents comparisons with ECM beyond the 52-week point assessed in the SINUS-52 trial. Additionally, the only outcome presented from AROMA in the CS was SNOT-22 score, restricting the longer-term assessment of dupilumab to its effects on HRQoL.
What alternative approach has the EAG suggested?	The EAG incorporated the results of AROMA into the evaluation of clinical effectiveness, discussing its impact on SNOT-22 scores beyond the 52 weeks covered by the SINUS trials, but acknowledging the limitations of this analysis. The EAG also requested a scenario analysis using the AROMA data to explore uncertainty in the long-term treatment effectiveness in the economic model. Although no justification was provided, the company updated their base-case analysis to use the analysis undertaken on AROMA. While the EAG considers the analysis provided by the company useful to explore uncertainty, there are several limitations with the analysis undertaken, which the EAG considers make it inappropriate to use in its base case (Section 4.2.4.1). In light of the uncertainty in the long-term treatment effect duration, the EAG also conducted an exploratory scenario of increasing the proportion of patients discontinuing dupilumab for any reason from year 5 onwards in the model to 15.6% (██████████% derived from the SINUS trials), to test the sensitivity of the results to a higher discontinuation rate due to lack of effectiveness.
What is the expected effect on the cost-effectiveness estimates?	The EAG notes that using the same approach as the company to inform transition probabilities based on an analysis of the AROMA study reduced the EAG's preferred ICER by ≈£2,000 (probabilistic). The EAG's exploratory scenario in which the proportion of patients who lose control each year from year five onwards is ██████████ used in the base-case analysis, increased the EAG's preferred base case ICER by less than £2,000 to £61,488.
What additional evidence or analyses might help to resolve this key issue?	Results from the prior NP surgery subgroup of SINUS-52 would provide evidence of the benefits of dupilumab beyond 24 weeks in the population for which dupilumab has been proposed by the company. Additional evidence comparing dupilumab with ECM beyond 52 weeks would provide a greater understanding of the longer-term effects of dupilumab, and how long any benefits over ECM are maintained. An updated analysis of the AROMA study, in which patients are formally matched to patients in the SINUS 24/52 trials would be more appropriate to inform any treatment effect beyond the 52-week trial period than that conducted by the company. The EAG notes, however, that this should also account for differences in how responders are classified between the two studies (e.g. SNOT-22 data only, use of rescue therapies, etc.).
Abbreviations: CS, company submission; EAG, External Assessment Group; ECM; established clinical management; HRQoL, health-related quality of life; NP, nasal polyps; ICER, incremental cost-effectiveness ratio; SNOT-22, 22-item Sinonasal Outcomes Test.	

Table 5. Key issue 4: Uncertainty in transition probability from post-op controlled to uncontrolled health state

Report section	Section 4.2.5
Description of issue and why the EAG has identified it as important	The EAG considers there to uncertainty in the rate of loss of control following revision surgery and, therefore, the transition probability to the uncontrolled health state. As much of the identified data on rate of revision surgery is based on time from previous surgery, this is not fully applicable to how the model structure is set up. In addition, clinical experts to the EAG noted how the rate of loss of control and revision surgery is highly variable. The EAG had some concerns with the approach used to derive the transition probability, resulting in uncertainty, yet notes that the resulting estimates appear to be aligned with alternative data sources on loss of response and clinical expert opinion.
What alternative approach has the EAG suggested?	The EAG was unable to source an alternative value to inform the annual probability of moving from the post-op controlled to uncontrolled and uses the same values as the company in its base-case analysis. To investigate the impact of any uncertainty on the ICER, an exploratory scenario analysis has been conducted by the EAG in which the transition probabilities were derived using the same approach as the company but the adjustments made to account for surgery waiting time in the UK is changed from two years to one year (i.e. one model cycle). This results in an annual transition probability from the post-op controlled to uncontrolled of 12.1% compared to 42.8% used in the base-case.
What is the expected effect on the cost-effectiveness estimates?	The exploratory analysis increased the company's post-clarification ICER (EAG model corrected) to £25,643 (deterministic). The EAG notes that due to the smaller incremental QALYs in the EAG base-case analysis, the use of a lower transition probability to the uncontrolled health state had a larger impact on the ICER when applied to the EAG's preferred base-case analysis, with a resulting ICER of £72,073 (probabilistic).
What additional evidence or analyses might help to resolve this key issue?	The EAG is unaware of any robust data appropriate to directly inform the company's model structure, specifically transition probability from the post-op controlled to uncontrolled health state. However, the EAG considers its exploratory scenario analysis to represent an upper boundary on what the ICER may be with a lower transition rate applied.
Abbreviations: CS, company submission; EAG, External Assessment Group; ECM; established clinical management; HRQoL, health-related quality of life; NP, nasal polyps; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SNOT-22, 22-item Sinonasal Outcomes Test.	

Table 6. Key issue 5: Inappropriate utility values used in the economic model

Report section	Section 4.2.7.4
Description of issue and why the EAG has identified it as important	Despite EQ-5D being collected in the SINUS trials, the company's base-case analysis applies health state utility values derived from mapping SNOT-22 from the clinical trials to EQ-5D. The company states that this is due to EQ-5D producing utility values higher than age–sex matched general population values for patients responding to treatment. The company considers that the EQ-5D instrument performs poorly at capturing the quality

	of life for patients with CRSwNP, particularly as anosmia and sleep are not covered by the EQ-5D measure. The EAG does not consider the company's departure from the NICE reference case and argument for the use of mapping SNOT-22 to EQ-5D, rather than using the trial-based EQ-5D, to be justified and also considers the model used for mapping (Crump <i>et al.</i>) to be inappropriate due to generalisability issues. Therefore, the EAG considers the use of EQ-5D-5L (mapped to EQ-5D-3L) directly from the key clinical trials to be most appropriate. The EAG notes that the use of the company's mapped utility values in the base-case analysis results in an incremental QALY gain of ■■■ for dupilumab. As dupilumab has not demonstrated a survival benefit in patients with CRSwNP, the EAG considers this to be a substantial benefit. The EAG notes that the choice of utility values used in the economic model is the key driver of the ICER and is therefore considered the main key issue of this appraisal. In addition, the company's base-case analysis applies a utility gain resulting from surgery of 0.051, sourced from Soler <i>et al.</i> 2011. The EAG notes this is based on SF-6D data and the time of study is considered relatively out of date.
What alternative approach has the EAG suggested?	During clarification, the EAG requested a scenario in which the utility values derived from the observed trial EQ-5D were capped at general population age–sex matched utility values and a multiplier applied to subsequent health states in order to retain the proportional differences between health states. The EAG considers the trial observed change from baseline (CFB) EQ-5D-5L (mapped to -3L) with the adjustment applied to be the most appropriate for the base-case analysis. The company also provided a scenario analysis in which the utility gain of surgery (0.08) was sourced from Remenschneider <i>et al.</i> 2015 which is based on more recent data and uses EQ-5D-5L and preferred by the EAG.
What is the expected effect on the cost-effectiveness estimates?	The scenario analysis using health state utilities derived from CFB EQ-5D increased the company's base-case post clarification ICER to £48,956 (deterministic). A separate scenario analysis using trial-based EQ-5D derived using a linear regression analysis best fitting model (with adjustments for general population utility cap applied) also had a substantial impact on the company's base case ICER, increasing it to £50,042. While the EAG's preference would be EQ-5D derived from a regression model over EQ-5D CFB, the EAG considers the regression conducted by the company to be methodologically flawed.
What additional evidence or analyses might help to resolve this key issue?	The EAG considers the range of scenarios provided highlights the sensitivity of the results to the approach taken to derive utility values. While the EAG considers the CFB analysis to be the best of the data available, the preferred option would be a regression model excluding SNOT-22 as it is not an independent variable.

In relation to the surgery utility gain, the EAG does not consider any alternative analyses to be available and prefers the use of Remenschneider *et al.* in the base-case

Abbreviations: CS, company submission; EAG, External Assessment Group; EQ-5D, EuroQol five dimension; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SNOT-22, 22-item Sinonasal Outcomes Test.

1.4 Other key issues: summary of the EAG's view

A number of additional issues were identified. These have a less significant impact on results than the key issues identified in Section 1.3 but they still represent areas of uncertainty or required the EAG to make changes to the economic model.

1. The EAG's clinical experts highlighted the importance of decisions about dupilumab being made in specialist centres, overseen by a multidisciplinary care team (MDT) who have experience in the treatment of patients with CRSwNP. This does not impact on the evaluation of clinical effectiveness, but following a clarification request, an MDT appointment was incorporated into the economic base case. The EAG notes that any requirements for prescribing to be made in clinical practice will need to be made clear in any NICE recommendation, if committee decides to approve dupilumab – Sections 2.2.1 and 4.2.8;
2. Two of the subgroups in the NICE final scope (patients who have asthma and patients who have NSAID-ERD) were combined in the CS. The EAG's clinical experts were uncertain whether there would be a difference in treatment response between these two groups and so the EAG requested the results for each group separately. The company provided the results for patients with NSAID-ERD, but not for those who only had asthma – Section 2.3.5 and 3.3.5;
3. In line with the primary outcome analysis of the clinical trials, in the company's economic analysis, patients who required a course of rescue therapy were classed as non-responders. Clinical experts to both the company and EAG noted that they would not necessarily discontinue patients if only one course of oral corticosteroids (OCS) was required during treatment and that timing from treatment initiation would be a factor to consider. While the EAG is unable to comment on the ICER impact, if patients would not be considered non-responders in clinical practice after requiring one course of rescue therapy, then the results of the model are unlikely to represent clinical practical – Section 4.2.4.1;
4. No inclusion of mortality or cost benefits due to dupilumab on asthma patients – Section 4.2.6 and 4.2.8;

5. Utility values for post-op controlled disease do not differ between treatment arms, i.e. no prolonged treatment benefit following loss of control – Section 4.2.7.4;
6. 5% of patients receive assistance with dupilumab administration, provided by a nurse home care visit – Section 4.2.8.5;
7. Inclusion of two year follow-up costs post-surgery – Section 4.2.8.5.

1.5 Summary of EAG's preferred assumptions and resulting ICER

Table 7 presents the EAG's preferred model assumptions and resulting cumulative change in the ICER from the company's base-case analysis. Results of each scenario presented are probabilistic, with the EAG's base-case ICER presented as both deterministic and probabilistic. Modelling errors identified and corrected by the EAG are described in Section 6.1. For further details of the exploratory and sensitivity analyses done by the EAG, see Sections 6.4.

Table 7. EAG preferred assumptions and probabilistic base-case ICER

Preferred assumption	Section in EAG report	Cumulative incremental costs	Cumulative incremental QALYs	Cumulative ICER (£/QALY)
Corrected company base case	Section 6.1	■	■	£23,499
General population mortality based on ONS life tables 2017-19	Section 4.2.6.1	■	■	£23,542
Controlled to inadequately controlled transition based on SINUS 24/52 responders	Section 4.2.4	■	■	£23,960
No asthma mortality included	Section 4.2.6.1	■	■	£24,356
Utility values based on observed trial based EQ-5D (change from baseline)	Section 4.2.7.4	■	■	£53,497
Surgery utility gain based on Remenschneider <i>et al.</i> 2015	Section 4.2.7.4	■	■	£57,087
Utility values for post-op controlled disease do not differ between treatment arms	Section 4.2.7.4	■	■	£56,683
Removal of differences in costs related to asthma control.	Section 4.2.8.5	■	■	£59,175
5% of patients receive assistance with dupilumab administration, provided by a nurse home care visit	Section 4.2.8.5	■	■	£59,030

Inclusion of two year follow-up costs post-surgery	Section 4.2.8.5	■	■	£59,379
EAG preferred base case, probabilistic	-	■	■	£59,379
EAG preferred base case, deterministic		■	■	£60,551

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; ONS, office of national statistics; QALY, quality adjusted life year; SNOT-22, Sino-Nasal Outcome Test-22

2 Introduction and background

2.1 Introduction

This report contains the External Assessment Group (EAG)'s critique of the clinical and cost-effectiveness evidence submitted for the Single Technology Appraisal (STA) of dupilumab (Dupixent®, Sanofi) for the treatment of people with uncontrolled chronic rhinosinusitis with nasal polyposis (CRSwNP). The marketing authorisation for dupilumab in this indication is, "as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control".^{1, 2}

2.2 Background

The company submission (CS) provides an overview of CRSwNP, including the causes, prevalence, diagnosis, pathology, and symptom burden (Section 1.2 of the CS). It also provides a description of dupilumab, its mechanism of action, indication, and methods of administration and dosage (Section 1.1 of the CS). Included below is the EAG's summary of the key background information presented in the CS, supplemented by information provided by the EAG's clinical experts.

Chronic rhinosinusitis is predominantly a form of Type 2 inflammatory disease, resulting in symptomatic inflammation of tissues in the paranasal sinuses and nasal cavity, with symptoms that last longer than 12 weeks. For some people, chronic rhinosinusitis occurs alongside nasal polyps (CRSwNP), which are non-cancerous soft tissue growths that develop along the mucosal layer of the sinonasal passages or sinuses. Nasal polyps occur bilaterally for most people and can cause partial or total obstruction of the nasal cavities. CRSwNP can cause a range of symptoms including loss of smell and taste, sinonasal congestion and discharge, impaired breathing, facial pain or pressure, fatigue and sleep disturbance, recurrent respiratory infections, eustachian dysfunction, hearing impairment and post-nasal drip. CRSwNP most commonly occurs in adults between 45 to 60 years, with an estimated prevalence of 4.76 per 100,000 individuals in the UK adult population in 2018.³

Diagnosis of CRSwNP begins when patients present to a GP with symptoms of sinonasal inflammation. The diagnostic criteria commonly used for CRSwNP is based on the 2020 European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS).⁴ This includes:

- Two or more symptoms present for over 12 weeks, one of which must include sinonasal blockage, obstruction, congestion, or nasal discharge. This can also include facial pain or pressure, and reduction or loss of smell;

And either:

- Endoscopic signs, such as presence of nasal polyps, mucopurulent discharge from the middle meatus, or oedema or mucosal obstruction primarily in the middle meatus; or
- CT changes, shown as mucosal changes within the ostiomeatal complex and/or sinuses.

CRSwNP is a disease with a high symptom burden, with the company reporting that loss of sense of smell and taste is the symptom that has the greatest impact on a patient's quality of life. This view was supported by the EAG's clinical experts, although they highlighted that this can also be one of the most difficult symptoms to resolve. Other important symptoms raised in the CS include nasal blockage, post-nasal discharge, thick nasal discharge and poor sleep quality. In addition to the symptoms directly associated with CRSwNP, patients often have comorbidities associated with Type 2 inflammation, including asthma, allergies, and non-steroidal anti-inflammatory drug-exacerbated respiratory disease (NSAID-ERD). The most common comorbidity is asthma, which is estimated to affect 46.9% to 62.3% of patients who have CRSwNP.⁵⁻⁷ The CS reports that the presence of comorbidities correlates with an increased severity of CRSwNP symptoms, and often results in an increased need for revision surgery.⁸

The severity of CRSwNP can be determined based on the level of disease control, as defined in the EPOS 2020 paper.⁴ It can either be controlled (patients either have no symptoms, or their symptoms do not affect quality of life, in addition to a healthy or almost healthy mucosa and only the need for local medication) or uncontrolled (patients have symptoms of nasal blockage, discharge, facial pain or pressure, reduced sense of smell, sleep disturbance, nasal endoscopy findings and the need for rescue medication). Patients with uncontrolled CRSwNP are referred to an Ear, Nose and Throat (ENT) or Rhinology clinic for further treatment. These patients are the focus of this submission.

2.2.1 Current treatment pathway

Current UK management of CRSwNP is based on the EPOS 2020 recommendations.⁴ Inhaled nasal corticosteroids (INCS) are recommended throughout the treatment pathway to reduce symptoms, while short-term systemic corticosteroids (SCS) are recommended for treatment of acute exacerbations to reduce polyp size and provide rapid symptom relief. For people who meet the criteria for uncontrolled CRSwNP there are currently three main treatment options:

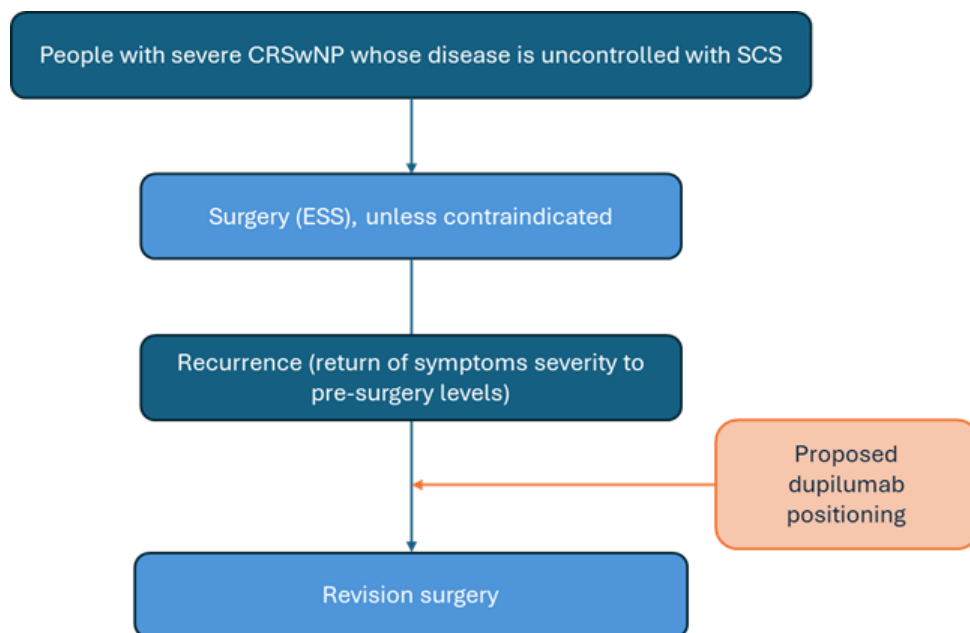
- Endoscopic sinus surgery (ESS) — involving the removal of polyps, ESS is recommended to alleviate the symptoms of CRSwNP and improve the delivery of INCS;

- Saline rinses and INCS — these are recommended following ESS to maintain the benefits of surgery; and
- Short courses of SCS — these are used to treat acute exacerbations both before and after ESS for patients who do not respond to INCS.

Some patients will continue to experience symptoms despite the above treatment options, and the EPOS 2020 recommendations state that either revision surgery, aspirin desensitisation (for patients with NSAID-ERD) or treatment with a biologic should be considered.⁴ The CS highlights limitations to these existing treatment options, such as surgery, which does not target the driver of the disease (Type 2 inflammation), and therefore while it provides temporary symptom relief, it does not guarantee that polyps will not recur. Aspirin desensitisation is only offered in a few UK centres and therefore not currently considered established clinical management (ECM), and while biologics have regulatory approval for CRSwNP in the UK, these are not yet available in the NHS.

The proposed positioning of dupilumab for people with CRSwNP is after initial surgery, but prior to revision surgery (Figure 1). The company expects that dupilumab will be used alongside INCS, with the aim of reducing inflammation and symptoms, thereby reducing the need for revision surgery and SCS that may otherwise be needed later in the treatment pathway.

Figure 1. Proposed positioning of dupilumab for patients with uncontrolled CRSwNP (reproduced from Figure 8 in the CS).



Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyposis; ESS, endoscopic sinus surgery; SCS, systemic corticosteroids

The company's suggested positioning of dupilumab broadly matches that expected by the EAG's clinical experts. Some of the clinical experts highlighted subgroups of patients with more severe disease who they thought may benefit from revision surgery prior to dupilumab. One group comprises patients who have initial surgery which is inadequate relative to the severity of disease and could therefore benefit from comprehensive revision surgery. The other group includes patients with very high SNOT-22 scores and high polyp disease burden, such as those with the Samter's triad or NSAID-ERD, and those who are refractory to nasal steroid or oral burst therapy. However, another of the EAG's clinical experts thought that this second group could still benefit from dupilumab after initial surgery, but prior to revision surgery. Randomisation of the key trials in the CS (SINUS-24 and SINUS-52) was not stratified on the characteristics outlined above, and so it is not possible to determine whether there are any differences in the treatment response for this group, but the EAG considers it an important issue to highlight. However, the EAG's clinical experts agreed that the positioning in Figure 1 is expected to be appropriate for the majority of patients.

An additional consideration highlighted by the EAG's clinical experts is how decisions about prescribing dupilumab will be made. The experts stressed the importance of these decisions being made in specialist centres, overseen by a multidisciplinary care team (MDT) who have experience in the treatment of patients with CRSwNP (additional issue 1 in section 1.4). This was considered preferable to decisions being made by a single clinician, such as a rhinologist, and is similar to the way in which biologics are prescribed for patients with asthma. While this does not impact the interpretation of the results of the clinical analysis, the EAG considers this an important point to highlight, given the importance that the clinical experts placed on this point. Following a clarification request from the EAG, the inclusion of an MDT appointment has also been considered by the company and is incorporated in the base case, which is discussed in more detail in Section 4.2.8.

2.3 Critique of the company's definition of the decision problem

The company provided a summary of the final scope issued by the National Institute for Health and Care Excellence (NICE), together with a rationale for any deviations from the decision problem. The CS covers most patients who are indicated in the marketing authorisation for dupilumab and matches the majority of the NICE final scope, with some differences in the population and subgroups. Overall, the EAG considers that the CS appears appropriate and justified. A summary of the final scope issued by NICE, the decision problem addressed in the CS, and the EAG's critique of this is provided in Table 8. Further detail about the EAG's critique is provided in Sections 2.3.1 to 2.3.5.

Table 8. Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope	EAG comment
Population	People with previously treated severe chronic rhinosinusitis with nasal polyps	The company's base case focuses on adults with uncontrolled CRSwNP following one or more surgeries	The NICE scope does not state the failure of, or intolerance to, previous treatments. Clinical experts advised the company that surgery works for some people and should therefore be recommended prior to dupilumab. However, patients who require revision surgery following a successful sinus surgery should have access to biologic therapy, with further revision surgery avoided where possible.	The EAG's clinical experts generally agreed with the company's proposed positioning of dupilumab after surgery. This is in line with the advice from the company's clinical experts and supports the company's decision to focus on people who have already had surgery for nasal polyps in their base case. Clinical experts for both the company and the EAG highlighted that very few patients are ineligible for surgery in clinical practice, and so the population proposed by the company covers most of the patients who would be seen by the NHS in England. While the EAG supports the company's decision to include only people who have had prior surgery in their base case, the clinical evidence in the company submission focuses on the ITT population of the SINUS studies, including both people who had and did not have prior surgery. The EAG requested additional results for the prior surgery group, and this group is the focus of the assessment of clinical effectiveness in this report.

Intervention	Dupilumab as add on to maintenance treatment	Dupilumab as an add on to maintenance treatment with INCS	N/A	N/A
Comparator(s)	Established clinical management (ECM) without dupilumab, including surgery	As per NICE scope	N/A	N/A
Outcomes	The outcome measures to be considered include: • nasal congestion and/or obstruction • sense of smell • sinus opacifications • need for surgery • need for SCS • adverse effects of treatment • HRQoL.	As per NICE scope, measured using: • nasal congestion and/or obstruction: NC, NPS • sense of smell: UPSIT, LoS • sinus opacifications: LMK-CT • need for surgery: % • need for SCS: % • adverse effects of treatment: TEAEs • HRQoL: SNOT-22	N/A	N/A
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent	As per NICE scope	N/A	The economic analysis adheres to the NICE reference case. The EAG notes that while the utility values used in the model are mapped to EQ-5D-3L, the directly observed EQ-5D values from the clinical trials are not used in the company's base case analysis.

	treatment technologies will be taken into account.			
Subgroups to be considered	• People who have asthma • People who are ineligible for surgery • People who are ineligible for systemic corticosteroids • People with non-steroidal anti-inflammatory drug-exacerbated respiratory disease (NSAID-ERD)	• People who have had one (or more) surgery • People with any prior type 2 medical history (including asthma/NSAID-ERD) • People who have had one (or more) surgery AND with any prior type 2 medical history (including asthma/NSAID-ERD)	People who are ineligible for surgery: • The base case focuses on people who have had one (or) more prior surgeries and remain uncontrolled. No patients in the SINUS studies had no prior surgery and were ineligible for revision surgery, and only 23.74% were ineligible for revision surgery. An analysis of those ineligible for surgery would therefore be highly uncertain. People who are ineligible for SCS: • Only 5.25% of patients in the SINUS studies were ineligible for SCS, and so meaningful subgroup analysis is not possible. • Clinical experts advised the company that this population is rarely seen in clinical practice. People who have asthma / People with NSAID-ERD: • NSAID-ERD is defined as the presence of CRSwNP with asthma and NSAID sensitivity and is predominantly a type 2 inflammatory disease.	People who are ineligible for surgery: • As noted for the population, the EAG agrees with the company's decision to focus on people who had prior surgery for nasal polyps. As such, people who are ineligible for surgery would not be included in the group used by the company for the base case, or in the results requested by the EAG for the clinical analysis. Clinical experts for both the company and EAG highlighted that very few people are ineligible for surgery. People who are ineligible for SCS: • The EAG's clinical experts agreed with the company's assumption that very few patients would be ineligible for SCS. In addition, the small number of people who were ineligible for SCS in the SINUS studies means that the interpretation of the results for this subgroup is likely to be associated with considerable uncertainty, particularly when the population is restricted to only those patients who had prior surgery. The EAG therefore agrees with the company's decision not to include this subgroup as part of the analysis.

			• There is a high prevalence of people with CRSwNP and comorbid asthma (up to 60%) and many also present with NSAID-ERD. • The high prevalence of comorbid asthma and NSAID-ERD in this population, and the increased surgery burden in this group, means these subgroups were combined as “people with any prior type 2 medical history”.	People who have asthma/People with NSAID-ERD: • The EAG’s clinical experts advised that these groups tend to be considered in a similar way in clinical practice. However, they were unsure whether both groups would respond to treatment in exactly the same way, as patients in the NSAID-ERD subgroup may have more severe disease than some of the patients who only have asthma. The EAG therefore requested information for the two subgroups separately, as stated in the NICE final scope.
Special considerations, including issues related to equity or equality	N/A	N/A	N/A	N/A

Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polypsis; EAG, External Assessment Group; EQ-5D, EuroQoL 5-Dimension 5-Level; HRQoL, health-related quality of life; ITT, intention-to-treat; LMK-CT, Lund-Mackay Computed Tomography; LoS, loss of smell; NC, nasal congestion score; NICE, National Institute for Health and Care Excellence; NPS, nasal polyp score; NSAID-ERD, non-steroidal anti-inflammatory drug exacerbated respiratory disease; PSS, Personal Social Services; QALY, Quality-adjusted life year; SCS, systemic corticosteroids; SNOT-22, 22-item Sinonasal Outcomes Test; TEAE, treatment emergent adverse event; TSS, total symptom score; UPSIT, University of Pennsylvania Smell Identification Test.

