Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende mepolizumab til behandling af svær CRSwNP

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. mepolizumab
2. Forhandlingsnotat fra Amgros vedr. mepolizumab
3. Ansøgers endelige ansøgning vedr. mepolizumab

Til medicinrådet

Høringssvar vedr. vurdering af mepolizumab til behandling af kronisk rhinosinuitis med næsepolypper(CRSwNP)

1. Juli 2022

GSK takker for modtagelsen af vurderingsrapporten for mepolizumab til behandling af patienter med kronisk rhinosinuitis med næsepolypper (CRSwNP).

Vi noterer os, at populationen i SYNAPSE studiet anses som værende mere syge end den danske population med CRSwNP. SYNAPSE studiet er det første og eneste fase III studie, hvor alle inkluderede patienter har været igennem mindst én FESS operation inden inklusion i studiet. Denne tilgang er for at imødekomme den population af patienter, for hvem behandling med systemiske kortikosteorider og/eller kirurgi ikke har ydet tilstrækkelig sygdomskontrol. Dette er i tråd med de danske nyopstillede kriterier for opstart af biologisk behandling, hvor det fremgår som et krav, at patienten har været opereret mindst én gang inden opstart af biologisk behandling. GSK anerkender dog, at 30% af de inkluderede patienter i SYNAPSE studiet havde ≥3 operationer, hvilket kan indikere en patientgruppe med sværere sygdom.

I studiet blev der udført en yderligere præ-specifik analyse på ændringen fra baseline i VAS-score for tab af lugtesans ud fra antallet af tidligere kirurgiske indgreb (Appendix tabel S4). Analysen viser, at der er en større forbedring af lugtesansen (set som et fald i VAS-scoren) for de patienter, der kun har fået udført et kirurgisk indgreb sammenlignet med de patienter, der har fået udført hhv. to eller flere kirurgiske indgreb. Der skal tages højde for, at det er en præ-specifik analyse og udført på en mindre patientgruppe, men det giver et billede af en bedre effekt af mepolizumab på lugtesansen for de patienter, der er mindst syge i SYNAPSE studiet defineret ud fra antallet af tidligere kirurgiske indgreb.

Dertil bemærkes det, at fagudvalget vurderer, at effekten af mepolizumab kan være underestimeret, da en større andel af patienterne i mepolizumab-armen modtog behandling med systemiske kortikosteroider indenfor 12 måneder. Behandling med kortikosteroider reducerer patienternes NPS, og det er derfor muligt at flere patienter i mepolizumab-armen end i komparator-armen stadig har effekt af den sidste behandling med systemiske kortikosteroider.

GSK anerkender og er enige i de betragtninger, som fagudvalget og sekretariatet har gjort sig vedr. effekten af mepolizumab. GSK har ikke yderligere kommentarer til vurderingsrapporten.

Med venlig hilsen

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29.06.2022

ECH og DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	31.08.2022
Leverandør	GSK
Lægemiddel	Nucala (mepolizumab)
Ansøgt indikation	Behandling af svær kronisk rhinosinuitis med næsepolypper

Forhandlingsresultat

Amgros har følgende pris på Nucala (mepolizumab):

Tabel 1: Pris

Lægemiddel	Styrke/dosis/form	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP (DKK)	Rabatprocent ift. AIP
Nucala (mepolizumab)	100 mg/100 mg hver 4. uge/pen	1 stk.	7.772,89	[redacted]	[redacted]
Nucala (mepolizumab)	100 mg/100 mg hver 4. uge/pen	3 stk.	23.318,68	[redacted]	[redacted]
Nucala (mepolizumab)	100 mg/100 mg hver 4. uge/sprøjte	1 stk.	7.772,89	[redacted]	[redacted]

Nucala (mepolizumab) indgik i det udbud, som blev gennemført på baggrund af behandlingsvejledningen indenfor svær astma. Nuværende aftale løber indtil 31.03.2023.

Konkurrencesituationen

Dupixent (dupilumab) er det første lægemiddel til svær kronisk rhinosinuitis med næsepolypper, hvilket betyder, at der med introduktionen af Nucala (mepolizumab) er kommet konkurrence på denne indikation. Dette er naturligvis kun tilfældet såfremt begge lægemidler bliver anbefalet. Både Dupixent (dupilumab) og Nucala (mepolizumab) indgår i behandlingsvejledningen for svær astma.

[redacted]

Samtidig med denne prisregulering vil Amgros publicere et udbud med aftalestart den 01.04.2023 for lægemidler til disse indikationer: svær astma, atopisk eksem og svær kronisk rhinosinuitis med næsepolypper.

Tabel 2: Sammenligning af lægemiddelpriser

Lægemiddel	Styrke/dosis/form	Pakningsstr.	Pakningspris SAIP (DKK)	Antal pakninger pr. 52 uger	Lægemiddelpris pr. 52 uger SAIP (DKK)
Dupixent (dupilumab)	300 mg hver 2 uge	2 stk	[redacted]	13 pakninger	[redacted]
Nucala (mepolizumab)	100 mg hver 4 uge	1 stk	[redacted]	13 pakninger	[redacted]

Status fra andre lande

Norge: Vurdering i gang[1].
England: Endnu ikke anbefalet, der er igangsat er revurdering[2].

Konklusion

[redacted]

[1] Mepolizumab (Nucala) - Indikasjon III (nyemetoder.no)
[2] Project information | Mepolizumab for previously treated severe chronic rhinosinusitis with nasal polyps [ID3817] | Guidance | NICE

Medicinrådet

Application for the assessment of mepolizumab (Nucala®) as an add-on therapy with intranasal corticosteroids for the treatment of adult patients with severe chronic rhinosinusitis with nasal polyps (CRSwNP) for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control

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1. Basic information

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Overview of the pharmaceutical	
Proprietary name	Nucala®
Generic name	Mepolizumab
Marketing authorization holder in Denmark	GSK A/S Delta Park 37, 2665 Vallensbæk Strand, Denmark
ATC code	R03DX09
Pharmacotherapeutic group	Obstructive airways diseases
Active substance(s)	Mepolizumab
Pharmaceutical form(s)	Subcutaneous (SC) injection
Mechanism of action	Mepolizumab is a humanized IgG1 kappa monoclonal antibody specific for interleukin 5 (IL-5). Mepolizumab binds to IL-5 and therefore stops IL-5 from binding to its receptor on the surface of eosinophils. Inhibiting IL-5 binding to eosinophils reduces blood, tissue, and sputum eosinophil levels.
Dosage regimen	The recommended dosage of Nucala® is 100 mg administered subcutaneously every 4 weeks.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Nucala® is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adult patients with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.
Other approved therapeutic indications	Severe eosinophilic asthma

Overview of the pharmaceutical	
Will dispensing be restricted to hospitals?	Yes, BEGR
Combination therapy and/or co-medication	Intranasal corticosteroids as described in the indication for Nucala®.
Packaging – types, sizes/number of units, and concentrations	100 mg/mL, single-dose, prefilled autoinjector or single-dose prefilled syringe. Store in the refrigerator between 2°C to 8°C. Do not freeze or shake.
Orphan drug designation	Nucala® had orphan drug status, however, was withdrawn when the new indications were submitted in October 2020.

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2. Abbreviations

AE	Adverse event
AERD	Aspirin-exacerbated respiratory disease
CFB	Change from baseline
CFTR	Cystic fibrosis transmembrane conductance regulator
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CRS	Chronic rhinosinusitis
CRSsNP	Chronic rhinosinusitis without nasal polyps
CRSwNP	Chronic rhinosinusitis with nasal polyps
CT	Computed tomography
DMC	Danish Medicines Council
DRG	Diagnosis related group
DSAR	Danish Severe Asthma Registry
EPOS	European Position Paper on Rhinosinusitis and Nasal Polyps
EU	European Union
FESS	Functional Endoscopic Sinus Surgery
GSK	GlaxoSmithKline
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health related quality of life
IL-5	Interleukin 5
INCS	Intranasal corticosteroids
IQR	Interquartile range
ITT	Intention-to-treat
KG	Kilogram
Mcg	Microgram
MCID	Minimum clinically important difference
Mg	Milligram
NCS	Nasal Congestion Score (Nasal Obstruction VAS)
NLM	National Library of Medicine
NP	Nasal polyp
NSAID	Nonsteroidal anti-inflammatory drugs
NSAID-ERD	NSAID-exacerbated respiratory disease
OCS	Oral corticosteroids
OR	Odds ratio
QALY	Quality adjusted life years
Q4W	Once every 4 weeks
QoL	Quality of life
RR	Relative risk
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SF-36	36-Item Short Form Survey
SF-6D	Short-Form Six-Dimension
SmPC	Summary of Product Characteristics

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SNOT-22	Sinonasal outcome test-22
SoC	Standard of care
SYNAPSE	StudY in NAsal Polyps Patients to Assess the Safety and Efficacy of Mepolizumab
TH2	Type two helper cells
US NIH	United States National Institute of Health
VAS	Visual analogue scale
WOCBP	Woman of childbearing potential

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3. Tables and Figures

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4. Summary

Indication and population covered in this application

Mepolizumab (Nucala®) is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adult patients with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control. The indication of mepolizumab is in line with the population covered in the SYNAPSE study - all patients included in the SYNAPSE study had undergone surgery for nasal polyps. Chronic rhinosinusitis (CRS) is a condition with chronic inflammation in nose and sinonasal cavity, which affects 5-12% of the population[4]. Nasal polyps are inflammatory outgrowths of sinonasal tissue that are frequently associated with a subset of chronic rhinosinusitis (CRS), named chronic rhinosinusitis with nasal polyps (CRSwNP). CRS can also occur without nasal polyps (CRSsNP). In CRSwNP, nasal polyps are benign and typically develop bilaterally in the sinonasal cavity. Among all patients with chronic rhinosinusitis (CRS), approximately 25% to 30% have CRSwNP. CRSwNP is associated with other important medical conditions that can influence disease severity, including acute rhinosinusitis, allergic rhinitis, chronic rhinitis, asthma, gastroesophageal reflux disease, and sleep apnea[7]. The underlying mechanisms that contribute to the chronic sinonasal inflammation observed in CRSwNP are not completely defined. CRSwNP is typically characterized by eosinophilic inflammation driven by an increased number of eosinophils in tissue or the bloodstream. Inflammation in eosinophilic CRSwNP is controlled by type 2 cytokines such as interleukin (IL)-13 and IL-5. IL-5 is known to be a key driver of eosinophil infiltration and associated tissue inflammation and damage, and therefore plays an important role in the development of the more severe clinical symptoms associated with eosinophilic CRSwNP compared to non-eosinophilic CRSwNP[15]. CRSwNP carries a substantial burden that has a significant impact on health-related quality of life (HRQoL) making this disease clinically important to identify, evaluate, and treat[1].

Commonly used therapeutic options for CRSwNP including use of corticosteroids or endoscopic sinus surgery in more advanced cases is insufficient, especially when CRSwNP is recurrent. Patients presenting with a symptomatic recurrence within 3 years of surgery are reported to have a high risk of treatment failure, defined as the need for further surgery[12]. Thus, there is an unmet need for effective therapeutic strategies in this area.

There is significant direct and indirect patient and society costs associated with CRSwNP. Among patients with CRSwNP and comorbid asthma or non-steroidal anti-inflammatory drugs- exacerbated respiratory disease (NSAID-ERD), increased disease severity associated with type 2 inflammation is additionally characterized by higher costs and health care utilization[9-11].

In Denmark, it is estimated that the prevalence of CRS is 9% of the population and 4% of the population is diagnosed with CRSwNP [13]. A study published in 2021 in Denmark reported that an average of 120 operated patients annually, will have revision surgery within seven years and therefore, may benefit from treatment with biologics as an alternative option to revision surgery [14].

Mepolizumab is expected to be used according to the indication: If CRSwNP is recurrent and refractory among patients who have undergone nasal polyp surgery and where the disease is still not controlled and are eligible for anti-IL-5 treatment. The patient population eligible for treatment with mepolizumab is expected to be in line with the estimated population for treatment with biologic drugs, provided by the scientific committee, i.e., 120 patients in 2021.

The intervention

Mepolizumab is a humanised monoclonal antibody that selectively binds to and inactivates interleukin-5 (IL-5). IL-5, which is derived from type two helper cells (TH2), plays a major role in the development and release of eosinophils. Mepolizumab inactivates IL-5, thereby inhibiting eosinophilic inflammation[15]. Multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) are involved in inflammation. Mepolizumab, by inhibiting IL-5 signaling, reduces the production and survival

of eosinophils; however, the mechanism of mepolizumab action in asthma and CRSwNP has not been definitively established.
Patients with severe chronic rhinosinusitis with nasal polyps often require nasal surgery, and those with eosinophil-rich nasal polyps have a higher postoperative recurrence rate. As such, anti-interleukin (IL)-5 therapies might be an effective treatment option for these patients[15].
Mepolizumab is expected to be used as an add-on with intranasal corticosteroids if CRSwNP is not controlled on corticosteroids or surgery or both[16]. Mepolizumab may be self-administered by the patient or administered by a caregiver if their healthcare professional determines that it is appropriate, and the patient or caregiver are trained in injection techniques. For CRSwNP patients, the dosage in clinical practice is expected to be 100 mg administered as a single subcutaneous (SC) injection into the upper arm, thigh, or abdomen once every 4 weeks.

Mepolizumab administered as a pre-filled pen or syringe can be self-administered by the patient or a caregiver once every four weeks. This ease of administration can be an advantage for patients who either cannot or are not willing to visit healthcare providers.
European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020 recommends minimizing systemic corticosteroid courses to fewer than two per year in partly controlled or uncontrolled nasal polyps and reduce the proportion of patients receiving surgery[4].
By deactivating and reducing the survival time of eosinophils in NP through IL-5 inhibition, mepolizumab can potentially reduce number of surgeries and courses of corticosteroids[15].

Comparators
Comparator for mepolizumab is placebo in addition to the standard of care (which includes mometasone furoate intranasal spray for at least 8 weeks, saline nasal irrigations, systemic corticosteroids, or antibiotics, or both). This is in line with EPOS 2020[4].
Efficacy Outcomes
Primary and secondary efficacy endpoints from the SYNAPSE (StudY in NAsal Polyps Patients to Assess the Safety and Efficacy of Mepolizumab) study [15], a phase 3 clinical trial, comparing mepolizumab and placebo patients were assessed in the application. The co-primary endpoints in the SYNAPSE study were:

- change from baseline in total endoscopic nasal polyp score at week 52 and
- change from baseline in mean nasal obstruction visual analogue scale (VAS) score during weeks 49–52

Secondary endpoints included were:

- time-to-first nasal surgery until week 52 (key secondary endpoint)
- change from baseline in mean overall VAS symptom score during weeks 49–52
- change from baseline in Sinonasal Outcomes Test (SNOT)-22 total score at week 52
- proportion of patients requiring systemic corticosteroids for nasal polyps until week 52
- change from baseline in mean composite VAS score (combining scores for nasal obstruction, nasal discharge, throat mucus, and loss of smell) during weeks 49–52
- change from baseline in mean VAS score for loss of smell during weeks 49–52

Relevant exploratory endpoints included were:

- proportion of proportion of patients with a decrease of 8.9 points or more from baseline in SNOT-22 total score in the absence of surgery

The efficacy endpoints chosen are representative of the outcomes available in the medical literature for nasal polyps and also mentioned in the Danish Medicines Council (DMC) protocol for assessment regarding dupilumab for treatment of CRSwNP.
Efficacy results
Mepolizumab significantly reduced the risk of repeat surgery for nasal Patients in the mepolizumab group had 57% reduction in the risk of nasal polyp surgery compared to placebo. Efficacy results demonstrate that both co-primary

endpoints (nasal polyp size and nasal obstruction) showed a significant benefit at 52 weeks with mepolizumab when compared with placebo, administered in addition to the standard of care.
The co-primary endpoints in the SYNAPSE showed:

- Mepolizumab significantly reduced baseline NPS at Week 52. Patients in the mepolizumab group had a significantly greater reduction in the total NPS compared to placebo (median difference in total endoscopic NPS: -0.73 [95%CI: -1.11, -0.34], p<0.0001); reductions in baseline NPS was seen as early as 4 weeks in the group of patients treated with mepolizumab.
- Mepolizumab significantly reduced nasal obstruction VAS score patients in the mepolizumab group had a significantly greater reduction in the nasal obstruction VAS score during weeks 49-52 (median difference in nasal obstruction VAS score: -3.14 [95%CI: -4.09, -2.18; p<0.0001); reductions nasal obstruction VAS score was seen as early as 4-8 weeks in the group of patients treated with mepolizumab.
- The secondary endpoints included in SYNAPSE: Mepolizumab led to significant improvements in loss of smell and composite VAS scores. During weeks 49-52 the median reduction from baseline in the loss of smell VAS symptom score was significantly greater in the mepolizumab group compared with placebo (-0.53 vs 0; p=<0.001; adjusted p-value=0.020). from week 4 onwards, loss of smell VAS scores was consistently greater in the mepolizumab group than the placebo group
- Mepolizumab led to significant improvements in baseline HRQoL as measured with SNOT-22. The total SNOT-22 score was assessed every 4 weeks until week 52 (adjusted difference in medians= –16.49, 95% confidence interval (CI) (–23.57 to –9.42)), p=0.0032). The proportion of mepolizumab patients achieving minimal clinically important difference (MCID) of 8.9 points or more for SNOT-22 scores from baseline was significantly higher than placebo patients.

Given that the goal of the treatment of CRSwNP is to reduce the number and the severity of the symptoms[25] mepolizumab was shown to be an effective add-on treatment option targeting the eosinophilic inflammation.

Safety of mepolizumab [redacted] The following safety outcomes were compared: adverse events (AE), serious adverse events (SAE), treatment discontinuation due to AE, study withdrawal due to AE. There was no statistical difference between mepolizumab and placebo for any of the safety outcomes which indicates similar safety profiles. Though, based on the percentages of patients with AE, mepolizumab tends to have a more favourable safety profile compared to placebo. Findings reported in Summary of Product Characteristics (SmPC) for Nucala® indicate that no additional adverse reactions were identified to those reported in the severe eosinophilic asthma studies. The safety profile for mepolizumab in patients with severe refractory eosinophilic asthma has been studied in open extended studies with an average treatment of 2.8 years (between 4 weeks to 4.5 years) showed that the side effect profile was in general consistent with the three placebo controlled registration studies[16].
[redacted]

Relevance to the Danish context
The population included in the SYNAPSE study in this application are generally comparable with the Danish patients. Patients enrolled in the SYNAPSE study were recruited from different countries around the world, including countries from Europe. Guidance from DMC regarding use of biologic drugs for CRSwNP recommends patient criteria that are very similar to the inclusion criteria of the SYNAPSE study. A recently published study in Denmark included all adult patients registered in the Danish National Patient Registry who had undergone first endoscopic sinus surgery for CRSwNP from 2012–2018. The authors reported that an average of 120 operated patients annually, will have revision surgery within seven years and may benefit from treatment with biologics as an alternative option to revision surgery [14].

Structure and results of the health economic analysis

A cost-effectiveness model including QALY has been carried out in Excel. The model will take a restricted societal perspective including drug-, administration-, surgery, patient- and transportation costs. The model will compare mepolizumab to standard of care, using a lifetime time horizon.

The results from the cost-effectiveness model showed total treatment costs of mepolizumab of DKK 1,612,411 and for the comparator standard of care DKK 34,217. The incremental cost-effectiveness ratio was [redacted] per QALY. The incremental QALY gain for treatment with mepolizumab compared to standard of care was [redacted]
The budget impact of recommendation of mepolizumab as standard treatment for patients with CRSwNP was DKK 4,087,811 year 1 and DKK 9,343,569 year 5.

Conclusion
Findings from the SYNAPSE study show that the addition of mepolizumab to the current standard of care for patients with refractory, recurrent CRSwNP generally results in significant improvements in efficacy outcomes. By deactivating and reducing the survival time of eosinophils in CRSwNP through IL-5 inhibition, mepolizumab can potentially reduce inflammation of the mucosa, and restore aeration of the nasal passage and sinuses through polyp volume reduction." Moreover, with a favorable safety profile and as pre-filled syringe or pen administered by patient or caregiver once every 4 weeks, it has the potential to remove any adherence challenges that may be encountered and thus, in the long term, potentially result in better disease control. From the economic model it can be concluded that there are additional costs associated with treatment with mepolizumab, however, data suggest a potential to prevent revision surgery for a number of these patients, reduce symptoms and improve HRQoL.

5. The patient population, the intervention and choice of comparators

5.1 The medical condition and patient population

5.1.1 CRSwNP

Nasal polyps are inflammatory outgrowths of sinonasal tissue that are frequently associated with a subset of chronic rhinosinusitis, called chronic rhinosinusitis with nasal polyps (CRSwNP). In this condition, nasal polyps are benign and typically develop bilaterally in the sinonasal cavity. Among all patients with chronic rhinosinusitis (CRS), approximately 25% to 30% have CRSwNP. However, CRSwNP is associated with significant morbidity and decreased quality of life making this disease clinically important to identify, evaluate, and treat[6].

In order to diagnose CRSwNP, patients must report the presence of anterior or posterior rhinorrhea, nasal congestion, hyposmia and/or facial pressure or pain lasting for greater than 12 weeks duration. However, these subjective findings are neither sensitive nor specific for CRSwNP alone and are used to also characterize patients who have chronic rhinosinusitis without nasal polyps (CRSsNP)[2]. Therefore, in addition to subjective assessments of CRSwNP, there must be objective evidence of sinonasal inflammation and nasal polyps on sinus computed tomography (CT) scan and/or nasal endoscopy. Patients with CRSwNP on average have more extensive sinus disease, have worse health outcomes after surgery and are more likely to require revision sinus surgeries than CRSsNP patients[17].
CRSwNP is a disease of middle age with the average age of onset being 42 years and the typical age of diagnosis ranging from 40–60 years[2]. Most commonly, nasal polyps present as bilateral inflammatory lesions originating in the ethmoid sinuses and projecting into the nasal airway beneath the middle turbinate. In contrast, isolated nasal lesions that present medial to the middle turbinate are concerning for neoplasm. Presumptive nasal polyps found in patients younger than 20 years or older than 80 years also raise suspicion for other clinical conditions. In children, cystic fibrosis becomes a concern[18] and unilateral nasal growths suggest a possible encephalocele. In adults, new onset polyps at an advanced age or in atypical locations suggest the possibility of neoplasm[6].

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In the SYNAPSE study the study participants were 49 years of age and 65% were men. When compared to males, females had significantly enhanced radiographic evidence of sinus disease, were more likely to be taking systemic corticosteroids at the time of sinus surgery, and more often required revision sinus surgeries[3].
However, a 2015 study by Stevens and colleagues examining CRSwNP patients undergoing sinus surgery at a tertiary care centre reported that females with CRSwNP had more severe disease than males Higher prevalence of CRSwNP was reported among men than women[4]. A 2021 national calculation found the male/female-ratio in the study population was 2:1 and the mean age was 53 years[19].
The underlying mechanisms that contribute to the chronic sinonasal inflammation observed in CRSwNP are not completely defined. It is hypothesized that an impaired sinonasal epithelial barrier could lead to increased exposures to inhaled pathogens, antigens and particulates that, in the setting of a dysregulated host immune response, could promote chronic inflammation[6]. The genetics of this disease are also not well understood, and no single polymorphism or genetic mutation has been consistently or reproducibly associated with CRSwNP to date with the exception of the cystic fibrosis transmembrane conductance regulator (CFTR) mutation in cystic fibrosis[5]. There is also no single validated biomarker that can reliably predict if a patient has CRSwNP versus CRSsNP, acute sinusitis, or no sinus disease at all.

CRSwNP is typically characterized by eosinophilic inflammation driven by an increased number of eosinophils in tissue or the bloodstream. Inflammation in eosinophilic CRSwNP is controlled by type 2 cytokines such as interleukin (IL)-13 and IL-5. IL-5 is known to be a key driver of eosinophil infiltration and associated tissue inflammation and damage, and therefore plays an important role in the development of the more severe clinical symptoms associated with eosinophilic CRSwNP compared to non-eosinophilic CRSwNP[15].

In a recently published Danish study the potential role of biological treatment for CRSwNP in Denmark is discussed and the number of eligible patients is estimated based on the calculation of patients receiving multiple surgeries for CRSwNP. This calculation links very well to the eligibility criteria for biological treatment stated by the EPOS 2020 and the population included in the SYNAPSE study. Data on Type 2 inflammation was not part of the Danish study but out

of the number of CRSwNP patients who had revision surgery, 34% were registered with a diagnosis of asthma, and 8,2% with allergic rhinitis. The number of patients with comorbidity were lower than expected, compared to a previous study performed at Rigshospitalet, Denmark. This study found that 65% of patients operated for CRSwNP had comorbid asthma when tested and that half were undiagnosed prior to the study[19].

CRSwNP is often associated with other important medical conditions that can influence disease severity, including acute rhinosinusitis, allergic rhinitis, chronic rhinitis, asthma, gastroesophageal reflux disease, and sleep apnea[7]. It is unclear, however, how these conditions could contribute to the development of CRSwNP[6]. In patients with CRSwNP, the prevalence of comorbid asthma is reported to be much higher[19, 20] than the prevalence of asthma in the general US population[21]. Apart from these comorbidities, NSAID-ERD is one of the most serious, recurrent, and treatment-resistant comorbidities associated with CRSwNP, placing an especially high clinical burden on affected patients. NSAID-ERD is a difficult-to-treat disease both from a pharmacologic (a requirement for high-dose systemic corticosteroids to manage asthma, if present) and a surgical perspective (frequent recurrence after surgeries).

From a patient perspective, CRSwNP carries a substantial burden that has a significant impact on health-related quality of life (HRQoL). Compared to those with CRSsNP, patients with CRSwNP experience higher symptom scores and greater severity of clinical disease[8]. The presence of CRSwNP is not only associated with greater burden of disease at presentation but also with worse disease severity despite sinonasal surgery. The impact of CRSwNP on overall HRQoL has been reported to be comparable with other chronic diseases such as chronic obstructive pulmonary disease (COPD), asthma, and diabetes [22]. CRSwNP not only has a major impact on general and disease-specific HRQoL but also impairs sleep quality and nasal patency, and increases daytime sleepiness and the risk of sleep apnea[23], all of which may negatively affect patient mental health.

CRSwNP has significant direct and indirect costs to patients and society. Among patients with CRSwNP and comorbid asthma or NSAID-ERD, increased disease severity associated with type 2 inflammation is additionally characterized by higher costs and health care utilization[9]. Costs to the patient with CRS relating to absenteeism, presenteeism, and lost work productivity are likely to be substantial[10, 11].

Commonly used therapeutic options for CRSwNP including use of corticosteroids or even endoscopic sinus surgery in more advanced cases is insufficient, especially when CRSwNP is recurrent. It has been reported that patients presenting with a symptomatic recurrence within 3 years of surgery have a high risk of treatment failure, defined as the need for further surgery[12]. Time to failure after previous surgery may be used to help select patients who may not benefit from current treatment pathways and may be good candidates for alternative strategies, including biologicals[12]. Thus, there is an unmet need for effective therapeutic strategies in this area.

Recent advances in the understanding of the distinct inflammatory mechanisms involved have led to encouraging progress in the development of targeted biologic pharmacotherapies[24]. Patients who may not benefit from current treatment pathways can be good candidates for alternative strategies, including biologicals.

Figure 1: Place of mepolizumab in the treatment pathway.

The underlying mechanisms that contribute to the chronic sinonasal inflammation observed in CRSwNP are not completely defined and is multifactorial[5, 6] The most common cause of CRSwNP is type 2 inflammation and approximately 50% of the patients with CRSwNP in a Danish ear-nose-throat practice also suffers from asthma disease but also this number varies depending on the reference[25]. The reason for the conflicting data on the number of patients with asthma or allergic rhinitis as comorbidity could be that the treatment of CRSwNP patients with biological compounds are new and good clinical practice requires a collaboration between a specialist within Ear-nose-throat

specialist and a pulmonologist in order to determine if the patient is suffering from type 2 inflammation. CRSwNP is often associated with other important medical conditions that can influence disease severity, including acute rhinosinusitis, allergic rhinitis, chronic rhinitis, asthma, gastroesophageal reflux disease, and sleep apnea[7].

5.2 Patient populations relevant for this application

The patient populations relevant for this application are:

- adult patients with severe, refractory, CRSwNP despite previous surgery and standard treatment with corticosteroids, and therefore require add-on treatment.

In Denmark, it is estimated that prevalence of CRS is 9% of the population and 4% of them diagnosed with CRSwNP [13]. A recently published study in Denmark included all adult patients registered in the Danish National Patient Registry who had undergone first endoscopic sinus surgery for CRSwNP between 2012–2018. The authors reported that an average of 120 operated patients annually will have revision surgery within seven years and may benefit from treatment with biologics as an alternative option to revision surgery[14]. A recent protocol from DMC for assessment regarding dupilumab for treatment of CRSwNP has also suggested that approximately 120 patients annually with refractory CRSwNP can benefit from biologic use.

The calculations are based on repeated surgery(more than one), the number of patients who do not respond to surgery (or patients that are not eligible or do not wish to be operated) and the estimated number of patient without sufficient disease control.[25].

Based on the guidance from DMC[25] and the study published by Eriksen et al.[14], it is expected that the number of patients eligible for new biologic treatments annually will be around 120. This population estimate will be used to inform the budget impact calculation in the economic part of this application.

Table 1: CRSwNP: Incidence and prevalence in the past 5 years

Year	2016	2017	2018	2019	2020
Incidence in Denmark	3602[1]	3623[2]	3640[3]	3653[4]	3659[5]
Prevalence in Denmark	229,821¥	231,142¥	232,240¥	233,098¥	233,488¥

[1]Incidence rate of 0.627/1000 patients as reported by Larsen et al**[26]** multiplied with Danish population in 2016 (5,745,526 inhabitants)**[27]**.
[2]Incidence rate of 0.627/1000 patients as reported by Larsen et al **[26]** multiplied with Danish population in 2017 (5,778,570 inhabitants)**[27]**.
[3]Incidence rate of 0.627/1000 patients as reported by Larsen et al **[26]**multiplied with Danish population in 2018 (5,806,015 inhabitants)**[27]**.
[4]Incidence rate of 0.627/1000 patients as reported by Larsen et al **[26]** multiplied with Danish population in 2019 (5,827,463 inhabitants)**[27]**.
[5]Incidence rate of 0.627/1000 patients as reported by Larsen et al **[26]** multiplied with Danish population in 2020 (5,837,213 inhabitants)**[27]**.

¥ Prevalences calculated by multiplying 0.04 with the population reported in the respective year. Population of each year included in the above footnote. CRSwNP, Chronic rhinosinusitis with nasal polyps.

The expected number of patients eligible for the new treatment during the next 5 years is shown in Table 2 below:

Table 2: Estimated number of patients eligible for treatment

Year	2021*	2022*	2023*	2024*	2025*
Number of patients in Denmark who are expected to use the biologic pharmaceutical in the coming years	120	240	360	480	600

*Using 120 as annual number of refractory CRSwNP patients expected to use biologic pharmaceuticals in coming years[14, 25]
CRSwNP, Chronic rhinosinusitis with nasal polyps.

Severe CRSwNP is by EPOS2020 characterized by a patient reported VAS-score (Visual Analog Scale) > 7. The scale goes from 0 to 10 and 10 is related to the highest disease burden.
In the recent DMC protocol[25] the following criteria has been suggested for the treatment of severe CRSwNP with biological treatment:
The patient has to have bilateral polyps and have undergone one or more FESS-surgeries (or not able to tolerate surgery) as well as meet three of the following criteria

- Type 2 inflammation
- In need of systemic corticosteroid courses (or systemic corticosteroid courses is contraindicated)
- Significantly impaired quality of life
- Significantly impaired sense of smell
- Diagnosed with asthma

In the SYNAPSE trial the patients had to have at least one nasal surgery (defined as any incision (cutting open) of the paranasal sinuses and removal of polyp tissue from the nasal cavity(polypectomy) and the sinuses) in the past 10 years. In addition, patients required stable maintenance therapy with intranasal spray medication for at least 8 weeks before screening and displayed 2 or more different symptoms for at least 12 weeks before screening (nasal blockage, obstruction, and congestion, or nasal discharge (anterior or posterior drip), with one or more of the following symptoms: nasal discharge, facial pain or pressure, and reduction or loss of smell. These symptoms are relatable to the description of an uncontrolled CRSwNP patient defined in the EPOS 2020 guideline.

The baseline characteristics for the patients included in the SYNAPSE study did fulfil several of the above criteria:

- All patients had at least one nasal surgery
- The mean overall symptom VAS score in the SYNAPSE study reported as baseline characteristics was 9 (15).
- 50% of the participants had systemic corticoid courses for nasal polyps in the past 12 months
- Mean loss of smell VAS score (scale 0-10) on 9,6.
- 68-74% had an asthma diagnosis

5.2.1 Subpopulations

In the SYNAPSE study, an overall number of patients 289 (71%) had comorbid asthma and 108 (27%) had AERD. Blood eosinophilic count at baseline overall was 395 cells/µL. [redacted] Patients with uncontrolled asthma disease was excluded by the following exclusion criteria:

- Patients who had an asthma exacerbation requiring admission to hospital within 4 weeks of screening.
- Patients that have taken part in previous mepolizumab, reslizumab, dupilumab, or benralizumab studies.
- Use of systemic corticosteroids (SCS; including oral corticosteroids) within 4 weeks prior to screening or planned use of such medications during the double-blind period.
- Intranasal corticosteroid dose changes within 1 month prior to screening.

In the randomization asthma exacerbation were not allowed during run-in period. An asthma exacerbation is defined as worsening of asthma requiring SCS (intravenous or oral corticosteroids) for at least 3 days or a single intramuscular corticosteroid dose and/or emergency department visit, or hospitalisation.
Overall, 289 (71%) of patients had comorbid asthma and 108 (27%) had AERD. In patients with comorbid asthma, exacerbation rates were 67% lower (rate ratio 0·33 [95% confidence interval (CI): 0·12, 0·95]) and mean Asthma Control Questionnaire (ACQ)-5 score improved by 0·66 points (least squares mean difference: -0·66 [95% CI: -0·92, -0·40]) with mepolizumab compared with placebo. Mepolizumab improved endoscopic NP score and nasal obstruction VAS score irrespective of comorbid asthma or AERD[15].

5.3 Current treatment options and choice of comparators

5.3.1 Current treatment options

Treatments of CRSwNP is primarily symptom relieving as no cure is available. The purpose of treatment is to reduce the number of symptoms. Medical treatment for CRS, consists of daily saline irrigations and nasal steroid for affected patients. Intranasal corticosteroids can also be used to decrease nasal polyp size, lessen sinonasal symptoms, and improve patient quality of life[29]. In case of narrowing of the sinonasal space, with thick mucous membrane and polyps, one can advantageously switch from spray of nasal steroid to drops. In case of secretion, supplement with antibiotic treatment might be needed, and in case of polyp disease the use of systemic corticosteroids can be beneficial to reduce the symptom severity. Oral corticosteroids can also reduce polyp size and improve symptoms, however, long term use of corticosteroids should be administered with caution due to the well-documented adverse effects associated with chronic and/or intermittent use of OCS[30].
Patients with significant sinonasal disease and/or those who fail medical management should be evaluated for functional endoscopic sinus surgery (FESS)[6]. FESS surgery is performed in general anesthesia and is most often assisted with a CT-scan (CAS-FESS). The aim of surgery is to complete polyp removal from relevant subsites and wide opening to the sinuses. Nasal sinus surgery improves air flow in the nose and headache, however, in severe cases and especially in patients with asthma, the effect is often transient. In patients with impaired sense of smell and secretion, surgery does not always help, and here biological treatment could be beneficial to decrease the patient's symptoms and improve quality of life[4].

Surgery does not control the eosinophilic inflammation in CRSwNP and therefore nasal polyps have a strong tendency to recur after surgery, often requiring repeated surgery. 40% of patients who undergo nasal polyp surgery experience polyp and associated symptom recurrence within 18 months of surgery. Importantly, patients with elevated eosinophil levels are up to three times more likely to require repeat treatment than patients with lower levels (81.8% vs. 25.0%, respectively) [38].
Mepolizumab, an established treatment for eosinophilic disease, is the first IL-5 targeted biologic that addresses the underlying cause of CRSwNP and effectively inhibits the eosinophilic inflammation which drives nasal polyp recurrence in CRSwNP patients[16].

5.3.2 Choice of comparators

The comparator for mepolizumab was placebo in addition to the standard of care (which included mometasone furoate intranasal spray for at least 8 weeks before screening and during the study, saline nasal irrigations, systemic corticosteroids or antibiotics, or both)[15].
This is in line with EPOS 2020 which states that the standard of care consisted of intranasal corticosteroids, short courses of systemic corticosteroids, and nasal surgery [4].

5.3.3 Description of the comparators

The placebo used was a clear to opalescent, colourless sterile solution for SC injection supplied in a single-use, safety syringe. Placebo was used in conjunction with standard of care (mometasone furoate intranasal spray, saline nasal irrigations, systemic corticosteroids or antibiotics, or both).

5.4 The intervention

Mepolizumab is a humanised monoclonal antibody that selectively binds to and inactivates interleukin-5 (IL-5). IL-5, which is derived from TH2, plays a major role in the development and release of eosinophils. Mepolizumab inactivates IL-5, thereby inhibiting eosinophilic inflammation[15]. Multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) are involved in

inflammation. Mepolizumab, by inhibiting IL-5 signaling, reduces the production and survival of eosinophils; however, the mechanism of mepolizumab action in asthma and CRSwNP has not been definitively established[16].

Mepolizumab is currently recommended in the DMC's drug recommendation and treatment guidelines regarding biological drugs for the treatment of patients with severe eosinophilic asthma [31]. The recommended dose is 100 mg mepolizumab administered as a single subcutaneous (SC) injection into the upper arm, thigh, or abdomen every 4 weeks, for asthma patients 12 years and older. For CRSwNP adult patients the dosage in clinical practice is also expected to be 100 mg administered as a single SC injection into the upper arm, thigh, or abdomen once every 4 weeks[16].

Mepolizumab injection is intended for use under the guidance of a healthcare provider. The pre-filled pen or pre-filled syringe should be used for SC injection only. Mepolizumab may be self-administered by the patient or administered by a caregiver if their healthcare professional determines that it is appropriate, and the patient or caregiver are trained in injection techniques. For self-administration, the recommended injection sites are the abdomen or thigh. A caregiver can also inject mepolizumab into the upper arm. Proper training is required in SC injection technique and on the preparation and administration of injection prior to use[16].

Treatment with mepolizumab is intended for long term treatment. The need to continue mepolizumab therapy should be considered at least on an annual basis as determined by physician assessment of the patient's disease severity and level of symptom control, according to the Summary of Product Characteristics (SmPC)(Table 68). Mepolizumab is expected to be used as an add-on if CRSwNP is not controlled on corticosteroids. Systemic or intranasal corticosteroids should not be stopped abruptly upon initiation of therapy with mepolizumab. Corticosteroids should be decreased appropriately, if necessary, under medical supervision[16].

Monitoring of the initial treatment of mepolizumab can occur during healthcare visits. Acute and delayed systemic reactions, including hypersensitivity reactions (e.g., anaphylaxis, urticaria, angioedema, rash, bronchospasm, hypotension), have occurred following administration of mepolizumab. These reactions generally occur within hours of administration, but in some instances have a delayed onset (i.e., typically within several days). These reactions may occur for the first time after a long duration of treatment[16]. In a placebo-controlled study in patients with CRSwNP, the most commonly reported adverse reactions during treatment were nasopharyngitis (25%) and headache (18%)[15].

A benefit of clinical significance with mepolizumab is the minimal training required and ease of administration by the patient or caregiver, at home. Administration of the drug once every 4 weeks either by the patient or caregiver is advantageous for patients who either cannot or are not willing to visit healthcare settings.

6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

Literature searches were performed on 13 August 2021. The searches were performed in Cochrane Central Register of Controlled Trials (Wiley) and PubMed via National Library of Medicine (NLM). To identify information on trials in progress, searches were performed in Clinicaltrials.gov (via https://clinicaltrials.gov/) and the EU clinical trials register (via https://www.clinicaltrialsregister.eu/). The search on the clinical trials registers was performed on 15 August 2021. The search strategies are provided in Appendix A – Literature search for efficacy and safety of intervention and comparators.

Based on the objectives of the literature search as described in Appendix A – Literature search for efficacy and safety of intervention and comparators., a phase 3 study by Han et al. 2021 evaluating mepolizumab for CRSwNP was considered as the only appropriate study to be included in this application [15].

6.2 List of relevant studies

The relevant study is listed below in Table 3. For detailed information about this included study, please refer to Appendix B Main characteristics of included studies.

Table 3: Relevant studies included in the assessment

Reference	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of
Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomised, double-blind, placebo-controlled, phase 3 trial Han et al., Lancet Respir Med 2021 [15]	SYNAPSE	NCT03085797	Start date: March 21, 2017 Results first posted: December 17, 2020 Last updated posted: August 3, 2021	Mepolizumab vs. placebo for adults with recurrent, refractory CRSwNP

CRSwNP, Chronic rhinosinusitis with nasal polyps

Risk of bias of the above study is shown in Table 62 , Appendix A – Literature search for efficacy and safety of intervention and comparators

7. Efficacy and safety

7.1 Efficacy and safety of mepolizumab compared to placebo for patients with recurrent, refractory CRSwNP

7.1.1 Relevant studies for the recurrent, refractory CRSwNP population

As stated in the previous section, SYNAPSE, the phase 3 trial comparing mepolizumab with placebo, administered in addition to the standard of care among refractory CRSwNP patients, was considered as the most relevant study for this application.

An overview of the study is shown in Table 4. Detailed study characteristics for the study are described in Appendix B Main characteristics of included studies. For baseline characteristics of patients included in the study, please see Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety. Relevant results for the study are discussed in Section 7.1.2.

Table 4: Overview of the included study

Study ID	Duration of treatment	Eligible intervention arms	Number(N)	AE n(%)	SAE n (%)	Study withdrawal due to AE n (%)	Treatment discontinuation due to AE n (%)
NCT03085797[15] , ITT population	52 weeks	Mepolizumab 100mg q4w	206	169 (82%)	12 (6%)	0	4 (2%)

Study ID	Duration of treatment	Eligible intervention arms	Number(N)	AE n(%)	SAE n (%)	Study withdrawal due to AE n (%)	Treatment discontinuation due to AE n (%)
		Placebo	201	168 (84%)	13 (6%)	1 (1%)	4 (2%)

AE, Adverse Event; SAE, Serious Adverse Events; q4w, once every fourth week; ITT, intention-to-treat

7.1.1.1 Differences between studies

Not relevant as only one study is discussed in this application.

7.1.1.2 Validity of studies

Using the guidance document to assess risk of bias in randomised controlled trials(RCT) provided by Cochrane reviews[32], a summary of the risk of bias for the SYNAPSE study is provided in Table 62, Appendix A – Literature search for efficacy and safety of intervention and comparators. Risk of bias for different domains as indicated in Table 62 are considered 'high', 'low' or 'unclear' dependent on whether the information regarding the domain is available in the published study. The SYNAPSE study had a low risk of bias regarding randomisation among patients, adequate concealment of patient allocation, blinding of site staff, the central study team, patients to treatment, as well as blinding of outcome assessment for the central study team. The study included an intention-to-treat (ITT) analysis, indicating low bias of risk. It was observed that there was an imbalance between the treatment groups in baseline characteristics of prognostic variables, indicating an unclear risk. There were no unexpected imbalances due to dropouts between the groups and no evidence to suggest that the authors measured more outcomes than reported. Overall, the SYNAPSE study provided unclear risk of bias for baseline differences between both treatment groups, and low risk of bias for all other domains.

7.1.2 Efficacy and safety – results per study

Based on the objectives of literature search as described in Appendix A – Literature search for efficacy and safety of intervention and comparators, SYNAPSE was the only relevant study for the present application.

Efficacy

Primary and secondary efficacy endpoints in the SYNAPSE study were assessed in the intention-to-treat (ITT) population, defined as all randomly assigned patients who received at least one dose of the study drug, analysed according to the allocated treatment. Results from the primary and secondary efficacy outcomes are provided in detail in the sections below. Exploratory endpoints from the SYNAPSE study, (except one endpoint that described the proportion of patients reporting 8.9 points or more in change from baseline SNOT-22 scores) are not reported in detail in this assessment.

The co-primary endpoints in the SYNAPSE study were:

- change from baseline in total endoscopic nasal polyp score at week 52 and
- change from baseline in mean nasal obstruction VAS score during weeks 49–52

Secondary endpoints in the SYNAPSE study included:

- time-to-first nasal surgery until week 52 (key secondary endpoint)
- change from baseline in mean overall VAS symptom score during weeks 49–52
- change from baseline in SNOT-22 total score at week 52
- proportion of patients requiring systemic corticosteroids for nasal polyps until week 52

- change from baseline in mean composite VAS score (combining scores for nasal obstruction, nasal discharge, throat mucus, and loss of smell) during weeks 49–52
- change from baseline in mean VAS score for loss of smell during weeks 49–52

Relevant exploratory endpoints from the SYNAPSE study included:

- proportion of patients with a decrease of 8.9 points or more from baseline in SNOT-22 total score in the absence of surgery.

The efficacy endpoints chosen are representative of the outcomes available in the medical literature for nasal polyps and also mentioned in the DMC protocol for assessment regarding dupilumab for the treatment of CRSwNP[25].

Results overview for the SYNAPSE study are provided in Appendix D Efficacy and safety results per study,Table 65 and Table 67. Statistical considerations related to single-study statistical analyses are provided in Appendix K – Statistical methods.

Co-primary endpoints

Change from baseline in total endoscopic nasal polyp score at week 52

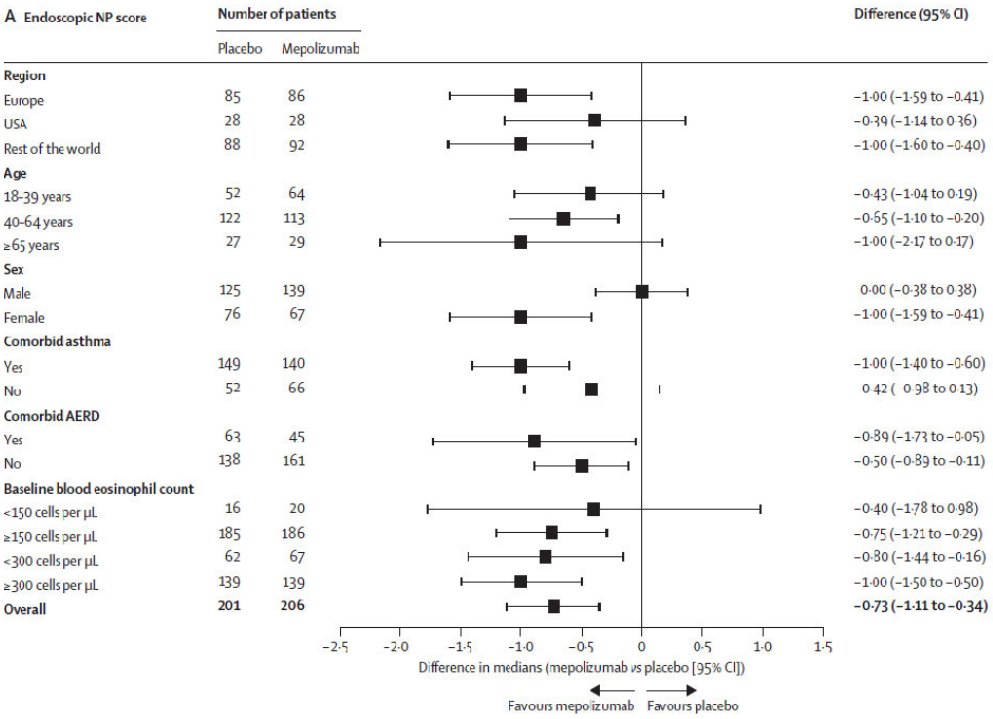
Total endoscopic nasal polyp score was the sum of left and right nostril scores ranging from 0 (no polyps) to 4 (large polyps causing complete obstruction of the inferior meatus) for each nostril, giving a total score of up to 8 [15].

Data from the SYNAPSE study showed that after 52 weeks, mean change and 95% confidence interval (CI) from baseline till week 52 for the placebo group was –0.1(–0.30; 0.10) as compared to mepolizumab group with –0.9(–1.16; –0.64), also provided in Table 65. The mean difference and 95% CI between mepolizumab and placebo were calculated at –0.8 (–1.13; –0.47), in favour of mepolizumab (p<0.001) (Table 65).

In a subgroup analysis, the authors of the SYNAPSE study also reported significant improvement in total endoscopic nasal polyp score at week 52 from baseline with mepolizumab compared to placebo, by estimating adjusted difference in median scores. The adjusted difference in median scores was calculated by the authors using quantile regression with covariates including treatment group, geographic region, baseline score, and natural logarithm of baseline blood eosinophil count (–0.73, 95% CI –1.11 ; –0.34; p<0.0001) (Figure 2, Table 65)[15].

No well-defined minimal clinically relevant difference (MCID) has been established in literature, but the DMC protocol for assessment regarding dupilumab for treatment of CRSwNP recommends an average difference of 1 point between groups as the smallest clinically relevant difference[25].

Figure 2: Subgroup analyses of change from baseline in total endoscopic nasal polyp score at week 52



AERD, Aspirin Exacerbated Respiratory Disease; CI, Confidence Interval; NP, Nasal Polyps. Han et al. 2021[15]

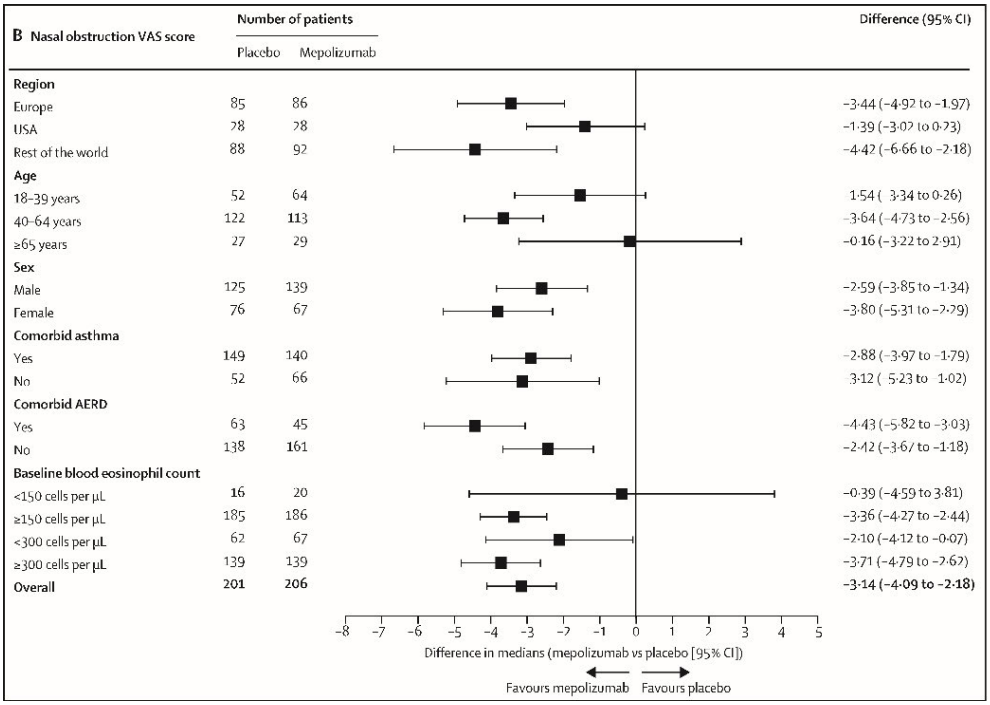
Change from baseline in mean nasal obstruction VAS score during weeks 49–52

Nasal obstruction using VAS scores was measured on a scale of 0 ('none') to 10 ('as bad as you can imagine'), where the score best corresponded to their status for severity of nasal obstruction. Higher score indicated worse obstruction. Patients who required nasal surgery before the visit or time period (weeks 49-52) were assigned their worst observed score recorded before surgery; patients with no nasal surgery who withdrew before the visit or time period were assigned their worst observed score before study withdrawal; patients with missing data were assigned their worst observed score before the missing visit [15].