2.3.1 Population

The NICE final scope focuses on all people who have previously treated severe CRSwNP, while the marketing authorisation states that dupilumab is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control. The CS states that while the NICE scope includes the relevant population, it does not specifically state that previous treatments should have failed to control the disease. In addition, the company notes that their clinical experts recommended that people should have surgery prior to being prescribed dupilumab, as this is an effective treatment option for some people. One of the company's clinical experts estimated that less than 10% of patients with CRSwNP would be ineligible for surgery (CS, Appendix R.2). This was supported by the EAG's clinical experts who indicated that the company's definition covers most of the population who would be seen in clinical practice in England. As such, the company's decision to focus on patients who have had previous surgery appears reasonable, and in line with clinical practice.

The EAG noted that while the company's proposed positioning of dupilumab focused on only patients who had previous surgery for nasal polyps (NP), the clinical section of the submission was based on the pooled ITT population (including both those who had, and had not, had prior NP surgery) (**Key issue 1** in section 1.1). Given the company's case for the prior NP surgery subgroup, and the views of both the company and EAG's clinical experts that surgery should take place before dupilumab is prescribed, the EAG requested the pooled clinical outcomes from SINUS-24 and SINUS-52 solely for the subgroup of patients who had prior NP surgery. The EAG's assessment of the clinical data for dupilumab is therefore based primarily on this subgroup of the population in the NICE final scope, rather than all patients in the ITT population.

The inclusion criteria for the key trials in this appraisal (SINUS-24 and SINUS-52) were discussed with the EAG's clinical experts. Both used the same criteria, including patients with bilateral sinonasal polyposis that persisted despite prior treatment with SCS within the past 2 years; and/or had a medical contraindication/intolerance to SCS; and/or had prior sinonasal surgery for nasal polyps, and had:

- An endoscopic bilateral NPS ≥ 5 at Visit 1 (maximum score of 8) with a minimum score of 2 in each nasal cavity; and

- Ongoing symptoms (for at least 8 weeks before Visit 1) of nasal congestion or obstruction (moderate or severe: score 2 or 3 at Visit 1 and a weekly average severity of >1 at Visit 2), and either loss of smell (partial or total) or rhinorrhoea (anterior or posterior).

The EAG's clinical experts thought the inclusion and exclusion criteria accurately reflected the patients they see in clinical practice, and represented those they would expect to be eligible for dupilumab treatment. As discussed above, they also agreed with the restriction of the trial population in the CS to only those who had prior NP surgery, as they considered this to be the group who would gain the most benefit from treatment with dupilumab.

One potential limitation of the SINUS trials is the limited number of patients from England. Only the SINUS-24 trial included any patients from the UK (19 patients from 6 sites), with 64% of patients in SINUS-24 from the EU, compared to 19% in SINUS-52. This could limit the generalisability of the results if patient characteristics or clinical practice differ considerably between the countries included in the trial and those in the NHS. However, the EAG's clinical experts considered the populations in both trials to be generalisable to the patient population that would be eligible for dupilumab in England. They noted that there may be some differences in practice, such as earlier surgery offered in the USA. However, they did not expect the differences in practice between countries to be sufficient to affect a patient's response to dupilumab. As such, the location of the trials does not appear to be a major concern. All other inclusion criteria and baseline characteristics appeared reasonable and so the EAG considers that the submission reflects the patient population in the decision problem.

2.3.2 *Intervention*

The intervention matches that stated in the NICE final scope. Dupilumab (brand name Dupixent®) has a marketing authorisation for adults as add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.

Dupilumab is a recombinant human IgG4 monoclonal antibody that inhibits IL-4 and IL-13 signalling, both of which are drivers of Type 2 inflammatory disease, including CRSwNP. By inhibiting the action of IL-4 and IL-13, dupilumab decreases the mediators of Type 2 inflammation. The recommended dose for dupilumab is 300 mg every other week, administered using a subcutaneous injection via either a pre-filled syringe or pen. Most people can self-administer dupilumab at home, although

some may need a carer or healthcare worker to administer the injection for them. The EAG's clinical experts expected that the number of people who would need assistance in delivering dupilumab would be very small.

The SINUS-24 and SINUS-52 trials assessed the use of dupilumab over 24 and 52 weeks, respectively, and the EAG's clinical experts considered this to be an acceptable time over which to assess someone's response to treatment. They noted that patients would likely remain on treatment beyond 52 weeks if they did show a response, and these longer-term effects are not reflected in the existing evidence base. Given that the dose, method of administration and assessment time points reflect what the clinical experts would expect to see in practice, the intervention used in the trials appears suitable to address the decision problem, although it is important to note the lack of longer-term data (**Key issue 3** in section 1.1).

The AROMA trial was discussed in the CS as a source of longer-term data for dupilumab for CRSwNP. This was an observational, open-label, single-arm, real-world registry study, with results currently available up to 24 months. AROMA assessed most of the outcomes that were reported in the SINUS trials, although only the results of one measure (SNOT-22) was reported in the CS. Although AROMA included a relevant intervention, the difference in trial design, with no comparator treatment, meant that it could not be incorporated into the pooled analysis. Other limitations included a lack of restrictions on rescue medication or concomitant medications during the trial, which could affect response to treatment. These limitations, alongside the limited reporting of the outcomes in the CS, limits the ability to assess the effects of dupilumab beyond the 52-week period covered by the SINUS-52 trial. With the lack of effectiveness data beyond 52 weeks, during clarification, the EAG requested a scenario analysis using the AROMA data to explore uncertainty in the long-term treatment effectiveness in the economic model. Although no justification was provided, the company updated their base-case analysis to use the analysis undertaken on AROMA. The EAG notes that no formal matching methods were used to account for differences in the patient population between the AROMA and SINUS studies (see Section 4.2.1 for further details).

2.3.3 Comparators

The comparator matches that in the NICE final scope of established clinical management (ECM) without dupilumab, including surgery. As discussed in Section 2.2.1, ECM for CRSwNP includes the use of INCS throughout the treatment pathway (before and after surgery), and the option of short courses of SCS if people have acute exacerbations. If a patient continues to have uncontrolled

symptoms following initial INCS, they can also be offered ESS. This is followed by a combination of INCS and saline rinses to maintain the benefits gained from surgery. The EAG's clinical experts confirmed that the clinical management used in the SINUS-24 and SINUS-52 trials reflected clinical practice in England, and the results are therefore considered generalisable to the NHS.

2.3.4 Outcomes

The outcomes in the CS match those in the NICE final scope (see Table 8). Change in nasal congestion (NC) and nasal polyp score (NPS) were the co-primary endpoints in the SINUS-24 and SINUS-52 trials. The EAG's clinical experts confirmed that these outcomes are often used in clinical practice to assess whether a patient is responding to treatment, although it was noted that these measures can be variable. Similar concerns about the variability of these outcomes were also reported by some of the company's clinical experts (CS, Appendix R.2). In addition, the EAG's clinical experts noted that while patient-reported outcomes (PROs) are often considered important outcomes when determining the effects of treatments for CRSwNP, NC score is not always considered the most reliable PRO.

An additional PRO highlighted by the EAG's clinical experts as commonly used in clinical practice was the 22-item Sinonasal Outcomes Test (SNOT-22), which was a key secondary outcome in the CS and the SINUS trials. SNOT-22 is used to assess a person's HRQoL based on a range of symptoms associated with CRSwNP. The EAG notes that there appears to be some variation in practice in relation to the preferred measures used to assess response to treatment for people with CRSwNP. As such, all three outcomes (NPS, NC and SNOT-22) should be considered when assessing the effectiveness of dupilumab in this population.

The NICE final scope also included outcomes relating to sense of smell and sinus opacifications. These were reported by the company as key secondary outcomes, with sense of smell measured using the University of Pennsylvania Smell Identification Test (UPSIT) and the loss of smell test (LoS), and sinus opacification measured using Lund-Mackay Computed Tomography (LMK-CT). The EAG's clinical experts discussed how loss of sense of smell is one of the most concerning outcomes for patients but noted that the results of the tests can be variable. As many patients never regain their sense of smell, it is not considered one of the main aims of treatment. Sense of smell outcomes are also covered to some degree as part of the SNOT-22 questionnaire. When discussing sinus opacification, the EAG's clinical experts highlighted that while LMK-CT was once a common measure in clinical practice, it is no longer consistently used and, while it can be useful for guiding decisions on surgery, it is a less useful method of assessing treatment outcomes. LMK-CT outcomes are,

therefore, potentially less useful for assessing the effectiveness of dupilumab than the NPS, NC and SNOT-22. As such, the focus of the EAG's assessment of clinical effectiveness is primarily on the co-primary endpoints (NC and NPS) and the outcomes from SNOT-22, rather than those associated with sense of smell or sinus opacifications.

Of note is the different combination of outcomes used to assess clinical effectiveness compared to those used to define response to treatment in the economic model (**Key issue 2** in section 1.1). While the clinical trials' results focused on NPS and NC, the economic model used a response criterion based on a combination of NPS and SNOT-22 scores. This choice of outcomes appears reasonable, based on the feedback from the EAG's clinical experts (outlined above), but there is a lack of clarity over the decision to use different outcomes for the clinical and economic analyses. For this reason, the EAG requested alternative economic analyses based on NPS alone and SNOT-22 only, to better align the clinical and economic comparisons, and to identify the impact of the alternative measures used in the base case. More information on the outcomes used for the assessment of cost-effectiveness is provided in Section 4.2.4.

2.3.5 Subgroups

Two of the subgroups stated in the NICE final scope (people who are ineligible for surgery and people who are ineligible for SCS) were not included in the CS. As noted in Table 8, the EAG considers the rationale for the exclusion of both subgroups to be reasonable. Given that the company's proposed positioning of dupilumab and the EAG's assessment of the clinical evidence focuses on people who had prior NP surgery, no one in this group would meet the criterion to be included in the subgroup of people who are ineligible for surgery.

The EAG's clinical experts discussed how very few patients would be ineligible for SCS, and this was reflected by the small number of patients who met the criterion for this subgroup in the SINUS trials (5.25%). The EAG therefore agrees with the company's statement that there are insufficient data to allow for meaningful subgroup analysis. As this group is rarely seen in clinical practice, the EAG does not consider it a major concern that this subgroup could not be included in the analysis.

The company combined two of the subgroups from the NICE final scope (people who have asthma and people who have NSAID-ERD). The EAG's clinical experts discussed how people in both groups tend to have more severe disease than other people with CRSwNP and agreed with the company's statements that many patients have both comorbid asthma and NSAID-ERD. Additionally, they noted

that patients who have NSAID-ERD and those who have asthma without NSAID-ERD are often treated in the same way in clinical practice. However, they also noted that patients who have NSAID-ERD can have more severe disease than those who only have asthma and they were unsure whether this would affect the magnitude of their response to treatment. The EAG, therefore, requested separate results for the two subgroups in a clarification question, to determine whether there are any differences in treatment response. The company provided results for the NSAID-ERD subgroup but stated that, because the presentation of NSAID-ERD includes asthma, removing NSAID-ERD patients from the asthma only subgroup would introduce bias to the results (additional issue 2 in section 1.4). It is therefore difficult to assess the extent to which treatment response differs between patients who have asthma (without NSAID-ERD) and those who have NSAID-ERD. It is unclear to the EAG why removing NSAID-ERD patients from the asthma subgroup would introduce bias, given that some patients who have asthma do not have NSAID-ERD. However, the company did provide the results for a subgroup who have asthma (including both those who do and do not have NSAID), and so this can be compared against the overall results for patients who had prior NP surgery to provide an indication of any potential differences in response.

3 Clinical effectiveness

3.1 Critique of the methods review

The company conducted a systematic literature review (SLR) to identify randomised controlled trials (RCTs), *post-hoc* analyses or pooled analyses of RCTs that compared the efficacy and safety of dupilumab or other approved and recommended treatments in adults with uncontrolled CRSwNP.

Methods used for the SLR are summarised in **Error! Not a valid bookmark self-reference..** The EAG considers the methods used to be appropriate to meet the NICE final scope. The SLR was updated in October 2024, three months prior to the submission, and so is unlikely to have missed any substantial, more recent, evidence.

Table 9. Summary of EAG's critique of the methods implemented by the company to identify evidence relevant this appraisal

Systematic review step	Section of CS in which methods are reported	EAG's assessment of robustness of methods
Data sources	CS Appendix D, Section D.1.1	Appropriate The following databases were searched: • MEDLINE via Ovid • Embase via Ovid • Cochrane Database of Systematic Reviews (CDSR) via Ovid • Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid Grey literature searches for conference proceedings for the following conferences of interest were searched using Embase: • American College of Allergy Asthma and Immunology • European Academy of Allergy and Clinical Immunology • American Academy of Otolaryngology–Head and Neck Surgery Foundation • European Respiratory Society • American Academy of Allergy, Asthma, and Immunology References lists of relevant SLRs were also searched in addition to the following clinical trial registries: • ClinicalTrials.gov of the United States (US) National Institute of Health • World Health Organisation meta-registry "International Clinical Trials Registry Platform Search Portal" (ICTRP)
Search strategies	CS Appendix D, Section D.1.1	Appropriate Searches included the relevant population, interventions and study designs. The initial search when the SLR was originally conducted was performed in September 2019, followed by further updates in June to October 2020 and October 2024. The final update of the search was 3 months prior to submission and so the likelihood of missing key references appears low. The two main trials in the CS were both identified in the SLR.

Inclusion criteria	CS Appendix D, Section D.1.2	Appropriate The population, intervention and comparators match those in the NICE final scope and decision problem. The efficacy and safety outcomes were appropriate to meet those specified in the scope. The SLR appears unlikely to have missed any relevant studies based on the inclusion criteria.
Screening	CS Appendix D, Section D.1.2	Appropriate Abstract and full-text screening was completed by two independent investigators, with discrepancies resolved by a third reviewer.
Data extraction	CS Appendix D, Section D.1.2.1	Appropriate Data was extracted by a single reviewer in an Excel-based data extraction workbook. All extracted data was validated by a second independent reviewer.
Tool for quality assessment of included study or studies	CS Appendix D, Section D.3	Appropriate The Cochrane Risk of Bias Assessment Tool 2.0 was used for quality assessment which is appropriate. Explanations for the quality judgement for each domain were not provided but the EAG performed its own quality assessment of the key trials from the CS (SINUS-24 and SINUS-52) and agrees with the assessment for both trials.
Abbreviations: CS, company submission; EAG, External Assessment Group; NICE, National Institute for Health and Care Excellence; SLR, systematic literature review.		

The SLR identified 15,359 records after deduplication (Figure 1, CS Appendix D). A total of 465 full-text articles were screened, with 141 publications representing 39 trials, identified as relevant. Of these, 19 assessed biologic treatments, four assessed surgery and 16 assessed other interventions, such as corticosteroids, leukotriene receptor antagonists and corticosteroid implants.

While 39 trials reported on treatment in the population specified in the decision problem, only three included the intervention relevant to the scope. These were:

- SINUS-24: Dupilumab vs placebo (ECM) (Phase III RCT);
- SINUS-52: Dupilumab vs placebo (ECM) (Phase III RCT);
- Bachert 2016: Dupilumab vs placebo (ECM) (Phase II trial).

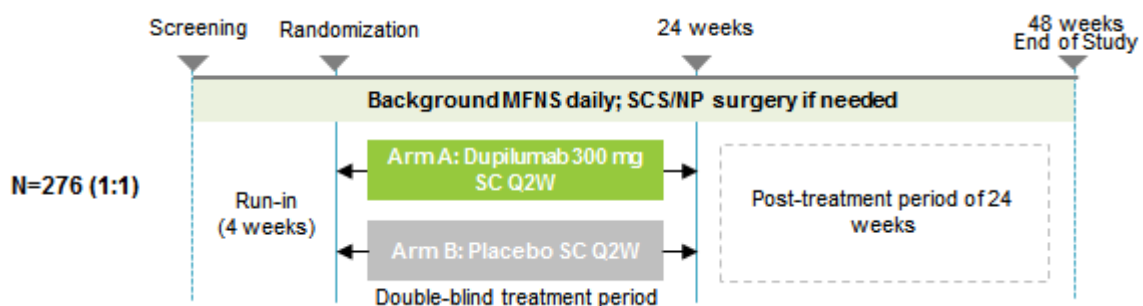
The interventions assessed by the other 36 trials were either not recommended by NICE for the treatment of CRSwNP or did not include the population of interest. Therefore, based on the available evidence, the EAG agrees that the direct evidence between dupilumab and ECM from the SINUS-24 and SINUS-52 trials is the most appropriate method to assess the effectiveness of dupilumab.

3.2 Critique of trials of the technology of interest

Two RCTs (SINUS-24 [NCT02912468] and SINUS-52 [NCT02898454]), both comparing dupilumab to ECM without dupilumab, were the focus of this submission. Both were Phase III, placebo-controlled, double-blind, randomised multicentre trials. In SINUS-24, participants were randomised to either dupilumab 300 mg delivered subcutaneously once every two weeks (as specified in the marketing authorisation) or placebo over a period of 24 weeks (Figure 2). SINUS-52 was a 52-week trial, with participants randomised to one of three arms; dupilumab 300 mg delivered subcutaneously once every two weeks (as for SINUS-24), dupilumab 300 mg once every two weeks for the first 24 weeks, followed by once every four weeks for the final 24 weeks, or placebo (Figure 3). In both trials, all patients also received standard of care (mometasone furoate nasal spray, 100 µg in each nostril twice per day) throughout the trial period. The EAG notes that both trials included prior surgery as a stratification factor during randomisation, supporting the use of the prior surgery subgroup without the concerns associated with the breaking of randomisation.

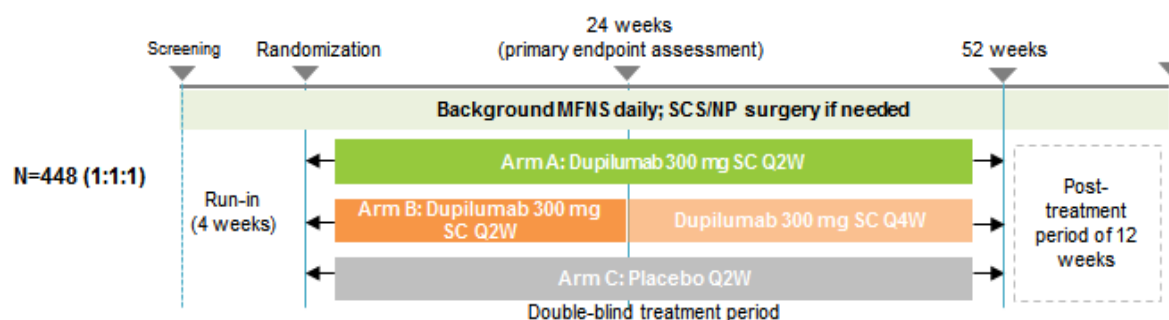
In addition to the treatment period, the SINUS-24 study included a 24-week post-treatment period (weeks 24 to 48), where treatment was withdrawn, and patient responses were monitored. Results of this period are summarised in Section 3.3.4 to inform what may happen to patients who discontinue treatment.

Figure 2. Study design of the SINUS-24 trial. Reproduced from Figure 9 of the CS.



Abbreviations: MFNS, mometasone furoate nasal spray; NP, nasal polyps; Q2W, once every 2 weeks; SCS, systemic corticosteroids.

Figure 3. Study design of the SINUS-52 trial. Reproduced from Figure 10 of the CS.



Abbreviations: MFNS, mometasone furoate nasal spray; NP, nasal polyps; Q2W, once every 2 weeks; Q4W, once every 4 weeks; SCS, systemic corticosteroids.

Both studies used the same methods for the imputation of missing data. A hybrid approach was used, with a combination of worst observation carried forward (WOCF) and multiple imputation (MI) methods. The EAG notes that WOCF can be considered a conservative approach to imputation in some situations. However, in other circumstances, such as when an intervention is effective and has few adverse effects, it can make comparisons against placebo appear more favourable. To identify the potential impact of this hybrid approach, the EAG requested further information about the quantity of missing data for each treatment arm. Alternative versions of the results were also requested using no data imputation and using only the MI approach.

The company provided information on missing data for the ITT population for both trials, and the EAG notes that a considerably higher percentage of patients in the ECM group had missing data, resulting in more missing data being imputed using the WOCF method than in the dupilumab group (Table 10). The use of either no imputation, or MI without the addition of WOCF, resulted in marginally greater changes from baseline for bilateral NPS, NC score and SNOT-22 score in both groups. At 24 weeks, differences between groups were slightly smaller than when the hybrid approach with WOCF was used, suggesting that the WOCF method may have resulted in marginally worse scores for placebo. However, the alternative methods of imputing the missing data appear to have a very limited impact on the results and do not change the interpretation of any of the comparisons between dupilumab and ECM.

Table 10. Method of imputation of missing data from the SINUS-24 and SINUS-52 trials.

Method of imputation	SINUS-24		SINUS-52	
	ECM (%)	Dupilumab (%)	ECM (%)	Dupilumab (%)
Bilateral NPS				
WOCF	18.8	7.0	28.8	8.1
MI	3.0	3.5	3.9	3.7
NC score				
WOCF	18.8	6.3	28.8	8.5
MI	1.5	0.7	2.6	1.7
SNOT-22				
WOCF	18.8	7.0	28.8	8.5
MI	1.5	1.4	3.9	3.1
Abbreviations: ECM, established clinical management; MI, multiple imputation; NC, nasal congestion score; NPS, nasal polyp score; SNOT-22, 22-item Sinonasal Outcomes Test; WOCF, worst observation carried forward				

The company reported that both trials were at low risk of bias (Table 20 in the CS). The EAG's quality assessment is presented in Table 11, and aligns with the company's assessment.

Table 11. EAG's summary of the design, conduct and analysis of SINUS-24 and SINUS-52.

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Randomisation	• SINUS-24 CSR – Section 8.4.4 • SINUS-52 CSR – Section 8.4.4	Appropriate Participants were randomised using 1:1 randomisation for SINUS-24 and 1:1:1 randomisation for SINUS-52. Randomisation for both trials was stratified based on asthma status, prior surgery for nasal polyps and country. Randomisation was achieved using a centralised treatment allocation system, with treatment kit numbers provided at the time of randomisation and follow-up visits via an Interactive Voice Response System/Interactive Web Response System.
Blinding and allocation concealment	• SINUS-24 CSR – Section 8.4.7 • SINUS-52 CSR – Section 8.4.7	Appropriate Dupilumab and placebo treatment kits were identical and indistinguishable. In SINUS-52, placebo doses were provided every other week for patients who were not in the dupilumab Q4W group. Patients, investigators and site study personnel were blinded to the assigned treatment at all times unless there were emergency safety concerns.

Eligibility criteria	CS Table 15	Appropriate The EAG's clinical experts agreed that the inclusion and exclusion criteria for the SINUS trials were appropriate and similar to patients they would expect to see in clinical practice.
Baseline characteristics	CS Table 17	Appropriate Baseline characteristics were similar between trial arms for SINUS-52. There were some differences between trial arms for SINUS-24 including sex, peak nasal inspiratory flow and age at onset of asthma (a greater percentage of males, higher peak inspiratory flow and older age of onset of asthma in the dupilumab arm). However, the EAG's clinical experts did not expect these to affect treatment response. Some differences were also evident between the mean baseline characteristics for the two trials (see Table 12). The EAG's clinical experts did not think most of these would affect treatment response, although the mean number of days using SCS was higher in SINUS-52 than would be expected in practice. Pooled baseline characteristics were similar between trial arms, both for the ITT population and the prior NP surgery subgroup.
Dropouts	• SINUS-24 CSR – Section 9.1 • SINUS-52 CSR – Section 9.1	Some concerns Over the first 24 weeks, dropouts in the dupilumab arm were relatively low for both trials (SINUS-24: 0.7%; SINUS-52: 2.4%). Dropouts in the placebo arm were similar to dupilumab in SINUS-24 (2.3%) but notably higher than dupilumab in SINUS-52 (9.8%). It is unclear why the relative proportion of dropouts was higher in the placebo arm for SINUS-52 than SINUS-24. In SINUS-52, discontinuations between weeks 24 and 52 were similar for the dupilumab (2.0%) and placebo (4.6%) arms.
Statistical analysis		
Sample size and power	CS Table 18	Appropriate Both studies were designed to have >90% power to detect a difference in the co-primary endpoints between dupilumab 300 mg Q2W and placebo at a 2-sided significance level of $\alpha=0.05$.
Handling of missing data	CS Table 18. Clarification responses, A1 and A2	Appropriate Each of the co-primary efficacy endpoints and key secondary endpoints were multiplicity-adjusted and analysed using a hybrid method of the WOCF and MI methods. Although more data were imputed using the WOCF method in the ECM arm, results provided by the company using other methods of imputation or no imputation do not affect the interpretation of the effects of dupilumab.
Outcome assessment	CS Table 16	Appropriate Clinical response outcomes were assessed using measures that are commonly used in practice. HRQoL was assessed using a validated tool.
Abbreviations: CS, company submission; CSR, clinical study report; EAG, External Assessment Group; HRQoL, health-related quality of life; MI, multiple imputation; Q2W, once every two weeks; Q4W, once every four weeks; WOCF, worst observation carried forward.		

The matching trial design, population, interventions, comparators and outcomes meant that the company chose to pool the analysis of the two trials. The EAG notes that there were some differences between the mean baseline characteristics from the trials (Table 12). The EAG's clinical experts did not expect most of these differences to affect treatment response. However, they discussed how the mean number of days with SCS use in the previous two years seemed higher in SINUS-52 than they would expect in clinical practice. This may indicate that the patients in SINUS-52 had more severe disease than those in the SINUS-24 trial, which could lead to a greater relative response to treatment than patients in SINUS-24. However, as these are a part of the patient population, the clinical experts did not think it was a major concern when interpreting the results of the trials.

Table 12. Key differences between baseline characteristics of the SINUS-24 and SINUS-52 trials.

Baseline characteristics	SINUS-24	SINUS-52
Race: White (%)	95.7	83.0
Race: Black/African descent (%)	3.3	1.6
Race: Asian (%)	0.4	12.1
% males	57.2	62.3
Prior surgery for nasal polyposis (%)	71.7	58.3
Number of previous surgeries for nasal polyposis (mean, SD)	2.24 (1.73)	1.75 (1.39)
Systemic corticosteroid use in the previous 2 years (%)	64.9	80.1
Mean number of days with SCS use in the previous 2 years (mean, SD)	14.44 (15.72)	45.46 (120.03)
% with history of epistaxis (%)	9.8	19.0
Months since last asthma exacerbation (mean, SD)	72.86 (105.11)	44.13 (67.67)

Overall, the EAG considers the pooling of results from the two trials to be an acceptable approach for outcome assessment. The pooled baseline characteristics were similar between the dupilumab and ECM arms, both in the ITT population and the prior NP surgery subgroup (Table 4 and Table 71 of company clarification responses). Most of the baseline characteristics in the prior NP surgery subgroup were similar to the full ITT population, with the exception of the percentage of patients with comorbid asthma or comorbid NSAID-ERD, which were slightly higher in the prior NP surgery subgroup (approximately 5% more with asthma and 6% more with NSAID-ERD). However, the percentage with each comorbidity was similar between trial arms in the prior NP surgery group, and

as such, is not expected to have a major impact on the results. As the pooled trials were the only evidence for dupilumab in this population, no meta-analysis was required.