Mean (95% CI) change from baseline nasal obstruction VAS score during weeks 49–52 in the SYNAPSE study for the placebo group was –2.5(–2.94; –2.06) as compared to mepolizumab group with –4.2(–4.67; –3.73). The mean difference and 95% CI between mepolizumab and placebo were calculated at –1.7 (–2.34; –1.06) in favour of mepolizumab (p<0.001). Table 65 provides the calculated mean difference in change from baseline for placebo and mepolizumab groups.

Similar to the previous co-primary endpoint, subgroup analyses also reported significant improvement in adjusted difference in nasal obstruction VAS median scores at weeks 49-52 from baseline with mepolizumab versus placebo, based on quantile regression (–3.14, 95% CI –4.09 ; –2.18; p<0.0001). The adjusted difference in median scores was calculated by the authors using quantile regression with covariates including treatment group, geographic region, baseline score, and natural logarithm of baseline blood eosinophil count (Figure 3, Table 65)[15].

Figure 3: Subgroup analyses of change from baseline mean nasal obstruction VAS score during weeks 49-52



AERD, Aspirin exacerbated respiratory disease; CI, Confidence interval; VAS, Visual analogue scale. Han et al. 2021[15]

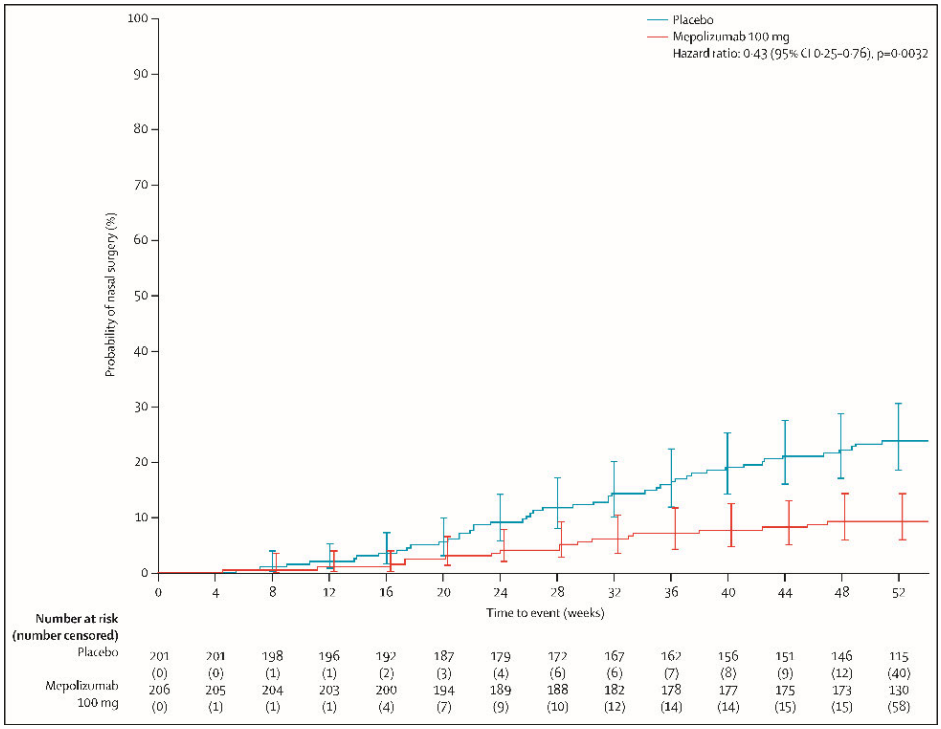
Secondary endpoints

Time-to-first nasal surgery until week 52 (key secondary endpoint)

Time-to-nasal surgery until week 52 was analyzed using a cox proportional hazards model with covariates of treatment group, baseline nasal polyp score (centrally read), baseline nasal obstruction VAS score, natural logarithm of baseline blood eosinophil count, number of previous surgeries (one, two, or more than two), and geographical region. The risk of nasal surgery was significantly lower for mepolizumab as compared to placebo (18 [8.7%] vs 46 [22.9%] patients; hazard ratio [HR] 0.43 (95% CI 0.25;0.76; p=0.0032) (Table 65).

Figure 4 provides the published Kaplan-Meier plot from the SYNAPSE study[15].

Figure 4: Kaplan-Meier plot of time-to-first nasal surgery (Intention-to-treat (ITT) population)



Han et al. 2021[15]

Change from baseline in mean overall VAS symptom score during weeks 49–52

Overall VAS symptoms scores were measured across a range from 0 ('none') to 10 ('as bad as you can imagine'). Patients who required nasal surgery before the visit or time period (weeks 49-52) were assigned their worst observed score recorded before surgery; patients with no nasal surgery who withdrew before the visit or time period were assigned their worst observed score before study withdrawal; patients with missing data were assigned their worst observed score before the missing visit[15].

Mean (95% CI) change from baseline overall VAS symptom score during weeks 49–52 for the placebo group was –2.5 (–2.93; –2.07) as compared to mepolizumab group –4.3 (–4.77; –3.83).

Change from baseline in mean overall VAS symptom score during weeks 49–52 had significantly improved in the mepolizumab group versus the placebo group (mean difference between mepolizumab and placebo= –1.8; 95% CI= –2.43; –1.17; p<0.001). Table 65 provides the calculated mean difference in change from baseline for placebo and mepolizumab groups.

Subgroup analyses in the study reported significant improvement in adjusted difference in median scores at weeks 49-52 from baseline with mepolizumab versus placebo, based on quantile regression (–3.18, 95% CI –4.10; –2.26; p=0.0032). The adjusted difference for overall VAS scores was calculated by the authors using quantile regression with covariates including treatment group, geographic region, baseline score, and natural logarithm of baseline blood eosinophil count (Table 65)[15].

Change from baseline in SNOT-22 total score at week 52

The validated 22-question Sinonasal Outcomes Test (SNOT-22) is a widely adopted instrument to evaluate CRS treatment outcomes. Each of its 22 items is scored on a scale from 0 ('no problem') to 5 ('problem as bad as it can be'). The SNOT-22 domain scores can be found in Appendix D Efficacy and safety results per study. The range of the global score is 0 to 110, and lower scores indicate less impact. Studies have reported that SNOT-22 has a minimal

clinically important difference (MCID) of 8.9 points [33]. This is an established MCID and was incorporated into the 2020 EUFOREA guidelines as a means to evaluate response to biologic treatment in the treatment of CRSwNP. However, guidance from EPOS 2020 has indicated that in a large surgical cohort, the MCID has been shown to be a change in 8.9 points on the SNOT-22, while for patients undergoing medical intervention, an MCID of 12 has been proposed[4].

At the end of the 52-week treatment period, a greater proportion of participants in the mepolizumab group than the placebo group demonstrated an improvement (decrease) at least 1 point in their SNOT-22 score (77% compared with 60%, respectively). A ≥ 45-point improvement (decrease) was observed for 27% of participants in the mepolizumab group compared with 13% in the placebo group. Analysis performed using mixed model repeated measures with covariates of treatment group, demographic region, baseline, log(e) baseline blood eosinophil count, visit plus interaction terms for visit by baseline and visit by treatment group. Estimates are based on weighting applied to each level of class variable determined from observed proportions. Missing visit data were assigned their worst observed score prior to the missing visit. 1 participant in the mepolizumab group and 3 in the placebo group with missing baseline scores were excluded from the analysis.

Mean (95% CI) change from baseline in SNOT-22 total score for the placebo group was –15.7 (–19.01; –12.39) as compared to mepolizumab group with –29.4(–32.77; –26.03) (Table 65). Change from baseline in SNOT-22 score significantly improved for mepolizumab as compared to placebo (mean difference between mepolizumab and placebo= –13.7; 95% CI –18.42; –8.98; p<0.001).

Subgroup analyses in the study reported significant improvement in adjusted difference in median scores at week 52 from baseline with mepolizumab versus placebo, based on quantile regression (–16.49, 95% CI –23.57; –9.42; p=0.0032). The adjusted difference in median for SNOT-22 scores were calculated by the authors using quantile regression with covariates including treatment group, geographic region, baseline score, and natural logarithm of baseline blood eosinophil count (Table 65)[15].

As mentioned, EPOS 2020 recommended a MCID of 12.0-point improvement in SNOT-22 for biological treatment options. The same MCID was included, by the scientific committee, in the protocol for the assessment of dupilumab. An additional responder analysis was therefore performed with the use of a MCID of 12-point improvement for SNOT-22 to accommodate this. [redacted] A summary of the responder analysis is illustrated in [redacted]. The full analysis is included in Appendix D Efficacy and safety results per study.

[redacted]

Proportion of patients requiring systemic corticosteroids for nasal polyps until week 52

The proportion of patients requiring systemic corticosteroids (≥1 course) for nasal polyps until week 52 was analyzed using a logistic regression model with covariates of treatment group, baseline nasal polyp score (centrally read), baseline nasal obstruction VAS score, natural logarithm of baseline blood eosinophil count, number of systemic corticosteroids courses in the previous 12 months, and geographic region.

Regarding systemic corticosteroids courses, 52 (25.2%) patients in the mepolizumab group and 74 (36.8%) in the placebo group had received one or more courses of systemic corticosteroids for nasal polyps by week 52 (odds ratio [OR] 0.58; 95% CI 0.36;0.92; p=0.020) (Table 65).

Change from baseline in mean composite VAS score (combining scores for nasal obstruction, nasal discharge, throat mucus, and loss of smell) during weeks 49–52

The composite VAS score was calculated as average of individual scores of nasal obstruction, nasal discharge, mucus in the throat and loss of smell and ranged between 0 and 10, with higher scores indicating greater disease severity.
Mean (95% CI) change from baseline in mean composite VAS score for the placebo group was estimated at –2.2 (-2.59; -1.81) as compared–3.8 (-4.24; -3.36) with mepolizumab group (Table 65). Change from baseline in mean composite VAS score was significantly improved for mepolizumab as compared to placebo (mean difference between mepolizumab and placebo= –1.6; 95% CI –2.18; –1.02; p<0.001).
Subgroup analyses were reported in the study, using quantile regression with covariates including treatment group, geographic region, baseline score, and natural logarithm of baseline blood eosinophil count. Significant improvement in adjusted difference in median scores at weeks 49-52 from baseline was reported for mepolizumab group as compared to placebo (–2.68, 95% CI –3.44; –1.91; p=0.020) (Table 65)[15].

Change from baseline in mean VAS score for loss of smell during weeks 49–52

VAS scores for loss of smell were measured across a range from 0 ('none') to 10 ('as bad as you can imagine').
Mean (95% CI) change from baseline in mean VAS score loss of smell for the placebo group was –1.4 (–1.77; -1.03) as compared to mepolizumab group with –2.8 (–3.29; –2.31). Change from baseline in mean VAS score for loss of smell was significantly improved for mepolizumab as compared to placebo (mean difference between mepolizumab and placebo= –1.4; 95% CI= –2.01; –0.79; p<0.001) (Table 65).
Similar to the previous endpoints, subgroup analyses for VAS score for loss of smell showed significant improvement in adjusted difference in median scores at week 52 from baseline for mepolizumab group, as compared to placebo (–0.37, 95% CI –0.65 ; –0.08; p=0.020) (Table 65)[15].
In the SYNAPSE study Improvement in loss of smell were greater in patients with fewer previous surgeries. The same tendency has been reported in the literature. In Table 5 the loss of smell VAS score and the number of previous surgeries is illustrated.

Table 5: Change from baseline in loss of sense of smell VAS score at weeks 49-52, by number of previous surgeries.

	Placebo (n=201)	Mepolizumab 100 mg SC (n=206)
1 previous surgery		
n	81	108

	Median change from baseline	-0.7	-1.87
	Difference in medians (95% CI)*	-1.29 (-2.27, -0.31)	
2 previous surgeries			
	n	47	47
	Median change from baseline	-0.02	-0.48
	Difference in medians (95% CI)*	-0.23 (-0.83, 0.37)	
>2 previous surgeries			
	n	73	51
	Median change from baseline	0.00	-0.07
	Difference in medians (95% CI)*	-0.07 (-0.19, 0.05)	

*Quantile regression with covariates of treatment group, geographic region, baseline score and Log(e) baseline blood eosinophil count. Patients with nasal surgery prior to visit/time period assigned their worst observed score prior to surgery; patients with no nasal surgery who withdrew prior visit/time period assigned their worst observed score prior to study withdrawal; patients with missing data assigned their worst observed score prior to the missing visit.

CI, confidence interval; SC, subcutaneous; VAS, visual analogue scale.

Exploratory endpoint

To provide more context to MCID for SNOT-22, results published from an exploratory endpoint in SYNAPSE is included in this application. This endpoint was also measured in the ITT population. Analysis was performed using a logistic regression model with covariates of treatment group, geographic region, baseline score and loge baseline blood eosinophil count. The proportion of patients with a 8.9 points (MCID suggested in the literature [33]) or higher, in SNOT-22 score from baseline to week 52, in the absence of surgery, was significantly higher for mepolizumab patients as compared to placebo (150 [73%] vs 106 [54%]; OR 2.44, 1.60;3.73; p<0.0001)[15]. No data, published or otherwise, was provided regarding the proportion of patients with a MCID cut-off of 12 points or higher.

Other exploratory endpoints that were not assessed in this application are:

- The proportion of patients with a decrease of 1 or more points from baseline in nasal polyps score at week 52 in the absence of surgery; number of courses of systemic corticosteroids; antibiotics up to week 52
- The proportion of patients with a decrease of 8·9 points or more from baseline in SNOT-22 total score in the absence of surgery
- The proportion of patients no longer needing surgery (defined as an overall symptom VAS score of ≤7 during weeks 49–52, a total endoscopic score of <5 at week 52, and no nasal surgery during the treatment period)
- Change from baseline in UPSIT (maximum score 40)
- Change from baseline on-treatment blood eosinophil count.
- Change from baseline in: loss of smell VAS score by the number of previous surgeries (one, two, or more than two) at week 49–52 and peak nasal inspiratory flow at week 52.
- Post-hoc analysis were the exacerbation rates and Asthma Control Questionnaire-5 scores at week 52 in patients with comorbid asthma.

UPSIT

The SYNAPSE study was not statistically powered to show any changes in UPSIT. However, this exploratory endpoint might be of interest for Danish physicians and will therefore shortly be described.
The UPSIT was completed by 108 participants (54 in each treatment group). UPSIT was completed at sites in Canada, the UK and the US only. The test was administered by a health care professional at visit 2 (Randomisation), and at alternative visits (Visits 3, 5, 7, 9, 11, 13). Up to an including visit 15 (Week 52) or early withdrawal UPSIT scores were similar in both treatment groups at baseline. In the mepolizumab group, the [redacted] At Week 52, the median change from baseline in UPSIT was 0.0 in both treatment groups. The difference between treatment groups was not statistically significant (p=0.302). Accounting for treatment group, country, baseline score and log(e) baseline blood eosinophil count, the difference in adjusted medians between treatment groups was [redacted]
UPSIT was only measured for a fourth of the patient population included in the SYNAPSE study (n=54 placebo arm, n=54 mepolizumab arm). It should be noticed that the patients included in the SYANPSE trial had at least ≥1 previous surgery before entering the study. 60% of the patients included in the placebo arm and 48% in the mepolizumab arm had ≥2 previous surgeries. The number of surgeries is well known to correlate with the loss of smell as also illustrated in
Table **5**. Based on this and the statistical bias there should not be placed too much emphasis on this exploratory endpoint.

[redacted]

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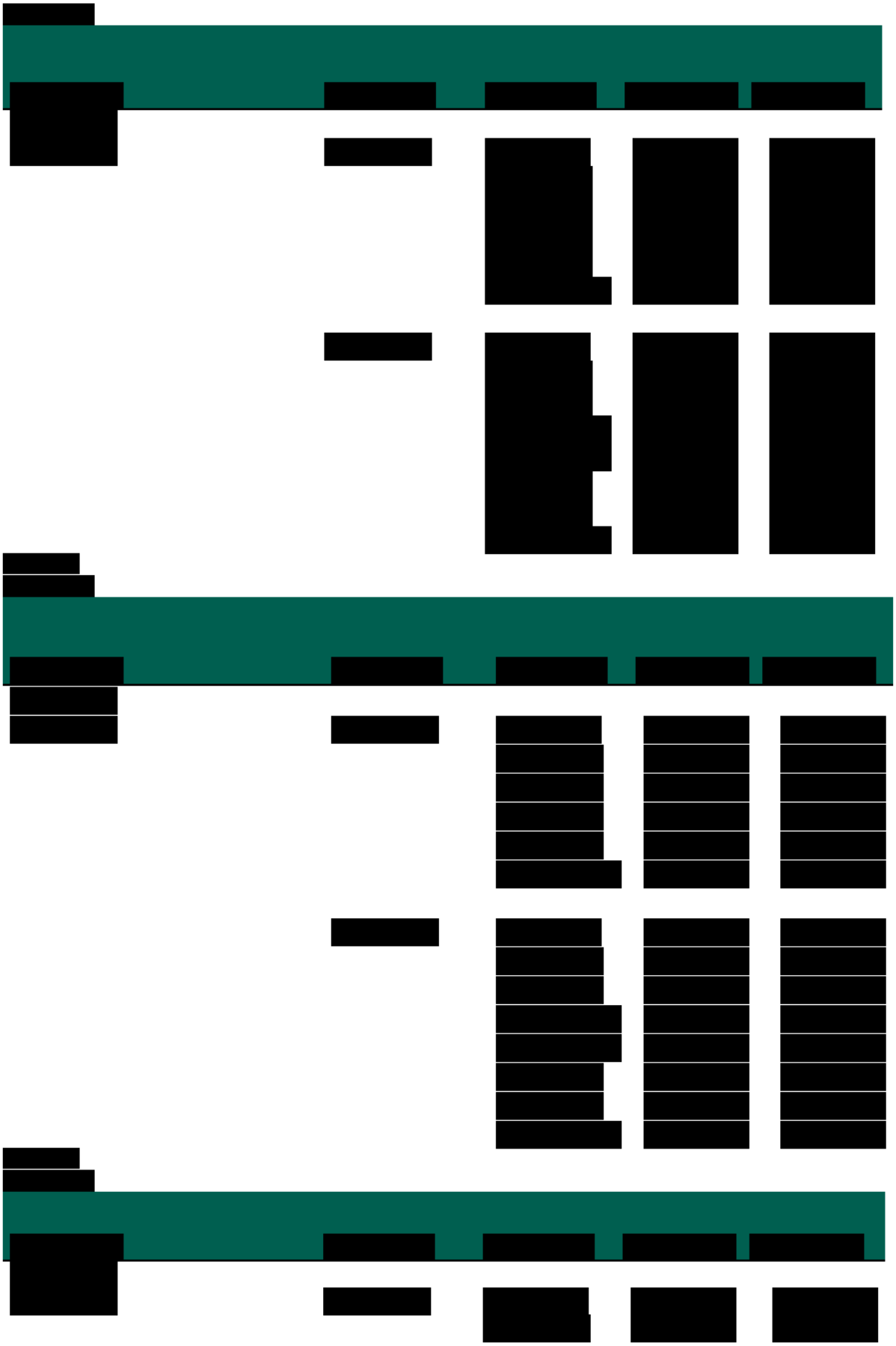

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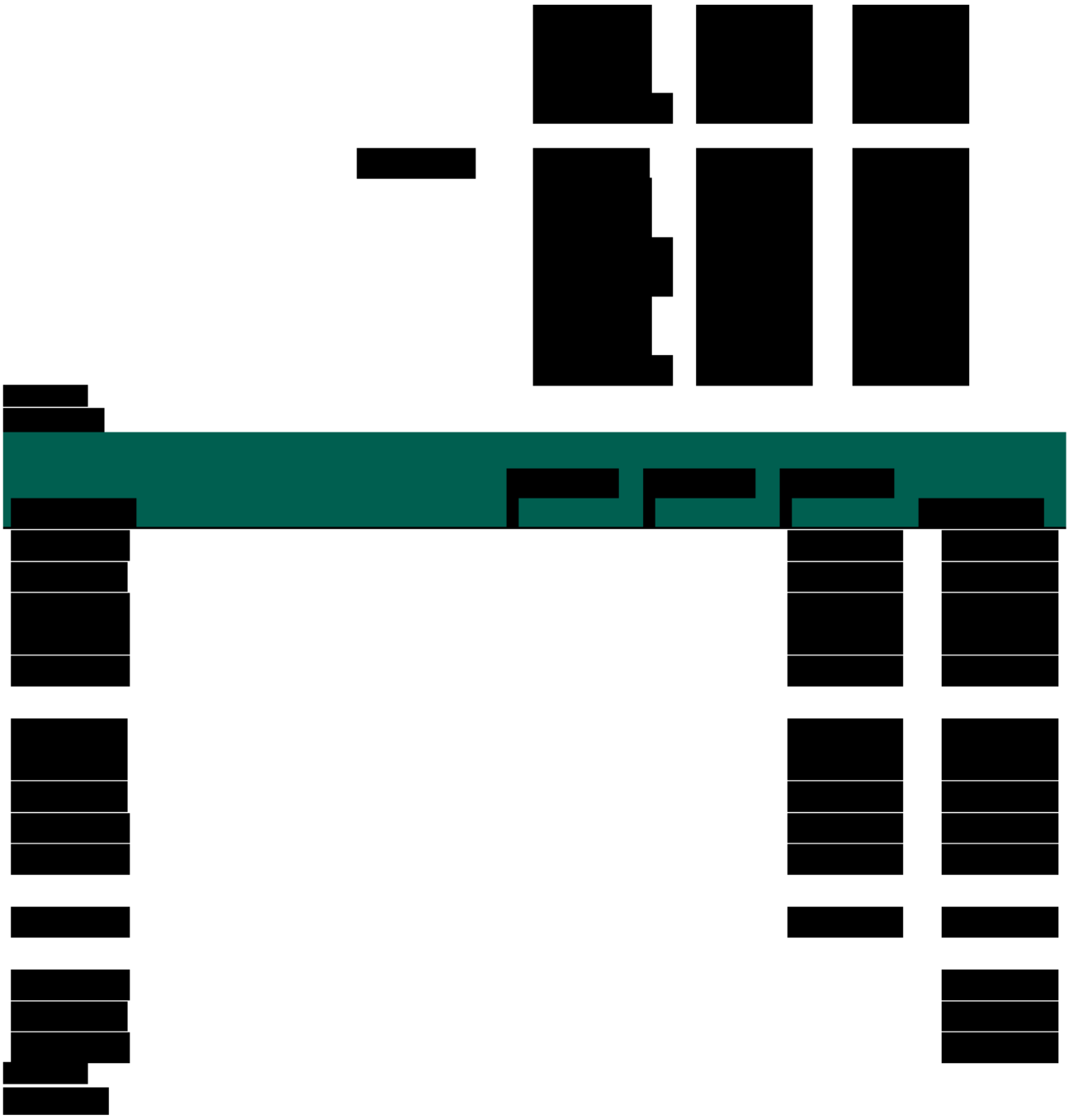

Safety

AE and SAE were coded in the SYNAPSE study per the Medical Dictionary for Regulatory Activities, V22.1 [34]. In terms of safety analysis, the proportion of patients who had on-treatment adverse events was similar between the two groups (169 [82%] in the mepolizumab group and 168 [84%] in the placebo group). According to the approved SmPC, no additional adverse reactions were identified than those reported in the severe eosinophilic asthma studies (Table 68).

The most frequently reported AE tended to be lower for mepolizumab as compared to placebo (nasopharyngitis (25% vs 23%), headache (18% vs 22%), epistaxis (8% vs 9%), and sinusitis (5% vs 11%), respectively). Injection site reactions (e.g., erythema, pruritus) occurred in 2% of patients receiving mepolizumab 100 mg compared to <1% in patients receiving placebo.

AE considered related to study treatment by the investigator were reported in 30 (15%) patients receiving mepolizumab and 19 (9%) receiving placebo. On-treatment serious AE occurred in 12 (6%) patients receiving mepolizumab and 13 (6%) for patients receiving placebo. One death was reported in the placebo group (myocardial infarction occurring 99 days after the patient's last dose of study treatment); this death was not considered related to study treatment (

For complete summary of AE from the SYNAPSE study, please see, Appendix E Safety data for intervention and comparators. An extract of SmPC is provided in Table 68.

Following the guidance from the DMC for assessment of new drugs[35], the proportion of patients experiencing the following outcomes are also presented for the SYNAPSE study, in Table 67. These include:

- Any AE
- SAE
- Treatment discontinuation due to AE
- Study withdrawal due to AE

Any AE

Treatment with mepolizumab was not significantly different from placebo in terms of any adverse events after 52 weeks. The absolute difference (95% CI) was calculated at –1.54% (–8.87; 5.79) corresponding to a relative risk(RR) (95% CI) of 0.982 (0.90; 1.07), p=0.6799 (Table 67).

SAE

Mepolizumab patients also did not report significant differences from placebo patients in terms of serious adverse events after 52 weeks. The absolute difference (95% CI) was –0.64% (-5.31; 4.03) corresponding to a RR (95% CI) of 0.901 (0.42; 1.93), p= 0.7874 (Table 67).

Treatment discontinuation due to AE

No significant differences were observed between mepolizumab and placebo patients with respect to discontinuation of treatment due to adverse event. The absolute difference (95% CI) was –0.05% (-2.75; 2.65) corresponding to a RR (95% CI) of 0.976 (0.25; 3.85), p= 0.9720 (Table 67).

Study withdrawal due to AE

No significant differences were observed between mepolizumab and placebo patients with respect to study withdrawal due to AE. The absolute difference (95% CI) was –0.05% (-2.16; 1.15) corresponding to a RR (95% CI) of 0.488 (0.04; 5.34), p= 0.5567 (Table 67).

Table 6: Summary of adverse events(AE)

	Placebo	Mepolizumab
All adverse events		
Any on-treatment event	168 (84%)	169 (82%)
Treatment-related event	19 (9%)	30 (15%)
Leading to treatment discontinuation	4 (2%)	4 (2%)
Leading to study withdrawal	1 (1%)	0
Serious adverse events		
Any on-treatment event	13 (6%)	12 (6%)

Treatment-related event*	1 (1%)	0
Resulting in death†	1 (1%)	0
Systemic or local injection-site reactions		
Systemic reaction	1 (1%)	2 (1%)
Local injection-site reaction	2 (1%)	5 (2%)
Anaphylaxis	0	0
Most common adverse events‡		
Nasopharyngitis	46 (23%)	52 (25%)
Headache	44 (22%)	37 (18%)
Epistaxis	18 (9%)	17 (8%)
Sinusitis	22 (11%)	10 (5%)
Back pain	14 (7%)	15 (7%)
Acute sinusitis	13 (6%)	13 (6%)
Oropharyngeal pain	10 (5%)	16 (8%)
Upper respiratory tract infection	14 (7%)	12 (6%)
Nasal polyps	16 (8%)	8 (4%)
Bronchitis	13 (6%)	10 (5%)
Asthma	18 (9%)	4 (2%)
Cough	13 (6%)	7 (3%)
Arthralgia	5 (2%)	13 (6%)
Otitis media	10 (5%)	5 (2%)

*Transient ischaemic attack. †Due to myocardial infarction during the follow-up period. ‡Reported in 5% or more patients in any treatment group.

Discussion The SYNAPSE study is assessing the safety and efficacy of Mepolizumab for patients with CRSwNP. The endpoints chosen in the SYNAPSE trial is in line with the EPOS 2020 guidance and the DMC protocol for dupilumab. The diagnosis of CRSwNP is made based on an objective and subjective measurement, through endoscopic nasal polyp score and nasal obstruction VAS score. These two endpoints are the co-primary endpoints included in the SYNAPSE trial. Similar endpoints were used in the studies with dupilumab and omalizumab studies.
The introduction of biologics as add-on therapy provides an opportunity to reduce the need for recurrent surgery and reduce the number of OCS courses.
Synapse this is the first large, multinational, phase 3 study to show the safety and efficacy of an anti-IL-5 biologic in patients with recurrent, refractory, severe chronic rhinosinusitis with nasal polyps, despite continuous medical treatment and previous surgical treatment, who were eligible for repeat nasal surgery.[15] SYNAPSE was designed with a sufficient sample size to detect important differences in the key secondary endpoint of time-to-first actual nasal surgery up to week 52. Only surgery stopped endpoint measures meaning that subject received systemic corticosteroids throughout. This is in contrast to other studies, where surgery and systemic corticosteroids stopped endpoint measures. Use of actual surgery provides a more objective endpoint as this describes a confirmed event rather than an intention to perform the event. In contrast, other biologics evaluated the time-to-first (actual and planned) nasal surgery.

Loss of smell is mentioned as an important measure by Danish physicians and in EPOS 2020. In the SYNAPSE trial all patients had at least one surgery prior to inclusion in the study, where 30% had ≥3 surgeries. From the literature and the subgroup analysis for the SYNAPSE study, we know that patients with fewer previous surgeries have greater improvements in sense of smell.

Adverse events from long term data on severe eosinophilic asthma.
Adverse events and long-term safety data are available on the treatment with mepolizumab within severe eosinophilic

asthma. In placebo-controlled studies on adults and young patients with severe refractory eosinophilic asthma the most common reported adverse events on treatment headache (20 %), injection site reactions (8 %) and back pain (6 %).
Open extension studies with severe refractory eosinophilic asthma COLOMBA, COSMOS og COSMEX. The prolonged side effect profile for mepolizumab in patients with severe refractory eosinophilic asthma(n=998) treated for an average of 2.8 years (between 4 weeks to 4.5 years) in the open extended studies COLOMBA, COSMOS og COSMEX was in general consistent with the 3 placebo-controlled registration studies.

7.1.2.1 Conclusion on efficacy and safety for patients with CRSwNP

The SYNAPSE study included all patients who had one or more nasal surgery before study entry, and CRSwNP for these patients was considered refractory to medical and surgical treatment.
Efficacy results demonstrate that both co-primary endpoints (nasal polyp score and nasal obstruction) showed a significant benefit at 52 weeks with mepolizumab compared with placebo, when administered in addition to the standard of care. The change from baseline in overall symptom VAS score, composite VAS score, and loss of smell VAS score during weeks 49–52, and SNOT-22 total score at week 52 had significantly improved in the mepolizumab group versus the placebo group. Risk of nasal surgery was also significantly lower for mepolizumab versus placebo. Subgroup analyses favoured mepolizumab over placebo for most of the subgroups analysed.

Guidance from EPOS 2020 has indicated that, in a large surgical cohort, the MCID is a change of 8.9 points on the SNOT-22, while for patients undergoing medical intervention, an MCID of 12 was proposed. Proportion of mepolizumab patients achieving MCID (8.9 points) or more for SNOT-22 scores from baseline to week 52 in the SYNAPSE study was significantly higher than placebo patients. No data was provided for patients achieving 12 points or more for change from baseline in SNOT-22 scores.

There was no statistical difference between mepolizumab and placebo for any of the safety outcomes which indicates similar safety profiles. Though, based on the proportion of patients with AE, mepolizumab seems to have a more favourable safety profile as compared to placebo. Findings reported in SmPC indicate that no additional adverse reactions were identified than those reported in the severe eosinophilic asthma studies. Long term data are, however, still limited.

The efficacy and safety findings show that the addition of mepolizumab to the current standard of care for patients with refractory CRSwNP generally results in statistically significant improvements in CRSwNP patients with severe disease who have not responded to the standard of care treatment and are eligible for repeat surgery.

7.1.3 Comparative analyses of efficacy and safety

Not applicable as only one study is included for this application.

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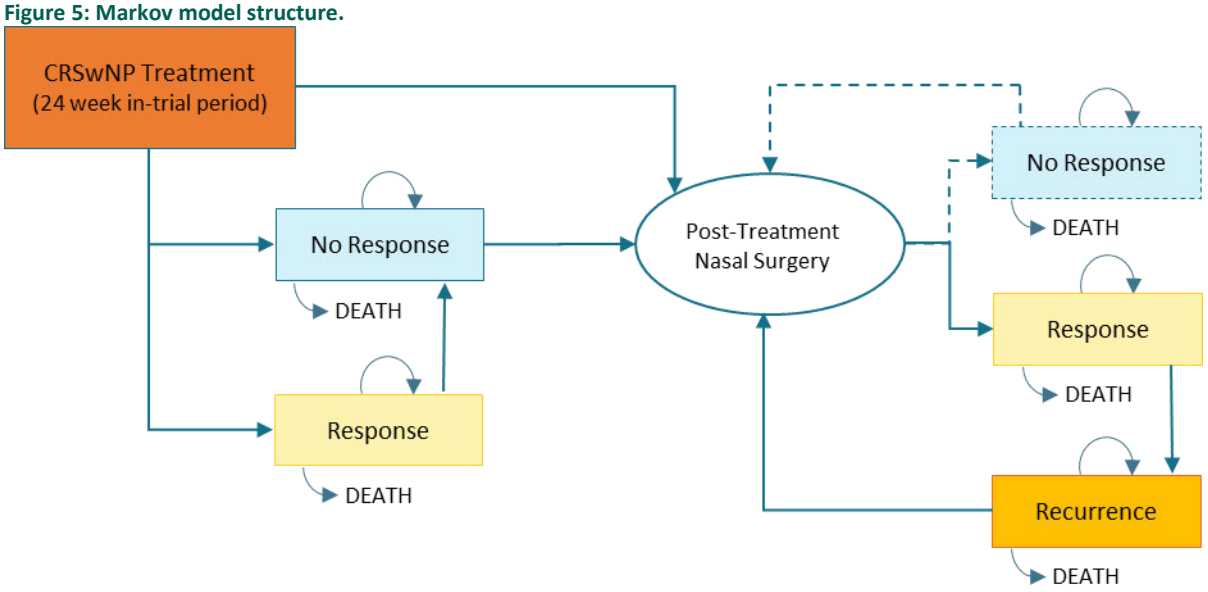
8. Health Economic analysis

A health economic model and a budget impact analysis was conducted to investigate the costs and outcomes associated with the add-on treatment with mepolizumab of patients with CRSwNP. A systematic literature review (SLR) was conducted to inform the data used in the model together with the SYNAPSE trial. A detailed description on the SLR is found in Appendix H.

8.1 Model structure

The model is designed as a Markov model with 4-week cycles with a lifetime time horizon. CRSwNP patients enter the model in need of treatment, reflective of patients enrolled in the SYNAPSE trial. During the first 24 weeks, all patients are treated with either mepolizumab or standard of care (SoC). In the base-case analysis, response is assessed at Week 24. Patients who do not achieve response at Week 24 will discontinue mepolizumab and subsequently incur the cost and outcomes of non-responders on SoC. Patients with response to mepolizumab at Week 24 are assumed to continue use of mepolizumab with a second assessment timepoint at Week 52. Patients who lose response between Week 24 and Week 52 discontinue mepolizumab and subsequently incur the cost and outcomes of non-responders on SoC. A scenario analysis is available which assumes all patients receive a 52-week trial of mepolizumab or SoC, with response only assessed at Week 52. Responders are not at risk of requiring surgery. Non-responders have a constant per-cycle probability of subsequent surgery. Subsequent surgery has a user defined effectiveness rate (100% in the base case), after which there is a probability of post-surgical disease recurrence for which patients can receive subsequent surgeries. The model includes a user-defined parameter for a surgical waiting period. In some jurisdictions, waiting periods might be extensive. Patients are kept in the non-response health state during their waiting period. Mortality is included as a separate health state. A small risk of surgical-related mortality is also included. All-cause mortality is derived from the statistics Denmark and used in the model. Costs and outcomes are discounted at 3.5% the first 35 years and after that with 2.5% per year in accordance with the recommended from the Ministry of Finance. Due to short cycle length, within-cycle correction (Simpson's 1/3 rule) is not applied in the base case.

Figure 5: Markov model structure.



The base-case analysis compares mepolizumab to the SoC with efficacy and utility data from the SYNAPSE Phase 3 trial (NCT03085797). Data from the SYNAPSE[15] trial used within the model includes treatment response, proportion of patients undergoing surgery, annual rate of clinically significant asthma exacerbations, mean courses of oral

corticosteroids (OCS), mean courses of antibiotics, and health utility. Clinically significant asthma exacerbations are classified into three severity types (requiring OCS, requiring an emergency visit, or requiring hospitalization), each associated with a cost and reduction in utility. Model outputs include total and treatment-related costs, number of surgeries, and quality-adjusted life years (QALYs), from a Danish health care perspective. The primary analysis is the incremental cost per QALY of mepolizumab vs SoC. The influence of individual parameters as well as overall uncertainty in the model results is tested in one-way and probabilistic sensitivity analysis, respectively.

8.1.1.1 Patient population

The model simulates patients with CRSwNP in alignment with the enrolment for the mepolizumab Phase 3 SYNAPSE trial. Patients had recurrent severe bilateral nasal polyps with a nasal obstruction visual analogue scale (VAS) score of >5. All patients had a history of ≥1 prior surgery for nasal polyps in the previous 10 years and were eligible for repeat nasal surgery (overall symptoms VAS score >7 and endoscopic NPS of ≥5 [maximum 8], with a minimum score of 2 in each nasal cavity), despite SoC treatment [15]. This is in line with the population suggested by the scientific committee in the protocol for dupilumab[25].

The following subpopulations can also be explored in the model:

- Comorbid asthma
- Baseline blood eosinophil count ≥150 cells/µL
- Baseline blood eosinophil count ≥300 cells/µL
- Comorbid aspirin exacerbated respiratory disease (AERD)
- Baseline blood eosinophil count ≥300 cells/µL and comorbid asthma

For the overall population and subpopulations, data for response, asthma exacerbation rates, OCS use, antibiotic use, and utility, by treatment arm, were derived from the SYNAPSE trial and accounted for within the model.

Table 7: Population Demographic Characteristics

Population parameters	Used in the model (number/value including source)	95% CI	Se	Distribution	Danish clinical practice (including source)
Age (mean)	48.8 (SYNAPSE)	N/A	2.5	normal	55 ±14.6 [14]
% Male	64.9% (SYNAPSE)	9.2%	2.4%	beta	Male/female-ratio 2:1 [14]

CI – confidence interval; SE – standard error.

8.1.1.2 Intervention

Mepolizumab is a fully humanized IgG monoclonal antibody specific for IL-5, which selectively and effectively inhibits eosinophilic airway inflammation. Mepolizumab reduced nasal polyp size, sinonasal symptoms, need for nasal polyp surgery, and use of oral corticosteroids (OCS) in adults with severe CRSwNP compared to SoC in the SYNAPSE study, a Phase 3 randomized controlled trial [15].

Mepolizumab is expected to be used as an add-on treatment if CRSwNP is not controlled on corticosteroids or surgery or both[16]. Mepolizumab may be self-administered by the patient or administered by a caregiver if their healthcare professional determines that it is appropriate, and the patient or caregiver are trained in injection techniques. For

CRSwNP patients, the dosage in clinical practice is expected to be 100 mg administered as a single subcutaneous (SC) injection into the upper arm, thigh, or abdomen once every 4 weeks.

Table 8 Intervention

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Dose	100 mg administered every 4 weeks (SYNAPSE)	100 mg administered every 4 weeks (SmPC)	100 mg administered every 4 weeks (SmPC)
Administration	Subcutaneously administered	Subcutaneous self-administration with a lead-in phase at the hospital	Subcutaneous self-administration with a lead-in phase at the hospital
Length of treatment	Treatment efficacy assessed at week 24 and 52 weeks.	Treatment efficacy assessed until 52 weeks. Response after week 52 is assumed to be lifelong	Intended for long-term
Mepolizumab position in Danish clinical practice	Add-on treatment to SoC (SYNAPSE)	Add-on treatment to SoC (SmPC)	Add-on treatment option to current Danish clinical practice

8.1.1.3 Comparators

The cost-effectiveness of mepolizumab is compared with the in-trial placebo arm as a proxy for SoC. The SoC for CRSwNP is typically intranasal corticosteroids (e.g., mometasone nasal spray). Patients entering the model will use mometasone nasal spray alone (SoC group) or mometasone with mepolizumab (mepolizumab group). No other comparators are included in the model. Placebo is used as a proxy for the SoC arm in both the clinical and economic application. This is in line with the protocol for dupilumab and European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020, which states that the SoC consists of intranasal corticosteroids, short courses of systemic corticosteroids, and nasal surgery [4].

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

8.2.1 Treatment response

In the base case two sets of criteria were used to define response: 1) achieving NPS improvement ≥1 or NCS improvement ≥3 (recommended as base-case analysis); 2) achieving a ≥8.9-point improvement in the sinonasal outcomes test 22-item (SNOT-22), the established minimum clinically important difference (MCID)[36]. In both sets, "Non-responder" is defined as achieving neither of the criteria defined or having surgery, regardless of whether one or both criteria above is achieved.

8.2.1.1 Incidence of surgery

The proportion of patients with surgery is derived from the SYNAPSE trial directly, by treatment arm, up to Week 24, then by response status and treatment arm for Weeks 24 to 52. Patients who receive surgery are considered treatment non-responders and assumed to discontinue treatment and transition to the post-surgery health state.

After 52 weeks, non-responders are assumed to require surgery at a constant annual rate based on published literature. The patients included in the SYNAPSE trial have had one or more previous surgery prior to entering in the trial. It is expected that the same will be a requirement for treatment with biologics in clinical practise, as surgery is successful in removing the nasal polyps in a number of cases.

8.2.1.2 Asthma exacerbations

The annualized rate of clinically significant asthma exacerbations by treatment arm are taken from the SYNAPSE trial. During the first 24 weeks, the in-trial rate is used, by treatment arm. Between 24 and 52 weeks as well as after 52 weeks, the rate is determined by response status and treatment arm. Asthma exacerbations are stratified by severity as requiring OCS, emergency visit, or hospitalisation.

8.2.1.3 Oral corticosteroid use

The mean number of OCS courses by treatment arm was derived from the SYNAPSE trial. During the first 24 weeks, the in-trial rate is used by treatment arm. After 24 weeks, the rate is determined by response status and treatment arm. The recommended dose of OCS used in clinical practice is derived from a danish treating physician. Treatment with systemic steroids (referred to as OCS) are often initiated as an effective treatment to reduce the nasal polyp size and thereby relieve the patients symptoms.

8.2.1.4 Antibiotic use

The mean number of antibiotic courses used in treatment of CRSwNP by treatment arm is derived from the SYNAPSE trial. During the first 24 weeks, the in-trial rate is used by treatment arm. After 24 weeks, the rate is determined by response status and treatment arm.

8.3 Utilities

All patients enter the model with baseline utility based on the pooled trial population at the start of the trial. Between Week 0 and Week 24, utilities are modelled by least squares mean change from baseline (CFB) by treatment arm at each assessment timepoint (i.e., each 4-week cycle) using a mixed model repeated measures analysis. Utility scores for SoC are calculated by adding the CFB with SoC to the baseline utility value. Utilities for mepolizumab are calculated by adding the difference from SoC in the CFB at each timepoint to the SoC utility. At Week 24, response is measured, and patients are classified as responder and non-responder. Starting at Week 24, utilities for responders are modelled as CFB by treatment arms, that were directly observed in SYNAPSE. Non-responders in the mepolizumab arm are assumed to discontinue mepolizumab and have the same utility as the SoC non-responder arm. The responder utility beyond Week 52 is based upon responders at Week 52 who were also responders at Week 24 for each arm. Non-responders beyond Week 52 for both the standard of care and mepolizumab arms are based on the utility of non-responders at Week 52 in the standard of care arm. Utility gain from surgery was derived from the SYNAPSE study by taking the difference in utility scores prior to surgery to scores 3 months post-surgery in the placebo arm. The utility values were adjusted related to age, according to the recommended in the DMC methods guidance Appendix, to capture the natural age-related decrease in HRQoL.

8.4 Inputs

8.4.1 Treatment Response

Treatment response in terms of response and no response, rates of surgery, rates of asthma exacerbations, rates of OCS use, and rates of antibiotic use under treatments with mepolizumab and SoC were derived from the SYNAPSE clinical trial. Inputs for the distribution of treatment response in the all-trial population are listed in the tables below. Treatment response for the included subpopulations is not included in the base case analysis and can therefore be found in Appendix L. Response is assessed at Week 24. At Week 24, responders continue receiving treatment. Non-responders stop treatment and remain non-responders for the duration of the model time horizon. Some patients who achieve response at Week 24 can lose response by Week 52. It is assumed responders at Week 24 continue treatment until Week 52, at which response is again assessed. Non-responders at Week 52 discontinue treatment for the duration of the model time horizon. Responders at Week 24 who were also responders at Week 52 are assumed to remain responders for the duration of the model time horizon. The model allows for both a post-trial annual loss of effect and post-trial annual discontinuation as a potential scenario analysis. All patients are assumed to respond to surgery in the base-case analysis.

Response is defined as having NPS ≥1 or NCS ≥3. Regarding NPS a MCID has been defined of ≥1 and is therefore used to define response. For the Nasal congestion score (NCS) no MCID has been defined in the literature. GSK has performed a post-hoc anchor-based analysis using data from baseline and week 52 in the psychometric analysis population, which included all patients from the ITT population. Polyserial correlation coefficient calculations were used to assess the relationship between potential anchors and change in NCS (nasal obstruction VAS score). Anchors with a coefficient of ≥3 were selected. Selected anchors were used to define patients as minimally improved or stable. Details on the anchor-based analysis can be found in Appendix K – Statistical methods

8.4.1.1 Response based on NPS ≥1 or NCS ≥3, all trial population

Table 9: NPS ≥1 or NCS ≥3, all trial population

	Value	95% CI	SE	Distribution	Source
Response at Week 24					
Mepolizumab	69.9%	(66.7%, 73.1%)	1.6%	beta	SYNAPSE
Standard of Care	47.3%	(43.7%, 50.8%)	1.8%	beta	SYNAPSE
Proportion of Responders at Week 24 with Response at Week 52					
Mepolizumab	86.8%	(84.0%, 89.6%)	1.4%	beta	SYNAPSE
Standard of Care	68.4%	(63.7%, 73.2%)	2.4%	beta	SYNAPSE

CI – confidence interval; NCS – nasal congestion score; NPS – nasal polyp score; SE – standard error

8.4.1.2 Response based on SNOT-22 ≥8.9, all trial population

Response assessed on SNOT-22 with a MCID of ≥8.9 was used as the base case analysis as this is an established MCID for SNOT-22 (Table 10).

Table 10: Response (%) based on SNOT-22 ≥8.9, All Trial Population

	Value	95% CI	SE	Distribution	Source
Response at Week 24					
Mepolizumab	81.1%	(78.3%, 83.8%)	1.4%	beta	SYNAPSE
Standard of Care	60.7%	(57.3%, 64.1%)	1.8%	beta	SYNAPSE
Proportion of Responders at Week 24 with Response at Week 52					
Mepolizumab	85.6%	(82.9%, 88.3%)	1.4%	beta	SYNAPSE
Standard of Care	75.4%	(71.5%, 79.3%)	2.0%	beta	SYNAPSE

CI – confidence interval; SNOT-22 – sino-nasal outcomes test 22-item; SE – standard error.

Response assessed at week 24 and week 52 based on SNOT-22 with a MCID of 12-point improvement was included as an option in the model, however, data was not available to support a full analysis based on a 12-point improvement, as data on the number of patients responding to treatment in week 24 that also responded in week 52 was not available. Therefore, only the responder analysis was included in the model (Table 11).

Table 11: Response Assessed at Week 24 and 52, based on SNOT-22 ≥12-point, All Trial Population

	Value	95% CI	SE	Distribution	Source
Response at Week 24					
Mepolizumab	[redacted]	[redacted]	NA	Beta	SYNAPSE
Standard of Care	[redacted]	[redacted]	NA	Beta	SYNAPSE
Response at Week 52					
Mepolizumab	[redacted]	[redacted]	NA	Beta	SYNAPSE
Standard of Care	[redacted]	[redacted]	NA	beta	SYNAPSE

CI – confidence interval; SNOT-22 – sino-nasal outcomes test 22-item; SE – standard error.

[redacted]

8.4.1.3 Scenario Analysis: Response Assessed Only at Week 52

A scenario analysis was conducted based on assessing response at Week 52 only using the criteria of SNOT-22 ≥8.9 as well as a scenario using the criteria of NPS ≥1 or NCS ≥3. Prior to Week 52, patients stay on treatment regardless of response except for those who receive surgery. After Week 52, patients are evaluated for response and either continue treatment or discontinue.

Table 12: Response Assessed at Week 52, based on NPS≥1 or NCS≥3 Response criteria, All Trial Population

	Value	95% CI	SE	Distribution	Source
Response at Week 52					
Mepolizumab	70.9%	(67.7%, 74.0%)	1.6%	beta	SYNAPSE
Standard of Care	47.3%	(43.7%, 50.8%)	1.8%	beta	SYNAPSE

CI – confidence interval; NCS – nasal congestion score; NPS – nasal polyp score; SE – standard error.

Table 13: Response Assessed at Week 52, based on SNOT-22 ≥8.9 response criteria, All Trial Population

	Value	95% CI	SE	Distribution	Source
Response at Week 52					
Mepolizumab	72.8%	(69.7%, 75.9%)	1.6%	beta	SYNAPSE

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Standard of Care	52.7%	(49.2%, 56.3%)	1.8%	beta	SYNAPSE

CI – confidence interval; SNOT-22 – sino-nasal outcomes test 22-item; SE – standard error.