3.3 Critique of the clinical effectiveness analysis and interpretation

Summaries of the individual trial results of SINUS-24 and SINUS-52 are presented in Appendix N of the CS, while the sections below focus on the results of the pooled analysis of the two trials, considering the effectiveness and safety of dupilumab compared to ECM. As outlined in Section 2.3, most of the clinical evidence in the CS is based on the full pooled ITT population of the two SINUS trials, while the company is positioning dupilumab for the subgroup of patients who had prior NP surgery (**Key issue 1** in section 1.1). The EAG's critique in the following sections will, therefore, focus on the prior NP surgery subgroup, in line with the company's proposed positioning of dupilumab, and to ensure consistency between the assessment of the clinical and economic evidence.

The CS reports the thresholds used to indicate a minimal clinically important difference (MCID) between dupilumab and ECM (Table 13). The company notes that most of the outcomes for CRSwNP are subjective and that the thresholds for patient-reported outcomes (PROs) are not well defined. As such, while SNOT-22 has a clinically validated threshold, all other MCIDs reported by the company are instead based on a *post-hoc* analysis of the SINUS trials. These values were discussed with the EAG's clinical experts, who considered them to be similar to those used in clinical practice. One exception was the UPSIT score, which the experts reported to be more variable between patients, and therefore more difficult to confidently assign a threshold for a MCID. The EAG's clinical experts were not aware of any other validated MCIDs used for the outcomes reported in the trials for patients with CRSwNP. Therefore, with the exception of UPSIT, for which there is some uncertainty, the values presented by the company appear to be reasonable estimates of a clinically meaningful difference between dupilumab and ECM.

Table 13. Minimal clinically important differences (MCIDs) used for each outcome.

Outcome	Validated MCID?	Company justification for other MCID
NC	No	1 point based on <i>post-hoc</i> analysis of SINUS-24 and SINUS-52 data using an anchor-based method.
NPS	No	1 point based on <i>post-hoc</i> analysis of SINUS-24 and SINUS-52 data using an anchor-based method.
LMK-CT	No	5 points based on <i>post-hoc</i> analysis of SINUS-24 and SINUS-52 data using an anchor-based method.
TSS	No	3 points based on <i>post-hoc</i> analysis of SINUS-24 and SINUS-52 data using an anchor-based method.
UPSIT	No	8 points based on <i>post-hoc</i> analysis of SINUS-24 and SINUS-52 data using an anchor-based method.
LoS	No	1 point based on <i>post-hoc</i> analysis of SINUS-24 and SINUS-52 data using an anchor-based method.

SNOT-22	Yes (change ≥ 8.9 points)	N/A
Abbreviations: LMK-CT, Lund-Mackay Computed Tomography; LoS, loss of smell; MCID, minimal clinically important difference; NC, nasal congestion score; NPS, nasal polyp score; SNOT-22, 22-item Sinonasal Outcomes Test; TSS, total symptom score; UPSIT, University of Pennsylvania Smell Identification Test.		

3.3.1 Primary outcome

3.3.1.1 Bilateral NPS and NC score

The co-primary endpoints for both trials were change from baseline in bilateral NPS and NC score at 24 weeks. Dupilumab resulted in improvements in both bilateral NPS and NC score over 24 weeks (Table 14), with the change from baseline for both outcomes exceeding the company's thresholds for a MCID. While ECM also resulted in improvements in NC score, the change from baseline was smaller than that seen for dupilumab, and did not reach the MCID threshold. No improvements were seen for bilateral NPS with ECM, with an increase of 0.16 points instead reflecting a marginal increase in disease severity.

Change from baseline for both outcomes was statistically significantly greater with dupilumab than ECM (Table 14), and a clinically meaningful difference was seen between groups for bilateral NPS. The difference between groups for NC score did not exceed the MCID, but was close to the 1-point threshold. As such, it appears that, following 24 weeks of treatment, dupilumab results in greater reductions in both polyp severity and patient-reported symptom severity than treatment with ECM alone.

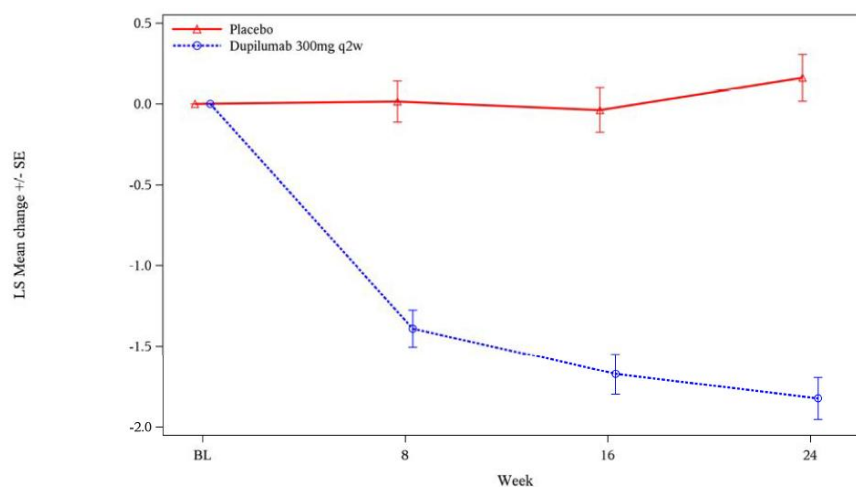
Table 14. Results of the co-primary endpoints of the pooled SINUS-24 and SINUS-52 trials for patients who had prior NP surgery (reproduced from Table 9 of the company's response to clarification questions).

Endpoint	ECM (n=187)		Dupilumab (n=272)		
	Mean change from baseline (SD)	LS mean change from baseline (SE)	Mean change from baseline (SD)	LS mean change from baseline (SE)	LS mean difference vs ECM (95% CI; p value)
Primary endpoints at Week 24					
Bilateral NPS	0.13 (1.23)	0.16 (0.14)	-1.89 (1.88)	-1.82 (0.13)	-1.99 (-2.29 to -1.68; p<0.0001)
NC score	-0.47 (0.79)	-0.38 (0.07)	-1.38 (0.92)	-1.36 (0.06)	-0.98 (-1.13 to -0.83, p<0.0001)
Abbreviations: ECM, established clinical management; LS mean, least squares mean; NC, nasal congestion score; NPS, nasal polyp score					

In response to clarification questions, the company provided the results for change from baseline at each assessment point up to 24 weeks (Figure 4 and Figure 5). Dupilumab resulted in reductions in bilateral NPS from week 8 onwards, and reductions in NC score from week 4 onwards.

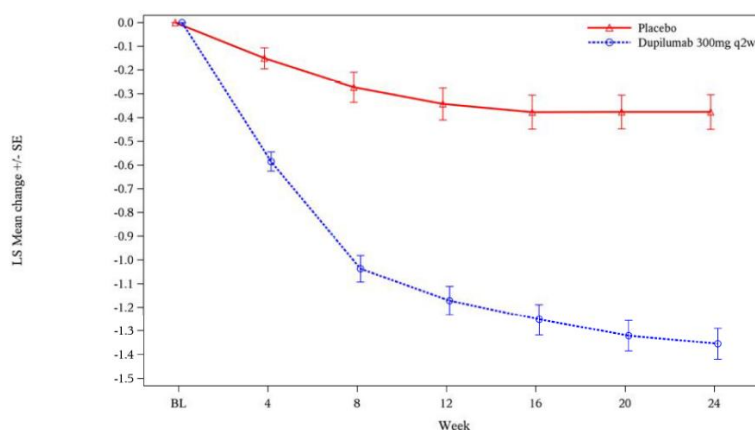
Improvements continued until week 24, suggesting ongoing benefits of dupilumab throughout the treatment period. Changes in the ECM group were less pronounced, with bilateral NPS remaining relatively stable until week 16 and then marginally increasing, while marginal reductions were seen in NC score over the first 16 weeks before stabilising. The relatively stable scores observed with ECM are not unexpected, given that this is an established method of controlling CRSwNP symptoms. However, the increasing differences between groups throughout the trial period highlights the additional benefits of dupilumab over ECM during the first 24 weeks of treatment.

Figure 4. LS mean change from baseline in bilateral NPS up to Week 24 in patients with prior NP surgery. Reproduced from Figure 33 of the company's clarification response



Abbreviations: LS mean, least squares mean; NPS, nasal polyps score; Q2W, once every two weeks; SE, standard error

Figure 5. LS mean change from baseline in NC score up to Week 24 in patients with prior NP surgery. Reproduced from Figure 34 of the company's clarification response



Abbreviations: LS mean, least squares mean; NC, nasal congestion; Q2W, once every two weeks; SE, standard error

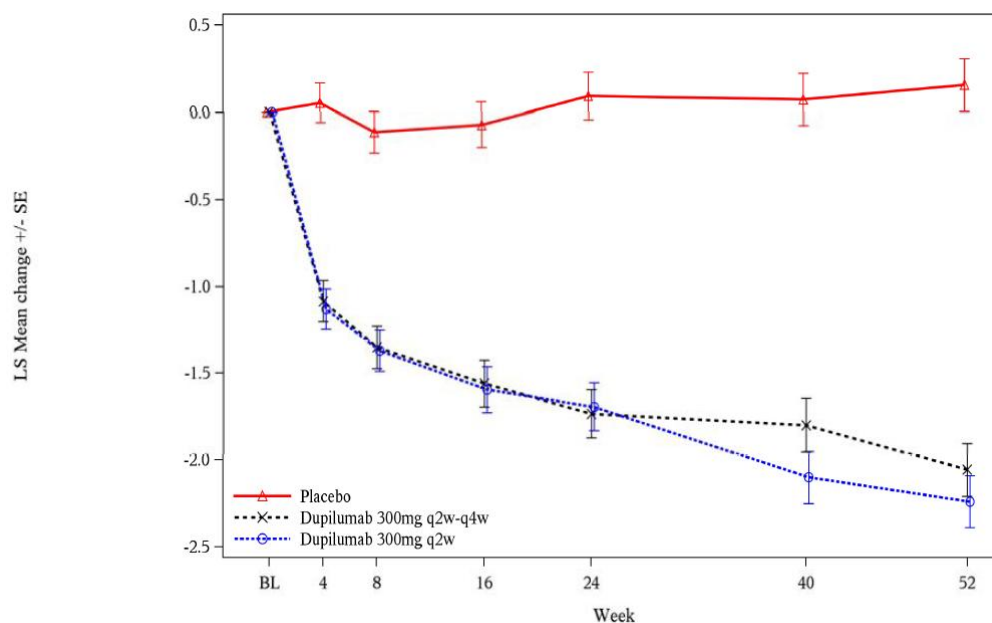
The SINUS-52 trial reported the benefits of dupilumab compared to ECM beyond the 24-week time point assessed in the pooled analysis. At 52 weeks, improvements from baseline were statistically significantly greater with dupilumab than ECM for both co-primary endpoints (Table 15). Differences between groups were greater at 52 weeks than at 24 weeks, suggesting that the benefits of dupilumab over ECM continue to increase for at least the first year of treatment.

Table 15. Results of the co-primary endpoints of the SINUS-52 trial for the ITT population.

Endpoint	ECM (n=187)		Dupilumab (n=272)		
	Mean change from baseline (SD)	LS mean change from baseline (SE)	Mean change from baseline (SD)	LS mean change from baseline (SE)	LS mean difference vs ECM (95% CI; p value)
Primary endpoints at Week 24					
Bilateral NPS	0.12 (0.95)	0.10 (0.14)	-1.72 (1.77)	-1.71 (0.11)	-1.80 (-2.10 to -1.51; p<0.0001)
NC score	-0.36 (0.73)	-0.38 (0.07)	-1.28 (0.95)	-1.25 (0.06)	-0.87 (-1.03 to -0.71; p<0.0001)
Primary endpoints at Week 52					
Bilateral NPS	0.12 (1.20)	0.15 (0.15)	-2.30 (1.97)	-2.24 (0.15)	-2.40 (-2.77 to -2.02; p<0.0001)
NC score	-0.34 (0.72)	-0.37 (0.08)	-1.39 (0.98)	-1.35 (0.07)	-0.98 (-1.17 to -0.79; p<0.0001)
Abbreviations: ECM, established clinical management; LS mean, least squares mean; NC, nasal congestion score; NPS, nasal polyp score; SD, standard deviation; SE, standard error					

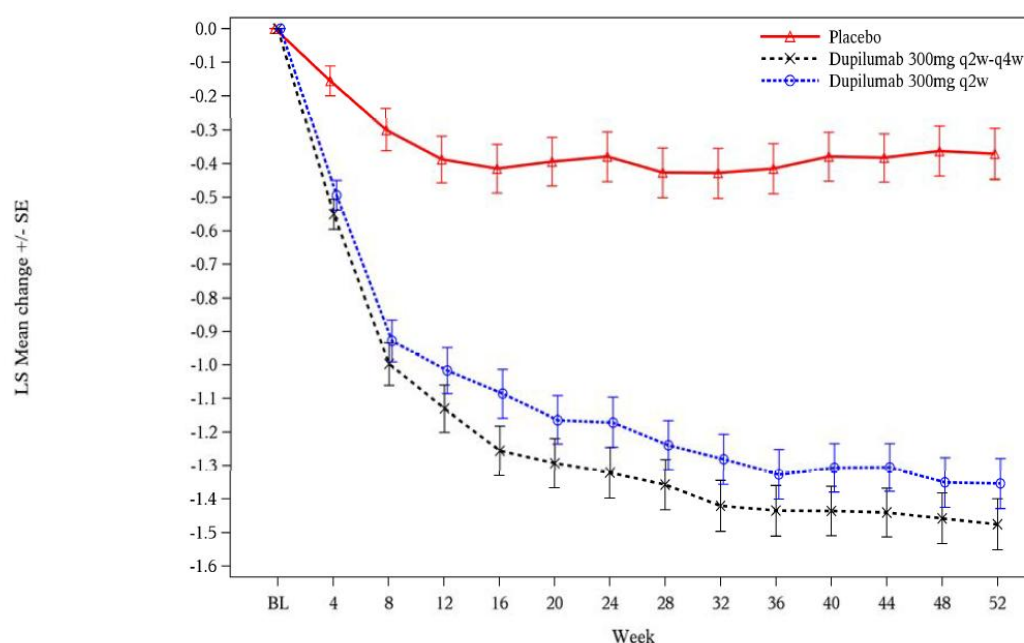
While SINUS-52 indicates ongoing benefits of dupilumab over ECM for the first year of treatment, there are some limitations which should be considered when interpreting these results. As discussed in Section 3.2, patients in the SINUS-52 trial may have had more severe disease than those in SINUS-24. However, as the response reported in the two trials was similar over the first 24 weeks, it may be reasonable to assume that the ongoing benefits seen for the patients in SINUS-52 may also be applicable to those in SINUS-24. Analysis of SINUS-52 was also based on the ITT population, rather than the prior NP surgery subgroup (**Key issue 3** in section 1.1). However, given the similarities in results for the ITT population and prior surgery subgroup in the pooled analysis, the EAG considers the results likely to be a reasonable surrogate for response in the prior NP surgery group.

Figure 6. LS mean change from baseline in bilateral NPS up to Week 52 in the ITT population of the SINUS-52 trial. Reproduced from Figure 4 of the SINUS-52 CSR.



Note: The dupilumab 300 mg q2w-q4w arm of SINUS-52 (black dashed line) is not a relevant comparator for this appraisal.
Abbreviations: LS mean, least squares mean; Q2W, once every two weeks; Q2W, once every four weeks; SE, standard error

Figure 7. LS mean change from baseline in NC score up to Week 52 in the ITT population of the SINUS-52 trial. Reproduced from Figure 9 of the SINUS-52 CSR.



Note: The dupilumab 300 mg q2w-q4w arm of SINUS-52 (black dashed line) is not a relevant comparator for this appraisal.
Abbreviations: LS mean, least squares mean; Q2W, once every two weeks; Q2W, once every four weeks; SE, standard error

3.3.2 Secondary outcomes

Key secondary endpoints reported in the CS related to changes in HRQoL (SNOT-22 score), sense of smell (UPSIT score, LoS score), overall symptoms (TSS) and sinus opacification (LMK-CT score) at 24 weeks. Based on feedback from the EAG's clinical experts, as outlined in Section 2.3.4, the EAG considers the outcomes of the SNOT-22 questionnaire to be the most relevant to clinical practice, and this is therefore considered in the most detail in the section below.

3.3.2.1 SNOT-22

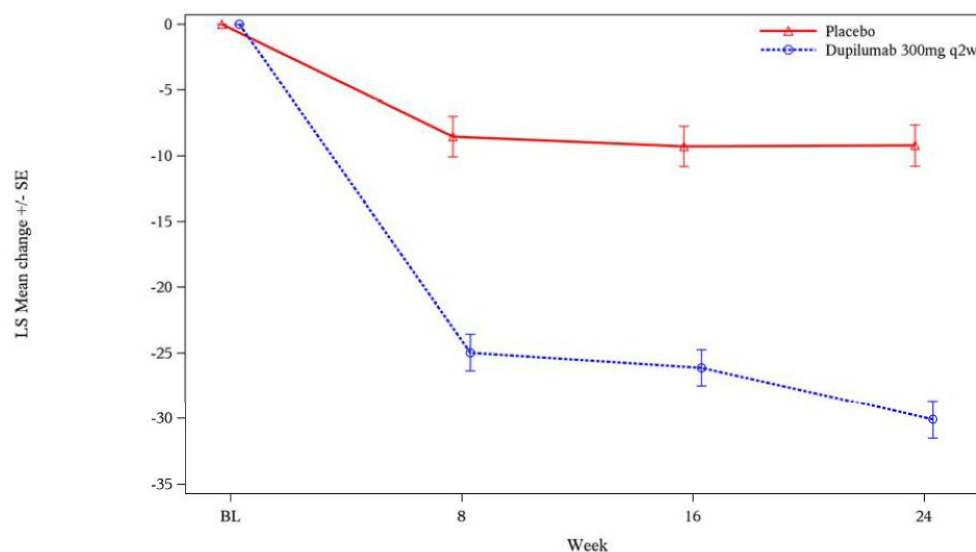
Both dupilumab and ECM resulted in statistically significant reductions in SNOT-22 scores from baseline, indicating improvements in HRQoL (Table 16). At 24 weeks, the mean difference between trial arms was -20.89 (95% CI -24.18 to -17.60), demonstrating that while both treatment options improved HRQoL, there was a statistically significant and clinically meaningful benefit of dupilumab over ECM.

Initial improvements in HRQoL, as indicated by reduction in SNOT-22 scores, were seen in both groups by week 8 (Figure 8). While scores in the ECM group remained relatively stable from this point onwards, improvements were seen throughout the study period for dupilumab, albeit to a lesser extent than during the initial 8 weeks. These ongoing improvements, alongside those seen for the co-primary endpoints, highlight the benefits of dupilumab over ECM for both clinical outcomes and PROs during the first 24 weeks of treatment.

Table 16. Results of the key secondary endpoints of the pooled SINUS-24 and SINUS-52 trials for patients who had prior NP surgery (reproduced from Table 9 of the company's response to clarification questions).

Endpoint	ECM (n=187)		Dupilumab (n=272)		
	Mean change from baseline (SD)	LS mean change from baseline (SE)	Mean change from baseline (SD)	LS mean change from baseline (SE)	LS mean difference vs ECM (95% CI; p value)
Key secondary endpoints at Week 24					
SNOT-22 score	-9.93 (19.01)	-9.23 (1.57)	-28.89 (21.85)	-30.12 (1.41)	-20.89 (-24.18 to -17.60; p<0.0001)
Abbreviations: ECM, established clinical management; LS mean, least squares mean; SNOT-22, 22-item Sinonasal Outcomes Test					

Figure 8. LS mean change from baseline in SNOT-22 score up to Week 24 in patients with prior NP surgery. Reproduced from Figure 36 of the company's clarification response



Abbreviations: LS mean, least squares mean; Q2W, once every two weeks; SE, standard error

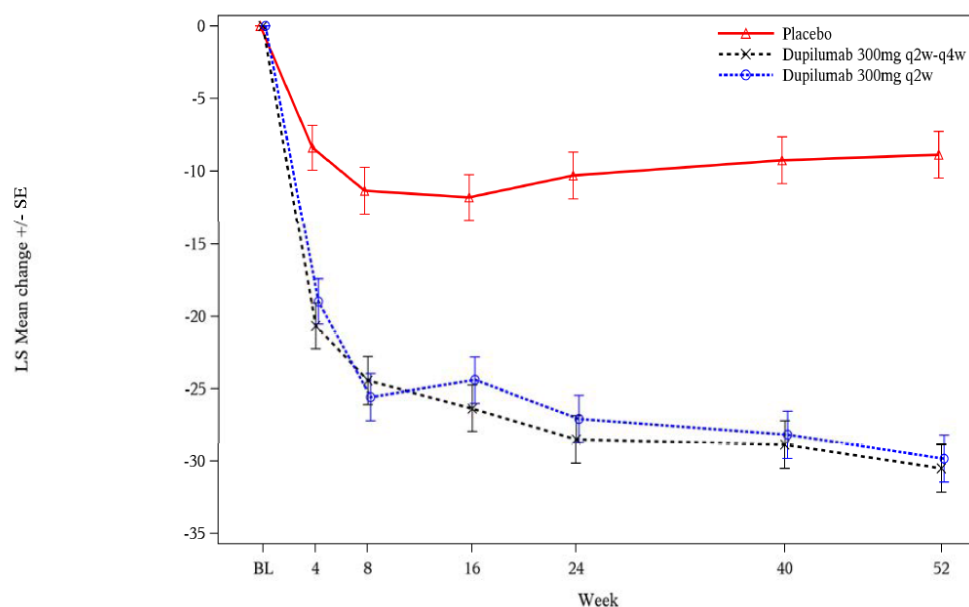
As for the co-primary endpoints, the SINUS-52 trial highlighted the benefits of dupilumab beyond the 24-week time point of the pooled analysis. Statistically significantly greater improvements in SNOT-22 score were seen with dupilumab than ECM at 52 weeks (Table 17). Differences between groups were similar to those seen at 24 weeks, indicating a sustained benefit of dupilumab on HRQoL throughout the first year of treatment. These results are subject to the same considerations outlined for the co-primary endpoints, including the greater disease severity of the SINUS-52 population and the use of the ITT population (**Key issue 3** in section 1.1). However, as outlined in Section 3.3.1.1, the EAG considers these results a reasonable surrogate for response for the prior NP surgery subgroup.

Table 17. SNOT-22 scores in the SINUS-52 trial for the ITT population.

Endpoint	ECM		Dupilumab		
	Mean change from baseline (SD)	LS mean change from baseline (SE)	Mean change from baseline (SD)	LS mean change from baseline (SE)	LS mean difference vs ECM (95% CI; p value)
Week 24					
SNOT-22	-10.94 (19.29)	-10.40 (1.61)	-27.32 (21.88)	-27.77 (1.26)	-17.36 (-20.87 to -13.85; p<0.0001)
Week 52					
SNOT-22	-9.06 (18.32)	-8.88 (1.61)	-28.66 (21.55)	-29.84 (1.63)	-20.96 (-25.03 to -16.89; p<0.0001)
Abbreviations: ECM, established clinical management; LS mean, least squares mean; SD, standard deviation; SE, standard error; SNOT-22, 22-item Sinonasal Outcomes Test					

Longer-term data are available for SNOT-22 than the other outcomes, with the AROMA trial providing an analysis of the effects of dupilumab over 24 months. The mean change from baseline in SNOT-22 score for patients in AROMA was -27.3 (SD 22.61) points at 12 months, which declined to -18.0 (SD 16.63) points at 24 months. This suggests that the benefits of dupilumab may begin to wane beyond the 52-week time point assessed by the SINUS trials. However, with no comparator arm in the AROMA trial, it is unclear whether the same effect would be seen with ECM, or if the difference between treatments would reduce beyond the 52-week point. As such, uncertainties remain over the long-term benefits of dupilumab (**Key issue 3** in section 1.1).

Figure 9. LS mean change from baseline in SNOT-22 score up to Week 52 in the ITT population of the SINUS-52 trial. Reproduced from Figure 24 of the SINUS-52 CSR.



Note: The dupilumab 300 mg q2w-q4w arm of SINUS-52 (black dashed line) is not a relevant comparator for this appraisal. Abbreviations: LS mean, least squares mean; Q2W, once every two weeks; Q4W, once every four weeks; SE, standard error

3.3.2.2 Other secondary outcomes

As discussed in Section 2.3.4, the EAG's clinical experts noted that the other secondary outcomes (LMK-CT, TSS, UPSIT score, LoS score) were less relevant to decision-making in clinical practice. However, the EAG notes that, as for the co-primary endpoints and SNOT-22 scores, dupilumab resulted in a clinically meaningful reduction from baseline for each of these outcomes (Table 18). In contrast, changes from baseline with ECM for each outcome were small, with none reaching the

MCID threshold. As a result, dupilumab resulted in statistically significant and clinically meaningful improvements in each outcome compared to ECM alone (Table 18). Comparisons throughout the trial showed similar trends to those reported for NPS, NC and SNOT-22 scores, with dupilumab showing ongoing improvements at each assessment point. In contrast, scores for the ECM group were either stable throughout the trial period or demonstrated small improvements which did not meet the MCID. This supports the results of the co-primary endpoints and SNOT-22 scores, demonstrating increasing benefits of dupilumab over ECM throughout the first 24 weeks of treatment.

Table 18. Results of the other key secondary endpoints of the pooled SINUS-24 and SINUS-52 trials for patients who had prior NP surgery (reproduced from Table 9 of the company's response to clarification questions).

Endpoint	ECM (n=187)		Dupilumab (n=272)		
	Mean change from baseline (SD)	LS mean change from baseline (SE)	Mean change from baseline (SD)	LS mean change from baseline (SE)	LS mean difference vs ECM (95% CI; p value)
Key secondary endpoints at Week 24					
LMK-CT score	-0.31 (2.24)	-0.05 (0.33)	-6.38 (4.90)	-6.32 (0.30)	-6.27 (-6.97 to -5.57; p<0.0001)
TSS	-1.13 (1.68)	-0.90 (0.18)	-3.71 (2.30)	-3.58 (0.16)	-2.69 (-3.06 to -2.31; p<0.0001)
UPSIT score	-0.10 (5.46)	-0.34 (0.71)	10.59 (10.06)	10.23 (0.64)	10.57 (9.07 to 12.06; p<0.0001)
LoS score	-0.16 (0.52)	-0.12 (0.08)	-1.22 (1.03)	-1.20 (0.07)	-1.07 (-1.23 to -0.91; p<0.0001)
Abbreviations: ECM, established clinical management; LMK-CT, Lund-Mackay Computed Tomography; LoS, loss of smell; LS mean, least squares mean; TSS, total symptom score; UPSIT, University of Pennsylvania Smell Identification Test.					

Results of the SINUS-52 trial again demonstrated that the benefits of dupilumab continued beyond the 24-week timepoint covered by the pooled analysis. Differences between dupilumab and ECM remained relatively stable for each of the secondary outcomes (Table 19), indicating sustained benefits of dupilumab throughout the first year of treatment.

Table 19. Results of the other key secondary endpoints of the SINUS-52 trial for the ITT population.

Endpoint	ECM		Dupilumab		
	Mean change from baseline (SD)	LS mean change from baseline (SE)	Mean change from baseline (SD)	LS mean change from baseline (SE)	LS mean difference vs ECM (95% CI; p value)
Week 24					
LMK-CT score	0.11 (1.88)	-0.09 (0.31)	-5.23 (4.42)	-5.21 (0.24)	-5.13 (-5.80 to -4.46; p<0.0001)
TSS	-1.03 (1.66)	-1.00 (0.20)	-3.54 (2.47)	-3.45 (0.15)	-2.44 (-2.87 to -2.02; p<0.0001)
UPSIT	-0.21 (5.15)	-0.81 (0.71)	10.28 (10.17)	9.71 (0.56)	10.52 (8.98 to 12.07; p<0.0001)
LoS score	-0.23 (0.56)	-0.23 (0.08)	-1.21 (1.02)	-1.21 (0.06)	-0.98 (-1.15 to -0.81; p<0.0001)
Week 52					
LMK-CT score	0.16 (2.05)	0.11 (0.37)	-7.08 (5.34)	-6.83 (0.37)	-6.94 (-7.87 to -6.01; p<0.0001)
TSS	-0.89 (1.63)	-0.94 (0.20)	-3.88 (2.58)	-3.79 (0.20)	-2.85 (-3.35 to -2.35; p<0.0001)
UPSIT	-0.14 (5.07)	-0.77 (0.71)	10.19 (10.32)	9.53 (0.72)	10.30 (8.50 to 12.10; p<0.0001)
LoS score	-0.18 (0.56)	-0.19 (0.09)	-1.31 (1.09)	-1.29 (0.08)	-1.10 (-1.31 to -0.89; p<0.0001)
Abbreviations: ECM, established clinical management; LMK-CT Lund-Mackay Computed Tomography; LOS, loss of smell; LS mean, least squares mean; SD, standard deviation; SE, standard error; TSS, total symptom score; UPSIT, University of Pennsylvania Smell Identification Test					

3.3.3 Safety

The CS reported information on treatment-emergent adverse events (TEAEs), serious TEAEs, TEAEs leading to treatment discontinuation and TEAEs leading to death (Table 20). The frequency of TEAEs was similar between ECM and dupilumab, suggesting no serious safety concerns. The EAG's clinical experts stated that the frequencies reported are similar to those they would expect to see in clinical practice. Specific TEAEs that occurred in ≥5% of the patients in either group were also presented, with the frequency of TEAEs consistently lower for dupilumab than ECM (Table 21).

In response to clarification questions, the company provided information on common serious TEAEs and TEAEs leading to treatment discontinuation (Table 21). Very few of these TEAEs occurred in ≥5% of the patients in either group and none occurred more frequently with dupilumab than ECM. As such, there do not appear to be any major safety concerns regarding the use of dupilumab in

comparison to ECM. The reported common TEAE's in Table 21 were included in the economic model, apart from worsening of nasal polyps (see Section 4.2.8.4 for further details).

Table 20. Pooled TEAEs from SINUS-24 and SINUS-52 at 24 weeks (ITT population). Reproduced from Table 32 of CS

TEAE, n (%)	ECM (N=282)	Dupilumab (N=440)	Risk difference, % (95% CI) dupilumab vs ECM
Any	208 (74)	305 (69)	-6.48 (-13.04 to 0.08)
Any serious	16 (6)	15 (3)	-2.80 (-6.30 to 0.70)
Leading to permanent treatment discontinuation	15 (5)	11 (3)	-2.66 (-6.01 to 0.69)
Leading to death	0	0	0
Abbreviations: ECM, established clinical management; TEAE, treatment emergent adverse event			

Table 21. Pooled common TEAEs from SINUS-24 and SINUS-52 at 24 weeks (ITT population – occurring in ≥5% of either treatment arm). Reproduced from Table 33 of CS and Tables 10 and 11 of clarification responses

TEAE, n (%)	ECM (N=282)	Dupilumab (N=440)
Common TEAEs		
Asthma*	20 (7.1)	7 (1.6)
Epistaxis	20 (7.1)	25 (5.7)
Headache	24 (8.5)	32 (7.3)
Injection-site erythema	22 (7.8)	28 (6.4)
Nasal polyps†	33 (11.7)	12 (2.7)
Nasopharyngitis	41 (14.5)	55 (12.5)
Common serious TEAEs		
Asthma*	2 (0.7)	0
Facial bones fracture	2 (0.7)	0
Nasal polyps†	2 (0.7)	1 (0.2)
Common TEAEs leading to permanent treatment discontinuation		
Nasal polyps†	5 (1.8)	2 (0.5)
Abbreviations: ECM, established clinical management; TEAE, treatment emergent adverse event		

* Worsening of asthma from baseline

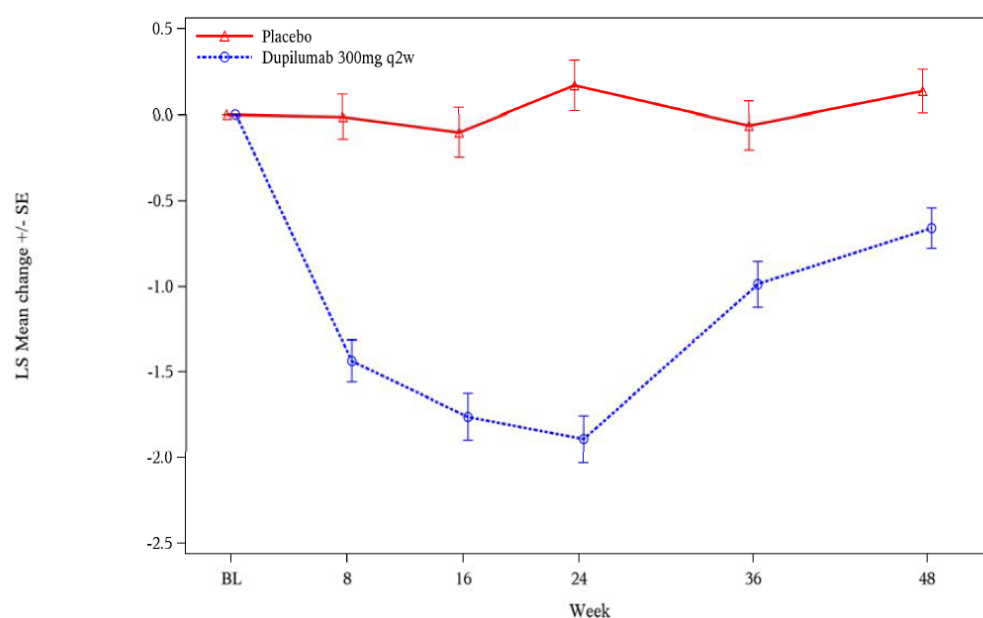
† Worsening of nasal polyps resulting in sinonasal surgery or SCS treatment

3.3.4 Post-treatment outcomes

SINUS-24 included a 24-week post-treatment period, from week 24 to 48. Results for the co-primary endpoints were reported in the CS, demonstrating patient's responses once treatment was stopped. While bilateral NPS remained relatively stable in the ECM group, there was a gradual increase in scores in the dupilumab group, reflecting worsening disease severity (Figure 10). Although scores in the dupilumab group remained lower than those recorded at baseline (LS mean difference -0.66, SE 0.12), the difference at week 48 was no longer clinically meaningful. The LS mean difference compared to ECM at week 48 was -0.80 (95% CI -1.11 to -0.48), also below the threshold for the MCID.

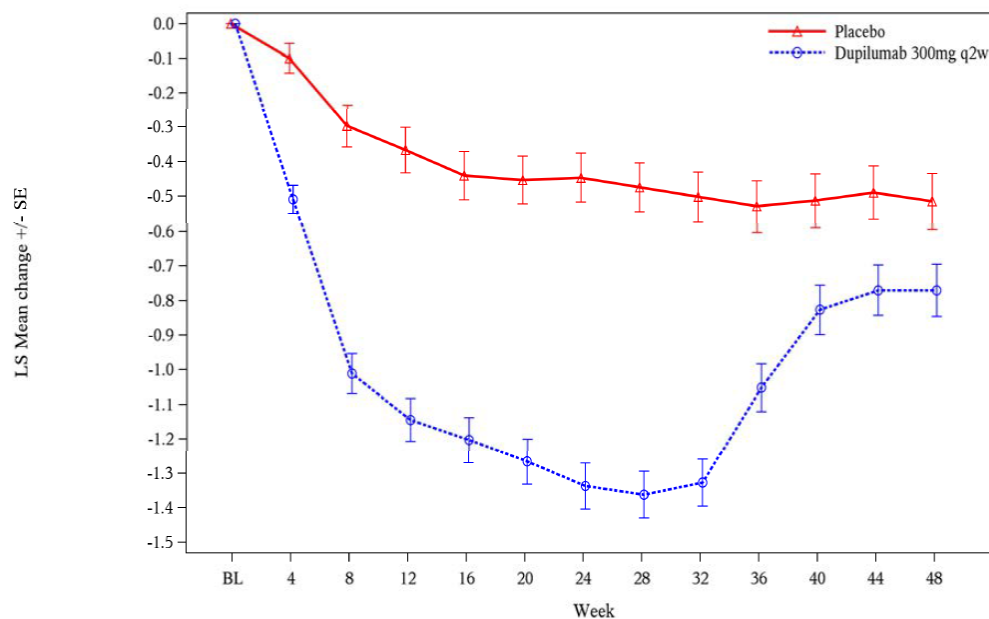
NC score was relatively stable in the ECM group throughout the post-treatment period. Scores were also relatively stable in the dupilumab group between weeks 24 and 32 before beginning to rise from week 36 onwards (Figure 11), reflecting increasing severity of symptoms. As for bilateral NPS, scores remained lower than baseline, but the LS mean difference (-0.77, SE 0.07), and the difference compared to ECM (-0.26 (95% CI -0.46 to -0.06), were both below the threshold to be considered clinically meaningful.

Figure 10. LS mean change from baseline in bilateral NPS up to Week 48 in SINUS-24 (weeks 24 to 48 represent the post-treatment period). Reproduced from Figure 11 of CS (Appendix N)



Abbreviations: LS mean, least squares mean; Q2W, once every two weeks; SE, standard error

Figure 11. LS mean change from baseline in NC score up to Week 48 in SINUS-24 (weeks 24 to 48 represent the post-treatment period). Reproduced from Figure 12 of CS (Appendix N)



Abbreviations: LS mean, least squares mean; Q2W, once every two weeks; SE, standard error

In response to clarification questions, the company provided the results from the post-treatment period for the other outcomes. SNOT-22 scores showed a similar pattern of decline to NC and NPS, although the LS mean difference compared to ECM was -9.30 (no 95% CI reported), which is greater than the validated MCID. This suggests there were some residual benefits of dupilumab on HRQoL once dupilumab treatment was stopped. Other secondary outcomes (LMK-CT, TSS, UPSIT and LoS) showed a similar decline to the co-primary endpoints, with no clinically meaningful benefits compared to ECM by week 48.

Result from the post-treatment phase indicate that, while there may be some residual benefits once dupilumab treatment is stopped, these decline over time. Although there may be some ongoing benefits for HRQoL, other outcomes indicate that patients reach a similar severity of disease to those on ECM within 6 months of the end of treatment. However, it should be acknowledged that the post-treatment outcomes reported are for the full ITT population and not the prior surgery subgroup (**Key issue 1** in section 1.1).

3.3.5 Subgroups

As for the main analysis, the EAG's critique of the subgroup analyses focuses on the results for the prior NP surgery subgroup. As discussed in Section 2.3.5, subgroup analysis was not performed for either the patients who are ineligible for surgery (who are not relevant to the base case population) or those who are ineligible for SCS. However, as outlined in Section 2.3.5, the company provided results for the comorbid asthma and comorbid NSAID-ERD subgroups as part of their response to clarification questions.

Results were similar between the comorbid asthma and comorbid NSAID-ERD subgroups, with neither group showing any major differences in response to treatment to the overall prior surgery group (Table 22 and Table 23). In both the asthma and NSAID-ERD subgroups, all outcomes demonstrated a clinically meaningful improvement with dupilumab, while for ECM, only SNOT-22 scores in the asthma subgroup met the MCID threshold. Change from baseline at 24 weeks was significantly greater with dupilumab than with ECM, with all outcomes apart from TSS meeting the company's MCID thresholds. It therefore appears that, while patients who have a comorbidity of asthma or NSAID-ERD may have more severe disease, their response to dupilumab treatment, and its relative benefits over ECM, are similar to the wider patient population who have had prior NP surgery.

As discussed in Section 2.3.5, no information was provided for the subgroup of patients who have asthma without NSAID-ERD (additional issue 2 in section 1.4). The benefits that this group of patients may experience in comparison to other patients therefore cannot be determined. However, as patients with NSAID-ERD are considered to have more serious disease than those who only have comorbid asthma, and results for this subgroup indicated similar benefits to the wider patient population, it may be assumed that the asthma subgroup would also show a similar response. This appears to be a reasonable assumption, as the EAG's clinical experts highlighted that both groups tend to be treated in a similar way in clinical practice.

Table 22. LS mean change from baseline for patients who had prior NP surgery in the comorbid asthma subgroup. Reproduced from Table 8 of the company's clarification response

LS mean change from baseline at Week 24	ECM	Dupilumab	LSM difference vs ECM (p-value)
Bilateral NPS	0.03	-2.05	-2.08 (<0.0001)
NC score	-0.34	-1.39	-1.05 (<0.0001)
UPSIT score	-0.76	10.33	11.09 (<0.0001)
SNOT-22 total score	-8.48	-30.90	-22.42 (<0.0001)
TSS	-0.78	-3.56	-2.78 (<0.0001)
Daily loss of smell score	-0.06	-1.12	-1.06 (<0.0001)
Abbreviations: ECM, established clinical management; LS mean, least squares mean; NC score, nasal congestion score; NPS, nasal polyp score; UPSIT, University of Pennsylvania Smell Identification Test; SNOT-22, Sino-Nasal Outcome Test-22; TSS, total symptom score			

Table 23. LS mean change from baseline for patients who had prior NP surgery in the comorbid NSAID-ERD subgroup. Reproduced from Table 6 of the company's clarification response

LS mean change from baseline at Week 24	ECM	Dupilumab	LSM difference vs ECM (p-value)
Bilateral NPS	-0.12	-2.10	-1.97 (<0.0001)
NC score	-0.42	-1.59	-1.18 (<0.0001)
UPSIT score	-0.28	9.97	10.25 (<0.0001)
SNOT-22 total score	-6.59	-31.17	-24.58 (<0.0001)
TSS	-0.98	-3.94	-2.96 (<0.0001)
Daily loss of smell score	-0.13	-1.11	-0.98 (<0.0001)
Abbreviations: ECM, established clinical management; LS mean, least squares mean; NC score, nasal congestion score; NPS, nasal polyp score; UPSIT, University of Pennsylvania Smell Identification Test; SNOT-22, Sino-Nasal Outcome Test-22; TSS, total symptom score			

Results were provided for patients with any comorbid type 2 medical history, including asthma or NSAID-ERD (Table 24). As with the asthma and NSAID-ERD subgroups, the results for each outcome were similar to the full patient population who had prior NP surgery, with each outcome apart from TSS demonstrating a clinically meaningful difference between dupilumab and ECM.

Table 24. LS mean change from baseline for patients who had any comorbid type 2 medical history, including asthma or NSAID-ERD.

LS mean change from baseline at Week 24	LSM difference vs ECM
Bilateral NPS	-2.05 (-2.38 to -1.71)
NC score	-1.05 (-1.21 to -0.89)
UPSIT score	10.79 (9.13 to 12.44)
SNOT-22 total score	-21.53 (-25.15 to -17.90)
TSS	-2.78 (-3.19 to -2.38)
Daily loss of smell score	-1.06 (-1.24 to -0.88)
Abbreviations: ECM, established clinical management; LSM, least squares mean; NC score, nasal congestion score; NPS, nasal polyp score; SNOT-22, Sino-Nasal Outcome Test-22; TSS, total symptom score; UPSIT, University of Pennsylvania Smell Identification Test	

3.4 Critique of the indirect comparison

The company highlighted how there are currently no targeted systemic treatments for patients with previously treated uncontrolled CRSwNP that are recommended by NICE. In addition, none of the comparators identified in the company's SLR are recommended for current practice in the NHS in England. As a result, the company did not perform any indirect treatment comparisons. The EAG is satisfied with this approach, and with the company's decision that the direct comparisons between dupilumab and ECM from the SINUS-24 and SINUS-52 trials are the most appropriate against which to assess the clinical effectiveness and safety of dupilumab for CRSwNP.

3.5 Conclusions of the clinical effectiveness section

The EAG considers that the evidence provided by the company is appropriate to address the decision problem, and any differences between the NICE final scope and the CS are justified (Section 2.3). The SLR was performed using appropriate methods and is likely to have identified the most relevant and current evidence (Section 3.1).

While the NICE final scope included all people with previously treated severe CRSwNP, the company chose to position dupilumab for patients who had prior NP surgery. This appears to be a reasonable decision, based on feedback from clinical experts for both the company and the EAG, who noted that surgery is an effective treatment option for some patients. However, the company's assessment of the clinical evidence was based on the ITT population, including both patients who had, and had not had, prior NP surgery. To align the evidence used for the EAG's clinical and economic evaluation, the company provided evidence for the prior NP surgery subgroup for all outcomes. This was the focus of the EAG's assessment, although it should be noted that there was limited difference between the results of the overall ITT population and those who had prior NP surgery.

Two trials (SINUS-24 and SINUS-52) provided direct comparisons between ECM with dupilumab and ECM alone. The EAG considers both trials to be at low risk of bias, and with the identical methods used for each trial, alongside similar baseline characteristics for the two trials, the use of a pooled analysis for all outcomes appears appropriate. None of the comparators identified in the company's SLR are currently recommended by NICE as treatment for CRSwNP and so no indirect treatment comparisons were performed. The EAG considers this to be a reasonable approach and therefore agrees with the company's decision to focus on the direct evidence from the pooled analysis of the SINUS-24 and SINUS-52 trials.

For the assessment of clinical effectiveness, only one outcome (SNOT-22) had a validated MCID, but the EAG's clinical experts considered that the MCIDs used for other outcomes appeared reasonable and reflective of clinical practice. Significant improvements were seen with dupilumab for both of the co-primary endpoints of bilateral NPS and NC score, resulting in greater improvements from baseline with dupilumab than with ECM alone (Section 3.3). SNOT-22, which is also considered an important outcome in clinical practice, demonstrated similar benefits with clinically meaningful improvements from baseline in comparison to ECM. Other secondary outcomes (LMK-CT, TSS, UPSIT score, LoS score) also demonstrated the benefits of dupilumab across the 24-week treatment period. When comparing change throughout the treatment period, outcomes with ECM either remained stable or showed an initial improvement during the first 8 weeks, before stabilising. In contrast, dupilumab resulted in gradual improvements in all outcomes throughout the 24-week period. These results indicate the ongoing, and increasing, benefits of dupilumab over ECM for both clinical and patient-reported outcomes in the first 24 weeks of treatment. While the pooled results were only available for the first 24 weeks of treatment, the SINUS-52 trial assessed response up to 52 weeks. Greater differences were seen between dupilumab and ECM at 52 than 24 weeks for bilateral NPS, NC score and SNOT-22 scores, indicating ongoing benefits of dupilumab throughout the first year of treatment.

One limitation which should be considered when interpreting the results of the SINUS-24 and SINUS-52 trials is the lack of long-term data. While dupilumab appears to have benefits over ECM over 52 weeks, the effects beyond this point are unclear. The AROMA trial indicates that the improvements seen in HRQoL may begin to decline between 12 and 24 months, but with no comparator arm in the study, it is unclear whether any benefits over ECM are maintained or also decline. It is also unclear whether this decline is evident for all outcomes, as only SNOT-22 scores were available from the

AROMA trial. As such, it is currently unclear how long the benefits of dupilumab may last beyond the 52-week period reported by the SINUS trials.

Patients who tend to have more severe symptoms of CRSwNP were included as subgroups in the CS (Section 3.3.5), including patients with comorbid asthma, comorbid NSAID-ERD, or any comorbid type-2 condition. Results were similar to those of the wider patient population who had prior NP surgery, with all subgroups demonstrating greater improvements with dupilumab than ECM. Most of these differences were considered clinically meaningful, demonstrating consistent benefits of dupilumab over ECM across subgroups.

Safety outcomes showed little difference between dupilumab and ECM (Section 3.3.3). Few serious TEAEs or TEAEs leading to treatment discontinuation were reported, and common TEAEs (those occurring in at least 5% of either treatment arm) were consistently lower for dupilumab. As such, there do not appear to be any major safety concerns associated with the use of dupilumab for people with CRSwNP.

Effectiveness and safety outcomes were also provided for the post-treatment period of the SINUS-24 trial (weeks 24-48). When treatment was stopped, bilateral NPS and NC remained relatively stable for the ECM group (Section 3.3.4), but gradually increased for the dupilumab group, reflecting increasing disease severity. By the end of the post-treatment period, outcomes remained better for the dupilumab than ECM group, but were not considered clinically meaningful, indicating that any benefits of dupilumab wane once treatment is stopped.

For patients who have CRSwNP, dupilumab appears to result in reduced disease severity and improvements in patient-reported outcomes in comparison to ECM over the first year of treatment. In addition to clinical benefits, the evidence suggests there are few safety concerns associated with the use of dupilumab in this population. However, it should be noted that while the results of the SINUS-24 and SINUS-52 trials demonstrate an effect of dupilumab up to 52 weeks after the start of treatment, a lack of long-term data means it is currently unclear how long the benefits are sustained beyond this point.

4 Cost effectiveness

Table 25 below presents the incremental cost-effectiveness results of the company's base case cost-effectiveness analysis. Results presented in this document are inclusive of a [REDACTED] % patient access scheme (PAS) discount for dupilumab, representing a price of [REDACTED] per pack.

Table 25. Company's base case results, post-clarification

Interventions	Total Costs (£)	Total LY*	Total QALYs	Δcosts (£)	ΔLYs	Δ QALYs	ICER (£/QALY)
Deterministic results							
ECM only	[REDACTED]	[REDACTED]	[REDACTED]	-	-	-	-
Dupilumab + ECM	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	£23,410
Probabilistic results							
ECM only	[REDACTED]	[REDACTED]	[REDACTED]				
Dupilumab + ECM	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	£23,793
*Undiscounted							
Abbreviations: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; LY, life year; NR, not reported; QALY, quality-adjusted life-year							

4.1 EAG comment on the company's review of cost effectiveness evidence

In June 2019, the company conducted a systematic literature review (SLRs) to identify existing evidence on cost-effectiveness, health-related quality of life (HRQoL), and resource use and costs for treatments in patients with mild, moderate, and severe: chronic rhinosinusitis with nasal polyps/polypoid. Updated searches were performed in September 2024. A summary of the External Assessment Group's (EAG's) critique of the methods implemented by the company to identify relevant evidence is presented in Table 26.

The company also performed grey literature searches and hand-searching to identify relevant evidence, such as conference abstracts and health technology appraisals (HTAs) published after 2022.

Table 26. EAG's critique of company's systematic literature review

Systematic review step	Section of CS in which methods are reported			EAG assessment of robustness of methods
	Cost effectiveness evidence	HRQoL evidence	Resource use and costs evidence	
Search strategy	Appendix G.1	Appendix G.1	Appendix G.1	Appropriate. The EAG notes that the SLR for CE HRQoL and resource use evidence appears to be done as one combined search.
Inclusion/ exclusion criteria	Appendix G.1	Appendix G.1	Appendix G.1	Appropriate
Screening	Appendix G.2	Appendix G.2	Appendix G.2	Appropriate
Data extraction	Appendix G.3	Appendix G.3	Appendix G.3	Appropriate
Quality assessment of included studies	Appendix G.4	Appendix H.4.3	Appendix I.4.3	The Drummond checklist was used to assess the quality of cost-effectiveness studies. Compliance with NICE reference case was done for HRQoL evidence. No assessment done for resource use and cost evidence.
Abbreviations: CE, cost-effectiveness; CS, company submission; EAG, External Assessment Group; HRQoL, health related quality of life; SLR, systematic literature review.				

In total (original search and September 2024 update), the SLRs identified 2,048 records (cost-effectiveness, HRQoL and resource use studies were all searched for). Following title/ abstract and full text screening, the company included 96 unique reports (six of which were not selected for data extraction); 19 economic evaluations, 55 reports of cost and resource use and 16 were HRQoL studies.

Of the 19 unique economic evaluations identified 10 were Markov/decision tree models, six were Markov/decision tree with microsimulation components and three took some other novel approach. Seven of the 19 papers used a 1-year cycle length. The company's model is based on those used for prior submissions related to dupilumab (atopic dermatitis, prurigo nodularis, asthma and COPD), though the structure appears to be in line with prior models for this disease.

Of the 16 HRQoL studies, only five reported EQ-5D with SF-6D being more commonly used. Notably, these five studies all had relatively high utility scores compared to those used in the company's model, this is further explored in Section 4.2.7. The paper used by the company, Crump, *et al.* 2017⁹, was excluded for being an “instrument design” study type (as opposed to a study explicitly trying to find HRQoL for health states) though the included paper Kumar *et al.* 2020¹⁰ used the Crump mapping algorithm to derive health states.

Of the 55 cost studies only four were based in England. Of these Benson *et al.* 2023¹¹ was used to help inform the cost of surgery in the company model and Wahid *et al.* 2020¹² was used in scenario analysis.

Overall, the EAG considers the company's SLR was thorough and comprehensive.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 27 summarises the EAG's assessment of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base-case analysis, with reference to the NICE final scope outlined in Section 2.2.