8.4.2 Surgery incidence

The following tables list the inputs used for the proportion of patients needing surgery at Week 24 and Week 52 by treatment arm as well as the proportion of responders and non-responders at Week 24 requiring surgery at Week 52 from the SYNAPSE trial. During the first 24 weeks, risk of surgery is derived from the proportion of patients with surgery at Week 24 in the SYNAPSE trial by treatment arm, assuming a constant per-cycle probability of surgery between Weeks 0 and 24. For the 52-week assessment timepoint scenario analysis, the proportion of patients in each treatment arm with surgery at week 52 is used. Patients who receive surgery during the trial are considered treatment non-responders and assumed to discontinue treatment and transition to the post-surgery health state.
Between Weeks 24 and 52, there are two subsets of patients who may require surgery: 1) those who were responders at Week 24 and 2) those who were non-responders at Week 24.
Surgery rates from the SYNAPSE trial by treatment arm are applied for responders at Week 24. For non-responders at Week 24, surgery rates from the SYNAPSE trial for the placebo arm are applied for both SoC and mepolizumab, as the model assumes that mepolizumab-treated patients who are non-responders at Week 24 will discontinue mepolizumab and switch to SoC. Data for surgery rates for mepolizumab non-responders at Week 24 for the trial period from Week 24 to Week 52 are not used within the model, as patients in the SYNAPSE continued to be treated with mepolizumab for 52 weeks regardless of response status at week 24. In the model, non-responders at Week 24 discontinue treatment, thus the surgery rate from the standard of care arm was used instead.

Table 14: Probability of Surgery, NPS ≥1 or NCS ≥3 response criteria, All Trial Population

	Value	95% CI	SE	Distribution	Source
Surgery at Week 24					
Mepolizumab	3.9%	(2.5%, 5.2%)	0.7%	beta	SYNAPSE
Standard of Care	9.0%	(6.9%, 11.0%)	1.0%	beta	SYNAPSE
Surgery at Week 52					
Mepolizumab	8.7%	(6.8%, 10.7%)	1.0%	beta	SYNAPSE
Standard of Care	22.9%	(19.9%, 25.8%)	1.5%	beta	SYNAPSE
Proportion of Responders at Week 24 Needing Surgery by Week 52					
Mepolizumab	4.2%	(2.5%, 5.8%)	0.8%	beta	SYNAPSE
Standard of Care	16.8%	(13.0%, 20.7%)	2.0%	beta	SYNAPSE
Proportion of Non-Responders at Week 24 Needing Surgery by Week 52	13.6%	(10.0%, 17.3%)	1.9%	beta	SYNAPSE

CI – confidence interval; SE – standard error.

Table 15: Probability of Surgery, based on SNOT-22 ≥8.9, All Trial Population

	Value	95% CI	SE	Distribution	Source
Surgery at Week 24					
Mepolizumab	3.9%	(2.5%, 5.2%)	0.7%	beta	SYNAPSE

Standard of Care	9.0%	(6.9%, 11.0%)	1.0%	beta	SYNAPSE
Surgery at Week 52					
Mepolizumab	8.7%	(6.8%, 10.7%)	1.0%	beta	SYNAPSE
Standard of Care	22.9%	(19.9%, 25.8%)	1.5%	beta	SYNAPSE
Proportion of Responders at Week 24 Needing Surgery by Week 52					
Mepolizumab	4.8%	(3.1%, 6.4%)	0.8%	beta	SYNAPSE
Standard of Care	8.2%	(5.7%, 10.7%)	1.3%	beta	SYNAPSE
Proportion of Non-Responders at Week 24 Needing Surgery by Week 52	29.5%	(23.7%, 35.3%)	3.0%	beta	SYNAPSE

CI – confidence interval; SNOT-22 – sino-nasal outcomes test 22-item; SE – standard error.

Table 16: Probability of surgery, response assessed at week 52, all trial population

	Value	95% CI	SE	Distribution	Source
Surgery at Week 52					
Mepolizumab	8.7%	(6.7%, 10.7%)	1.6%	beta	SYNAPSE
Standard of Care	22.9%	(19.9%, 25.8%)	1.5%	beta	SYNAPSE

CI – confidence interval; SE – standard error.

Table 17 lists additional inputs for surgery derived from the SLR. After 52 weeks non-responders are assumed to require surgery at a constant annual rate of 11.4% per year based on 4.36% of all patients per year require surgery[37] compared to 38.4% lose response[38]. Upon receiving surgery, patients enter the post-surgery response state. Post-surgery responders are assumed to lose response at a constant rate of 38.4% per year [38], at which point they are eligible to receive another surgery. There is no limit to how many surgeries a patient can undergo. In the base case, all patients are assumed to respond to surgery. When the surgery success rate is set to less than 100%, patients who receive an ineffectual surgery enter a post-surgery non-responder state, analogous to the CRSwNP recurrence state. The base case also assumes patients have no wait time to receive surgery. The model also allows for an up to a 52-week waiting period as a scenario analysis to capture issue of limited surgery resource/capacity in certain markets. When the waiting period is non-zero, patients needing surgery, but waiting are assumed to stay in the non-responder or post-surgery recurrence state until their waiting period has passed.

Table 17: Probability of subsequent surgery

	Value	SE	Source
Non-Responder Annual Probability of Surgery	11.4%	0.6%	[37]

Waiting Period Before Surgery (weeks)	0	0	Assumption
Surgery Success Rate	100%	5.1%	Assumption
Annual Probability of Recurrence	38.4%	2.0%	[38]

CI – confidence interval; SE – standard error.

8.4.3 Asthma exacerbation rate

Clinically significant asthma exacerbations by treatment arm are taken from the SYNAPSE trial. The rate of asthma exacerbations by treatment arm for the overall trial population are listed in Table 18 and Table 19. Asthma exacerbation rates for the subpopulations are included in Appendix L. During the first 24 weeks, the in-trial rate is used, by treatment arm. Between 24 and 52 weeks as well as after 52 weeks, the rate is determined by response status and treatment arm. After week 24, non-responders in the mepolizumab arm discontinue treatment and switch to SoC, thus have the same rate as non-responders in the SoC arm between Week 24 and Week 52 weeks and after 52 weeks.

Table 18: Asthma Exacerbation Rate, NPS ≥1 or NCS ≥3 response criteria, All Trial Population

	Value	95% CI	Log(SE)	Distribution	Source
In-Trial (24 weeks) Annual Rate					
Mepolizumab	0.02	N/A	0.77	lognormal	SYNAPSE
Standard of Care	0.06	N/A	0.57	lognormal	SYNAPSE
Responder Annual Rate (Weeks 24-52)					
Mepolizumab	0.01	N/A	1.06	lognormal	SYNAPSE
Standard of Care	0.08	N/A	0.58	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 24-52)	0.06	N/A	0.63	lognormal	SYNAPSE
Responder Annual Rate (Weeks 52+)					
Mepolizumab	0.01	N/A	1.27	lognormal	SYNAPSE
Standard of Care	0.05	N/A	1.08	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 52+)	0.11	N/A	0.50	lognormal	SYNAPSE

CI – confidence interval; SE – standard error.

Table 19: Asthma Exacerbation Rate, SNOT-22 ≥8.9, All Trial Population

	Value	95% CI	Log(SE)	Distribution	Source
In-Trial (24 weeks) Annual Rate					

Mepolizumab	0.02	N/A	0.77	lognormal	SYNAPSE
Standard of Care	0.06	N/A	0.57	lognormal	SYNAPSE
Responder Annual Rate (Weeks 24-52)					
Mepolizumab	0.01	N/A	1.01	lognormal	SYNAPSE
Standard of Care	0.03	N/A	0.71	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 24-52)	0.13	N/A	0.83	lognormal	SYNAPSE
Responder Annual Rate (Weeks 52+)					
Mepolizumab	0.01	N/A	1.00	lognormal	SYNAPSE
Standard of Care	0.04	N/A	0.71	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 52+)	0.15	N/A	0.63	lognormal	SYNAPSE

CI – confidence interval; SNOT-22 – sino-nasal outcomes test 22-item; SE – standard error.

Table 20: Asthma Exacerbation Rate, Response Assessed at Week 52, All Trial Population

	Value	95% CI	Log(SE)	Distribution	Source
In-Trial (24 weeks) Annual Rate					
Mepolizumab	0.02	N/A	0.55	lognormal	SYNAPSE
Standard of Care	0.06	N/A	0.42	lognormal	SYNAPSE

CI – confidence interval; SE – standard error.

Asthma exacerbations are stratified as requiring OCS, emergency visit, or hospitalisation. Due to relatively low rates during the SYNAPSE trial, it is assumed that the stratification of asthma exacerbation resource utilization is the same for both arms, both in-trial and post-trial. Most clinically significant asthma exacerbations in the SYNAPSE trials were managed with OCS (90.5%). This is considered a conservative estimate, higher rates of outpatient visits have been reported in previous assessments in severe asthma, however, no estimates are available for this patient population therefore the rates reported in the SYNAPSE trial was used.

Table 21: Asthma Exacerbation Severity

	Value	95% CI	SE	Distribution	Source
Asthma Exacerbations Requiring OCS	90.5%	(absorbing)	N/A	(absorbing)	SYNAPSE
Asthma Exacerbations Requiring emergency Visit	4.8%	(0.01%,9.4%)	2.4%	beta	SYNAPSE
Asthma Exacerbations Requiring Hospitalisation	4.8%	(0.01%,9.4%)	0.57	beta	SYNAPSE

CI – confidence interval; OCS – oral corticosteroids; SE – standard error.

8.4.4 Oral corticosteroids

The mean number of OCS courses over 52 weeks by treatment arm for the overall trial population is listed in the tables below. During the first 24 weeks, the in-trial rate is used by treatment arm. Between 24 and 52 weeks as well as after 52 weeks, the rate is determined by response status and treatment arm. After week 24, non-responders in the mepolizumab arm discontinue treatment and switch to SoC, thus have the same rate as non-responders in the SoC arm between 24 and 52 weeks as well as after 52 weeks.

Table 22: OCS Use, NPS ≥1 or NCS ≥3, All Trial Population

	Value	95% CI	Log(SE)	Distribution	Source
In-Trial (24 weeks) Annual Rate					
Mepolizumab	0.42	N/A	0.17	lognormal	SYNAPSE
Standard of Care	0.45	N/A	0.17	lognormal	SYNAPSE
Responder Annual Rate (Weeks 24-52)					
Mepolizumab	0.26	N/A	0.26	lognormal	SYNAPSE
Standard of Care	0.51	N/A	0.26	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 24-52)	0.54	N/A	0.24	lognormal	SYNAPSE
Responder Annual Rate (Weeks 52+)					
Mepolizumab	0.17	N/A	0.34	lognormal	SYNAPSE
Standard of Care	0.36	N/A	0.33	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 52+)	0.76	N/A	0.23	lognormal	SYNAPSE

CI – confidence interval; OCS – oral corticosteroids; SE – standard error.

Table 23: OCS Use, SNOT-22 ≥8.9, All Trial Population

	Value	95% CI	Log(SE)	Distribution	Source
In-Trial (24 weeks) Annual Rate					
Mepolizumab	0.42	N/A	0.17	lognormal	SYNAPSE
Standard of Care	0.45	N/A	0.17	lognormal	SYNAPSE
Responder Annual Rate (Weeks 24-52)					
Mepolizumab	0.24	N/A	0.23	lognormal	SYNAPSE
Standard of Care	0.43	N/A	0.21	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 24-52)	0.88	N/A	0.32	lognormal	SYNAPSE
Responder Annual Rate (Weeks 52+)					
Mepolizumab	0.24	N/A	0.26	lognormal	SYNAPSE
Standard of Care	0.44	N/A	0.26	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 52+)	0.96	N/A	0.26	lognormal	SYNAPSE

CI – confidence interval; OCS – oral corticosteroids; SE – standard error; SNOT-22 – sino-nasal outcomes test 22-item.

Table 24: OCS Use, Response Assessed at Week 52, All Trial Population

	Value	95% CI	Log(SE)	Distribution	Source
In-Trial (24 weeks) Annual Rate					
Mepolizumab	0.38	N/A	0.15	lognormal	SYNAPSE
Standard of Care	0.54	N/A	0.14	lognormal	SYNAPSE

CI – confidence interval; OCS – oral corticosteroids; SE – standard error.

8.4.5 Antibiotic Courses

The mean number of antibiotic courses over 52 weeks by treatment arm for the overall trial population are listed in the tables below. During the first 24 weeks, the in-trial rate is used by treatment arm. Between 24 and 52 weeks as well as after 52 weeks, the rate is determined by response status and treatment arm. After week 24, non-responders in the mepolizumab arm discontinue treatment and switch to SoC, thus have the same rate as non-responders in the SoC arm between 24 and 52 weeks as well as after 52 weeks.

Table 25: Antibiotic Use, NPS ≥1 or NCS ≥3, All Trial Population

	Value	95% CI	Log(SE)	Distribution	Source
In-Trial (24 weeks) Annual Rate					
Mepolizumab	0.25	N/A	0.21	lognormal	SYNAPSE
Standard of Care	0.26	N/A	0.21	lognormal	SYNAPSE
Responder Annual Rate (Weeks 24-52)					
Mepolizumab	0.17	N/A	0.29	lognormal	SYNAPSE
Standard of Care	0.54	N/A	0.23	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 24-52)	0.28	N/A	0.34	lognormal	SYNAPSE
Responder Annual Rate (Weeks 52+)					
Mepolizumab	0.12	N/A	0.23	lognormal	SYNAPSE
Standard of Care	0.40	N/A	0.27	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 52+)	0.53	N/A	0.30	lognormal	SYNAPSE

CI – confidence interval; SE – standard error.

Table 26: Antibiotic Use, SNOT-22 ≥8.9, All Trial Population

	Value	95% CI	Log(SE)	Distribution	Source
In-Trial (24 weeks) Annual Rate					
Mepolizumab	0.25	N/A	0.21	lognormal	SYNAPSE
Standard of Care	0.26	N/A	0.21	lognormal	SYNAPSE
Responder Annual Rate (Weeks 24-52)					
Mepolizumab	0.16	N/A	0.28	lognormal	SYNAPSE
Standard of Care	0.43	N/A	0.22	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 24-52)	0.11	N/A	0.77	lognormal	SYNAPSE
Responder Annual Rate (Weeks 52+)					
Mepolizumab	0.11	N/A	0.35	lognormal	SYNAPSE
Standard of Care	0.36	N/A	0.25	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 52+)	0.53	N/A	0.33	lognormal	SYNAPSE

CI – confidence interval; SE – standard error; SNOT-22 – sino-nasal outcomes test 22-item.

Table 27: Antibiotic Use, Response Assessed at Week 52, All Trial Population

	Value	95% CI	Log (SE)	Distribution	Source
In-Trial (24 weeks) Annual Rate					
Mepolizumab	0.21	N/A	0.18	lognormal	SYNAPSE
Standard of Care	0.34	N/A	0.15	lognormal	SYNAPSE

CI – confidence interval; SE – standard error.

8.5 Adverse reaction outcomes

The following safety outcomes were compared: adverse events (AE), serious adverse events (SAE), treatment discontinuation due to AE, study withdrawal due to AE. There was no statistical difference between mepolizumab and placebo for any of the safety outcomes which indicates similar safety profiles. Though, based on the percentages of patients with AE, mepolizumab tends to have a more favourable safety profile compared to placebo. Findings reported in Summary of Product Characteristics (SmPC) for Nucala® indicate that no additional adverse reactions were identified to those reported in the severe eosinophilic asthma studies. Based on this no adverse events are included in the base case analysis for mepolizumab or SoC. The model is programmed with the ability to account for adverse events and their associated costs and disutility as a scenario analysis.

8.5.1 Surgical complications

The rate of surgical complications was derived from the national comparative audit of surgery for nasal polyposis and chronic rhinosinusitis [39]. The report found that 3.8% of all patients were readmitted to hospital for a sinonasal problem within 3 months of their surgery. Complications that arise during surgery and are addressed peri-operatively are assumed to be accounted for in the DRG tariff used to estimate costs associated with surgery (FESS). Post-surgical complications are modelled as epistaxis and are costed accordingly.

Table 28: Probability of Surgical Complications

	Value	95% CI	SE	Distribution	Source
Probability of AE requiring revision	3.8%	N/A	0.2%	beta	[39]
Probability of major AE	0.4%	N/A	0.0%	beta	[39]
Probability of minor AE	5.0%	N/A	0.3%	beta	[39]

CI – confidence interval; SE – standard error.

8.6 Documentation of health-related quality of life (HRQoL)

8.6.1 Overview of health state utility values (HSUV)

The base case analysis relies on utility scores derived from mapping SNOT-22 scores from the SYNAPSE trial to the EQ-5D using an established mapping algorithm [40]. All patients enter the model with baseline utility based on the pooled trial population at the start of the trial. All utilities during and post-trial are modelled as changes from this baseline. All mepolizumab non-responders are assumed to stop treatment, meaning that the utility for non-responders in the mepolizumab arm will be equivalent and set to the utility of the non-responders in the SoC arm. Utility gain from surgery was derived from the SYNAPSE study by taking the difference in utility scores prior to surgery to scores 3 months post-surgery in the placebo arm. In scenario where response to surgery is not 100%, for surgery non-responders, it is assumed that the CFB in utility is zero, since the patient is essentially in the same state that they were prior to entering the trial (CRSwNP with prior surgery in need of treatment). The utility gain from surgery (FESS) was based on utility change before and after surgery in patients who underwent surgery from the placebo arm in

SYNAPSE. In total, 46 patients had surgery from the placebo arm. 35 patients had EQ-5D quantified before and 3-month after surgery, and these patients contributed to the surgery utility gain calculation.
The following table list the inputs for these treatment independent utilities. Utility inputs from the included subpopulations can be found in Appendix L.

Table 29: Treatment Independent Utilities, All Trial Population

	Value	95% CI	SE	Distribution	Source
Baseline	0.534	(0.518, 0.550)	0.008	beta	SYNAPSE
CFB Week 52+ Non-Responder	0.029	(-0.012, 0.070)	0.021	lognormal	SYNAPSE
Utility Gain from Surgery	0.107	(0.044, 0.170)	0.032	lognormal	SYNAPSE
CFB Post Surgery in Non-responders to Surgery (not used in base-case)	0.000	N/A	N/A	N/A	Assumption

CFB – change from baseline; CI – confidence interval; N/A – not applicable; SE – standard error.

Table 30: Treatment Independent Utilities, SNOT-22 ≥8.9, All Trial Population

	Value	95% CI	SE	Distribution	Source
Baseline	0.534	(0.518, 0.550)	0.008	beta	SYNAPSE
CFB Week 52+ Non-Responder	-0.048	(-0.073, -0.023)	0.013	lognormal	SYNAPSE
Utility Gain from Surgery	0.107	(0.044, 0.170)	0.032	lognormal	SYNAPSE
CFB Post Surgery in Non-responders to Surgery (not used in base-case)	0.000	N/A	N/A	N/A	Assumption

CFB – change from baseline; CI – confidence interval; N/A – not applicable; SE – standard error; SNOT-22 – sino-nasal outcomes test 22-item.

Between Week 0 and Week 24, utilities are modelled for all patients by each arm by an analysis of the least squares mean CFB for SoC and the difference between mepolizumab and SoC in CFB at each assessment timepoint using a mixed model repeated measures analysis with covariates of treatment group, geographic region, baseline, log(e) baseline blood eosinophil count, visit plus interaction terms for visit by baseline and visit by treatment group.

Utility scores for SoC are calculated by adding the CFB with SoC to the baseline utility value. Utilities for mepolizumab are calculated by adding the difference from SoC in the CFB at each timepoint to the SoC utility.

At Week 24, response is measured, and patients are classified as responder and non-responder. Starting at Week 24, utilities for responders in the mepolizumab arm are modelled as CFB. Non-responders in the mepolizumab arm are assumed to have the same utility as the SoC non-responder arm. Utilities for responders and non-responders in the SoC arm are modelled as CFB.

It is assumed that utility scores for responders and non-responders is constant beyond Week 52. The responder utility beyond Week 52 is based upon responders at Week 52 who were also responders at Week 24 for each arm. Non-responders beyond Week 52 for both the SoC and mepolizumab arms are based on the utility of non-responders at Week 52 in the SoC arm.

Table 31: Standard of Care EQ-5D Utilities, NPS ≥1 or NCS ≥3, All Trial Population

All Trial Population, Standard of Care	Value	95% CI	SE	Distribution	Source
CFB Week 4	0.070	(0.052, 0.088)	0.009	normal	SYNAPSE
CFB Week 8	0.090	(0.072, 0.108)	0.009	normal	SYNAPSE

CFB Week 12	0.104	(0.084, 0.124)	0.010	normal	SYNAPSE
CFB Week 16	0.118	(0.098, 0.138)	0.010	normal	SYNAPSE
CFB Week 20	0.119	(0.097, 0.141)	0.011	normal	SYNAPSE
CFB Week 24 Responder	0.157	(0.126, 0.188)	0.016	normal	SYNAPSE
CFB Week 28 Responder	0.158	(0.125, 0.191)	0.017	normal	SYNAPSE
CFB Week 32 Responder	0.160	(0.123, 0.197)	0.019	normal	SYNAPSE
CFB Week 36 Responder	0.144	(0.111, 0.177)	0.017	normal	SYNAPSE
CFB Week 40 Responder	0.167	(0.132, 0.202)	0.018	normal	SYNAPSE
CFB Week 44 Responder	0.158	(0.119, 0.197)	0.020	normal	SYNAPSE
CFB Week 48 Responder	0.147	(0.110, 0.184)	0.019	normal	SYNAPSE
CFB Week 52+ Responder	0.174	(0.135, 0.213)	0.020	normal	SYNAPSE
CFB Week 24 Non-Responder	0.065	(0.026, 0.104)	0.020	normal	SYNAPSE
CFB Week 28 Non-Responder	0.094	(0.055, 0.133)	0.020	normal	SYNAPSE
CFB Week 32 Non-Responder	0.090	(0.051, 0.129)	0.020	normal	SYNAPSE
CFB Week 36 Non-Responder	0.119	(0.082, 0.156)	0.019	normal	SYNAPSE
CFB Week 40 Non-Responder	0.089	(0.050, 0.128)	0.020	normal	SYNAPSE
CFB Week 44 Non-Responder	0.099	(0.058, 0.140)	0.021	normal	SYNAPSE
CFB Week 48 Non-Responder	0.108	(0.067, 0.149)	0.021	normal	SYNAPSE
CFB Week 52+ Non-Responder	0.029	(-0.012, 0.070)	0.021	normal	SYNAPSE

CFB – change from baseline; CI – confidence interval; SE – standard error.

Table 32: Mepolizumab EQ-5D Utilities, NPS ≥1 or NCS ≥3, All Trial Population

All Trial Population, Mepolizumab	Value	95% CI	SE	Distribution	Source
Difference from SOC in CFB Week 4	0.023	(-0.002, 0.048)	0.013	normal	SYNAPSE
Difference from SOC in CFB Week 8	0.028	(0.002, 0.054)	0.013	normal	SYNAPSE
Difference from SOC in CFB Week 12	0.031	(0.004, 0.059)	0.014	normal	SYNAPSE
Difference from SOC in CFB Week 16	0.029	(0.001, 0.057)	0.014	normal	SYNAPSE
Difference from SOC in CFB Week 20	0.036	(0.006, 0.065)	0.015	normal	SYNAPSE
CFB Week 24 Responder	0.182	(0.153, 0.211)	0.015	normal	SYNAPSE
CFB Week 28 Responder	0.179	(0.150, 0.208)	0.015	normal	SYNAPSE
CFB Week 32 Responder	0.185	(0.156, 0.214)	0.015	normal	SYNAPSE
CFB Week 36 Responder	0.181	(0.150, 0.212)	0.016	normal	SYNAPSE
CFB Week 40 Responder	0.179	(0.148, 0.210)	0.016	normal	SYNAPSE
CFB Week 44 Responder	0.180	(0.149, 0.211)	0.016	normal	SYNAPSE
CFB Week 48 Responder	0.185	(0.154, 0.216)	0.016	normal	SYNAPSE
CFB Week 52+ Responder	0.201	(0.170, 0.232)	0.016	normal	SYNAPSE

CFB – change from baseline; CI – confidence interval; SE – standard error; SOC – standard of care.

Table 33: Standard of Care EQ-5D Utilities, SNOT-22 ≥8.9, All Trial Population

All Trial Population, Standard of Care	Value	95% CI	SE	Distribution	Source

CFB Week 4	0.070	(0.052, 0.088)	0.009	normal	SYNAPSE
CFB Week 8	0.090	(0.072, 0.108)	0.009	normal	SYNAPSE
CFB Week 12	0.104	(0.084, 0.124)	0.010	normal	SYNAPSE
CFB Week 16	0.118	(0.098, 0.138)	0.010	normal	SYNAPSE
CFB Week 20	0.119	(0.097, 0.141)	0.011	normal	SYNAPSE
CFB Week 24 Responder	0.195	(0.171, 0.219)	0.012	normal	SYNAPSE
CFB Week 28 Responder	0.195	(0.170, 0.220)	0.013	normal	SYNAPSE
CFB Week 32 Responder	0.182	(0.151, 0.213)	0.016	normal	SYNAPSE
CFB Week 36 Responder	0.179	(0.152, 0.206)	0.014	normal	SYNAPSE
CFB Week 40 Responder	0.178	(0.149, 0.207)	0.015	normal	SYNAPSE
CFB Week 44 Responder	0.185	(0.154, 0.216)	0.016	normal	SYNAPSE
CFB Week 48 Responder	0.177	(0.146, 0.208)	0.016	normal	SYNAPSE
CFB Week 52+ Responder	0.213	(0.182, 0.244)	0.016	normal	SYNAPSE
CFB Week 24 Non-Responder	-0.057	(-0.086, -0.028)	0.015	normal	SYNAPSE
CFB Week 28 Non-Responder	-0.028	(-0.063, 0.007)	0.018	normal	SYNAPSE
CFB Week 32 Non-Responder	-0.007	(-0.042, 0.028)	0.018	normal	SYNAPSE
CFB Week 36 Non-Responder	0.011	(-0.024, 0.046)	0.018	normal	SYNAPSE
CFB Week 40 Non-Responder	0.001	(-0.030, 0.032)	0.016	normal	SYNAPSE
CFB Week 44 Non-Responder	-0.020	(-0.059, 0.019)	0.020	normal	SYNAPSE
CFB Week 48 Non-Responder	-0.002	(-0.039, 0.035)	0.019	normal	SYNAPSE
CFB Week 52+ Non-Responder	-0.048	(-0.073, -0.023)	0.013	normal	SYNAPSE

CFB – change from baseline; CI – confidence interval; SE – standard error; SNOT-22 – sino-nasal outcomes test 22-item.

Table 34: Mepolizumab EQ-5D Utilities, SNOT-22 ≥8.9, All Trial Population

All Trial Population, Mepolizumab	Value	95% CI	SE	Distribution	Source
Difference from SOC in CFB Week 4	0.023	(-0.002, 0.048)	0.013	normal	SYNAPSE
Difference from SOC in CFB Week 8	0.028	(0.002, 0.054)	0.013	normal	SYNAPSE
Difference from SOC in CFB Week 12	0.031	(0.004, 0.059)	0.014	normal	SYNAPSE
Difference from SOC in CFB Week 16	0.029	(0.001, 0.057)	0.014	normal	SYNAPSE
Difference from SOC in CFB Week 20	0.036	(0.006, 0.065)	0.015	normal	SYNAPSE
CFB Week 24 Responder	0.198	(0.174, 0.222)	0.012	normal	SYNAPSE
CFB Week 28 Responder	0.199	(0.175, 0.223)	0.012	normal	SYNAPSE
CFB Week 32 Responder	0.202	(0.178, 0.226)	0.012	normal	SYNAPSE
CFB Week 36 Responder	0.197	(0.172, 0.222)	0.013	normal	SYNAPSE
CFB Week 40 Responder	0.198	(0.173, 0.223)	0.013	normal	SYNAPSE
CFB Week 44 Responder	0.197	(0.170, 0.224)	0.014	normal	SYNAPSE
CFB Week 48 Responder	0.199	(0.172, 0.226)	0.014	normal	SYNAPSE
CFB Week 52+ Responder	0.236	(0.211, 0.261)	0.013	normal	SYNAPSE

CFB – change from baseline; CI – confidence interval; SE – standard error; SOC – standard of care; SNOT-22 – sino-nasal outcomes test 22-item.

8.6.1.1 Disutilities

Disutilities for relevant clinical events are listed in the following table. Disutility values are modelled as multiplicative decreases to utility (i.e., health state utility scores are multiplied by one minus the disutility), prior to adjusting for cycle length. The decrement to utility due to adverse events is applied for the duration of a single cycle (4 weeks). Surgery disutility is based on an estimate for reduction in utility due to non-packing post-procedure [41]. Disutility due to surgery is modelled in the cycle the surgery occurs. No disutility due to surgical complications was assumed, which is a conservative assumption, as some patients might experience a decrease in utility due to surgical complications, however, as no such data is available from the literature it was decided to use a conservative estimate. Asthma exacerbation disutility values are based on moderate to severe asthma patients in the UK that have been used in prior economic modelling of mepolizumab and other biologics in severe eosinophilic asthma [42]. These estimates were used as no such data is available in Denmark for this patient population. UK data is assumed to be representative for DK clinical practice. It is assumed that there is no additional disutility associated with disease worsening needing OCS or antibiotics. This assumption was made based on the lack of evidence to support the use of antibiotics in patients with CRSwNP, and that no disutility values was available for the use of OCS for patients with CRSwNP.

Table 35: Disutility Estimates

	Value	95% CI	SE	Distribution	Source
Surgery Disutility	0.028	N/A	0.001	lognormal	[41]
Surgery – AE requiring revision disutility per event	0.000	N/A	0.000	lognormal	Assumption
Surgery – Major AE disutility per event	0.000	N/A	0.000	lognormal	Assumption
Surgery – Minor AE disutility per event	0.000	N/A	0.000	lognormal	Assumption
Asthma Exacerbation Requiring OCS	0.100	N/A	0.005	lognormal	[43]
Asthma Exacerbation Requiring emergency Visit	0.150	N/A	0.008	lognormal	[43]
Asthma Exacerbation Requiring Hospitalisation	0.200	N/A	0.010	lognormal	[43]
OCS Use	0.000	N/A	0.000	lognormal	Assumption
Antibiotic Use	0.000	N/A	0.000	lognormal	Assumption

CI – confidence interval; N/A – not applicable; OCS – oral corticosteroids; SE – standard error.

8.6.1.2 Scenario Analysis: Response Assessed Only at Week 52

For the scenario where response is only assessed at Week 52, mean utilities by treatment arm, measured every 4 weeks, are used up to Week 52. At Week 52, patients are evaluated for response. Responders continue treatment and maintain the utility for response at Week 52. Non-responders discontinue mepolizumab have utility equivalent to non-responders on the SoC arm at Week 52.

Table 36: Treatment Independent Utilities, Response Assessed at Week 52, NPS ≥1 or NCS ≥3, All Trial Population

	Value	95% CI	SE	Distribution	Source
Baseline	0.534	(0.518, 0.550)	0.008	lognormal	SYNAPSE
CFB Week 52+ Non-Responder	0.029	(-0.012, 0.070)	0.021	normal	SYNAPSE
Utility Gain from Surgery	0.107	(0.044, 0.170)	0.032	normal	SYNAPSE
CFB Post Subsequent Surgery	0.000	N/A	N/A	N/A	Assumption

CFB – change from baseline; CI – confidence interval; N/A – not applicable; SE – standard error.

Table 37: Treatment independent utilities, response assessed at week 52, SNOT-22 ≥8.9, All population.

	Value	95% CI	SE	Distribution	Source
Baseline	0.534	(0.518, 0.550)	0.008	beta	SYNAPSE
CFB Week 52+ Non-Responder	-0.048	(-0.073, -0.023)	0.021	lognormal	SYNAPSE
Utility Gain from Surgery	0.107	(0.044, 0.170)	0.032	lognormal	SYNAPSE
CFB Post Subsequent Surgery	0.000	N/A	N/A	N/A	Assumption

CFB – change from baseline; CI – confidence interval; N/A – not applicable; SE – standard error.

Table 38: Standard of Care EQ-5D Utilities, Response Assessed at Week 52, NPS ≥1 or NCS ≥3, All Trial Population

All Trial Population, Standard of Care	Value	95% CI	SE	Distribution	Source
CFB Week 4	0.070	(0.052, 0.088)	0.009	normal	SYNAPSE
CFB Week 8	0.090	(0.072, 0.108)	0.009	normal	SYNAPSE
CFB Week 12	0.104	(0.084, 0.124)	0.010	normal	SYNAPSE
CFB Week 16	0.118	(0.098, 0.138)	0.010	normal	SYNAPSE
CFB Week 20	0.119	(0.097, 0.141)	0.011	normal	SYNAPSE
CFB Week 24	0.112	(0.090, 0.134)	0.011	normal	SYNAPSE
CFB Week 28	0.121	(0.099, 0.143)	0.011	normal	SYNAPSE
CFB Week 32	0.119	(0.097, 0.141)	0.011	normal	SYNAPSE
CFB Week 36	0.120	(0.098, 0.142)	0.011	normal	SYNAPSE
CFB Week 40	0.116	(0.094, 0.138)	0.011	normal	SYNAPSE
CFB Week 44	0.115	(0.091, 0.139)	0.012	normal	SYNAPSE
CFB Week 48	0.116	(0.094, 0.138)	0.011	normal	SYNAPSE
CFB Week 52+ Responder	0.179	(0.148, 0.210)	0.016	normal	SYNAPSE
CFB Week 52+ Non-Responder	0.029	(-0.012, 0.070)	0.021	normal	SYNAPSE

CFB – change from baseline; CI – confidence interval; SE – standard error.

Table 39: Mepolizumab EQ-5D Utilities, Response Assessed at Week 52, NPS ≥1 or NCS ≥3, All Trial Population

All Trial Population, Mepolizumab	Value	95% CI	SE	Distribution	Source
CFB Week 4	0.023	(-0.002, 0.048)	0.013	normal	SYNAPSE
CFB Week 8	0.028	(0.002, 0.054)	0.013	normal	SYNAPSE
CFB Week 12	0.031	(0.004, 0.059)	0.014	normal	SYNAPSE
CFB Week 16	0.029	(0.001, 0.057)	0.014	normal	SYNAPSE
CFB Week 20	0.036	(0.006, 0.065)	0.015	normal	SYNAPSE
CFB Week 24	0.046	(0.017, 0.075)	0.015	normal	SYNAPSE
CFB Week 28	0.040	(0.011, 0.069)	0.015	normal	SYNAPSE
CFB Week 32	0.042	(0.012, 0.073)	0.016	normal	SYNAPSE
CFB Week 36	0.037	(0.007, 0.067)	0.015	normal	SYNAPSE
CFB Week 40	0.042	(0.011, 0.073)	0.016	normal	SYNAPSE

CFB Week 44	0.041	(0.009, 0.073)	0.016	normal	SYNAPSE
CFB Week 48	0.045	(0.014, 0.076)	0.016	normal	SYNAPSE
CFB Week 52+ Responder	0.204	(0.175, 0.233)	0.015	normal	SYNAPSE

CFB – change from baseline; CI – confidence interval; SE – standard error.

Table 40: Standard of Care EQ-5D Utilities, Response Assessed at Week 52, SNOT-22 ≥8.9, All Trial Population.

All Trial Population, Standard of Care	Value	95% CI	SE	Distribution	Source
CFB Week 4	0.070	(0.052, 0.088)	0.009	lognormal	SYNAPSE
CFB Week 8	0.090	(0.072, 0.108)	0.009	lognormal	SYNAPSE
CFB Week 12	0.104	(0.084, 0.124)	0.010	lognormal	SYNAPSE
CFB Week 16	0.118	(0.098, 0.138)	0.010	lognormal	SYNAPSE
CFB Week 20	0.119	(0.097, 0.141)	0.011	lognormal	SYNAPSE
CFB Week 24	0.112	(0.090, 0.134)	0.011	lognormal	SYNAPSE
CFB Week 28	0.121	(0.099, 0.143)	0.011	lognormal	SYNAPSE
CFB Week 32	0.119	(0.097, 0.141)	0.011	lognormal	SYNAPSE
CFB Week 36	0.120	(0.098, 0.142)	0.011	lognormal	SYNAPSE
CFB Week 40	0.116	(0.094, 0.138)	0.011	lognormal	SYNAPSE
CFB Week 44	0.115	(0.091, 0.139)	0.012	lognormal	SYNAPSE
CFB Week 48	0.116	(0.094, 0.138)	0.011	lognormal	SYNAPSE
CFB Week 52+ Responder	0.198	(0.171, 0.225)	0.014	lognormal	SYNAPSE
CFB Week 52+ Non-Responder	-0.048	(-0.073, -0.023)	0.013	lognormal	SYNAPSE

CFB – change from baseline; CI – confidence interval; SE – standard error.

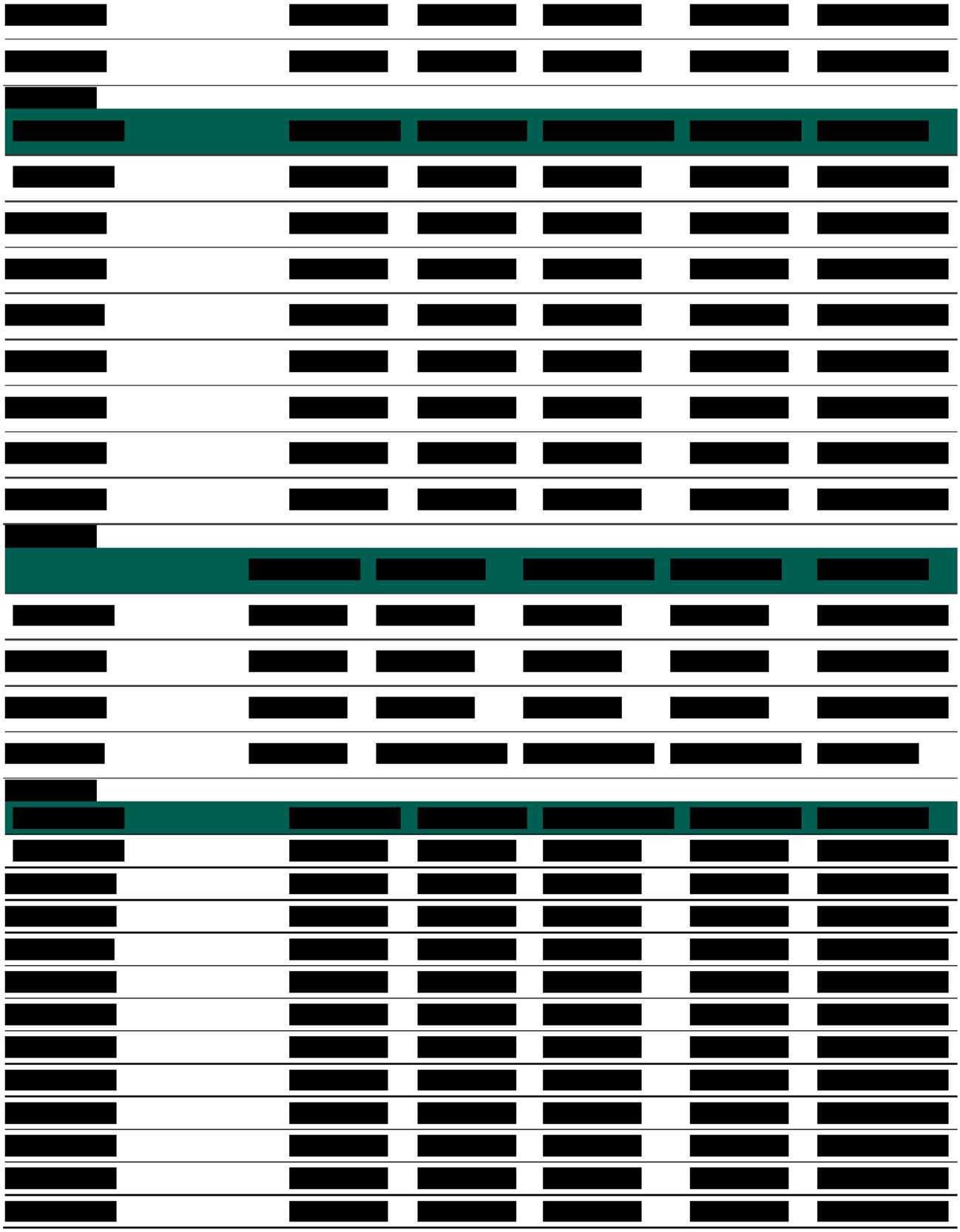
Table 41: Mepolizumab EQ-5D Utilities, Response Assessed at Week 52, SNOT-22 ≥8.9, All Trial Population.

All Trial Population, Mepolizumab	Value	95% CI	SE	Distribution	Source
CFB Week 4	0.023	(-0.002, 0.048)	0.013	lognormal	SYNAPSE
CFB Week 8	0.028	(0.002, 0.054)	0.013	lognormal	SYNAPSE
CFB Week 12	0.031	(0.004, 0.059)	0.014	lognormal	SYNAPSE
CFB Week 16	0.029	(0.001, 0.057)	0.014	lognormal	SYNAPSE
CFB Week 20	0.036	(0.006, 0.065)	0.015	lognormal	SYNAPSE
CFB Week 24	0.046	(0.017, 0.075)	0.015	lognormal	SYNAPSE
CFB Week 28	0.040	(0.011, 0.069)	0.015	lognormal	SYNAPSE
CFB Week 32	0.042	(0.012, 0.073)	0.016	lognormal	SYNAPSE
CFB Week 36	0.037	(0.007, 0.067)	0.015	lognormal	SYNAPSE
CFB Week 40	0.042	(0.011, 0.073)	0.016	lognormal	SYNAPSE
CFB Week 44	0.041	(0.009, 0.073)	0.016	lognormal	SYNAPSE
CFB Week 48	0.045	(0.014, 0.076)	0.016	lognormal	SYNAPSE
CFB Week 52+ Responder	0.229	(0.204, 0.254)	0.013	lognormal	SYNAPSE

CFB – change from baseline; CI – confidence interval; SE – standard error.

8.6.1.3 Scenario analysis: SF-6D

A scenario analysis including SF-6D was performed and included as an option in the health economic model. The SF-6D uses information on patient-reported health from the SF-36, a commonly used generic measure for general health in clinical studies. The Short-Form 36-Dimension (SF-36) was administered in the SYNAPSE trial every 8 weeks. The SF-36 questionnaire consists of 36 self-administered questions that cover eight health domains: physical functioning, role physical, bodily pain, general health, vitality, role emotional, social functioning, and mental health.
Utility values for SF-36 was established using the Short-Form Six-Dimension (SF-6D) health index designed for calculating quality adjusted life years (QALYs). The value set model 10 developed for the United Kingdom by Brazier et al. (2002) was used. Since the SYNAPSE study was conducted, an updated approach to the SF-6D instrument has been established (SF-6Dv2). However, SF-6Dv2 was not available for the use in the conversion of SF-36 at the time of analysis. Utilities for SF-6D were only captured every 8 weeks rather than for every 4-week cycle. Utilities for cycles not explicitly captured are assumed to be the average of the previous and next cycle. Utilities for responders and non-responders at Week 24 are assumed to be the responder and non-responder utilities at Week 28, respectively, due to lack of endpoint measurement at Week 24. All other inputs for the model are identical to the base case. The utility scores based on SF-6D were assessed assuming response based on ≥8.9-point improvement in SNOT-22 and NPS ≥1 or NCS ≥3.



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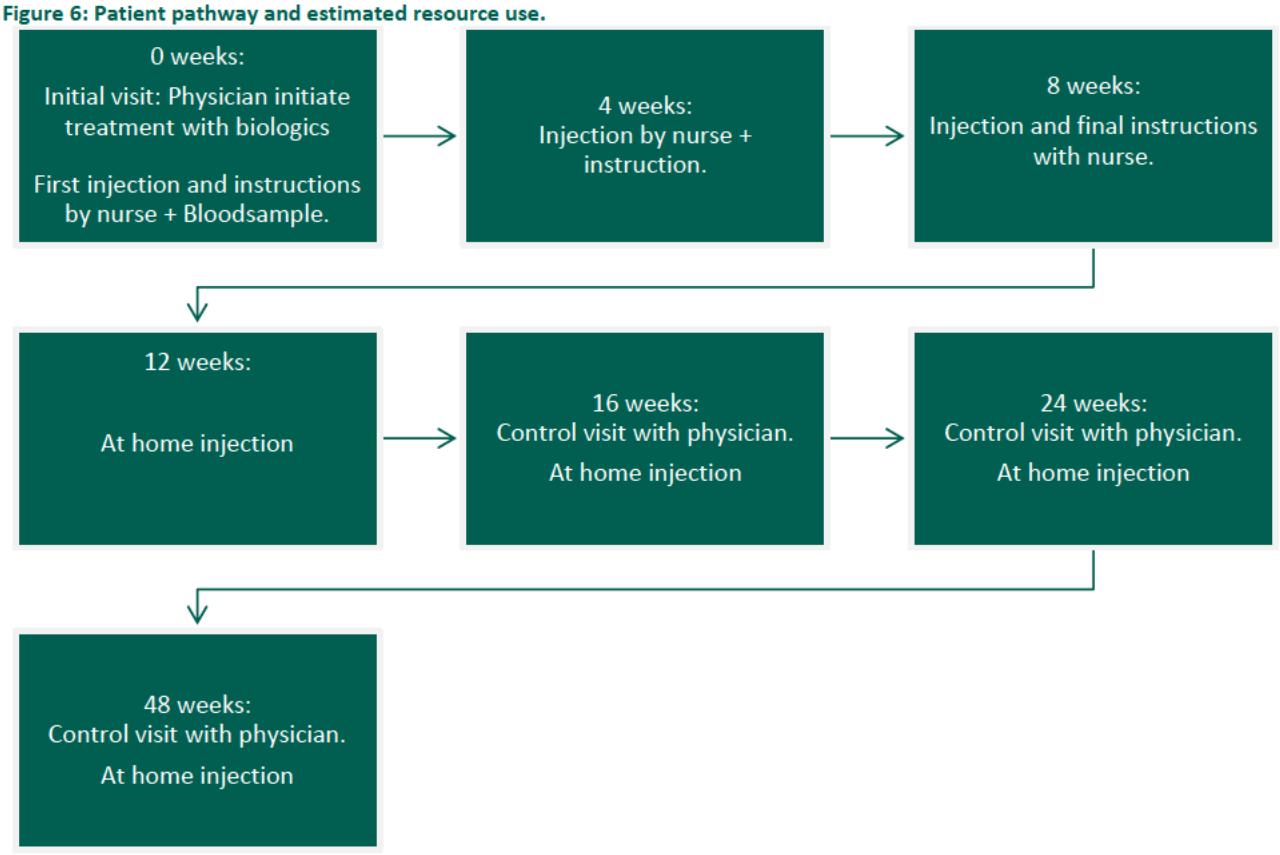
[redacted]

8.7 Resource use and costs

The estimated resource use associated with treatment with mepolizumab were obtained from interview with a treating physician in one of the Danish hospitals (specific details can be obtained by contacting GSK). The resource use is illustrated in the figure below. Prior to initiating treatment with mepolizumab, the patient will have a consultation with both a physician and a nurse at the department. Mepolizumab is administered every 4 weeks, the first 3 injections will be administered by a nurse at the clinic, following instructions for self-administration. From week 16, the patient will be trained and able to self-administer mepolizumab, either by prefilled syringe or prefilled autoinjector. Three trainings with a nurse is assumed for patients based on insights from the clinic. When the patient is trained and comfortable with the administration of mepolizumab, the patient will have two visits a year with the treating physician. This applies after the first year of treatment as well. The resource use associated with mepolizumab are therefore expected to decrease after the first year of treatment, the resource use after year 1 is therefore included in the model.

Figure 6: Patient pathway and estimated resource use.



8.7.1 Drug costs

Drug costs for SoC are assumed to be zero. Drug acquisition costs for mepolizumab are based on AIP derived from Medicinpriser.dk January 2022. Patients in the mepolizumab arm on treatment receive a single dose of 100 mg administered subcutaneously, every 4 weeks.

Table 42: Drug acquisition costs.

Item	Value	95% CI	Distribution	Source
SoC cost per dose	DKK 0.00	N/A	Fixed	Assumption
Mepolizumab cost per dose	DKK 7,772.89	N/A	gamma	Medicinpriser.dk
Mepolizumab doses per 4-week cycle	1	N/A	N/A	SmPC mepolizumab

8.7.2 Administration cost

Administration costs were derived from the DMC valuation of unit costs [36], Medicinpriser.dk [37] and the DRG. Mepolizumab is administered by subcutaneous injection, either by a provider or at home. It is assumed that 85% of the patients will use at-home administration. This rate can be modified in the model. Three at-home administration training with a nurse is expected based on experience from biological treatment of patients with severe asthma, this

estimate can be modified in the model. The costs associated with training and the first three at-hospital administrations by a provider is assumed to be covered by the DRG tariff used for the initiation costs.

Table 43: Drug administration costs.

	Value	95% CI	SE	Distribution	Source
% At Home Administration	85%	N/A	4%	beta	Assumption
Doses to Train At-Home Administration	3	N/A	N/A	N/A	Assumption

8.7.3 Initiation and monitoring costs

Initiation costs during the 1st year for mepolizumab include an initial consultation with a treating physician, followed by 3 control visits at week 16, 24 and 48, and 3 injections administered by a nurse at the hospital, together with At-home training. An eosinophilic blood sample is drawn once a year, this is expected to be captured within the DRG tariff used for injection. The costs associated with initiating treatment with mepolizumab and the following control visits at the outpatient clinic together with the administration costs of injecting mepolizumab, are estimated with the use of interactive DRG. Monitoring costs after the 1st year is assumed to consist of 2 outpatient visits with the treating physician and one eosinophilic blood sample.
Patient and transportation costs were derived from the valuation of unit costs provided by the DMC, where a fixed cost of DKK 100 was assumed for one visit at the hospital. Patient and transportation costs were estimated based on the patient pathway illustrated in Figure 6. No patient and transportation costs were assumed for SoC. The estimation of patient and transportation costs were based on the number of visits at the hospital and outpatient clinic illustrated in Table 44.

Table 44: Unit costs derived from the DMC "value of unit costs".

	Unit costs (DKK)	Unit	Value (DKK)	95% CI	SE (DKK)	Distribution	Source
Standard of Care Initiation Costs Year 1	0.00	0.00	0.00	N/A	0.00	gamma	Assumption
Mepolizumab Initiation Costs Year 1	1,364	7.00	9,548	N/A	487.14	gamma	DRG 2022, 03MA09
Standard of Care Monitoring Costs Year 2+	0.00	0.00	0.00	N/A	0.00	gamma	Assumption
Mepolizumab Monitoring Costs Year 2+	1,364	2.00	2,728	N/A	139.18	gamma	DRG 2022, 03MA09
Patient costs year 1	179	6.00	1,074	N/A	N/A	Fixed	DMC valuation of unit costs
Transportation costs year 1	100	6.00	600	N/A	N/A	Fixed	DMC valuation of unit costs

CI – confidence interval; N/A – not applicable; SE – standard error.

8.7.4 Surgery and complication costs

Surgery costs includes the costs of procedure and a CT scan prior to surgery. The costs were derived using the interactive DRG, where the diagnose code 03MP16 was used based on information from clinical practice. The DRG tariff used is expected to capture the costs associated with a CT-scan prior to surgery.