Table 27. NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Adheres to the NICE reference case.
Perspective on costs	NHS and PSS	Adheres to the NICE reference case.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Adheres to the NICE reference case.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Lifetime. Adheres to the NICE reference case.
Synthesis of evidence on health effects	Based on systematic review	Adheres to the NICE reference case.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	SNOT-22 data collected in the pooled SINUS-24 and SINUS-52 trials was mapped to EQ-5D-5L data, then cross-walked to EQ-5D-3L using the algorithm published

		by Hernández Alava <i>et al.</i> 2022, ¹³ as per the NICE health technology evaluation manual.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	SNOT-22 data and EQ-5D-5L used for mapping study was reported directly from patients.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Patients in SINUS-24 and SINUS-52 are generally representative of the UK patient population.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Adheres to the NICE reference case.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Adheres to the NICE reference case.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Adheres to the NICE reference case.
Abbreviations: EAG, External Assessment Group; EQ-5D-5L, EuroQol five dimension five level; NICE, National Institute of Health and Care Excellence; NHS, national health service; PSS, personal social services; QALY, quality adjusted life year; SNOT-22, Sino-Nasal Outcome Test-22; UK, United Kingdom		

4.2.2 Intervention and comparator

As noted in Section 2.3.2, the intervention evaluated in the economic model is dupilumab in combination with established clinical management (ECM). Dupilumab is given at a dose of 300mg subcutaneous injection every two weeks.

The comparator in the economic model is ECM only. As previously discussed, ECM consists of nasal irrigation saline solutions, intranasal corticosteroids (INCS), systemic corticosteroids (SCS), antibiotics and endoscopic sinonasal surgery (ESS). Although ESS is included in the economic modelling as an event for a specified proportion of patients (see Section 4.2.3 for further details), it is not included as a standalone comparator.

The company stated that the SINUS-24 and SINUS-52 trials used to inform the effectiveness data for dupilumab in this appraisal were not designed to demonstrate a difference in the usage of INCS. Therefore, costs for INCS were not included in the economic model as they were assumed to be equal. This approach was also taken for nasal irrigation solutions, although the company did not state this explicitly in the submission.

4.2.3 Modelling approach and model structure

The company produced a cohort-level short-term decision tree leading to a Markov state transition model, programmed in Microsoft Excel®, to assess the cost-effectiveness of dupilumab plus ECM for the treatment of uncontrolled chronic rhinosinusitis with nasal polyps (CRSwNP) following prior surgery. The analysis was carried out from an NHS and Personal Social Services (PSS) perspective. Costs and health effects are discounted at an annual rate of 3.5%, in line with the NICE Reference Case.¹⁴

The company's model structure was based on the published study by De Corsa *et al.* 2022,¹⁵ which was developed by the company to assess the effectiveness of dupilumab for people with uncontrolled CRSwNP from the Italian national health service perspective. Amendments were made to model inputs for the current submission to reflect the specific population of interest.

4.2.3.1 Short-term decision tree

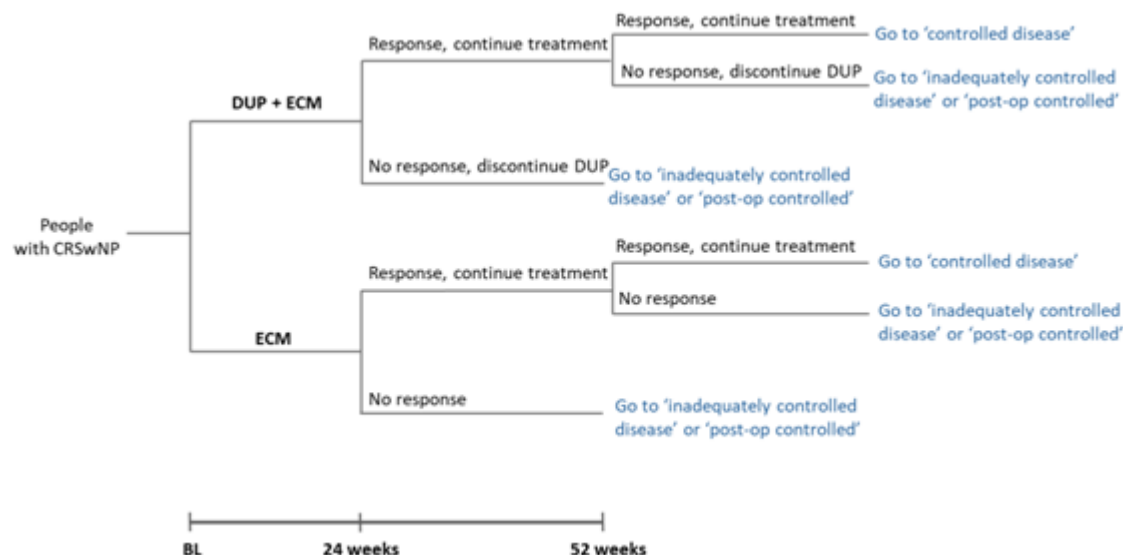
The short-term decision tree reflects the trial period of the longest available study (SINUS-52) of 52-weeks. Response to treatment was undertaken at both 24 and 52 weeks in the key clinical trials (SINUS-24 and SINUS-52), which is reflected in the decision tree. Patients receiving dupilumab who are classed as 'responders' during the first 24-weeks of the decision tree continue to receive dupilumab, whereas those who do not respond discontinue treatment and receive ECM only. Patients who continued to respond to dupilumab between 24 and 52 weeks continue on dupilumab treatment into the long-term Markov model, whereas those who are no longer classed as responders are assumed to discontinue treatment with dupilumab and receive ECM only, as shown in [Figure 12](#).

Based on pooled data from both the SINUS-24 and SINUS-52 trials, patients are assigned to one of three health states at the end of the decision tree, based on both the response to treatment during the trial period (either dupilumab + ECM or ECM alone) and surgery status.

A small proportion of patients in both treatment arms underwent ESS during the key clinical trial periods (see Section 4.2.4). Therefore, the equivalent proportion of patients in each treatment arm receive the costs of surgery during the decision tree period. These patients then enter the long-term Markov model in the 'post-op controlled' health state. Patients who did not meet the response criteria at week 52 and did not have surgery enter the Markov model in the 'inadequately controlled

disease health state'. Responders to treatment enter the Markov model in the 'controlled disease' health state.

Figure 12. Diagram of decision tree model structure used to represent the trial period, reproduced from Figure 17 of the CS



Abbreviations: BL, baseline; CRSwNP, chronic rhinosinusitis with nasal polyps; DUP, dupilumab; ECM, established clinical management.

4.2.3.2 Long-term Markov model

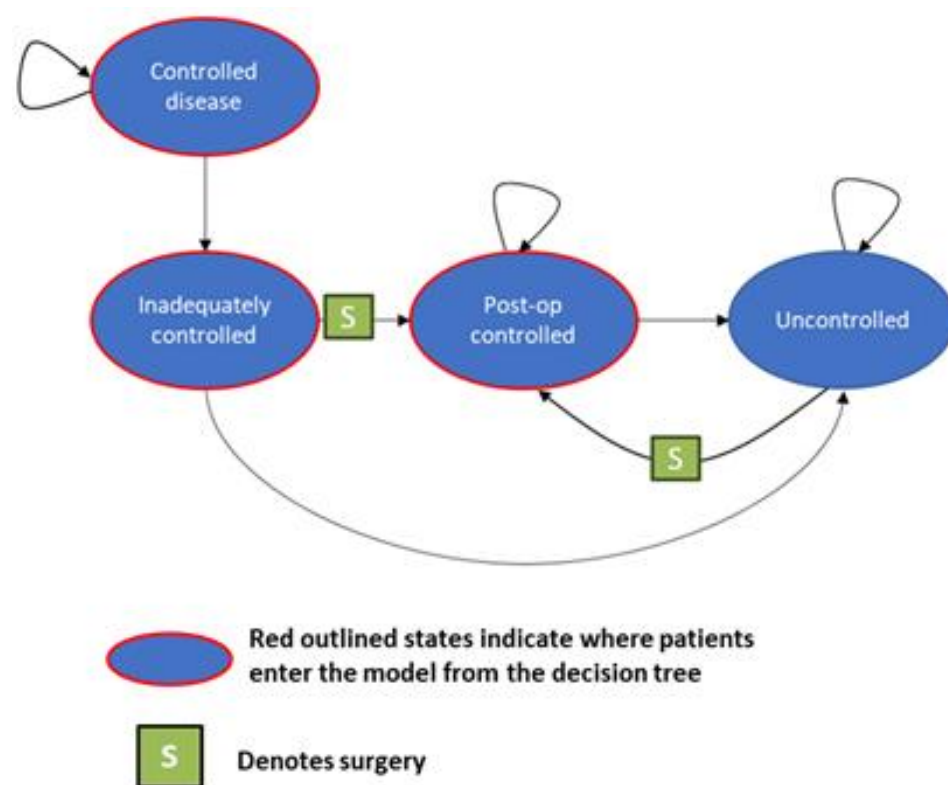
The Markov model uses a lifetime time horizon with an annual cycle length and a half-cycle correction is applied.

As noted above, patients enter the Markov state transition model in one of three health states: controlled disease, inadequately controlled disease or post-op controlled. The Markov model includes an additional health state for uncontrolled disease, which patients can either enter from the inadequately controlled disease health state, if ineligible for revision surgery, or from the post-op controlled state, once control via revision surgery is lost, shown in Figure 13. Patients who are ineligible for surgery remain in the uncontrolled disease state until death, whereas patients eligible for revision surgery may undergo a further ESS before returning to uncontrolled once post-op control is lost. The data used to inform the transition probabilities in each cycle are described in further detail in Section 4.2.5.

The inadequately controlled disease health state is a temporary tunnel state which patients can only remain in for one model cycle (one year). This temporary state is included to capture any decline in health-related quality of life (HRQoL) prior to patients becoming uncontrolled.

Patients may transition to death from any health state based on general population mortality.

Figure 13. Diagram of Markov model structure used to estimate the post-trial period, reproduced from Figure 18 of CS



4.2.3.3 EAG critique

Overall, the EAG is mainly satisfied that the model structure captures the main features of CRSwNP. Clinical experts to the EAG agreed with the model structure and confirmed that currently surgery is the only option available that would result in a patient moving out of the uncontrolled health state. They noted that although the surgery provides short-term improvement of symptoms, the main aim is to allow standard therapies such as INCS to work effectively, and therefore surgery alone does not provide full control of the disease.

The EAG notes that a one-year cycle length is not in line with the regularity of dupilumab administration and may not capture the timings of key clinical events. During clarification, the EAG

asked the company to justify the annual cycle length or adapt to a shorter cycle length. The company stated that the model is in line with the regularity of response assessments that will be undertaken in clinical practice and the initial decision tree captures response at both 24 and 52 weeks. In addition, the company noted that the one-year cycle length is consistent with clinical changes, such as discontinuation and disease progression. While the EAG considers that a shorter cycle length may have added to the accuracy of the economic model, it does not anticipate that this would have a substantial impact on any results.

4.2.4 *Treatment effectiveness*

The treatment effectiveness of dupilumab was informed by response rates observed in both the SINUS-24 and SINUS-52 trials. In the model base-case, the company measured response using a combination of the objective nasal polyp score (NPS) measure **and** a patient reported outcome measure (PROM) using SNOT-22, using the minimum clinically important difference (MCID) discussed in Section 3.3 . Therefore, response was defined as:

- NPS change from baseline of ≥ 1 ; and
- SNOT-22 change from baseline of ≥ 8.9 points.

The company stated that this criteria for response was tested with clinicians during an advisory board meeting who stated that the combined response criteria is in line with clinical practice.

The proportion of responders at Week 24 was based on pooled data from the SINUS-24 and SINUS-52 trials, resulting in ■■■% of responders in the ECM only (placebo) arm compared to ■■■% in the dupilumab arm, shown in [Table 28](#). This was used in the decision tree model to inform responders and non-responders at Week 24 in both treatment arms. Data was only available from SINUS-52 on patients who responded at Week 24 and continued to meet the response criteria at Week 52; this was used to inform the proportion of patients classed as responders at the end of the decision tree and beginning of the long-term Markov model. In the ECM only arm, ■■■% of patients showed a maintained response at Week 52 compared to ■■■% in the dupilumab arm.

In the company's original submission, the 28-week trial data on maintained response rates (week 24 to week 52) was converted to an annual probability to inform the long term probability of remaining in the controlled health state for each treatment arm (■■■% for the dupilumab + ECM arm versus ■■■% for the ECM only), and subsequently the annual probability of transitioning to the inadequately controlled health state (■■■% and ■■■%, respectively). However, during clarification,

the company undertook an analysis of the AROMA observational trial using response data based on SNOT-22 only, due to NPS not being available (see response to CQ B11). The company's updated economic model used these data to inform dupilumab treatment effectiveness beyond one-year, i.e. transition probability of moving from controlled to inadequately controlled). The updated analysis uses a probability of █% for years 1-2 and █% for all subsequent years. This is discussed further in Section 4.2.4.1.

The company apply the probability of remaining in the controlled health state for the duration of the lifetime Markov model, therefore, implying no decline in the treatment effect of dupilumab over time.

In line with how dupilumab will be prescribed in clinical practice in accordance with the SmPC, only data for patients in SINUS-52 on a once every two weeks (Q2W) dosing schedule were included in the base-case analysis.

Table 28. Number of responders based on combined criteria of improvement in SNOT-22 and NPS used to inform company base case

	Placebo (ECM only)	Dupilumab + ECM
Week 24	N=187	N=272
Responders	█	█
Non-responders	█	█
Week 24 to Week 52*	N=5	N=46
Responders	█	█
Non-responders	█	█
* Includes only patients from SINUS-52 who met the response criteria at Week 24 and had data available to assess response at Week 52		
Abbreviations: ECM, established clinical management		

Discontinuations for all reasons (i.e. loss of response, adverse events, patient choice) are captured in the proportion of patients leaving the controlled health state each annual cycle (█% in year 1-2 and █% for subsequent years), and therefore, no separate discontinuation rate is applied in the model. As a scenario analysis, the company used the annual discontinuation rate calculated from the SINUS-24/52 responder analysis of █% that was originally used in the company's base-case prior to the clarification stage.

Due to the short-term trial data available for dupilumab in CRSwNP patients (up to 52 weeks only), all further transition probabilities used in the economic model are informed by published literature and assumed not to differ between treatment arms. These are explained in further detail in Section 4.2.5.

In addition to improvements in NPS and SNOT-22, the company included additional benefits of dupilumab in the economic model through both a reduction in ECM drug usage (SCS and antibiotics) and improvement in asthma control for patients with comorbid asthma. Both of these aspects impact on costs (see Section 4.2.8) and asthma improvements are also assumed to influence mortality outcomes in the model (see Section 4.2.6 for further detail). During clarification, the company stated that due to differences in antibiotic use not being statistically significantly different between the two treatment arms these were removed from the economic model, which had a minimal impact on the ICER. The company clarified that the ITT population was used to inform differences in SCS use between treatment arms and responder status instead of the base case population due to “...the higher sample size and to improve statistical significance, while considering the minimal impact of ECM medication costs on the results”. While the EAG considers the use of a larger sample to ‘improve statistical significance’ to be inappropriate, the impact on the ICER is minimal.

The differences in SCS between the two treatment arms are applied in the short-term decision tree only (see Section 4.2.8.2 for further detail)

4.2.4.1 EAG critique

As discussed in Section 2.3, the company has positioned dupilumab within the population of patients who have had at least one prior surgery. As this differs to the clinical trial ITT population, it reduced the number of patients available for the base-case analysis. This, in addition to the response criteria requiring patients to meet the MCID in both SNOT-22 and NPS resulted in very small patient numbers available for those who responded at both Week 24 and Week 52. This is particularly evident in the ECM only arm in which there were only █ patients available, █ of which were classed as responders. The EAG acknowledges that the small patient numbers are a limitation of the data available and that there is large uncertainty associated with this parameter. During clarification, the EAG asked for further detail on the small patient numbers and asked the company to explore the

impacts of this uncertainty in the model further. The company noted that all patients who required either a course of rescue therapy or surgery during the trial period were also classed as non-responders. This, in addition to the dual response criteria needing to be met at both 24 and 52 weeks for the responder analysis resulted in low patient numbers available.

The company's base case analysis response criteria was chosen based on discussion with clinical experts who stated this would be used in clinical practice. While clinical experts to the EAG agreed with the response criteria used in the model, one noted that they would likely only use SNOT-22 response in clinical practice; i.e. if a patient was showing improvement in SNOT-22 outcomes and stated they felt better but had not met the >1 point change from baseline in NPS, they would not take them off treatment. The EAG notes that in the company clinical expert consultation, one expert also stated that symptom scores such as SNOT-22 are more important due to NPS (and Lund-Mackay) scores being highly variable and unreliable to assess patient outcomes. They also noted that NPS can be less useful as a patient may still have multiple polyps but are more concerned about their loss of sense of smell.

Therefore, the EAG requested an analysis in the model using only SNOT-22 outcome data to determine patient responder status. In addition, as the responder criteria used in the economic model is based on a *post-hoc* analysis of the trial data that was not pre-specified, the EAG also requested an analysis in the model using the primary outcome of the clinical trials. The EAG notes that using the SNOT-22 response data improves the small patient numbers available, with the number of patients with response data available in the ECM only arm increasing from ■ patients in the base-case analysis to ■ and from ■ in the dupilumab arm to ■, shown below in [Table 29](#).

While the EAG considers the combined response criteria used in the company's base case to be acceptable, it is noted that there is uncertainty associated if this is not what would be used in clinical practice and guidance may need to state that this is the criteria to be applied in order for any estimates of cost-effectiveness to accurately reflect the real world (**Key issue 2** in Section 1.1). The EAG notes that a similar situation occurred with TA534 for atopic dermatitis and the subsequent recommendation specified the combined outcome required for determining an adequate response.¹⁶ As the SNOT-22 only data increases the sample size available for the responder analysis and based on expert opinion from both the EAG's clinical experts and the company's, the EAG consider responder analysis based on SNOT-22 only to be a plausible scenario analysis (see Section 6). The EAG note that using SNOT-22 increased the company's ICER by ≈£4,700.

Table 29. Response data for patients who responded at both Week 24 and Week 52, using alternative responder criteria

	SNOT-22 total score and NPS (base-case)		SNOT-22 total score only		NPS only	
	Placebo (ECM only)	Dupilumab + ECM	Placebo (ECM only)	Dupilumab + ECM	Placebo (ECM only)	Dupilumab + ECM
Week 24						
	N=187	N=272	N=187	N=272	N=187	N=272
Responders	██████	██████	██████	██████	██████	██████
Non-responders	██████	██████	██████	██████	██████	██████
Week 24 to Week 52						
	N=5	N=46	N= 35	N=60	N=7	N=54
Responders	██████	██████	██████	██████	██████	██████
Non-responders	██████	██████	██████	██████	██████	██████
Abbreviations: ECM, established clinical management; NPS, nasal polyp score; SNOT-22, Sino-Nasal Outcome Test-22						

As noted in Section 4.2.4, during clarification, the company updated the long-term effectiveness of dupilumab (beyond one year) to be based on an analysis of the AROMA data. The EAG has a number of issues with this being included in the base case, detailed below:

- No formal matching of patients was undertaken, such as propensity score matching, to account for differences in the patient populations between the SINUS-24/52 RCTs and the AROMA observational study.
- The response analysis of AROMA was based on SNOT-22 only, due to NPS being unavailable. If using responder data based on SNOT-22 to inform dupilumab effectiveness beyond the trial period, the EAG consider it inappropriate to use different criteria to assess response during the trial period in the base case analysis.
- The company used data from the ITT population in the analysis from the SINUS trials as opposed to the prior surgery population. However, it is noted that the differences are minimal.
- It is unclear from the company's presented analysis if patients requiring rescue treatment and/or surgery were also classed as non-responders.

- The ECM only arm is still informed by the SINUS trial data, i.e. the [REDACTED] patients classed as non-responders in the clinical trials. The EAG considers it to be inconsistent to use the two alternative approaches for the different treatment arms.

While the EAG considers there to be uncertainty with the company's original base case approach, as previously stated, it does not consider using the analysis the company has undertaken on the AROMA data to reduce uncertainty and is more appropriate to be considered as a scenario analysis. The EAG notes that using the AROMA data analysis to inform the probability of moving to inadequately controlled in the dupilumab arm reduced the company's ICER by £619.

As previously noted, the company assumes no decline in the treatment effect of dupilumab over time. A clinical expert to the EAG considered that while they were unable to state how much effectiveness may decline in the long-term, it was likely that some decline in response would occur based on their experience with other biologics. As the longest randomised clinical trial (RCT) was only conducted for 52-weeks (SINUS-52), no RCT data are available to inform the long-term effectiveness of dupilumab for CRSwNP (**Key issue 3** in Section 1). The EAG considers this to introduce uncertainty in the results of the economic model. In response to clarification (see response to B12), in addition to the analysis of the AROMA dataset mentioned above, the company also provided evidence of the sustained benefits of dupilumab observed in other disease areas (asthma and atopic dermatitis) and of dupilumab and other biologics in CRSwNP. The EAG notes that this is an uncertain feature of the economic model and the EAG does not consider evidence of a sustained effect in other therapy areas to be robust evidence for a sustained effect in CRSwNP. However, the EAG conducted an exploratory scenario of increasing the proportion of patients discontinuing dupilumab for any reason from year 5 onwards in the model to 15.6% ([REDACTED] % derived from the SINUS trials), to test the sensitivity of the results to a higher discontinuation rate due to lack of efficacy; this increased the company's ICER by less than £1000.

In line with the primary outcome analysis of the clinical trials, in the company's base case analysis, patients who required a course of rescue therapy were classed as non-responders. A clinical expert to the company stated that when considering treatment response, the main criteria should be patients not requiring a course of rescue treatment in addition to symptom improvement. However, a second expert stated that they would not discontinue patients on dupilumab if one course of oral corticosteroids (OCS) was required during treatment. A clinical expert to the EAG suggested that

time from starting on dupilumab and then requiring a course of SCS would be a key factor to consider. For example, they would not consider a patient a non-responder if they only required one course of SCS in the first three months of treatment or two courses in the first six months; however, more courses of SCS in either time or frequency and would make them a non-responder. The EAG notes that if patients would not be considered non-responders in clinical practice after requiring one course of rescue therapy then the model may not be an accurate representation. Although classing patients who required SCS in the dupilumab arm will lower the proportion of patients in the model classed as non-responders, as more patients on ECM only required rescue therapy, this will have a greater impact on the ECM only arm. The EAG is unable to comment on the impact on the ICER that this will have as the data are unavailable for the EAG to run the analysis (additional issue 3 in Section 1.4).

4.2.5 Transition probabilities

Only transitions from the controlled health state are dictated by the clinical trial data and differ between treatment arms, as described above. All remaining transitions are informed by published literature, detailed below.

Inadequately controlled health state

As previously noted, the inadequately controlled health state is a temporary tunnel state that patients may only occupy for one annual cycle. Following this, patients may either enter the post-op controlled state or the uncontrolled health state.

Based on pooled SINUS-24 and SINUS-52 data, the company stated that 23.7% of patients were ineligible for revision surgery. Therefore, these patients can only transition to the uncontrolled health state and the annual transition probability 100%.

For patients eligible for surgery (76.3%), the probability of moving to the post-op controlled health state each year is 15.1%. In the CS, this figure is said to be sourced from Benson *et al.* 2023,¹¹ a retrospective cohort study of patients with CRSwNP in England which assessed the rate of surgery during a follow up period. This study used the UK Clinical Practice Research Datalink Aurum database with Hospital Episodes Statistics (HES) linkage for the period of 2007–2019. The EAG was unable to replicate the 15.1% from the Benson *et al.* 2023 study.¹¹ During clarification, the company provided further detail of the calculations undertaken to produce the 15.1%, stating that this was derived by dividing the number of surgeries by year by the total eligible population, after accounting for the

average wait time in the UK (see response to B7b for further details). The number of surgeries and eligible patients for surgery used data from patients who had two or more surgeries during follow up and the average time between second and third surgery.

All patients who are eligible for surgery, but who do not transition to the post-op controlled state, instead transition to the uncontrolled health state ($100\% - 15.1\% = 84.9\%$).

Post-op controlled health state

As noted in Section 4.2.3.1, a proportion of patients in each treatment arm of the pooled SINUS-24 and SINUS-52 trials underwent surgery, which is reflected in the decision tree and dictates the proportion of patients occupying the post-op controlled health state at the beginning of the Markov model. By Week 24, 1.2% of patients in the dupilumab arm and 5.5% in the ECM only arm had surgery. Between Week 24 and 52, 0% had surgery in the dupilumab arm compared to 4.7% in the ECM only arm.

The probability of losing disease control following revision surgery and therefore moving to the uncontrolled health state is also informed by Benson *et al.* 2023.¹¹ The company stated that this was based on data provided on the mean time to third surgery for patients who have already had two surgeries during the study follow-up period. It was noted in the CS that data were adjusted to account for average wait times of two years in England following discussions with clinical experts during an advisory board. This was to account for the fact that the data from Benson *et al.* only provides average time from second surgery to third (875 days/2.4 years) and this does not account for the timing of loss of control, i.e. moving from post-op controlled to uncontrolled. Experts consulted by the company stated that they expect around 40% of patients to lose control quickly. The company stated that this adjustment, therefore, accounts for patients losing control following surgery and remaining on the surgical waitlist. Following this adjustment, it resulted in an annual probability of 42.8% moving to the uncontrolled state and the corresponding 57.2% remaining in the post-op controlled health state. The 42.8% was derived based on the following calculation:

Annual probability = (proportion of patients having ≥ 3 surgeries/ proportion of patients having ≥ 2 surgeries) $\div$ (average time from second to third surgery – average surgery wait time)

Uncontrolled health state

The probability of having revision surgery in each cycle from the uncontrolled health state, for those eligible, is equal to that in the inadequately controlled health state (15.1%). Therefore, the probability of remaining in the uncontrolled health state is 84.9% for those eligible for surgery and 100% for those not eligible for surgery.

A summary of all transition probabilities for each treatment arm in each cycle is shown in [Table 30](#), split between those eligible and not eligible for revision surgery.

Table 30. Annual transition probabilities applied in the company's base-case analysis, split by patient's surgery eligibility

Dupilumab + ECM						ECM only			
Patients eligible for surgery (76.4%)									
	To	Controlled	Inadequately controlled	Post-op controlled	Uncontrolled	Controlled	Inadequately controlled	Post-op controlled	Uncontrolled
From	Controlled	■	■	0.00	0.00	■	■	0.00	0.00
	Inadequately controlled	0.00	0.00	0.15	0.85	0.00	0.00	0.15	0.85
	Post-op controlled	0.00	0.00	0.57	0.43	0.00	0.00	0.57	0.43
	Uncontrolled	0.00	0.00	0.15	0.85	0.00	0.00	0.15	0.85
Patients ineligible for surgery (23.6%)									
From	Controlled	■	■	0.00	0.00	■	■	0.00	0.00
	Inadequately controlled	0.00	0.00	0.00	1.00	0.00	0.00	0.00	1.00
	Post-op controlled	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Uncontrolled	0.00	0.00	0.00	1.00	0.00	0.00	0.00	1.00
*In years 1 to 2 this is equal to ■ and ■ for all subsequent years. Therefore, the probability of remaining in the controlled health state in years 1-2 is ■									
Abbreviations: ECM, established clinical management; post-op, post-operation									

4.2.5.1 EAG critique

Clinical experts to the EAG stated that they would not expect a high proportion of patients to be ineligible for revision surgery as it rarely occurs in their clinical practice, with an expected proportion of less than 10%. This is considerably lower than the 23.6% of patients ineligible in the company's base case economic model based on the SINUS-24 and SINUS-52 trial data. The EAG also notes that a clinical expert consulted by the company, considered that while some patients may not be fit enough for surgery, it would not be as many as the 23% suggested by the company and estimated it to be lower than 10%. During clarification, the EAG asked for further details of the criteria used to determine eligibility for surgery; it was stated that this was based solely on expert opinion during baseline screening visits. The company noted the 23.7% is based on those with prior surgery and proposed an alternative lower value of 15.1%, which is based on the ITT population. In addition, the EAG requested that the company included a scenario analysis using an alternative value based on their experts' feedback. The company included a rate of 10% in the economic model. This was then included in the company's updated base-case analysis. Based on feedback from the company's clinical experts, the EAG consider this lower value to be more reflective of UK clinical practice. The EAG notes that changing this parameter has a minor impact on the ICER.

The company used the Benson *et al.* 2023¹¹ study to derive the transitions from both the inadequately controlled and uncontrolled health state to post-op surgery (15.1% applied in both health states) and from the post-op controlled to uncontrolled (42.8%). The study provides data on the average time from second to third surgery during follow-up. While the EAG agrees that this study is an appropriate data source that is applicable for the population in the appraisal, there are a number of uncertainties in the annual transition probabilities derived (**Key issue 4** in Section 1.1).

The Benson *et al.* study, as with other studies reviewed by the EAG, provides the average time from revision surgery to subsequent surgery for nasal polyps. This therefore represents the 'loop' from post-op controlled to uncontrolled and back to post-op controlled. However, due to the model structure, separate transitions are required to represent the proportion of patients who lose control in an annual cycle following revision surgery and then the proportion of patients who are classed as uncontrolled who have revision surgery each year. In order to account for these transitions required, the company used the average time patients in the UK spend on the surgery wait list (two years), informed by clinical experts, to adjust the average time from second to third surgery to represent time to patients losing control following surgery and remaining on a waiting list. The EAG notes that

there is uncertainty in adjusting based on waiting times, as this incorporates issues with service provision, which can vary significantly across different regions in England and therefore the resulting annual probability of 42.8% is uncertain. The EAG notes, however, that in a submission received from SINUS UK as part of this submission, of 51 patients surveyed with CRSwNP, 60% of patients indicated that their symptoms returned in 12 months or less following surgery for nasal polyps, highlighting the short time to loss of control as noted by the company's clinical experts. A clinical expert to the EAG also noted that it is difficult to say how long a patient remains temporarily controlled post-surgery, particularly as this will be influenced by the type of surgery undertaken and surgeon expertise.

In addition, the EAG considers the appropriateness of the methods used by the company to derive the 15.1% revision rate to be unclear but notes the company also applied the same adjustment of two years to these calculations. As a result, the EAG considers the annual transition probability to be uncertain. The EAG also noticed an error in the company's calculation provided at clarification in which it is stated that the number of surgeries per year is 52, whereas based on the company's calculations this should be 50.93. The EAG corrected this (see Section **Error! Reference source not found.**) which resulted in an annual probability of 14.8% compared to the company's 15.1%.

The EAG notes that during the company's consultation with clinical experts, they presented an annual rate of revision surgery of 1.9%. During clarification, the company clarified that this rate was based on an earlier draft of the model and based on French hospital discharge data and so not relevant to the current base-case model. However, this was provided as a scenario to show the impact of using this lower estimate. It had a minimal impact on the ICER, highlighting that while the EAG considers the rates used in the base case to be uncertain, transitions to the post-surgery controlled state are not a key driver of the economic model. While the EAG consider that the annual probability of revision surgery may be lower than that used in the company base case, as this will have a greater impact on the ECM only arm, the higher probability used by the company could be considered a conservative estimate and notes that the surgery rate is not a key driver of the ICER.

While the EAG was unable to source an alternative value to inform the annual probability of moving from the post-op controlled to uncontrolled to explore the impact of any uncertainty on the ICER, a scenario analysis has been conducted by the EAG in which the transition probabilities used the same approach as the company (described in CQ B7b) but the adjustments made to account for surgery waiting time in the UK is changed from two years to one year (i.e. one model cycle). This results in an

annual transition probability from the post-op controlled to uncontrolled of 12.1%. The EAG notes that the same adjustment is not made to the uncontrolled to post-op controlled probability as the EAG consider this to result in much higher probabilities than the expected (41.3%) and, as previously noted, the value used by the company for the rate of revision could be considered a conservative option. Therefore, while the EAG considers these probabilities to also be uncertain, this scenario is included to show the impact of a lower probability in loss of control following surgery on the company's ICER, which increased it by ≈£2,000.

4.2.6 Mortality

The economic model uses UK national life tables from 2021–2023¹⁷ to represent general population mortality associated with age and no additional mortality risk specifically associated with CRSwNP is applied. However, the CS states that due to the increased risk of mortality with asthma, a relative risk (RR) for increased mortality is applied to all patients with comorbid asthma. The RR of 1.36 was sourced from a meta-analysis that aimed to evaluate the association of asthma on cardiovascular disease and all-cause mortality.

The EAG notes that the meta-analysis used to inform the relative risk for increased mortality in the company's original submission for asthma patients was based on four studies, none of which were UK based and none were published recently, which the EAG considers may affect the applicability of the study to current UK practice. During clarification the EAG asked the company if any more relevant studies had been searched for. In response to clarification, the company updated this based on a targeted literature review. This identified a study by Zhang *et al.* 2022, which is a meta-analysis of 18 studies evaluating the association between asthma and all-cause mortality and produced a similar RR of 1.38.

In the company submission, it is stated that there is an increased mortality risk with asthma; the economic model applies the increased risk to all patients with comorbid asthma and not just patients with severe asthma. During clarification, the company stated that the mention of severe asthma in the CS was a typing error and, based on the literature source used, the company considers that this should be applied to all comorbid asthma patients. The company also updated the proportion of patients with comorbid asthma from 59.1% to 66.2%, based on the updated analysis.

Due to the inclusion of increased mortality for asthma patients and the company applying separate rates of uncontrolled asthma for each treatment arm in the model, based on rates observed in the

pooled SINUS-24 and -52, this results in a difference in mortality between the two treatment arms and therefore in life years (LYs).

4.2.6.1 EAG critique

The EAG notes that dupilumab already has a positive NICE recommendation for treating severe asthma with type 2 inflammation, therefore patients with severe asthma and CRSwNP may already have access to dupilumab. In the published final guidance for TA751, it states, “... It [the committee] also heard that dupilumab is effective in people with comorbidities (such as nasal polyps and atopic dermatitis). It concluded that these additional benefits of dupilumab had not been adequately captured in the QALY calculation and took them into consideration in its decision making.”¹⁸

Therefore, the EAG considers that the crossover benefits of dupilumab for severe asthma and CRSwNP patients has already been accounted for in the decision making ICER threshold of the previous appraisal, and including them again may result in double counting of the benefit. In addition, the proportion of patients on ECM only with uncontrolled asthma in the clinical trials may be higher than in clinical practice as patients may be able to access alternative biologics approved by NICE for use in asthma. As a result, the EAG does not consider it appropriate to include the increased risk of mortality due to asthma in the base-case analysis (additional issue 4 in Section 1.4).

The company's use of 2021–2023 life tables for age-matched general population mortality was identified as a minor issue by the EAG. Guidance in the NICE decision support unit (DSU) technical support document (TSD) 23 recommends using the ONS life tables from 2017–2019 due to the uncertainty about the long-term impact of COVID-19 on the latest estimates.¹⁹ As such, the EAG ran a scenario using the ONS life tables for England from 2017–2019 (see Section 6.2). The EAG's scenario had minimal impact on the ICER but it is included in the EAG base case for adherence to the guidance in NICE DSU TSD 23.¹⁹

4.2.7 Health-related quality of life

4.2.7.1 Health-state utility

Health state utility values used in the company's economic model were informed by the SNOT-22 scores from SINUS-24 and SINUS-52 mapped to EQ-5D-3L. The scores were mapped using an algorithm published by Crump *et al.* 2017.⁹ The health state utility values used in the model are

shown in [Table 31](#) along with their source in the pooled analysis of SINUS 24 and SINUS 52 SNOT-22 data.

Table 31. Base case health state utility (Pooled analysis of SINUS 24 and SINUS 52 SNOT-22 scores mapped using Crump algorithm)

Health state	Dupilumab + ECM	ECM only	Source
Decision tree			
Week 0 - 12	0.524	0.524	Baseline utility weight from the studies.
Week 13-24	0.727	0.596	Utility weight at Week 24 by treatment arm.
Week 25 to 52 responders	0.793	0.734	Average of responder utility weight at Week 24 and Week 52 by treatment arm.
Week 25 to 52 non responders	0.673	0.587	Average of non-responder utility weight at Week 24 and Week 52
Markov model			
Controlled disease	0.809	0.809	All responder utility weight at Week 52
Inadequately controlled disease	0.594	0.594	Utility weight at Week 52 from patients on ECM, who did not respond at Week 24 and Week 52
Uncontrolled disease	0.524	0.524	Assumed to be the baseline utility.
Abbreviations: ECM, established clinical management; SNOT-22, Sino-Nasal Outcome Test-22			

There is a treatment-specific benefit for both responders and non-responders during the trial period (decision tree section) for patients receiving dupilumab. After this period (Markov section), there is assumed to be no difference in utility, within health states, between dupilumab and ECM pre-op patients (this is not the case for post-op patients, see Section 4.2.7.2). The inadequately controlled disease utility is intended to reflect the benefit of receiving optimised care, even if unresponsive to that care, as compared to uncontrolled disease, which reflects patients who lose any disease control.

The Crump *et al.* 2017⁹ paper used for mapping presents three model options based on a cross-sectional Canadian population of chronic rhinosinusitis patients, awaiting bilateral endoscopic sinus surgery. Model 1 in the paper is a simple regression against the SNOT-22 global score, model 2 regresses against each component of SNOT-22 and model 3 is the same as model 2 but it also includes age and percentage female. Model 1 was selected as the company base case as models 2

and 3 appeared to be over-specified leading to implausible coefficients that meant loss of sense of taste/smell or waking up tired had a positive impact on a patient's quality of life. In addition, model 1 appeared to have higher Spearman correlation coefficient levels with trial-observed EQ-5D. The EAG agrees with the company that of the models presented in the Crump paper, model 1 is the most appropriate.

The SINUS trials directly recorded EQ-5D-5L data. The Crump model was selected as the base case, over the trial utility data, because responders at week 52 showed a score higher than the UK general population. The company also stated that a baseline EQ-5D of 0.782 is high considering the significant impact of this disease on patients. These values are suggested to be higher than expected, since EQ-5D does not explicitly account for items related to anosmia and sleep. The company further goes on to show the Spearman's correlation coefficient between key disease-specific measures and EQ-5D is weak.

A linear mixed model regression based on directly observed EQ-5D utility values collected up to week 52 in the SINUS trials was provided as scenario analysis. Hernandez-Alava²⁰ crosswalk was used in the creation of the dependent variable (converting EQ-5D-5L to EQ-5D-3L). Four models were tested, all models included age, sex, baseline EQ-5D score, and SNOT-22 total score, while models 2–4 also included Nasal Polyps Score (NPS), and models 3 and 4 further tested interaction effects between SNOT-22 and NPS. Model 4 additionally included treatment as a coefficient. Model 1 was selected as the best-fit model because it had the lowest AIC (-3131.9) and BIC (-3122.8) values, indicating superior statistical performance. This model was preferred due to its simpler structure and better overall fit, focusing on the primary predictors of utility — SNOT-22 score, age, sex, and baseline utility — while excluding variables that did not significantly improve model accuracy. Notably, model 1 was selected despite it excluding NPS due to NPS not being a statistically significant factor, despite this being used to determine the definition of response.

During clarification, the EAG requested that the company reran the four regression analyses using change from baseline in SNOT-22 score rather than total, in order to limit issues with multicollinearity between SNOT-22 and baseline EQ-5D. These were provided and incorporated into the company's updated economic model, with models 5 to 8 being equivalent of 1 to 4, respectively, with the exception of SNOT-22, NPS and their interaction measured by change from baseline. The utility values by health state using the best fitting model (model 5) are shown in Table 32. Health state utilities derived from observed EQ-5D regression used in scenario analysis

Table 32. Health state utilities derived from observed EQ-5D regression used in scenario analysis

Health state	Dupilumab + ECM	ECM only	Source
Decision tree			
Week 0 - 12	0.782	0.782	Baseline utility weight from the studies, derived using regression.
Week 13-24	0.826	0.757	Utility weight at Week 24 by treatment arm, derived using regression.
Week 25 to 52 responders	0.858	0.828	Average of responder utility weight at Week 24 and Week 52 by treatment arm.
Week 25 to 52 non-responders	0.797	0.748	Average of non-responder utility weight at Week 24 and Week 52
Markov model			
Controlled disease	0.867	0.867	All responder utility weight at Week 52
Inadequately controlled disease	0.745	0.745	Utility weight at Week 52 from patients on ECM, who did not respond at Week 24 and Week 52
Uncontrolled disease	0.738	0.738	Assumed to be the baseline utility.
Abbreviations: DUP, dupilumab; ECM, established clinical management; SNOT-22, Sino-Nasal Outcome Test-22			

The company also included a scenario using the directly observed change from baseline (CFB) EQ-5D. This takes observed EQ-5D-5L in SINUS-24/52, converted into EQ-5D-3L using a crosswalk method (either Van Hout or Hernandez depending on scenarios). The company stated that this was not used as the base case due to issues with EQ-5D not capturing the burden of CRSwNP and the values being implausibly higher than age-related utility.

4.2.7.2 Surgery and AE utility

Post-operative patients experience a short-term disutility and a long-term utility gain, moving into the post-op controlled state. The short-term disutility comes indirectly from Scangas *et al.* 2017,²¹ it is -0.150 applied over 14 days. The source paper is a cost-utility analysis of endoscopic sinus surgery for patients with chronic rhinosinusitis, both with (CRSwNP) and without nasal polyps (CRSsNP). It is unclear how the company derived this disutility from the paper as health states are recorded

annually in the reported model and no short-term disutility is directly mentioned (although probabilities relating to post-op complications, which would involve short-term disutility, are recorded).

Long-term improvement in utility from surgery is 0.051, sourced from Soler *et al.* 2011.²² As this is applied as a utility gain, as opposed to a standalone health state, the health state a patient transitioned from determines the patient's utility in the post-op-controlled health state. Patients who are non-responders, inadequately controlled or uncontrolled can all require surgery and post-surgery, the health state they came from determines their subsequent utility. This means dupilumab non-responders who require surgery are expected to retain a treatment-specific benefit unless or until they transition from post-op controlled. The resulting health state-utility for post-op controlled patients from this calculation method are listed in [Table 33](#).

Table 33. Base case health state utility post-operative

Health state	Utility
Post-op controlled disease - patients from DUP+ECM No response HS	0.724
Post-op controlled disease - patients from ECM No response HS	0.638
Post-op controlled disease - patients from Inadequately controlled HS	0.645
Post-op controlled disease - patients from Uncontrolled HS	0.575
Abbreviations: DUP, dupilumab; ECM, established clinical management; HS, health state	

The Soler *et al.* 2011²² paper takes the SF-6D utility increase, following endoscopic surgery, in patients with nasal polyposis present. Scenario analysis is provided using Remenschneider *et al.* 2015,²³ which sources an EQ-5D improvement of 0.08 QALYs following surgery.

Adverse events do not have an impact on HRQoL as the impact of them is assumed to already be incorporated into the health state utilities.

4.2.7.3 Age related utility

The company used Ara and Brazier, 2011 to estimate relative decline in age related utility over time. At clarification the EAG requested the company use Health Survey for England (HSE) 2014 dataset in line with NICE methods guide. The company has since updated the base case to incorporate this.

4.2.7.4 EAG critique

The EAG notes that the company's use of a disease-specific measure (SNOT-22) mapped to EQ-5D is a departure from the NICE reference case, particularly when EQ-5D(-5L) is available from the clinical trials and notes that mapping is commonly used to bridge an evidence gap when EQ-5D data are not available.¹⁴

The EAG does not agree with the company view on observed EQ-5D being inappropriate. The issue of exceeding the general population is common in clinical trials and can be resolved by capping the responder utility values at general population for the baseline age and then applying a multiplier to subsequent health states in order to retain the proportional differences between states. The EAG requested that the company perform this analysis at clarification. The company provided this, producing a capping multiplier of 0.937 for the observed SINUS EQ-5D-3L crosswalked change from baseline data. This is the EAG's preferred base case (**Key issue 5** is Section 1.1; results are found in Section 5.2.2). In addition, Tashman *et al.* 2024, Wahid *et al.* 2020, Scangas 2018, Scangas 2017a and De Corso *et al.* 2022^{12, 15, 21, 24} identified in the company's SLR appear to show significantly higher utility values than used in the company's base case. Therefore, the company's statement about baseline utility being excessively high does not appear to be supported by the literature. The company reaffirmed their position on this at clarification by referring to the case they made in their submission, that the EQ-5D instrument performs poorly at capturing the quality of life for patients with CRSwNP, also noting that these papers appear to show baseline QoL close to age-related general population utility. The company emphasised that anosmia and sleep in particular are not explicitly covered by the EQ-5D measure.

Usual activities and pain/discomfort should, to some extent, cover issues with sleep or lack of smell, although the EAG acknowledges that there may be a lack of sensitivity of measurement when compared to SNOT-22. This is commonly the case when a generic instrument is compared to a disease-specific measure of QoL. However, the EAG does not consider the company's solution of using the Crump model's SNOT-22 overall score to be more appropriate. Models 2 and 3 from Crump (which use individual components of SNOT-22 in the regression) show a positive statistically non-significant relationship between EQ-5D and the "anosmia" and "lack of sleep" components of SNOT-22, which, as the company points out, implausibly suggests these negative health outcomes improve quality of life. Yet, by using model 1, this relationship is simply obscured by having these

components be combined with other components such as “facial pain/pressure” which have a large, statistically significant and negative impact on EQ-5D.

Furthermore, the EAG considers the Crump model to have generalisability issues, which also make it inferior to using the company’s trial-based EQ-5D data. The Crump model population is exclusively chronic rhinosinusitis patients awaiting surgery, meaning it effectively only includes patients who would be in the uncontrolled disease health state. This makes it a worse representative sample for determining the quality of life of those other health states. The company responded to this issue at clarification by identifying that the SNOT-22 scores have a large standard deviation (SD) suggesting a reasonable spread across the population, attempting to demonstrate this by producing a sample histogram for illustrative purposes. The EAG does not agree with this explanation, as while the SD is high, the issue is that the population selected likely has constraints on their SNOT-22 score due to their position in the care pathway (waiting for surgery). It cannot be assumed that these patients have a standard distribution (as was done in the company’s illustrative histogram) as there is likely to be a SNOT-22 threshold below which a patient is eligible for/requires surgery.

The EAG notes that the NICE reference case stipulates that in order to make the case that the EQ-5D is inappropriate, evidence should be derived from a synthesis of peer-reviewed literature. The EAG does not consider that this has been done. In addition, the validity of the argument made by the company that the EQ-5D instrument performs poorly at capturing the quality of life for patients with CRSwNP is also unclear as the company maps to the EQ-5D and therefore the utility values used in the model are still EQ-5D values, albeit derived from mapping. As noted in the NICE DSU TSD 22, *“Mapping to EQ-5D is not appropriate if EQ-5D is considered inappropriate for measuring health benefits in the condition under consideration”*,²⁵ therefore, the company’s argument does not match their approach taken.

The regression model provided by the company post-clarification alleviates some of the issues with Crump and using the trial data directly is preferable to using this external paper. However, the EAG notes that SNOT-22 is correlated to EQ-5D and other included variables and therefore including it as an independent variable in the regression analysis is likely to result in both multicollinearity and endogeneity. Although the EAG’s preferred analysis would usually be EQ-5D from the trial derived from a regression analysis, the EAG consider the regression analysis to be methodologically flawed due to the inclusion of SNOT-22, however as the EAG was unable to perform an analysis without this included, the extent to which it is flawed is unclear.

For these reasons, the EAG's preference is for the observed change from baseline in observed EQ-5D-5L data crosswalked to EQ-5D-3L in the base-case analysis (**Key issue 5** in Section 1).

At clarification, the company was asked to justify why dupilumab non-responders who receive surgery would have a higher utility than ECM non-responders. No clinical justification was provided, the company instead made the case that the two papers sourced for surgery-related utility benefit suggest ESS provides a one-off quality of life improvement post-surgery. The EAG does not consider this to be evidence that a continued benefit from dupilumab is appropriate, as this appears to be a presentational preference for these studies. No evidence has been provided that, as a non-responder, surgery will provide patients with a fixed benefit that improves the areas of the condition not affected by dupilumab. The EAG considers it more likely that surgery improves a patient's QoL to a similar point irrespective of what their prior treatment was. In addition, the company's assumption is inconsistent with the current model; it seems implausible that dupilumab provides no lasting benefit within health states after one year for non-surgery patients but it does if a patient has had surgery. Therefore, the EAG has assumed the surgery state is based on a fixed utility benefit applied to the post-decision tree ECM health states (additional issue 5 in Section 1).

The EAG consider the source used for the utility gain of surgery in the company's base case (Soler *et al.* 2011²²) to be inappropriate as it is based on SF-6D and uses data that the EAG considers relatively out of date (2004 – 2009). Therefore, the EAG prefers to use Remenschneider *et al.* 2015²³ in the base-case analysis both because it contains more recent data (2011–2012) and as it is based on EQ-5D-5L over SF-6D, which is more in line with the NICE reference case. The EAG acknowledges that the data in Remenschneider *et al.* 2015²³ is still considered relatively out of date, however, in light of a lack of an alternative source this is the EAG's preferred source (**Key issue 5** in Section 1.1).

Furthermore, the lack of confirmation of where the short-term surgery disutility came from in Scangas *et al.* 2017²¹ represents a minor uncertainty. The EAG acknowledges that surgery will likely result in a short-term disutility and the value has minimal impact but the lack of clear origin introduces uncertainty.

The utilities implemented by the EAG compared to the company are shown in [Table 34](#).

Table 34. EAG base case utility values

Health State	Utility DUP+ECM	Utility ECM	Source
Decision tree			
Week 0 to 12	0.782	0.782	Baseline utility weight from the studies.
Week 13 to 24	0.827	0.775	Utility weight at Week 24 by treatment arm.
Week 25 to 52 responders	0.856	0.832	Average of responder utility weight at Week 24 and Week 52 by treatment arm.
Week 25 to 52 non-responders	0.791	0.762	Average of non-responder utility weight at Week 24 and Week 52
Markov model			
Controlled disease	0.866	0.866	All responder utility weight at Week 52
Inadequately controlled disease	0.752	0.752	Utility weight at Week 52 from patients on ECM, who did not respond at Week 24 and Week 52
Uncontrolled disease	0.732	0.732	Assumed to be the baseline utility.
Surgery			
Post-op controlled disease Patients from no response HS	0.827	0.827	Based on applying 0.08 long-term surgery benefit from Remenschneider <i>et al.</i> 2015 ²³ to inadequately controlled state
Post-op controlled disease Patients from inadequately controlled HS	0.827	0.827	Based on applying 0.08 long-term surgery benefit from Remenschneider <i>et al.</i> 2015 ²³ to inadequately controlled state
Post-op controlled disease Patients from uncontrolled HS	0.807	0.807	Based on applying 0.08 long-term surgery benefit from Remenschneider <i>et al.</i> 2015 ²³ to uncontrolled controlled state
Short term disutility (per year)	-0.006	-0.006	Based on disutility of -0.15 applied over 14 days from Scangas <i>et al.</i> 2017
Abbreviations: DUP, dupilumab; ECM, established clinical management; HS, health state			

4.2.8 Resource use and costs

4.2.8.1 Health care resource use

Health care resource use (HCRU) was determined by a company advisory board of six clinicians held in June 2024. The experts were presented with resource use estimates from Davis *et al.* 2022.²⁶ This paper showed primary care, outpatient, emergency, nurse, and hospitalisation resource use rates for CRSwNP patients in the USA, either on or off SCS. The advisory board was asked to evaluate the data and reflect on what their expectations would be for the UK resource use rate. Based on this, the company obtained the base case values found in [Table 35](#).

Table 35. Health care resource use rate

Treatment state	Primary care	Outpatient	Emergency	Nurse	Hospitalisation
Decision tree					
DUP+ECM Response	0	2	0	0	0
DUP+ECM No response	6	3	0	0	0
ECM Response	0	1	0	0	0
ECM No response	6	3	0	0	0
Markov model					
Controlled disease First year	0	1	0	0	0
Controlled disease Sub year	0	1	0	0	0
Inadequately controlled	6	3	0	0	0
Post op controlled First year	0	0	0	0	0
Post op controlled Sub year	0	1	0	0	0
Uncontrolled First year	6	3	0	0	0
Uncontrolled Sub year	6	3	0	0	0
Abbreviations: DUP, dupilumab; ECM, established clinical management.					

Unit costs of these appointments can be found in [Table 36](#). Primary care is assumed to be the equivalent of a GP visit, outpatient is the equivalent of a specialist visit. The costs included in this

table are the updated values following a clarification request to update them to the latest publication.

Table 36. Health care resource use unit costs

Resource	Unit Cost	Cost used in the model (inflated to 2024 cost year)	Source
GP visit	£49.00	£50.42	PSSRU 2023
Specialist visit	£168.16	£168.16	NHS Schedule of Costs 2023/2024
Nurse visit	£48.00	£49.39	PSSRU 2023
Abbreviations: GP, general practitioner; NHS national health service; PSSRU, Personal Social Services Research Unit			

4.2.8.2 Drug and administration costs

Dupilumab is dosed at 300mg every other week and is provided by subcutaneous injection. The annual cost is £16,500, although there is a confidential patient access scheme in place with a discounted price of [REDACTED]. A one-time administration cost of £49.39 is applied based on the PSSRU cost for a band 6 nurse to account for a one-off training in dupilumab administration.

In the CS, dupilumab was assumed to have an adherence rate of 99.26% based on the average adherence between 300mg administered at Q2W-Q4W and Q2W arms from the SINUS trials. The company provided a scenario at clarification using just Q2W patients; they had an adherence of 99.34%. This was then updated as part of the company’s base-case.

The EAG was advised that if dupilumab were to be recommended for routine clinical practice, the decision to start a patient on treatment would be made as part of a multidisciplinary team (MDT). A cost of £220.78 based on the NHS reference cost data for Ear, Nose and Throat (ENT) service- Outpatient Care national average unit cost (multiprofessional - Consultant Led) was included in the company base case following clarification. The EAG agree this should be included in the base case.