Serious complications resulting from sinus surgeries are generally rare and are assumed to be primarily attributable to epitaxis events. Costs for surgical complications are split between those requiring revision, other major complications such as headache and migraine, and minor complications requiring an outpatient visit. The costs are included for both the intervention mepolizumab and the comparator SoC. The included costs are listed in Table 45.

Table 45: Costs of Functional Endoscopic Sinus Surgery (FESS)

	Value (DKK)	95% CI	SE (DKK)	Distribution	Source DRG-takster 2021 - Sundhedsdatastyrelsen
Surgery procedure	25,681	N/A	1,310	gamma	03MP16 operation on nose, category 1.
Surgery AE requiring revision	2,217	N/A	113	gamma	https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-202103MA98 dagsgruppe, pat. mindst 7 år (DR040 nosebleed).
Surgery Major AE	3,618	N/A	184.59	gamma	01MA98 MDC03 1-dagsgruppe pat. Mindst 7 år (DG439 migraine).
Surgery Minor AE	1,364	N/A	69.59	gamma	03MA09: DJ330 nasal polyp

8.7.5 Asthma exacerbation costs

Asthma exacerbations are stratified by those requiring at home OCS, ambulant treatment, and hospitalization. Asthma exacerbations rates has been identified by the scientific committee in the previous application for dupilumab for the treatment of severe asthma, however, there are some uncertainties whether this estimate can be used for CRSwNP patients, therefore it was decided to use the rates from the SYNAPSE trial for this application. This is considered a conservative estimate as the rates reported by the scientific committee are higher for patients treated in the outpatient clinic and hospitalized.

The OCS is defined as at home treatment; however, the patient is expected to either visit the GP or have a telephone consultation. As no data on the split is available, it was assumed that one half of the patients would visit the GP clinic and the other half would be consulted by telephone. The costs were obtained from the DMC valuation of unit costs and the DRG system. Asthma exacerbation costs were derived from the DRG system, using the tariff for chronic pulmonary disease with acute exacerbation, as no tariff is available for asthma patients.

Table 46: Resource use associated with asthma exacerbation

Resource	Rate	Description of unit cost	Unit costs (DKK)	Source
OCS use (at home)	90.5%	Practice visit or telephone consultation	143.44/170.27	Valuation of unit costs
Outpatient visit	4.8%	04MA98 – MDC04 1- dagsgruppe, pat. Mindst 7 år	2,180	DRG-takster 2021 - Sundhedsdatastyrelsen

Resource	Rate	Description of unit cost	Unit costs (DKK)	Source
Hospitalization	4.8%	04MA12 – obstructive pulmonary disease pat. 0-59 year	22,687	DRG-takster 2021 - Sundhedsdatastyrelsen

8.7.6 Oral corticosteroid cost

Short term costs resulting from a flare are modelled as a single practice visit and a course of prednisone. The average dose of prednisone per course is taken from sundhed.dk, where a dose of 10 mg prednisone daily for 1-2 weeks is recommended for CRSwNP patients. The use of antibiotic in case of exacerbation was estimated using the guideline for treating exacerbation provided by the Danish Pulmonary Medicine Society.

Table 47: Drug costs for OCS.

Costs	Description	Unit cost AIP (DKK)	Source
Oral corticosteroid cost	Prednisone, 10 mg daily for 1-2 weeks	36.38	Medicinpriser.dk, sundhed.dk (næsepolypper)

8.7.7 Antibiotic cost

Short term antibiotic costs resulting from a flare are modelled as a 3-day course of azithromycin 500 mg once daily, the mean duration of antibiotics use per course is derived from the SYNAPSE trial. There is insufficient evidence supporting the use of antibiotics for patients with CRSwNP, however, antibiotics is used in clinical practice for some patients and for that reason antibiotics was included in the model. The majority of patients is treated with azithromycin as the first option, as the penetrance of this medication is favorable for treating infection in the sinuses. It should be noted that there is variation in choice of medication depending on the patient and treating physician, however, the cost of antibiotics is rather similar in most cases.

Costs	Description	Unit cost AIP (DKK)	Source
Antibiotic cost	Azithromycin 500 mg, 3 pcs. tablets (blister)	9.20	Medicinpriser.dk (dec 2022)

8.8 Results

8.8.1 Base case overview

In the table below an overview of the base case is provided, with the central inputs from the model.

Example of table 48 Base case overview

Base case	CRSwNP (trial population)
Comparator	• Standard of care / placebo
Patient Subgroups	• Comorbid asthma • Baseline blood eosinophil count ≥150 cells/µL • Baseline blood eosinophil count ≥300 cells/µL • Comorbid aspirin exacerbated respiratory disease (AERD) • Baseline blood eosinophil count ≥300 cells/µL and comorbid asthma
Structure	Markov Model
Cycle Lengths	4-week cycles
Half Cycle Correction	Simpson's 1/3 rule (not applied in base case)
Time Horizon	User defined - Lifetime base case
Perspective	Restricted societal perspective
Intervention	Mepolizumab
Measurement and valuation of health effects	• Base case: Health-related quality of life measured with mapping SNOT-22 scores from SYNAPSE to EQ-5D [40] • Scenario: Health-related quality of life measured with mapping SF-6D.
Direct Costs	• Drug cost • Administration cost • Nasal polyp surgery • Asthma exacerbations • Oral corticosteroids (OCS) for treating CRSwNP • Antibiotics for treating CRSwNP • Patient costs • Transportation costs
Outcomes	• Treatment-related costs (acquisition + administration) • Disease-related costs (asthma exacerbations, OCS, antibiotics) • Surgeries • Life years (LY) • Quality-adjusted life years (QALYs)
Sensitivity Analysis	One-way sensitivity analysis to test the impact of individual parameters Probabilistic sensitivity analysis to assess the overall uncertainty in model results

8.8.2 Base case results

The base case results from the cost-effectiveness model is populated in the table below. The table consists base case results on costs, life years gained, QALY and the incremental cost per QALY.

Table 49 Base case results

Per patient	Intervention	Comparator	Difference
Life years gained			
Total life years gained	**19.79**	**19.78**	**0.1**
QALYs			
Total QALYs	[redacted]	[redacted]	[redacted]
QALYs in trial	[redacted]	[redacted]	[redacted]
QALYs Responder	[redacted]	[redacted]	[redacted]
QALYs Non-responder	[redacted]	[redacted]	[redacted]
QALYs Effective surgery	[redacted]	[redacted]	[redacted]
QALYs recurrence or failed	[redacted]	[redacted]	[redacted]
QALYs (adverse reactions)	**N/A**	**N/A**	**N/A**
Costs (DKK)			
Total costs	**1,612,411**	**34,217**	**1,578,194**
Drug costs	**1,448,427**	**0**	**1,448,427**
Administrative costs	**146,283**	**0**	**146,283**
Surgery	**16,692**	**32,090**	**15,398**
Asthma exacerbation	**1,008**	**2,126**	**1,119**
Other	**0.00**	**0.00**	**0.00**
Incremental results	**1,612,411**		
ICER (cost per QALY)	[redacted]		

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8.8.3 Scenario Analyses – SF-6D

Scenario analyses were conducted for utility scores based on SF-6D assuming response based on ≥8.9-point improvement SNOT-22 and NPS ≥1 or NCS ≥3. In the scenario, results show higher cost and greater QALYs for mepolizumab compared with the standard of care.

8.8.4 Utility Scores Based on SF-6D

[redacted]

8.9 Sensitivity analyses

8.9.1 Deterministic sensitivity analyses

The results from the one-way sensitivity analysis obtained in illustrated in the table below.

8.9.1.1 One-way sensitivity analysis results

Table 50: Results from the one-way sensitivity analysis

Parameter	Base Case	Low Value	High Value	Range	Low Result (DKK)	High Result (DKK)	Δ (DKK)
Mepolizumab - EQ-5D CFB @ Week 52+ Δ NPS ≥1 OR Δ NCS ≥3 Responder	0.201	0.170	0.23	95% CI	1,822,336	941,922	880,414
SOC - EQ-5D CFB @ Week 52+ Δ NPS ≥1	0.174	0.135	0.21	95% CI	1,024,686	1,576,050	551,364

OR Δ NCS ≥3 Responder							
Mepolizumab - Cost per Dose (DKK)	7,773	6,996	8,550	±10%	1,131,539	1,352,306	220,767
EQ-5D Utility Gain From Surgery	0.107	0.044	0.17	95% CI	1,164,346	1,330,576	166,230
SOC Response - Δ NPS ≥1 OR Δ NCS ≥3 @ Week 24 (Responder)	47%	44%	51%	95% CI	1,172,136	1,320,530	148,393
SOC Response - Proportion of Responders @ Week 24 with Response @ Week 52	68%	64%	73%	95% CI	1,177,360	1,313,966	136,606
Mepolizumab Response - Δ NPS ≥1 OR Δ NCS ≥3 @ Week 24 (Responder)	70%	67%	73%	95% CI	1,297,574	1,194,679	102,895
SOC - EQ-5D CFB @ Week 52+ Δ NPS ≥1 OR Δ NCS ≥3 Non-Responder	0.03	-0.01	0.07	95% CI	1,199,347	1,287,633	88,286
Mepolizumab Response - Proportion of Responders @ Week 24 with Response @ Week 52	87%	84%	90%	95% CI	1,280,303	1,207,688	72,616

8.9.2 Probabilistic sensitivity analyses

A probabilistic sensitivity analysis was carried out with 5,000 iterations. The model allows for the PSA to be run with 10,000 iterations. Results of probabilistic sensitivity analysis yielded higher ICERs on average for mepolizumab vs standard of care compared with deterministic estimates, driven by uncertainty in model parameters that resulted in outlier iterations with high cost and fewer QALYs gained.

Table 51: Probabilistic sensitivity analysis results.

Total Costs and QALYs		Incremental Cost and QALYs	
Mean	95% Credible Range	Mean	95% Credible Range

Standard of Care				
Total Costs	DKK 35,516	(DKK 28,500; DKK 47,325)	0.00	(DKK 0.000; DKK 0.000)
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]
ICER			0.00	0.00
Mepolizumab				
Total Costs	DKK 1,610,683	(DKK 1,450,734; DKK 1,762,604)	DKK 1,314,644	(DKK 1,416,263; DKK 1,725,385
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]
ICER			[redacted]	[redacted]

[redacted]

[redacted]

9. Budget impact analysis

The budget impact analysis was carried out in an excel spreadsheet. A newly published Danish study assessing the potential role of biological treatment of CRSwNP patients. The conclusion was that an average of 120 patients annually will have revision surgery and may therefore benefit from biological treatment. This was also provided by the scientific committee in the protocol for dupilumab and therefore included for this application[25].

9.1.1 Market uptake

The expected market uptake for mepolizumab is estimated based on insights and the uptake for mepolizumab when introduced for treatment of severe asthma. If mepolizumab is not recommended as standard treatment no patients are expected to be on treatment with mepolizumab.

Table 52: Expected market uptake if mepolizumab is recommended for standard treatment

	Year 1	Year 2	Year 3	Year 4	Year 5
Mepolizumab	35%	45%	55%	75%	80%
Standard of care	65%	55%	45%	25%	20%

Table 53: Expected market uptake if mepolizumab is NOT recommended as standard treatment

	Year 1	Year 2	Year 3	Year 4	Year 5
Mepolizumab	0%	0%	0%	0%	0%
Standard of care	100%	100%	100%	100%	100%

9.1.2 Number of patients

The estimated number of patients expected to be treated with mepolizumab over the next five years is based on the estimated market uptake for mepolizumab.

Table 54: Number of patients expected to be treated over the next five-year period - if mepolizumab is recommended for standard treatment

	Year 1	Year 2	Year 3	Year 4	Year 5
Mepolizumab	42	54	66	90	96
Standard of care	78	66	54	30	24
Total number of patients	120	120	120	120	120

Table 55: Number of patients expected to be treated over the next five-year period - if mepolizumab is NOT recommended for standard use

	Year 1	Year 2	Year 3	Year 4	Year 5
Mepolizumab	0	0	0	0	0
Standard of care	120	120	120	120	120
Total number of patients	120	120	120	120	120

9.1.3 Budget impact results

9.1.3.1 Budget impact per treated patient

The per patient costs associated with recommending mepolizumab as standard of care for patients with CRSwNP. The per treated patient costs are illustrated in the table below.

Table 56: Budget impact per treated individual per year – if mepolizumab is recommended [DKK].

Difference	Year 1	Year 2	Year 3	Year 4	Year 5
Mepolizumab	97,329	97,329	97,329	97,329	97,329

9.1.3.2 Budget impact per drug and medical cost

The per drug and medical costs associated with introducing mepolizumab as standard treatment is illustrated in Table 57.

Table 57: Budget impact per drug and medical costs [DKK].

Difference (standard - not standard)	Year 1	Year 2	Year 3	Year 4	Year 5
Drug cost budget impact	4,243,998	5,456,569	6,669,140	9,094,281	9,700,567
Medical cost budget impact	-156,186	-200,811	-245,436	-334,685	-356,998

9.1.3.3 Total budget impact

The budget impact if mepolizumab is recommended as standard treatment and if it is NOT recommended for standard treatment.

Table 58: Expected budget impact of recommending mepolizumab for standard treatment [DKK].

	Year 1	Year 2	Year 3	Year 4	Year 5
Total budget impact if mepolizumab is recommended	4,808,200	5,976,147	7,144,093	9,479,985	10,063,958
Total budget impact if mepolizumab is NOT recommended	720,389	720,389	720,389	720,389	720,389
Budget impact of the recommendation	4,087,811	5,255,758	6,423,704	8,759,596	9,343,569

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9.2 Summary of results

The results from the cost-effectiveness model showed an ICER of DKK [redacted]. The incremental QALY gain of [redacted] when comparing mepolizumab to SoC. Introducing Nucala as standard treatment for CRSwNP patients would result in approved quality of life compared to current standard practice. The results showed additional costs associated with introducing mepolizumab for standard treatment. The costs are primarily driven by the drug costs of Nucala. However, from the economic and clinical application it can be concluded that treatment with mepolizumab reduces the number of sinus surgeries needed and improves the quality of life for the patients.
The budget impact showed the health care costs over a 5-year period, the budget impact year 1 was DKK 4,087,811 and for year 5 DKK 9,343,569. Using the estimated number of eligible patients (120 each year).

10. Discussion on the submitted documentation

Efficacy

For all recurrent, refractory CRSwNP population evaluated, mepolizumab demonstrated a statistically significant benefit over placebo in terms of improved nasal polyp size and nasal obstruction. The findings also showed that overall symptom VAS score, composite VAS score, and loss of smell VAS score had significantly improved from the baseline in the mepolizumab group versus the placebo group. The risk of surgery over the treatment period was significantly lower for mepolizumab patients and subgroup analyses favoured mepolizumab over placebo.

The 2019 European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA) expert team proposed that biological treatment should be indicated in patients with bilateral nasal polyps who have undergone surgery in the past and meet at least three of the following criteria: evidence of type 2 inflammation, need for systemic corticosteroids in the past 2 years, substantial quality of life impairment, and a significant loss of smell or a diagnosis of comorbid asthma[38]. The inclusion criteria of patients in the SYNAPSE study are in line with these recommendations.

It was not possible to establish the MCID for change in total nasal polyp score based on published literature. However, the DMC protocol for assessment regarding dupilumab [25] for treatment of CRSwNP recommends an average difference of 1 point between groups as the smallest clinically relevant difference[25]. Regarding change in SNOT-22 scores, higher proportion of mepolizumab patients reported achieving MCID (8.9 points) or more on change in SNOT-22 scores from baseline to week 52 as compared to placebo patients[15].

Safety

There were no statistical difference between mepolizumab and placebo for any of the safety outcomes which indicates similar safety profiles. Compared to placebo patients however, the proportion of mepolizumab patients with AE was lower. Long term data are, however, still limited.
Mepolizumab administered as a pre-filled pen or syringe can be self-administered by the patient or a caregiver every four weeks. This ease of administration can be an advantage for patients who either cannot or are not willing to visit healthcare providers.

Relevance to the Danish context

The population included in the SYNAPSE study in this application are generally comparable with the Danish patients. Patients enrolled in the SYNAPSE study were recruited from different countries around the world, including countries from Europe. Guidance from DMC regarding use of biologic drugs for CRSwNP recommends patient criteria that are very similar to the inclusion criteria of the SYNAPSE study. A recently published study in Denmark included all adult patients registered in the Danish National Patient Registry who had undergone first endoscopic sinus surgery for CRSwNP between 2012–2018. The authors reported that an average of 120 operated patients annually will have revision surgery within seven years and may benefit from treatment with biologics as an alternative option to revision surgery [14]. Since the SYNAPSE study reported the benefits of using mepolizumab, a biologic drug for refractory, recurrent CRSwNP patients, these benefits will also be relevant for Danish patients who require an alternative to the standard of care.

Strengths and weaknesses of the health economic model

A weakness to the health economic model is that the utility values used for this application are mapped from SNOT-22 to utility values by using a mapping tool. This is the only existing study that has made an algorithm to map SNOT-22 values to utilities. There are therefore some uncertainties, as this is not a widely studied method. The model uses data from other countries, there might therefore be some demographic uncertainties linked to these parameters used in

the model. The model assumes that patients responding to mepolizumab after 52 weeks will remain in the response state. This assumption might be associated with some uncertainties. The strengths of the economic model are that it leviates a lifetime time horizon and includes the benefit of mepolizumab in reducing surgeries and increasing quality of life for the CRSwNP patients.

Conclusion

Findings from the SYNAPSE study show that the addition of mepolizumab to the current standard of care for patients with refractory, recurrent CRSwNP generally results in significant improvements in efficacy outcomes. With a favourable safety profile and as pre-filled syringe or pen administered by patient or caregiver once every 4 weeks, mepolizumab has the potential to remove the adherence challenges that may be encountered, and thus, in the long term, potentially result in better disease control. The budget impact analysis shows there are additional costs associated with treatment with mepolizumab compared to surgery. The costs associated with treatment are primarily driven by drug costs to mepolizumab. It was concluded from the Danish registry study that a group (120) of patients will be eligible for biologic treatment. Introducing mepolizumab as a treatment of CRSwNP will according to the data from the Synapse study result in better disease control, reduce the need for surgery and risk of treatment failure thus increasing the quality of life for the patient.

11. Other considerations

Subgroup analyses of SYNAPSE study examining the impact of mepolizumab on comorbidities and baseline blood eosinophil count in CRSwNP patients, is expected to be published in Journal of Allergy and Clinical Immunology later this year.

Newly published Danish national cohort data on incidence of CRSwNP showed that 34% of the patients who had revision surgery was diagnosed with asthma and 8.2% with allergic rhinitis. This data illustrates that potentially one third of the CRSwNP patients have a co-morbidity [14].
Another previous study conducted in a Danish department found 65% of patients operated for CRSwNP had comorbid asthma when tested. Half of them were undiagnosed prior to the study [19].For this group of patients biological treatment could be beneficial in order to achieve asthma control and reduce number of endoscopic sinus surgeries.

11.1 Additional data (asthma)

GSK has recently concluded a randomised, double-blind, placebo-controlled trial (COMET) to evaluate the impact of stopping long-term use (≥3 years) of mepolizumab in severe eosinophilic asthma patients. Patients who received continuous mepolizumab treatment for ≥3 years were randomized 1:1 to stop (switch to placebo) or continue SC mepolizumab 100 mg every 4 weeks for 52 weeks. Patients stopping (n=151) versus continuing (n=144) mepolizumab had significantly shorter times to first clinically significant exacerbation (HR: 1.61 [95% CI: 1.17,2.22]; *P*=0.004) and decrease in asthma control (HR: 1.52 [1.13,2.02]; P=0.005). The results indicate that patients who stopped mepolizumab showed an increase in exacerbations and reduced asthma control versus those who continued.
The results of this trial are currently in press and will be shortly published in European Respiratory Journal.

The long-term efficacy profile of mepolizumab in severe refractory eosinophilic asthma patients (n=998) treated for median of 2.8 years (range 4 weeks to 4.5 years) in open-label extension studies MEA115666, MEA115661 and 201312 was generally consistent with the 3 placebo-controlled studies.

12. List of experts

[redacted]

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Appendix A – Literature search for efficacy and safety of intervention and comparators

The objective of the literature search was to answer the following:
"What is the efficacy and safety of mepolizumab in patients with recurrent, refractory, severe chronic rhinosinusitis with nasal polyps, despite continuous medical treatment and previous surgical treatment who were eligible for repeat nasal surgery?"
The objectives more specifically were to:
•Identify published and unpublished randomised controlled trials (RCT) of the efficacy and safety of mepolizumab, and comparators in RCTs, for the treatment of recurrent, refractory, severe CRSwNP
•Present a narrative synthesis of outcome data reported in relevant studies of mepolizumab, and other comparators

Literature searches were performed 13 August 2021. The searches were performed in Cochrane Central Register of Controlled Trials (CENTRAL) and PubMed (MEDLINE).

To identify information on trials in progress, searches were performed in Clinicaltrials.gov (via https://clinicaltrials.gov/) and EU clinical trials register (via https://www.clinicaltrialsregister.eu/). The search was performed on 15 August 2021.

Table 59: Databases included in the search

Database	Platform	Relevant period for the search	Date of search completion
Cochrane Central Register of Controlled Trials	CENTRAL	Issue 8 of 12, August 2021	13 August 2021
PubMed	MEDLINE	1946-August 2021	13 August 2021

Table 60: Registers included in the search

Database	Platform	Search strategy	Date of search
US NIH registry & results database	https://clinicaltrials.gov	Search string run in expert search	15 August 2021
EU Clinical Trials Register	EU Clinical Trials Register	Search string run in the basic search box	15 August 2021

US NIH, United States National Institute of Health; EU, European Union.

Search strategy

The search strategy developed to meet the objective of the literature search was defined by the following inclusion and exclusion criteria.

Population:
The target population of patients include adults with recurrent, refractory, severe, bilateral chronic rhinosinusitis with nasal polyps who were eligible for mepolizumab.

Interventions:
Eligible intervention is mepolizumab.

Comparators:
Interventions including placebo (with or without background therapy) is considered as eligible comparators.

Outcomes:
Studies providing data on any of the efficacy outcomes listed below in the relevant patient populations were eligible for inclusion:

- Change from baseline in total nasal polyps score;
- Change from baseline in VAS nasal obstruction score;
- Change from baseline in overall VAS symptom score;
- Change from baseline in composite VAS score;
- Change from baseline in loss of smell VAS score;
- Change from baseline in SNOT-22 score;
- Proportion of patients having nasal surgery;
- Proportion of patients requiring systemic corticosteroids

The safety outcomes of interest are:

- Any adverse event (AE);
- Serious AE (SAE)
- Treatment discontinuation due to AE
- Study withdrawal due to AE

Study design:
Phase 3, randomised trials were eligible for inclusion.

Publication types:
Full-text, peer-reviewed publications of trials was the most desirable form of evidence eligible for inclusion. Abstracts or oral conference presentations from 2018-2020 reporting clinical trials were eligible for inclusion if sufficient data were reported or if they supplemented data from another relevant publication.

The following publication types were not part of the data synthesis: Systematic reviews with or without meta-analysis and guidelines. The following study designs and publication types were also not eligible for inclusion: Non-systematic reviews, expert opinion pieces, letters, editorials, press releases, case studies of individuals, in vitro studies, animal model studies.

Limits:
Bibliographic databases, and the trials registry and trials platform, were searched from inception to present. Study identification was limited to studies reporting randomised trials. No other limits (language, publication type or status) were applied to the search.

Search strings for the individual searches are provided below.

Bibliographic databases

PUBMED search, 13 Aug 2021

#	Searches	Results
1	(mepolizumab[Title/Abstract]) OR (mepolizumab)	947
2	(((chronic rhinosinusitis) OR (chronic rhinosinusitis[Text Word])) AND (nasal polyps)) OR (nasal polyps[Text Word])	8,755
3	#1 AND #2	76
4	((((Random* Controlled Trial) OR (Controlled clinical trial)) OR (pragmatic clinical trial)) OR (clinical trial, phase 3)).pt	3,069
5	#4 AND (double blind)	451
6	#5 OR (single blind)	57,048
7	#6 OR (triple blind)	58,954
8	#7 AND #1	4

COCHRANE central search, 13 Aug 2021

#	Searches	Results
1	(mepolizumab):kw OR (mepolizumab):ti,ab,kw	341
2	("chronic rhinosinusitis") OR ("chronic rhinosinusitis"):ti,ab,kw AND ("nasal polyp"):ti,ab,kw OR ("nasal polyp")	1,213
3	#1 AND #2	76
4	("randomised clinical trials") OR ("controlled clinical trial") OR ("clinical trial") OR ("phase 3 studies") OR ("clinical trial"):pt	683,357
5	#4 AND ("double blind") OR ("single blind") OR ("triple blind")	235,902
6	#5 AND #3	8

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Trial registers

Clinicaltrials.gov search, 15 August 2021

Records retrieved: 2

Mepolizumab OR Chronic Rhinosinusitis with Nasal Polyps AND Recruiting OR Not yet recruiting OR Active OR not recruiting OR Completed OR Enrolling by invitation OR Suspended OR Terminated OR Withdrawn OR Unknown status AND interventional Studies

EU clinical trials registry search, 15 August 2021

Records retrieved: 1

Mepolizumab OR Chronic Rhinosinusitis

Treatment arms excluded from the analysis

No treatment arms were excluded from the analysis. Both mepolizumab and placebo arms from the SYNAPSE study were included in the analysis.