Established clinical management (ECM) costs involve acute treatment of infections and inflammation using SCS and/or antibiotics; the unit cost of these treatments can be seen in Table 37. While ECM is provided to both arms, as treatment is acute and targeted means there are differences in drug use rates between the arms. These are recorded in Table 38 with unit costs found in Table 37. Following clarification, the company removed antibiotics drug use from the model as there was not a

statistically different rate of usage between placebo and treatment. The company also corrected the rate of SCS use for ECM non-responders. These changes are included in the tables below and the company's base case.

Table 37. Unit cost associated with ECM

Items	Cost per course	Daily cost
SCS (prednisolone 5mg)	£2.77	£0.28
Antibiotics (doxycycline 100mg)	£3.81	£0.18
Abbreviations: ECM, established clinical management; SCS, systemic corticosteroids		

Table 38. Base case drug-acquisition costs for SCS and antibiotics according to response

Response	SCS		Drug costs, £
	Drug use, %	Duration, days	
Week 0–Week 24			
DUP + ECM responders	0	0	0.00
DUP + ECM non-responders	17.9	19.2	0.95
ECM responders	0	0	0.00
ECM non-responders	26.7	13.1	0.96
Week 25–Week 52			
DUP + ECM responders	0	0	0.00
DUP + ECM non-responders	20.5	22.7	1.29
ECM responders	0	0	0.00
ECM non-responders	28.2	16.2	1.26
Markov Model			
Controlled Disease	0	0.0	0.00
Inadequately Controlled	28.2	36.0	2.81
Post-Op Controlled	0	0.0	0.00
Uncontrolled	28.2	36.0	2.81
Abbreviations: DUP, dupilumab; ECM, established clinical management; SCS, systemic corticosteroids			

Aside from dupilumab, all treatment costs are publicly available. As such, there is no confidential appendix for this EAG report.

4.2.8.3 Surgery costs

Surgery costs are taken from Clarke *et al.* 2022²⁷, an observational retrospective study of health service costs for patients receiving surgery for chronic rhinosinusitis in England.

Total per person NHS costs, from this paper, in the year following surgery, was estimated to be £2,547, which is used as the company's base case. A scenario analysis was conducted using the component costs listed in the paper, which states surgery is priced at £2,284.63 with follow on outpatient costs of £76.78 in the immediate quarter after and 2-year follow up costs of £59.62 per quarter. This would result in a total cost of £2,540.27 for the year containing surgery. Costs in the paper were in 2017-18 UK pound sterling and so have been inflated to 2024 prices. The explanation provided by the company for why the component costs summed differs from the total first year costs is that the 2-year follow up cost of £59.82 is a per quarter average over 2 years while the first year per patient cost includes the true value. The EAG agrees that this explanation is plausible.

Post-op costs are separated into first year and subsequent years. As previously shown [Table 35](#), no additional healthcare resource use cost is applied in the first year as this is assumed to be accounted for in the cost taken from the Clarke *et al.* 2022 paper.²⁷ In subsequent years, a single outpatient appointment cost is applied.

4.2.8.4 AE and asthma cost

Adverse event rates and costs are listed in [Table 39](#). Selection of AEs comes from the list of treatment-emergent adverse events in Bachert *et al.* 2019,²⁸ a paper reviewing the efficacy and safety in the SINUS 24 and 52 trials.

Table 39. Base case data inputs for adverse event costs (reproduced from Table 62 in CS)

TEAE	Annual incidence, %		TEAE unit cost, £	Cost used in the model (inflated to 2024 cost year), £	Source for cost
	DUP + ECM	ECM			
Nasopharyngitis	0.275	0.287	49.00	50.42	One GP visit
Headache	0.092	0.181	0	0	Assumed self-treated
Epistaxis	0.106	0.114	0	0	Assumed self-treated
Asthma	0.058	0.173	168.00	172.87	One specialist visit
Injection site reaction	0.395	0.000	273	280.92	One emergency care visit

Abbreviations: DUP, dupilumab; ECM, established clinical management; GP, general practitioner; TEAE, treatment-emergent adverse event.

Following TA751,¹⁸ dupilumab was recommended for treating severe asthma with type 2 inflammation. A significant portion of patients with CRSwNP have comorbid asthma; 59.6% and 58.3% of the SINUS 24 and SINUS 52 trials, respectively. Therefore, the company used the asthma control questionnaire ACQ-6 to assess levels of control of asthma following the trial in each arm. The company applied these control levels from the trial in the model and costed them using values from Wilson *et al.* 2014.²⁹ The values for controlled level and corresponding cost used in the model are shown in Table 40.

Table 40. Asthma control level and cost applied in model (reproduced from Table 63 from CS)

Control level	Dupilumab + ECM	ECM only	Cost
Controlled asthma	76.0%	16.7%	£960
Partially controlled asthma	10.0%	19.4%	£1,795
Uncontrolled asthma	14.0%	63.9%	£2,629

Abbreviations: DUP, dupilumab; ECM, established clinical management; GP.

4.2.8.5 EAG critique

At clarification the company was asked to provide the usage of SCS and antibiotics based on the decision problem as opposed to the ITT population. In response, the company has confirmed that the difference in antibiotic usage was not statistically significant between arms and has removed it from the model. Therefore, in the company's updated model, only differences in SCS use are included.

The company assumes that 100% of patients will be able to self-administer dupilumab but included a scenario analysis in which 5% of patients receive administration by a nurse. Based on clinical expert feedback, the EAG consider this to be more appropriate for the base-case analysis as it is unlikely that 100% of patients will be able to self-administer. The EAG notes that this has a minor impact on the ICER (additional issue 6 in Section 1.1).

The company provided two scenarios for surgery costs, one based on the sum of component costs for the first year of surgery for patients and the other, which is stated in the paper to be the total

per-person NHS costs for 1 year in patients receiving surgery. However, the paper lists per quarter follow-up costs of £59.62 up to 2 years that do not appear to have been incorporated into the model, with patients in subsequent years (post op) only receiving one outpatient appointment. The EAG base case incorporates these 2-year follow-up costs into its base case, subtracting the cost of 1 outpatient appointment to avoid double counting of resource use. Second year costs are discounted 3.5% and the costs are inflated to 2024 prices. This results in an overall cost of £3,205. The impact of incorporating this increases the cost of surgery, which improves the cost-effectiveness of dupilumab as fewer dupilumab patients receive surgery (additional issue 7 in Section 1.4) .

As previously discussed in relation to mortality, the EAG consider that some of the benefits of dupilumab in patients with comorbid asthma will have already been captured in the previous appraisal. Therefore, differences in asthma costs have been excluded from the EAG base case and provided as a scenario analysis only.

5 Cost effectiveness results

5.1 Company's cost effectiveness results

Table 41 presents the cost-effectiveness results of the company's updated (i.e. post clarification) base case deterministic and probabilistic analyses dupilumab plus background therapy. The company performed a probabilistic sensitivity analysis (PSA) to assess the joint parameter uncertainty around base case results. Incremental results from the company's PSA are based on 1,000 simulations.

In the base case probabilistic analysis, an incremental quality-adjusted life-year (QALY) gain of [REDACTED] over background therapy along with increased costs of [REDACTED] for dupilumab plus background therapy generates an incremental cost-effectiveness ratio (ICER) of £23,793.

The net health benefit (NHB) based on the deterministic results using the £20,000 and £30,000 threshold is [REDACTED] and [REDACTED], respectively. A positive NHB implies that overall population health would be increased because of the new intervention.

Table 41. Company base case results

Interventions	Total Costs (£)	Total LY*	Total QALYs	Δcosts (£)	ΔLYs*	Δ QALYs	ICER (£/QALY)
Deterministic results							
ECM only	[REDACTED]	[REDACTED]	[REDACTED]	-	-	-	-
Dupilumab + ECM	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	£23,410
Probabilistic results							
ECM only	[REDACTED]	[REDACTED]	[REDACTED]	-	-	-	-
Dupilumab + ECM	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	£23,793
*Undiscounted							
Abbreviations: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year							

A PSA scatterplot is presented in Figure 14 and a cost-effectiveness acceptability curve (CEAC) is presented in Figure 15. Based on these analyses, the probability that dupilumab plus background therapy is cost effective versus background therapy alone is approximately 0.1% at a willingness to pay (WTP) threshold of £20,000 and 100% at a WTP threshold of £30,000.

Figure 14. Scatterplot of PSA estimates, reproduced from the company's economic model, post clarification

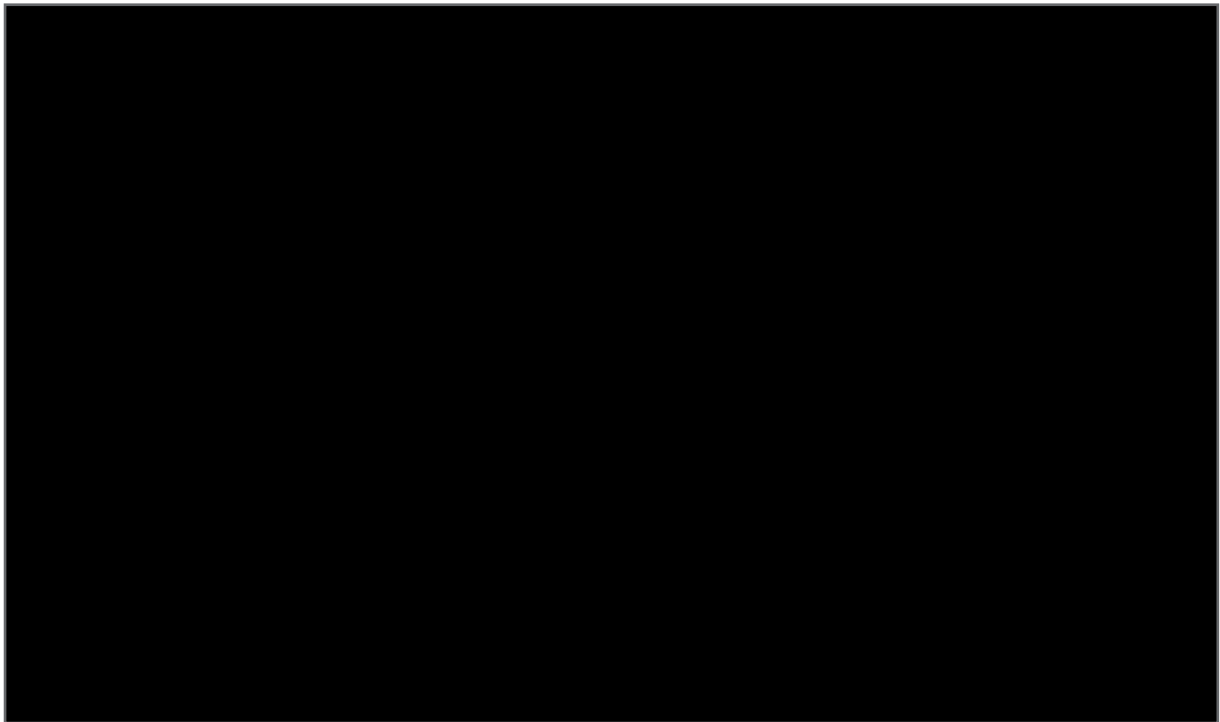
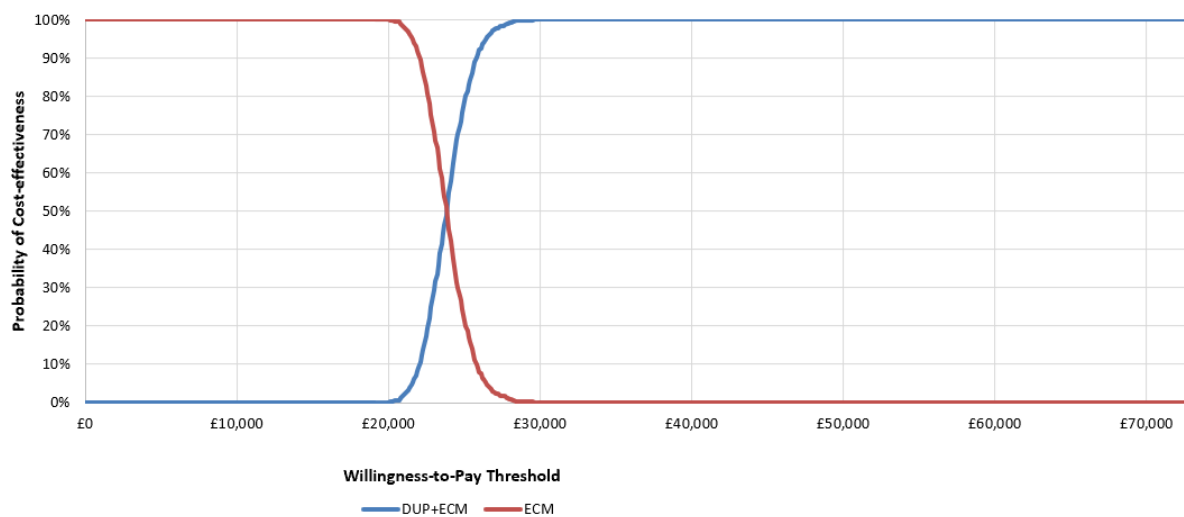


Figure 15. Cost-effectiveness acceptability curve. Reproduced from the company's economic model, post clarification



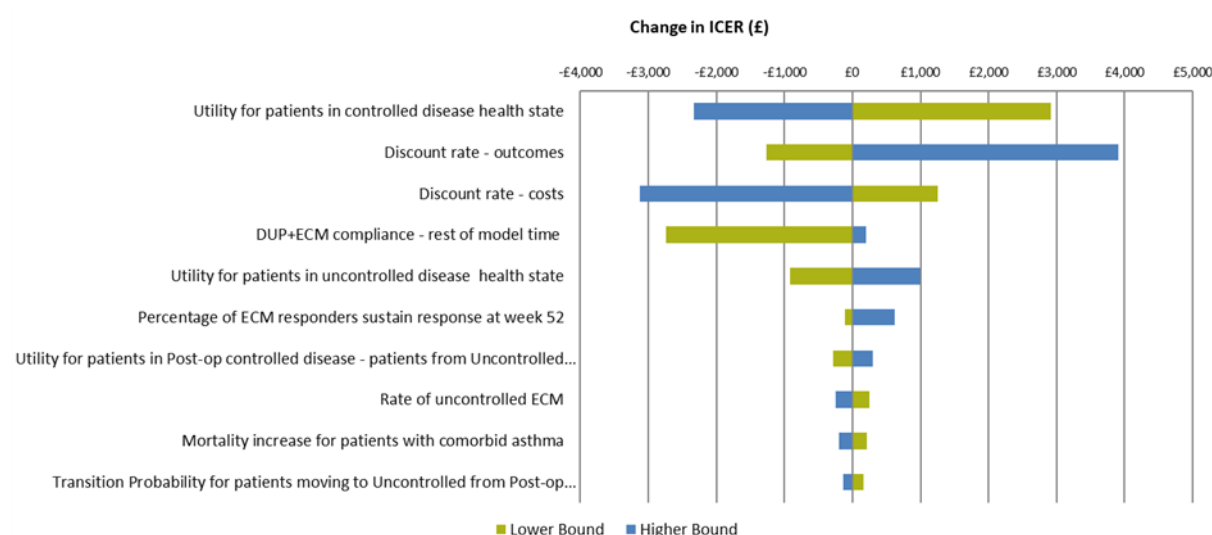
5.2 Company's sensitivity analyses

5.2.1 One-way sensitivity analyses

The company conducted one-way sensitivity analyses (OWSAs) to assess the impact on the ICER of varying specific parameters in isolation and to identify the main model drivers. Parameters were varied by 95% confidence intervals (CIs) when available and $\pm 10\%$ when these were not available.

The results are illustrated in the tornado diagram presented in [Figure 16](#), which depicts the change in the ICER from baseline. The ICER was most sensitive to the utility values for the controlled and uncontrolled disease health states, the proportion of patients with sustained response on dupilumab at week 52 (as this informs the long-term Markov model transition probabilities) and compliance rate of dupilumab.

Figure 16. Tornado plot (Figure 76 of the clarification response)



5.2.2 Scenario analyses

The company undertook an extensive series of scenario analyses to assess the impact of applying alternative assumptions to key model parameters. In addition, the EAG requested a range of scenarios during clarification. As a result of clarification, the company updated their base-case analysis and incorporated some of the requested analyses into the new base-case, therefore some scenario analyses changed from the original submission. The scenarios presented in

[Table 42](#) are a combination of those undertaken by the company and those requested by the EAG at clarification. The company only provided results deterministically, however, the EAG notes the probabilistic and deterministic analyses were largely similar.

As shown in Table 42, the utility values used in the company's base case analysis had the largest impact on the ICER, with all alternative options to the company's base case increasing the ICER substantially above the £20,000—£30,000 threshold.

Table 42. Company scenario analysis following clarification

No.	Scenario	Deterministic results		
		Δ QALYs	Δ costs (£)	ICER (£/QALY)
Company scenarios analyses				
0	Company base case	■	■	£23,410
1	Discount rate - 3%	■	■	£24,658
2	Discount rate – 5%	■	■	£23,675
4	Time horizon - 5 years	■	■	£27,485
5	Time horizon - 10 years	■	■	£24,814
6	Time horizon - 20 years	■	■	£23,784
7	Utility values SNOT-22 to EQ-5D mapping – Crump model 2	■	■	£37,990
8	Utility values SNOT-22 to EQ-5D mapping – Crump model 3	■	■	£38,306
9	Utility values EQ-5D regression - Hernandez Model 1*	■	■	£50,042
10	Utility values EQ-5D regression - Hernandez Model 2*	■	■	£50,042
11	Utility values EQ-5D regression - Hernandez Model 3*	■	■	£50,430
12	Utility values EQ-5D regression - Hernandez Model 4*	■	■	£51,751
13	Utility values based on observed change from baseline (Hernandez EQ-5D-5L to 3L CW)*	■	■	£48,956
14	Utility gain from surgery - Remenschneider, 2015	■	■	£23,997
15	Remove short-term disutility of surgery	■	■	£22,443
16	Utility age adjustment based on Ara and Brazier	■	■	£23,438
17	Long-term discontinuation of dupilumab – 7.8% based on responders in the SINUS-24/52 trials	■	■	£24,028
18	Long-term compliance of dupilumab - 95%	■	■	£22,234
19	5% of patients receive nurse administration of dupilumab	■	■	£23,578
20	Remove asthma related costs	■	■	£24,321
21	Remove asthma related mortality	■	■	£24,029
22	Linear increase in patients ineligible for surgery due to age	■	■	£23,424

23	Polynomial increase in patients ineligible for surgery due to age	■	■	£23,415
24	HCRU - Non-responder GP appointments increased to 7.64, Consultant appointments decreased to 2.0	■	■	£23,657
25	HCRU - 1 nurse visit instead of 1 consultant visit for responders	■	■	£23,381
26	Indirect costs included for presenteeism and absenteeism	■	■	£17,839
EAG requested scenarios				
B4	Responder analysis based on SNOT-22 response only	■	■	£28,128
B4	Responder analysis based on NPS response only	■	■	£25,885
B5	Analysis based on only SINUS-52 trial data	■	■	£23,261
B9	Transition probability of having surgery and moving to post-op controlled health state – 1.9%	■	■	£23,343
* These models all apply a cap on utility at general population and a multiplier is applied to subsequent health states in order to retain the proportional differences between states, as requested by the EAG at clarification Abbreviations: CW, crosswalk; EAG, External Assessment Group; EQ-5D-5L, EuroQoL 5-Dimensions 5-Level; GP, general practitioner; HCRU, health care resource use; ICER, incremental cost-effectiveness ratio; ITT, intent-to-treat; LS, least squares; N/A, not applicable; NICE, National Institute for Health and Care Excellence; NPS, nasal polyps score; QALY, quality-adjusted life-year				

5.2.3 Subgroup analyses

The company originally undertook two subgroup analyses and presented the accompanying cost-effectiveness results. The subgroups explored in the economic model were:

- Patients **without prior surgery** and with prior type 2 medical history including asthma/NSAID-ERD,
- Patients **with prior surgery** and with prior type 2 medical history including asthma/NSAID-ERD.

The cost-effectiveness results for the two subgroups are presented below. The EAG notes that these two subgroups differ slightly to the subgroups presented in the clinical evidence of the CS, which did not separate results based on patient's prior surgery status, discussed in Section 3.3.5.

As shown in [Table 43](#) and [Table 44](#), the subgroup analyses produced similar ICER's to the company's base-case analysis (post-clarification), particularly for those patients with prior surgery.

For patients with prior type 2 medical history, without prior surgery, the ICER was ≈£1,500 higher than the company's base case.

Table 43. Company subgroup analyses results for patients without prior surgery and with prior type 2 medical history including asthma/NSAID-ERD

Interventions	Total Costs (£)	Total LY	Total QALYs	Δcosts (£)	ΔLYs	Δ QALYs	ICER (£/QALY)
Deterministic results							
ECM only	■	■	■	-	-	-	-
Dupilumab + ECM	■	■	■	■	■	■	£24,955
Probabilistic results							
ECM only	■	■	■	-	-	-	-
Dupilumab + ECM	■	■	■	■		■	£25,528
Abbreviations: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; LY, life year; NR, not reported; QALY, quality-adjusted life-year							

Table 44. Company subgroup analyses results for patients with prior surgery and with prior type 2 medical history including asthma/NSAID-ERD

Interventions	Total Costs (£)	Total LY*	Total QALYs	Δcosts (£)	ΔLYs*	Δ QALYs	ICER (£/QALY)
Deterministic results							
ECM only	■	■	■	-	-	-	-
Dupilumab + ECM	■	■	■	■	■	■	£23,258
Probabilistic results							
ECM only	■	■	■	-	-	-	-
Dupilumab + ECM	■	■	■	■	■	■	£23,733
*Undiscounted Abbreviations: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; LY, life year; NR, not reported; QALY, quality-adjusted life-year							

As previously discussed in Section 3.3.5, the EAG also requested additional analyses in which patients with asthma and NSAID-ERD were considered separately, based on clinical expert advice, rather than a combined group. However, as previously discussed in Section 2.3.5, the results for the

comorbid asthma patients represents those with asthma and NSAID-ERD as the company stated “...have not conducted a subgroup analysis for the population of patients who have asthma (and specifically who do not also have NSAID-ERD)” The tables below present the results of the subgroup analyses requested by the EAG during clarification, only for those with prior surgery as the EAG note that this is applicable to the proposed positioning of dupilumab.

As shown in Table 45 and Table 46, when considered separately, both asthma (including NSAID-ERD) and NSAID-ERD subgroups resulted in an increased ICER of over £3,000. The EAG notes that this is mainly due to a reduction in the incremental QALYs.

Table 45. Subgroup analyses results for patients with prior surgery and comorbid asthma

Interventions	Total Costs (£)	Total LY*	Total QALYs	Δcosts (£)	ΔLYs*	Δ QALYs	ICER (£/QALY)
Deterministic results							
ECM only	■	■	■	-	-	-	-
Dupilumab + ECM	■	■	■	■	■	■	£26,009
Probabilistic results							
ECM only	■	■	■	-	-	-	-
Dupilumab + ECM	■	■	■	■	■	■	£26,705
*Undiscounted							
Abbreviations: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; LY, life year; NR, not reported; QALY, quality-adjusted life-year							

Table 46. Subgroup analyses results for patients with prior surgery and NSAID-ERD

Interventions	Total Costs (£)	Total LY*	Total QALYs	Δcosts (£)	ΔLYs*	Δ QALYs	ICER (£/QALY)
Deterministic results							
ECM only	■	■	■	-	-	-	-
Dupilumab + ECM	■	■	■	■	■	■	£26,217
Probabilistic results							
ECM only	■	■	■	-	-	-	-
Dupilumab + ECM	■	■	■	■	■	■	£26,816
*Undiscounted							

5.3 Model validation and face validity check

Section B.3.13 in the company submission outlines the company's approach to the validation of the economic model. The EAG is satisfied that the company's approach was thorough and robust. The EAG undertook their own validation of the model and checked the face validity of the assumptions and inputs with clinical experts. During clarification, the EAG highlighted some minor discrepancies between the CS and the economic model inputs, which were amended by the company.

6 Additional economic analysis undertaken by the EAG

6.1 Model corrections

As noted in Section 4.2.5.1, the EAG corrected an error in the company's calculation of the annual probability of revision surgery. Therefore, this was amended by the EAG to an annual probability of 14.8% compared to the company's 15.1%.

The EAG also amended the probabilistic values sampled for the proportion of patients with asthma as this was incorrectly sampling from the proportion of patients with severe asthma.

All additional scenarios performed by the EAG include these model corrections to the base-case.

6.2 EAG scenario analysis

As discussed in Section 4, the EAG identified a number of uncertainties that warranted further exploration in scenario analyses, in addition to the company's own sensitivity and scenario analyses. The majority of these were conducted by the company in response to clarification, as previously shown in

Table 42 in Section 5.2.2. The additional scenarios performed by the EAG are detailed below.

1. General population mortality based on ONS life tables 2017-19, in line with NICE DSU guidance¹⁹ (Section 4.2.6).
2. Annual probability of patients transitioning from controlled to inadequately controlled in the dupilumab arm beyond 5 years in the model is equal to 15.6%. This is an exploratory scenario based on [REDACTED] of discontinuation (including due to loss of response) at the end of the SINUS-52 trial [REDACTED] in order to explore the impact of a reduced treatment effect over time (Section 4.2.4).
3. Transition probabilities from post-op controlled to uncontrolled based on the company analysis of Benson *et al.* but using an adjustment of a one year wait time in the calculations as opposed to two years. This results in an annual probability of post-op controlled to uncontrolled of 12.1% as opposed to the company's 42.8% (Section 4.2.5.1).
4. Utility values for post-op controlled disease do not differ between treatment arms, i.e. no prolonged treatment benefit following loss of control (Section 4.2.7.4).
5. Inclusion of two year follow-up costs post-surgery (Section 4.2.8.5).

Results reported include the company's proposed patient access scheme (PAS) discount on the list price of [REDACTED] for dupilumab.

Table 47. Results of the EAG's scenario analyses, deterministic

	Results per patient	Intervention	Comparator	Incremental value
Company base case				
	Total costs (£)	[REDACTED]	[REDACTED]	[REDACTED]
	QALYs	[REDACTED]	[REDACTED]	[REDACTED]
	ICER (£/QALY)			£23,410
Model correction made by the EAG				
	Total costs (£)	[REDACTED]	[REDACTED]	[REDACTED]
	QALYs	[REDACTED]	[REDACTED]	[REDACTED]
	ICER (£/QALY)			£23,404
1	General population mortality based on ONS life tables 2017-19			
	Total costs (£)	[REDACTED]	[REDACTED]	[REDACTED]
	QALYs	[REDACTED]	[REDACTED]	[REDACTED]
	ICER (£/QALY)			£23,425
2	Annual probability of transitioning from controlled to inadequately controlled in the dupilumab arm beyond 5 years is equal to 15.6%			
	Total costs (£)	[REDACTED]	[REDACTED]	[REDACTED]
	QALYs	[REDACTED]	[REDACTED]	[REDACTED]
	ICER (£/QALY)			£24,288
3	Transition probabilities from post-op controlled to uncontrolled adjusted based on a one-year wait time			
	Total costs (£)	[REDACTED]	[REDACTED]	[REDACTED]
	QALYs	[REDACTED]	[REDACTED]	[REDACTED]
	ICER (£/QALY)			£25,643
4	Utility values for post-op controlled disease do not differ between treatment arms			
	Total costs (£)	[REDACTED]	[REDACTED]	[REDACTED]
	QALYs	[REDACTED]	[REDACTED]	[REDACTED]
	ICER (£/QALY)			£23,457
5	Inclusion of two year follow-up costs post-surgery			
	Total costs (£)	[REDACTED]	[REDACTED]	[REDACTED]
	QALYs	[REDACTED]	[REDACTED]	[REDACTED]
	ICER (£/QALY)			£23,167
Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year				

6.3 EAG preferred assumptions

In this section, the EAG presents its preferred analysis for the cost-effectiveness of dupilumab in combination with ECM for the treatment of uncontrolled chronic rhinosinusitis with nasal polyps (CRSwNP) following prior surgery. The assumptions that form the EAG's preferred base case are listed below, with the cumulative results of each analysis shown in Table 48. The EAG notes that the individual impact of each scenario on the company's base-case ICER has been previously presented in either

Table 42 or Table 47. The EAG ran probabilistic results over 1,000 iterations. It is noted that due to variability in the PSA, there may be small discrepancies in the incremental costs or QALYs between scenarios.

The EAG notes that due to changes in the base case preferences, corrections were applied to the sampled PSA utility values to ensure that the utility multiplier was also applied in the probabilistic version of the model and that utilities followed the expected ordering across health states. For scenarios including no mortality or costs associated with asthma, these values were set not to vary in the PSA.

- General population mortality based on ONS life tables 2017-19, in line with NICE DSU guidance¹⁹ (Section 4.2.6).
- Transition probability of controlled to inadequately controlled based analysis of responders from the SINUS 24/52 trials (■% annual probability) (Section 4.2.4).
- Removal of difference in mortality between treatment arms due to uncontrolled asthma (Section 4.2.6).
- Utility values based on observed EQ-5D SINUS trial data (change from baseline), with a cap applied to the responder utility values at general population for the baseline age and a multiplier applied to subsequent health states in order to retain the proportional differences between states (Section 4.2.7.4).
- Surgery utility gain based on Remenschneider *et al.* 2015 (Section 4.2.7.4).
- Utility values for post-op controlled disease do not differ between treatment arms, i.e. no prolonged treatment benefit following loss of control (Section 4.2.7.4).
- Removal of differences in costs related to asthma control (Section 4.2.8.5).
- 5% of patients receive assistance with dupilumab administration, provided by a nurse home care visit (Section 4.2.8.5).
- Inclusion of two year follow-up costs post-surgery (Section 4.2.8.5).

Table 48. EAG's preferred model assumptions, cumulative ICER (probabilistic)

Preferred assumption	Section in EAG report	Cumulative incremental costs	Cumulative incremental QALYs	Cumulative ICER (£/QALY)
Corrected company base case	Section 6.1	■	■	£23,499
General population mortality based on ONS life tables 2017-19	Section 4.2.6.1	■	■	£23,542
Controlled to inadequately controlled transition based on SINUS 24/52 responders	Section 4.2.4	■	■	£23,960
No asthma mortality included	Section 4.2.6.1	■	■	£24,356
Utility values based on observed trial based EQ-5D (change from baseline)	Section 4.2.7.4	■	■	£53,497
Surgery utility gain based on Remenschneider <i>et al.</i> 2015	Section 4.2.7.4	■	■	£57,087
Utility values for post-op controlled disease do not differ between treatment arms	Section 4.2.7.4	■	■	£56,683
Removal of differences in costs related to asthma control.	Section 4.2.8.5	■	■	£59,175
5% of patients receive assistance with dupilumab administration, provided by a nurse home care visit	Section 4.2.8.5	■	■	£59,030
Inclusion of two year follow-up costs post-surgery	Section 4.2.8.5	■	■	£59,379
EAG preferred base case	-	■	■	£59,379
Abbreviations: EAG, External Assessment Group; EQ-5D, EuroQol five dimension; ICER, incremental cost-effectiveness ratio; ONS, office of national statistics; QALY, quality adjusted life year; SNOT-22, Sino-Nasal Outcome Test-22				

As shown in Table 48, changes to the utility values used in the base-case analysis had the largest impact on the ICER. Full probabilistic and deterministic EAG base case analysis results are shown below in Table 49. The EAG notes that in the EAG-preferred analysis, the probabilistic ICER is ≈£1,000 lower than the deterministic results. This appears to be driven by both an increase in incremental costs and QALYs in the probabilistic model.

Table 49. EAG base case results

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
ECM only	■	■	■	-	-	-	-
Dupilumab + ECM	■	■	■	■	■	■	£60,551
Probabilistic results							
ECM only	■	■	■	-	-	-	-
Dupilumab + ECM	■	■	■	■	■	■	£59,379
Abbreviations: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; NR, not reported							

6.4 EAG additional sensitivity analysis

The following additional sensitivity analyses were also undertaken using the EAG's preferred analysis to explore the sensitivity to alternative assumptions:

1. Responder analysis based on SNOT-22 response only. This scenario applies data analysis on patients response from SINUS 24/52 based on SNOT-22 change from baseline of ≥ 8.9 points only, as opposed to the combined response. Based on feedback from clinical experts, the EAG considers it a reasonable alternative to the base-case analysis, dependent on the criteria that will be used in clinical practice.
2. Annual probability of patients transitioning from controlled to inadequately controlled in the dupilumab arm beyond 5 years in the model is equal to ■%. This is an exploratory scenario to explore the impact of a reduced treatment effect over time given the lack of availability of long-term comparative data.
3. Use of company's analysis of AROMA to inform long-term treatment effectiveness and discontinuation rates of dupilumab (transition from controlled to inadequately controlled), as used in the company's updated base case analysis post clarification.
4. Inclusion of asthma-related mortality and costs. While the EAG considers that costs for asthma control and mortality benefit related to asthma should not be included in the base-case analysis for CRSwNPs, it is considered an appropriate scenario analysis to explore the impact on the ICER. The EAG notes that as patients in clinical practice would have access to

other biologics for asthma that were not available during the clinical trials, the proportions of patients with uncontrolled asthma in the ECM arm may differ in the real world. In addition, some patients with severe asthma and CRSwNP will already have access to dupilumab.

5. Utility values based on observed EQ-5D derived from the regression model. This analysis used utility values based on observed EQ-5D SINUS trial data (linear regression model controlling for age, gender, baseline utility and SNOT-22 change from baseline), as opposed to the change from baseline used in the EAG preferred analysis.
6. Utility values based on the mapping of SNOT-22 to EQ-5D (-3L), as used in the company's base analysis.
7. Transition probability from post-op controlled to uncontrolled is based on the company analysis of Benson *et al.* but using an adjustment of a one year wait time in the calculations as opposed to two years. This results in an annual probability of post-op controlled to uncontrolled of 12.1% as opposed to the company's 42.8%. This exploratory scenario is included to explore the magnitude of the ICER impact when using a lower annual transition to the uncontrolled health state.

As shown in Table 50, the use of responder analysis measured using SNOT-22 had the largest increase on the EAG's ICER. The EAG notes that this scenario has a greater impact on the EAG's preferred analysis compared to the company's due to the smaller absolute QALYs in the EAG base case due to the utility values used and removal of survival benefit related to uncontrolled asthma (i.e. no difference in LYs). As previously discussed, the choice of method used to derive utility values has the greatest impact on the ICER, which is observed in additional analysis six, using the company's mapping. The EAG notes that this scenario results in considerably higher incremental QALYs (■■■■). As previously discussed, the EAG does not consider the company's mapping to be appropriate (see Section 4.2.7.4).

The reduced treatment effect beyond 5 years (additional analysis 2) had a small impact on the ICER as did the use of the AROMA study to inform the transition probability (additional analysis 3). The inclusion of asthma-related benefits reduced the EAG ICER by ≈£6,000, driven by both an increase in incremental QALYs due to a survival gain for dupilumab, and a reduction in incremental costs.

Table 50. Results of additional sensitivity analyses applied to the EAG's preferred base case, probabilistic

	Results per patient	Dupilumab + ECM	ECM only	Incremental value
EAG base case				
	Total costs (£)	████	████	████
	QALYs	██	██	██
	ICER (£/QALY)			£59,379
1	Responder analysis based on SNOT-22 response only			
	Total costs (£)	████	████	████
	QALYs	██	██	██
	ICER (£/QALY)			£76,832
2	Reduced treatment effectiveness beyond five years			
	Total costs (£)	████	████	████
	QALYs	██	██	██
	ICER (£/QALY)			£61,488
3	Transition from controlled to inadequately controlled for dupilumab informed by company analysis of AROMA			
	Total costs (£)	████	████	████
	QALYs	██	██	██
	ICER (£/QALY)			£57,446
4	Inclusion of asthma related costs and mortality			
	Total costs (£)	████	████	████
	QALYs	██	██	██
	ICER (£/QALY)			£53,549
5	Utility values based on observed EQ-5D from regression model			
	Total costs (£)	████	████	████
	QALYs	██	██	██
	ICER (£/QALY)			£61,068
6	Utility values based on mapping of SNOT-22			
	Total costs (£)	████	████	████
	QALYs	██	██	██
	ICER (£/QALY)			£26,229
7	Transition probabilities from post-op controlled to uncontrolled adjusted based on a one-year wait time			
	Total costs (£)	████	████	████
	QALYs	██	██	██
	ICER (£/QALY)			£72,073
Abbreviations: EAG, External Assessment Group; ECM, established clinical management; EQ-5D, EuroQol-five dimension; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SNOT-22, Sino-Nasal Outcome Test-22				

In addition, the EAG also conducted a subgroup analyses for patients with prior surgery and with a prior type 2 medical history including asthma/NSAID-ERD, using its preferred assumptions. This was included to highlight the impact of comorbidities in this population. As such, the EAG also included both the costs and increased risk of mortality due to asthma in the analyses presented. Although the EAG planned to also present subgroup analyses separately for patients with comorbid asthma and NSAID-ERD, the EAG notes that due to the small patient numbers available to inform these analyses, the EAG considered the utilities and responder proportions to be too uncertain to produce robust results. As the EAG base-case uses the trial based responder analysis (responders at week 24 and week 52) to inform the annual transition from controlled to inadequately controlled, small differences in the proportion has a larger impact than when the subgroup analyses were performed by the company, due to their use of the AROMA study to inform transitions.

The EAG notes that the subgroup results for patients with prior surgery and with a prior type 2 medical history (including asthma/NSAID-ERD) are similar to that of the entire population. Based on the similarities in the clinical effectiveness between the subgroups discussed in Section 2.3.5, the EAG anticipates that the ICERs for the comorbid asthma and NSAID-ERD subgroups would also be similar.

Table 51. Results of subgroup analyses on EAG preferred base-case, probabilistic

Results per patient	Dupilumab + ECM	ECM only	Incremental value
EAG base case			
Total costs (£)	████	████	████
QALYs	██	██	██
ICER (£/QALY)			£58,608
Patients with prior surgery and with prior type 2 medical history including asthma/NSAID-ERD			
Total costs (£)	████	████	████
QALYs	██	██	██
ICER (£/QALY)			£57,597
Abbreviations: EAG, External Assessment Group; ; ECM, established clinical management; ICER, incremental cost-effectiveness ratio; NSAID-ERD, non-steroidal anti-inflammatory drug-exacerbated respiratory disease; QALY, quality adjusted life year			

6.5 Conclusions of the cost effectiveness sections

Generally, the EAG considers the company's submitted cost-effective evidence to adhere to the NICE decision problem defined in the NICE final scope. The company compared dupilumab plus

established clinical management (ECM) to ECM only. Clinical experts to the EAG confirmed that endoscopic sinonasal surgery (ESS) is a component of ECM rather than a standalone comparator.

The inputs used in the model in relation to utility values are the key driver of the ICER and consequently are considered to be a key issue in this appraisal (**Key issue 5** in Section 1). As previously discussed in Section 4.2.7.4, the EAG does not consider the company's departure from the NICE reference case and argument for the use of mapping SNOT-22 to EQ-5D, rather than using the trial-based EQ-5D, to be justified and also considers the model used for mapping (Crump *et al.*) to be inappropriate due to generalisability issues). Therefore, the EAG considers the use of EQ-5D-5L (mapped to EQ-5D-3L) directly from the key clinical trials to be most appropriate. While the EAG preference would be trial EQ-5D derived from a regression model, as previously stated, the EAG considers the company's regression to be methodologically flawed due to the inclusion of SNOT-22 as an independent variable. Therefore, the EAG's preferred base case analysis used the trial observed EQ-5D change from baseline (CFB), resulting in a probabilistic ICER of £59,370 per QALY gained. As utility values produced using this approach for patients in the controlled health state resulted in a utility value higher than UK population norm, a cap on age-matched utility was used and a multiplier applied to subsequent health states in order to retain the proportional differences between states. The EAG notes that using the company's mapped utility values substantially increases the incremental QALY gain for dupilumab, which can be clearly seen in the company's scenario analysis using observed CFB utilities (

Table 42), whereby incremental QALYs reduced from [REDACTED] to [REDACTED]. As dupilumab has not demonstrated a survival benefit in patients with CRSwNP, the EAG considers an incremental QALY gain of [REDACTED] considerably high.

The EAG also considers the utility values used to represent the gain from surgery to be a key issue. The EAG's preferred analysis includes a gain of 0.08, sourced from Remenschneider *et al.* 2015.²³ This is considered more appropriate than the value used by the company (0.051 from Soler *et al.* 2011²²) due to it being derived from more recent data and as it is based on EQ-5D-5L rather than SF-6D, which is more in line with the NICE reference case and other utilities used in the base-case. The EAG acknowledges that the data in Remenschneider *et al.* 2015²³ is still considered relatively out of date (2011–2012); however, in light of a lack of an alternative source this is the EAG's preferred option.

While not changed in the EAG base-case analysis, the criteria used to measure response in clinical practice is an area of uncertainty if it differs to that used in the economic model (combination of SNOT-22 and nasal polyp score [NPS]). This is shown in the EAG's additional sensitivity analysis 1, in which the use of responder status based on SNOT-22 only increased the ICER to £76,832 per QALY gained. As discussed in the analysis of the clinical evidence (Section 2.3.4), the response criteria used in the model also differed to the primary outcomes of the clinical trials and, therefore, that used to

assess clinical effectiveness (NPS and nasal congestion [NC]). While the EAG considers the combined criteria used in the base-case analysis to be appropriate, based on feedback from clinical experts, there is uncertainty regarding if this is what will be applied in clinical practice and, therefore, is considered a key issue. The EAG notes that there is also uncertainty regarding whether patients requiring a course of rescue therapy while receiving dupilumab will be classed as non-responders, as was applied in the company's responder analysis. If patients would not be considered non-responders in clinical practice after requiring one course of rescue therapy, it is unlikely that the results of the model are an accurate reflection of this treatment strategy.

Based on patients only receiving dupilumab for the 52-week trial period (SINUS-52), no randomised controlled trial (RCT) data are available on the long-term treatment effect of dupilumab in CRSwNP patients, resulting in high uncertainty in this model input. Following the clarification stage, the company updated their estimates of the annual transition probability from controlled to inadequately controlled for dupilumab to be based on an analysis of the observational AROMA study. While the EAG consider these data to be useful to explore uncertainty in the long-term treatment effect beyond 52-weeks, the EAG has several concerns with the analysis undertaken and, therefore, deems it inappropriate for its base-case analysis (see Section 4.2.4.1 for further details). The EAG notes that using the same approach as the company to inform transition probabilities reduced the EAG's preferred ICER by $\approx$ £2000 (additional sensitivity analysis 3).

In order to further explore the uncertainty in the long-term treatment effect of dupilumab, the EAG conducted an exploratory scenario in which the proportion of patients who lose control each year from year five onwards is [REDACTED] used in the base-case analysis. The EAG notes that while the ICER increased, this was not by a substantial amount.

The EAG also considers there to be uncertainty in the rate of loss of control following revision surgery and so the transition probability to the uncontrolled health state. As much of the identified data on rate of revision surgery is based on time from previous surgery, this is not fully applicable to the model structure. In addition, clinical experts to the EAG noted how the rate of loss of control and revision surgery is highly variable. Although the EAG has some concerns with the methods used to derive the transition probabilities, it is noted that the resulting estimates appear to be aligned with alternative data sources on loss of response and clinical expert opinion. The EAG's exploratory additional sensitivity analysis 7 shows that the ICER increased by quite a large amount when using

the lower probability; the EAG consider this to represent an upper boundary on what the ICER may be with a lower transition rate.

The EAG considers the company's base case analysis to overestimate the cost-effectiveness of dupilumab when taken in addition to ECM. The EAG notes that there are several uncertainties in the assumptions and inputs used in the model, as previously discussed. However, the main driver of the ICER is the method and corresponding estimates used for HRQoL in the model.

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Single Technology Appraisal

Dupilumab for treating severe chronic rhinosinusitis with nasal polyposis [ID6480]

EAG report – factual accuracy check and confidential information check

“Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, [NICE health technology evaluations: the manual](#)).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 28 April 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as **confidential** should be highlighted in turquoise and all information submitted as **depersonalised data** in pink.

Issue 1 Prevalence of CRSwNP in England

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Section 2.2 Background (Page 25)</u>: The EAG reports “[...] an estimated prevalence of 1.6 per 100,000 individuals in the UK adult population in 2013.³”.	Please amend this by: “[...] an estimated prevalence of 4.76 per 100,000 individuals in the UK adult population in 2018.³	In the CS, the prevalence selected by the company to determine the epidemiology in England was based on the more recent source (Benson et al. 2023): “Benson et al. characterised the real-world burden of CRSwNP in the UK (analysis of CPRD and HES medical and prescribing records including 31,728 people with CRSwNP as of 31 December 2018, published in 2023) and reported the prevalence to be 0.476% of the population.¹⁶” Although the data cited by the EAG is referencing an older publication (Hopkins et al. 2021) that the company also presented in the CS, the company would like to amend this value to reflect the	Thank you for highlighting this discrepancy. The proposed amendment has been added to the report.

		prevalence agreed by NICE and NHSE in the BIT (in line with the most recent RW data in England). Please note this has a no impact on the conclusions of the EAR.	

Issue 2 Proportion of AROMA patients with prior surgery (amongst RAS) as a limitation

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Section 2.3.2 Intervention (Page 35)</u>: The EAG cites the “[...] relatively small number who had prior surgery (19.1%)” as a limitation of the AROMA trial in comparison to the SINUS trials to assess long-term outcomes of the intervention, as the patient population proposed by the company (subgroup of patients with prior surgery) was agreed by the EAG.	Please remove the statement: “[...] ~~the relatively small number of patients who had prior surgery (19.1%)~~” from the paragraph.	512 patients out of the 691 patients (74.2%) included in the AROMA trial had at least one prior surgery for CRSwNP at any time before inclusion in AROMA. The company notes that the number mentioned by the EAG concerns patients who had surgery for CRSwNP in the 12 months prior to inclusion in AROMA (132/691 patients, i.e. 19.1%), which is a more restrictive criterion than the one applied to the SINUS population to identify	Thank you for highlighting this factual inaccuracy. The proposed amendment has been added to the report.

		the base case patient population. The company would like to emphasise that the proportion of patients with prior surgery is therefore not a limitation of the AROMA trial (in comparison with the SINUS trials) to assess outcomes of dupilumab. The company notes that this represents about two third of the patients included in the study, which is a similar proportion to that observed in the SINUS trials (63%) and reported by clinicians during the company consultancy meetings.	

Issue 3 Inversion of co-primary endpoints

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Section 2.3.4 Outcomes (Page 36)</u>: The EAG's clinical experts noted that "[...] while patient-reported	Please amend to: "[...] while patient-reported outcomes (PROs) are often considered important outcomes when	Nasal Polyps Score (NPS) is not a patient-reported outcome (PRO), but an objective clinical measure	Thank you for highlighting this factual inaccuracy. The

outcomes (PROs) are often considered important outcomes when determining the effects of treatments for CRSwNP, NPS is not always considered the most reliable PRO”.	determining the effects of treatments for CRSwNP, NC is not always considered the most reliable PRO”.	(nasal polyp score assessed by the clinician via endoscopy). The company believes that the EAG meant Nasal Congestion score (NC) in this statement. Please note this has not impact on the EAR conclusions.	proposed amendment has been added to the report.

Issue 4 Importance of sensory deprivation to patients

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Section 2.3.4 Outcomes (Page 36)</u> : The EAG’s reports that “[...] clinical experts noted that “ As many patients never regain their sense of smell, it is not considered one of the main aims of treatment ”.	Please remove statement: “[...] ~~As many patients never regain their sense of smell, it is not considered one of the main aims of treatment~~ ” from the paragraph.	Sense of smell is one of the main aims of treatment of CRSwNP, and one of the symptoms most important to patients (as reported in Hopkins et al. 2024 – described in the CS) which has been confirmed by the company’s clinical experts, as well as the patient’s roundtable (submitted in the CS appendices). The company believes that this statement is not accurate	This is not a factual accuracy; no change is required. This reflects the views of the EAG’s clinical experts.

		(does not reflect clinical consensus in England, as per the company-led advisory board and consultancy meetings, provided as appendices in the original CS), and that it carries potential to be misinterpreted by the public, as well as the patient advocacy groups. Please note this has not impacted on the EAR conclusions, as the EAG agreed on the use of SNOT-22 to assess outcomes of dupilumab versus ECM, which includes sensory deprivation.	

Issue 5 Mislabelling of tables' columns in sections 3.3.1 and 3.3.2

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Section 3 Clinical Effectiveness (tables 14 to 19)</u> : In tables reporting clinical endpoints in sections 3.3.1 and 3.3.2, titles of the column reporting the mean	Please amend “ Mean (SD) ” by “ Mean change from baseline (SD) ” in tables throughout sections 3.3.1 to 3.3.2.	The company would like to confirm that the values reported in the tables are correct but refer to the mean change from baseline (CFB) rather than the mean value	Thank you for highlighting this factual inaccuracy. The proposed amendment has been added to the report.

change from baseline (CFB) are mislabelled.		(for each endpoint reported in these sections). Please note this has no impact on the EAR conclusions.	

Issue 6 Update of the company base case following clarification questions

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Section 4.2.4 Treatment Effectiveness (Page 72)</u> : “Despite not providing any explanation for the change or explicitly stating that this was part of their updated base-case”.	Please remove this statement from the paragraph.	The updates to the company base-case were clarified in the company post-clarification response document (Question B1).	Thank you for highlighting this factual inaccuracy. The EAG has removed the statement from the paragraph.

Issue 7 Asthma mortality risk ratio applies to all asthma patients

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Section 4.2.6 Mortality (Page 83)</u> : The EAG mentions the company’s use of “[...] increased risk of	Please remove the mention of “severe” from these statements: “[...] increased risk of mortality with ~~severe~~ asthma”.	The meta-analysis referenced in the CS (Xu et al. 2017), as well as the more recent meta-analysis provided in the clarification response (Zhang et al. 2022) both identified a	The EAG has amended the text as proposed by the company.

mortality with severe asthma”. AND “In the CS, it is stated that there is an increased mortality risk with severe asthma; however, the economic model applies the increased risk to all patients with comorbid asthma and not just patients with severe asthma.”	AND “In the company submission, it is stated that there is an increased mortality risk with severe asthma; however, the economic model applies the increased risk to all patients with comorbid asthma and not just patients with severe asthma”	similar mortality RR for all-asthma patients versus the general population mortality. Therefore, the company would like to amend these statements to avoid confusion (the mortality risk ratio [RR] applied to all asthma patients, not only severe asthma patients), as this input is one of the key issues identified by the EAG in the EAR.	

Issue 8 New SINUS EQ-5D regression models

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Section 4.2.7.1 Health-state utility (Page 86)</u>: The EAG mentions the new EQ-5D regression models provided by the company in the clarification response: “[...] with models 5 to 8 being equivalent of 1 to 4, respectively, with the exception of SNOT-22	Please amend this statement with: “[...] with models 5 to 8 being equivalent of 1 to 4, respectively, with the exception of SNOT-22, NPS and their interaction measured by change from baseline”.	As requested by the EAG, the company updated the EQ-5D regression models (based on the pooled SINUS observed data) with change from baseline (CFB) replacing the absolute value for both SNOT-22, NPS, as well as their interaction (in the relevant models). This was done in the clarification	Thank you for highlighting this factual inaccuracy. The proposed amendment has been added to the report.

measured by change from baseline”.		response (question B18). Please note this has no impact on the EAR conclusions.	

Issue 9 Asthma control level in the ECM only arm

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Table 40 Asthma control level (Page 97)</u> : The EAG reports the values from the original CS, which included one typing error (proportion of ECM only patients with controlled asthma).	Please amend “ 15.4% ” by “ 16.7% ” in table 40, for the proportion of patient with controlled asthma in the ECM only group.	The appropriate value of 16.7% was updated in the company clarification response and included in the EAG base case. Please note this has therefore no impact on the EAR conclusions.	Thank you for highlighting this factual inaccuracy. The EAG has updated the value in the report.

Issue 10 Definition of company original subgroup analyses

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Section 5.2.3 Subgroup analyses (Page 103)</u> : The EAG mentions one of the subgroup analyses explored in the original CS: “Patients without prior surgery and with prior type 2 medical	Please amend this statement with: “Patients with prior type 2 medical history including asthma/NSAID-ERD, irrespective of prior surgery status ,”.	As for the subgroup analyses requested by the EAG in the clarification questions and provided by the company in the clarification response, this subgroup of patients was provided in both the ITT	This is not a factual inaccuracy. The EAG’s statement reflects the wording used in the CS. For example, in the CS on page 152, where the company presents the subgroups being described in the EAG report it states “Patients

history including asthma/NSAID-ERD,”.		population, and the population with at least one prior surgery for CRSwNP. Therefore, this statement is inaccurate as it suggests that patients with prior surgery were removed. Please note this has therefore no impact on the EAR conclusions.	with prior type 2 medical history including asthma/NSAID-ERD (i.e., no prior surgery)”.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
<u>Section 4.2.4.1 EAG critique (page 74).</u>	“[...] the number of patients with response data available in the ECM only arm increasing from █ patients in the base-case analysis to █ and from █ in the dupilumab arm to █, shown below in Error! Reference source not found..”.	Please amend the marking to: “[...] the number of patients with response data available in the ECM only arm increasing from █ patients in the base-case analysis to █ and from █ in the dupilumab arm to █, shown below in Error! Reference source not found..”.	Thank you for highlighting the incorrect marking. This has been marked as confidential in the EAG's updated report.