Ongoing studies and studies that are completed but not yet published

A search was undertaken in clinicaltrials.gov on 15 August 2021 to identify ongoing studies and studies that were completed but had not yet been published. To identify ongoing studies, the filters “Not yet recruiting”, “Recruiting”, “Enrolling by invitation” and “Active, not recruiting” were applied. To identify completed but not yet published studies, the filter “completed” was applied.

Two studies were identified as ongoing studies and no study was identified as completed.

Table 61: Studies that are ongoing

ClinicalTrials.gov Search Results 08/15/2021

	NCT Number	Title	Status	Study Results	Conditions	Interventions	Dates
1	NCT04607005	Efficacy and Safety of Mepolizumab in Adults With Chronic Rhinosinusitis With Nasal Polyps (CRSwNP)/ Eosinophilic Chronic Rhinosinusitis (ECRS)	Recruiting	No Results Available	•Nasal Polyps	•Drug: Mepolizumab •Drug: Placebo •Drug: Standard of care	Study Start: February 8, 2021
2	NCT04823585	Aggravated Airway Inflammation: Research on Biological Treatment (Mepolizumab)	Recruiting	No Results Available	•Asthma, Aspirin-Induced •Chronic Rhinosinusitis With Nasal Polyps	•Drug: Mepolizumab •Drug: Placebo	Study Start: August 12, 2021

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

Risk of bias by study

Table 62: Summary of risk bias

Trial name/ ID	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants, and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in dropouts between groups?	Was the method of measuring the outcome inappropriate? If no, were the outcome assessors aware of the intervention received by the study participants?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
SYNAPSE/NCT03085797[15]								

Green represents 'low' risk bias and yellow represents 'unclear' risk bias.

From Cochrane. RoB 2: A revised Cochrane risk-of-bias tool for randomized trials 2021[32]

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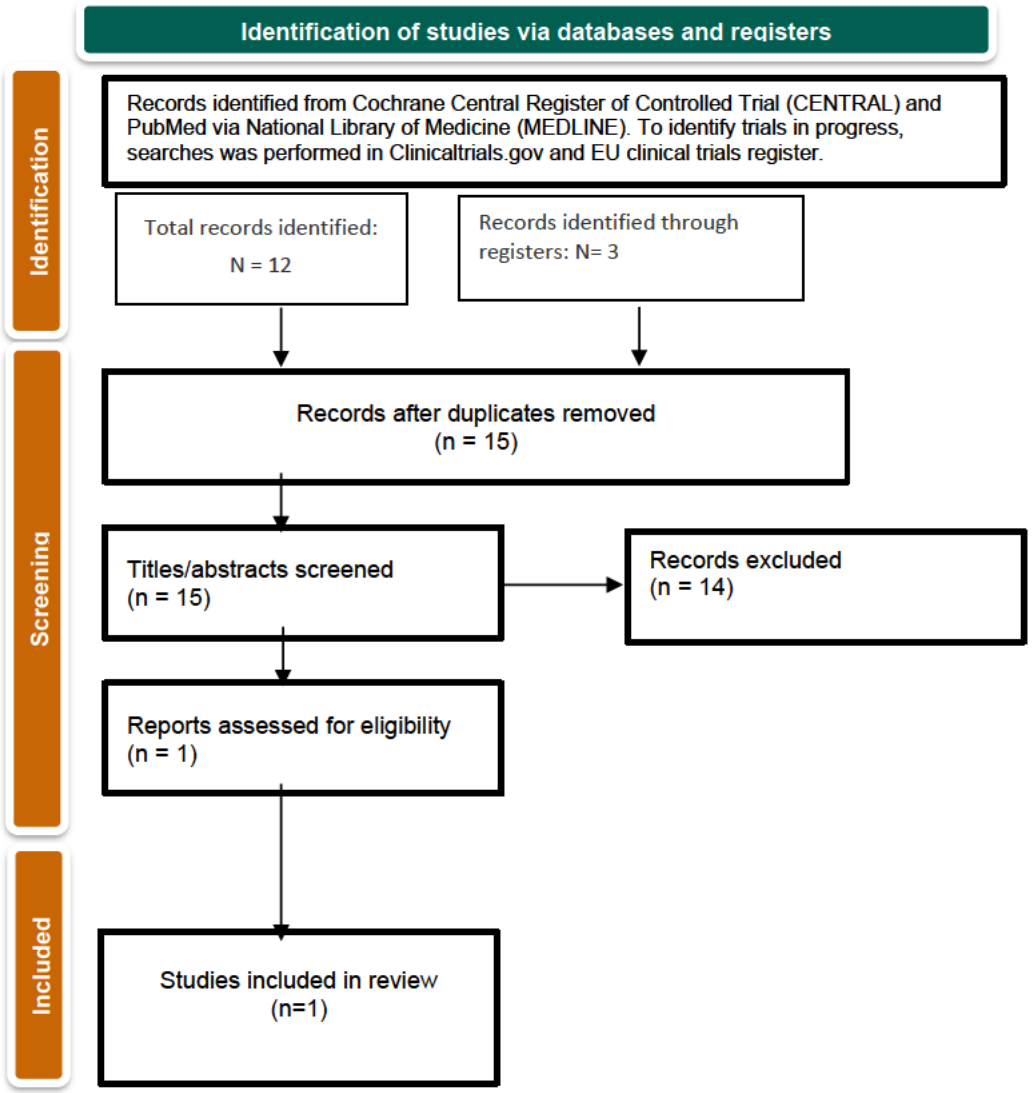
PRISMA diagram



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Quality assessment

The literature search was performed in August 2021. The literature search has in general been performed and documented in accordance with the methodology recommended by the Medicines Council.

Unpublished data

Not applicable.

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Appendix B Main characteristics of included studies

Mepolizumab study	
Trial name: SYNAPSE	**NCT number: NCT03085797**
Objective	To assess the clinical efficacy and safety of 100 milligram (mg) subcutaneous (SC) mepolizumab as an add on to maintenance treatment in adults with severe bilateral nasal polyps
Publications – title, author, journal, year	A Randomised, Double-blind, Parallel Group PhIII Study to Assess the Clinical Efficacy and Safety of 100 mg SC Mepolizumab as an Add on to Maintenance Treatment in Adults With Severe Bilateral Nasal Polyps - SYNAPSE (StudY in NAsal Polyps Patients to Assess the Safety and Efficacy of Mepolizumab) Han, JK et al Lancet Respir Med 2021[15]
Study type and design	randomised, double-blind, parallel group, phase 3 study
Sample size (n)	407 patients-206 assigned mepolizumab, 201 assigned placebo

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Main inclusion and exclusion criteria	Inclusion criteria: • 18 years of age and older inclusive, at the time of signing the informed consent • Body weight greater or equal to 40 kilogram (kg) • Male or female participants (with appropriate contraceptive methods) to be eligible for entry into the study. To be eligible for entry into the study, woman of childbearing potential (WOCBP) must commit to consistent and correct use of an acceptable method of birth control from the time of consent, for the duration of the trial, and for 105 days after last study drug administration • Participants who have had at least one previous surgery in the previous 10 years for the removal of nasal polyp (NP). NP surgery is defined as any procedure involving instruments with resulting incision (cutting open) and removal of polyp tissue from the nasal cavity (polypectomy). For the purpose of inclusion into this study, any procedure involving instrumentation in the nasal cavity resulting in dilatation of the nasal passage such as balloon sinuplasty, insertion of coated stents or direct injection of steroids or other medication without any removal of NP tissue is not accepted • Participants with bilateral NP as diagnosed by endoscopy or computed tomography (CT) scan • Presence of at least two of the following symptoms one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip) and either nasal discharge (anterior/posterior nasal drip); facial pain/pressure; reduction or loss of smell for at least 12 weeks prior to screening • Participants with severe NP symptoms defined as an obstruction VAS symptom score of >5. • Severity consistent with a need for surgery as described by: participants with an overall VAS symptom score >7, OR participants with an endoscopic bilateral NP score of at least 5 out of a maximum score of 8 (with a minimum score of 2 in each nasal cavity) • Treatment with intranasal corticosteroids (INCS) for at least 8 weeks prior to screening • Capable of giving signed informed consent Exclusion criteria: • As a result of medical interview, physical examination, or screening investigation, the physician responsible considers the participant unfit for the study • Cystic fibrosis • Eosinophilic granulomatosis with polyangiitis (also known as churg strauss syndrome), young's, kartagener's or dyskinetic ciliary syndromes. • Antrochoanal polyps • Nasal septal deviation occluding one nostril • Acute sinusitis or upper respiratory tract infection at screening or in 2 weeks prior to screening • Ongoing rhinitis medicamentosa (rebound or chemical induced rhinitis) • Participants who have had an asthma exacerbation requiring admission to hospital within 4 weeks of screening • Participants who have undergone any intranasal and/or sinus surgery (for example polypectomy, balloon dilatation or nasal stent insertion) within 6 months prior Visit 1 • Participants where NP surgery is contraindicated in the opinion of the Investigator • Participants with a known medical history of human immunodeficiency virus (HIV) infection • Participants with a known, pre-existing parasitic infestation within 6 months prior to Visit 1 • Participants who are currently receiving, or have received within 3 months (or 5 half lives - whatever is the longest) prior to first mepolizumab dose, chemotherapy, radiotherapy or investigational medications/therapies • Participants with a history of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or GSK

	medical monitor, contraindicates their participation. Aspirin-sensitive participants are acceptable • Participants with a history of allergic reaction to anti-IL-5 or other monoclonal antibody therapy • Participants on a waiting list for NP surgery while at screening • Participants that have taken part in previous mepolizumab, reslizumab, dupilumab or benralizumab studies • Use of systemic corticosteroids (including oral corticosteroids) or corticosteroid nasal solution (intranasal corticosteroid is accepted) within 4 weeks prior to Screening or planned use of such medications during the double-blind period • INCS dose changes within 1 month prior to screening • Treatments with biological or immunosuppressive treatment (other than omalizumab) treatment within 5 terminal phase half lives of Visit 1 • Omalizumab treatment in the 130 days prior to Visit 1 • Commencement of leukotriene antagonist treatment less than 30 days prior to Visit 1 • Allergen immunotherapy within the previous 3 months • Women who are pregnant or lactating or are planning on becoming pregnant during the study • Participants who currently smoke or have smoked in the last 6 months • Any participant who is considered unlikely to survive the duration of the study period or has any rapidly progressing disease or immediate life-threatening illness (e.g., cancer). In addition, any participant who has any other condition (e.g., neurological condition) that is likely to affect respiratory function should not be included in the study • Participants who have known, pre-existing, clinically significant endocrine, autoimmune, cardiovascular, metabolic, neurological, renal, gastrointestinal, hepatic, hematological or any other system abnormalities that are uncontrolled with standard treatment • Immunocompromized, other than that explained by the use of corticosteroids taken as therapy • A current malignancy or previous history of cancer in remission for less than 12 months prior to Screening. Participants with successfully treated basal cell carcinoma, squamous cell carcinoma of the skin, or cervical carcinoma in situ, with no evidence of recurrence may participate in the study • Current active liver or biliary disease (with the exception of gilbert's syndrome or asymptomatic gallstones or otherwise stable chronic liver disease per investigator assessment) • Corrected QT interval (QTc) >450 milliseconds (msec) or QTc >480 msec in participants with bundle branch block at visit 1 • A known or suspected history of alcohol or drug abuse within 2 years prior to Screening (Visit 1) that in the opinion of the investigator would prevent the participant from completing the study procedures • An investigator, sub-investigator, study coordinator, employee of a participating investigator or study site, or immediate family member of the aforementioned that is involved in this study • In the opinion of the investigator, any participant who is unable to read and/or would not be able to complete a questionnaire
Intervention	Mepolizumab 100 mg subcutaneous (SC) + Mometasone furoat 400 mcg, 2 actuations (50 mcg/actuation) in each nostril twice daily.
Comparator	Placebo SC + Mometasone furoat 400 mcg, 2 actuations (50 mcg/actuation) in each nostril twice daily

Follow-up time	52 weeks, by design, some randomised participants were eligible to enter a further 6-month no-treatment follow-up period to assess maintenance of response after cessation of treatment
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Co-primary endpoints: • Change from baseline in total endoscopic nasal polyp score at week 52 • Change from baseline in nasal obstruction visual analogue scale (VAS) score during the 4 weeks prior to week 52 Secondary endpoint: • time-to-first nasal surgery until week 52 (key secondary endpoint) • change from baseline in mean overall VAS symptom score during weeks 49–52 • change from baseline in Sinonasal Outcomes Test (SNOT)-22 total score at week 52 • proportion of patients requiring systemic corticosteroids for nasal polyps until week 52 • change from baseline in mean composite VAS score (combining scores for nasal obstruction, nasal discharge, throat mucus, and loss of smell) during weeks 49–52 • change from baseline in mean VAS score for loss of smell during weeks 49–52 Exploratory endpoint: • proportion of patients with a decrease of 8.9 points or more from baseline in SNOT-22 total score in the absence of surgery
Method of analysis	For the statistical analysis of the co-primary and key secondary endpoints, the treatment effect to be estimated was the comparison of mepolizumab SC 100 mg with placebo; for co-primary endpoints the summary measure of treatment effect was the difference between mepolizumab and placebo in the variable medians. For coprimary endpoints, VAS scores, SNOT-22 score, the non-parametric Wilcoxon rank-sum test was used to assess the difference in change from baseline scores between treatment groups. Time-to-nasal surgery was analyzed using a Cox proportional hazards model with covariates of treatment group, baseline nasal polyp score (centrally read), baseline nasal obstruction VAS score, natural logarithm of baseline blood eosinophil count, number of previous surgeries, and geographical region. The proportion of patients requiring systemic corticosteroids for nasal polyps was analyzed using a logistic regression model with covariates of treatment group, baseline nasal polyp score (centrally read), baseline nasal obstruction VAS score, natural logarithm of baseline blood eosinophil count, number of systemic corticosteroids courses in previous 12 months and geographic region. For the exploratory endpoint regarding proportion of patients with a decrease of 8.9 or more points in change in SNOT-22 scores, analysis performed using a logistic regression model with covariates of treatment group, geographic region, baseline score and loge baseline blood eosinophil count.

Subgroup analyses	Analysis of the co-primary endpoints was carried out to assess efficacy in subgroups by region, age, sex, presence of comorbid asthma, presence of comorbid aspirin-exacerbated respiratory disease (AERD) and baseline blood eosinophil count. For each subgroup, estimates of treatment effect were from a quantile regression model with covariates of treatment group, geographic region (except for analysis by region), baseline score and natural logarithm of baseline blood eosinophil count (except for analysis by blood eosinophil count).

Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Table 63: Baseline characteristics of the SYNAPSE study, (Intention-to-treat (ITT) population) [15]

	Placebo	Mepolizumab
Age, in years	48.9 (12.5)	48.6 (13.6)
Sex		
Men	125 (62%)	139 (67%)
Women	76 (38%)	67 (33%)
Demographic		
White and European	183 (91%)	190 (92%)
East Asian	7 (3%)	6 (3%)
Black and African American	4 (2%)	5 (2%)
Arabic and North African	4 (2%)	2 (1%)
Central and South Asian	1 (1%)	2 (1%)
South East Asian	1 (1%)	1 (1%)
Multiple	1 (1%)	0
Body mass index (kg/m^2)		
Median	27.2 (24.6–30.5)	27.4 (24.4–30.3)
Mean	28.2 (5.5)	28.2 (5.3)
Duration of nasal polyps, years		
Median	10.0 (5.3–16.0)	9.0 (5.0–15.3)
Mean	11.5 (8.3)	11.4 (8.5)
Previous nasal polyp surgery		
≥1	201 (100%)	206 (100%)
≥2	120 (60%)	98 (48%)
≥3	73 (36%)	51 (25%)
≥4	38 (19%)	24 (12%)
≥5	26 (13%)	11 (5%)
Time since most recent nasal surgery (years) *		
Median	3.0 (1.7–5.6)	3.8 (1.9–6.2)
Mean	3.8 (2.7)	4.2 (2.7)
Systemic corticosteroid use in preceding 12 months		
0	110 (55%)	100 (49%)
≥1	91 (45%)	106 (51%)
≥2	44 (22%)	42 (20%)
Total endoscopic score (scale 0–8)		
Median	6.0 (5.0–6.0)	5.0 (5.0–6.0)
Mean	5.6 (1.4)	5.4 (1.2)
Nasal obstruction VAS score (scale 0–10)†		
Median	9.1 (8.5–9.7)	9.0 (8.3–9.6)
Mean	9.0 (0.8)	8.9 (0.8)
Overall symptom VAS score (scale 0–10)†		
Median	9.2 (8.7–9.8)	9.1 (8.4–9.7)
Mean	9.1 (0.7)	9.0 (0.8)

Nasal symptom composite‡ score (scale 0–10)†		
Median	9.2 (8.6–9.6)	9.1 (8.5–9.6)
Mean	9.0 (0.8)	9.0 (0.8)
Loss of smell VAS score (scale 0–10)†		
Median	10.0 (9.6–10.0)	10.0 (9.6–10.0)
Mean	9.7 (0.6)	9.6 (0.8)
SNOT-22 total score†		
Median	64.0 (51.0–77.0)	64.0 (50.0–77.0)
Mean	64.4 (19.0)	63.7 (17.6)
Asthma	149 (74%)	140 (68%)
Patients with aspirin-exacerbated respiratory disease	63 (31%)	45 (22%)
Blood eosinophil count, cells per µL§	400 (0.91)	390 (0.88)

Data are n (%), mean (SD), or median (IQR). SNOT=Sino-Nasal Outcome Test. VAS=visual analogue scale. *Includes patients with partial dates for previous surgery; if day was missing, assumed as the last day of the month; if month was missing, assumed as December. †Higher scores indicate greater disease severity or worse quality of life. ‡Combining scores for nasal obstruction, nasal discharge, throat mucus, and loss of smell. §Geometric mean (coefficient of variation).

Comparability of patients across studies

Not applicable, since only one study is assessed.

Systematic selection of studies

After duplicates were removed from the total search result, a primary screening based on title and abstract was undertaken. Only one study (SYNAPSE), by Han et al. 2021 [15] satisfied the objective of the literature search. As a result, only this study was evaluated in this application.

Comparability of the study populations with Danish patients

Recent guidance by Danish Medicines Council provides criteria for the Danish patient population who can be eligible for biologics for treatment of CRSwNP[25]. One of the main criteria is the presence of severe CRSwNP with bilateral NP and one or more FESS operations (or patients who could not tolerate the operation).
Other criteria, of which any three may apply include:

- Type 2 inflammation
- Need for systemic corticosteroid therapy (or contraindicated for systemic corticosteroid therapy)
- Significantly reduced quality of life
- Significantly impaired sense of smell
- Diagnosed with asthma

Inclusion criteria for the SYNAPSE study required patients to have bilateral NP, at least one prior surgery to remove the polyps, treatment with corticosteroids, and severe CRSwNP as indicated by the VAS score. Since the patient population in SYNAPSE is comparable to the expected severe CRSwNP Danish patient population for biologics, these results can be considered transferable to Danish clinical practice. [redacted]

Appendix D Efficacy and safety results per study

Outcome measures

Table 64: Definition, validity and clinical relevance of included outcome measures

Outcome measure	Definition	Validity	Clinical relevance
Change in total endoscopic nasal polyp	**Change from baseline in total endoscopic nasal polyp score at week 52** Total endoscopic nasal polyp score was the sum of left and right nostril scores ranging from 0 (no polyps) to 4 (large polyps causing complete obstruction of the inferior meatus) for each nostril, giving a total score of up to 8 [15]	NR	Total nasal polyp score as an outcome has been investigated in patients with nasal polyps or asthma as a reliable outcome to indicate reduction of nasal polyps. Use of omalizumab in allergic and non-allergic asthma and nasal polyps patients resulted in reduction of total nasal endoscopic polyp scores over 16 weeks, confirmed by means of computed tomographic scanning (Lund-Mackay score) [32]. Use of dupilumab was shown to be more effective than placebo in reduction of total nasal polyp score [18]. **Minimal clinically important difference (MCID):** No well-defined minimum clinically relevant difference has been established in literature, but the subject committee considers an average difference of 1 point between groups as the smallest clinically relevant difference[25].
Mean nasal obstruction VAS score	Mean nasal obstruction VAS score measured during weeks 49–52. The VAS score could range from 0.0 (none) to 10.0 (as bad as you can imagine), as used in previous	NR	In CRS, VAS for total nasal symptom score (TNSS) is part of routine clinical practice to classify disease as mild, moderate, and severe. In research, VAS for TNSS and individual symptoms are frequently incorporated into studies as an instrument for estimating symptoms severity and burden of disease[39]. VAS scores for total nasal symptom score and individual symptoms have been reported to be correlated significantly with SNOT-22 [40].

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Outcome measure	Definition	Validity	Clinical relevance
	studies of nasal polyps [39]. Lower scores indicate less impact.		**Minimal clinically important difference (MCID):** Not available in literature. GSK performed an anchor-based analyses with SYNAPSE data and found the meaningful within-patient change threshold is -3.0-points (improvement) for Nasal Obstruction VAS.
Time-to-first nasal surgery	Time-to-first nasal surgery until week 52	NA	Generally used efficacy outcome. No well-defined MCID has been established in literature. Insights from the clinic suggest that the endpoint time to first surgery is relevant, as it is well known that loss of smell increases with the number of surgeries, and that in some cases surgery does not remove the underlying problem and repeated surgery is therefore needed.
Patients requiring systemic corticosteroids for nasal polyps	Proportion of patients that discontinue during the study period for nasal polyps until week 52	NA	Generally used efficacy outcome. No well-defined MCID has been established in literature. However, this endpoint was included as the use of corticosteroids is associated with long term complications.
Mean overall VAS symptom score	Change from baseline till during weeks 49-52 The VAS score could range from 0.0 (none) to 10.0 (as bad as you can imagine), as used in previous studies of nasal polyps [39]. Lower scores indicate less impact.	NR	Generally used efficacy outcome. No well-defined MCID has been established in literature. This endpoint was included to evaluate the overall improvement of symptoms.
SNOT-22 total score	Change from baseline till week 52 Each of SNOT-22 items is scored on a scale from 0 (no problem) to	Validity of SNOT-22 has been established in many studies [41-43] ,	Symptoms of CRS such as chronic nasal congestion, facial pressure or pain, headache, hyposmia, and anosmia can significantly reduce quality of life (QOL). Management, therefore, mainly aims to reduce its symptoms and thus improve

Outcome measure	Definition	Validity	Clinical relevance
	5 (problem as bad as it can be). The range of the global score is 0 to 110, and lower scores indicate less impact.	including in the Danish population [44].	QOL. Several questionnaires have been used to assess this disease-specific QOL, and the Sinonasal Outcome Test-22 (SNOT 22) is one among those which is frequently applied. It was originally developed in 1998, which consisted of 16 items, and then was later modified to be 20 items, and finally 22 items. The questionnaire had been tested and showed high reliability and validity, and significantly correlated with general QOL measured by the SF-36. In addition, the SNOT-22 has been translated to other languages worldwide[45]. **Minimal clinically important difference (MCID):** SNOT-22 scores ranged from 0 to 110, and have a minimal clinically important difference of 8.9 units [33]. Guidance from EPOS 2020 has indicated that in a large surgical cohort the MCID has been shown to be a change in 8.9 points on the SNOT-22, while for patients undergoing medical intervention, an MCID of 12 has been proposed[4].
Mean composite VAS score (combining scores for nasal obstruction, nasal discharge, throat mucus, and loss of smell)	Change from baseline till during weeks 49-52 The VAS score could range from 0.0 (none) to 10.0 (as bad as you can imagine), as used in previous studies of nasal polyps [39]. Lower scores indicate less impact.	NR	Generally used efficacy outcome. No well-defined MCID has been established in literature. This endpoint was included to evaluate the overall improvement of the most characteristic symptoms reported by the patients with CRSwNP.
Mean VAS score for loss of smell	change from baseline till during weeks 49-52 The VAS score could range from 0.0 (none) to 10.0 (as bad as you	NR	Generally used efficacy outcome. No well-defined MCID has been established in literature. This endpoint was included as loss of smell is known to impact the patient's quality of life significantly.

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Outcome measure	Definition	Validity	Clinical relevance
	can imagine), as used in previous studies of nasal polyps [39]. Lower scores indicate less impact.		

NA: Not available; NR: Not reported

Results per study

Table 65: Results for SYNAPSE study-co-primary and secondary endpoints

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Results of SYNAPSE study- co-primary and secondary endpoints

					Estimated absolute difference in effect			Adjusted treatment effect between mepolizumab vs. placebo in SYNAPSE			References
Outcome	**Treatment group**	**N**	**Mean change from baseline (CI)**	**Proportion of patients (%)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**	
Change from baseline in total endoscopic nasal polyp score at week 52*	Mepolizumab 100 mg q4w	206	–0.9(–1.16; –0.64)		–0.8	–1.13; –0.47	<0.001	–0.73 †	–1.11; –0.34†	P<0.001‡	[15]
	Placebo	201	–0.1(–0.30; 0.10)								
Change from baseline in nasal obstruction VAS score during weeks 49–52*	Mepolizumab 100 mg q4w	206	–4.2(–4.67; –3.73)		–1.7	–2.34; –1.06	<0.001	–3.14 †	–4.09; –2.18†	P<0.001‡	[15]
	Placebo	201	–2.5(–2.94; –2.06)								
Proportion of patients having nasal surgery up to week 52 (time-to-first nasal surgery)	Mepolizumab 100 mg q4w	206		18 (9%)	NA	NA	NA	0.43 §	0.25; 0.76§	0.0032	[15]
	Placebo	201		46 (23%)							
Change from baseline in overall symptom VAS score during weeks 49–52*	Mepolizumab 100 mg q4w	206	–4.3(–4.77; –3.83)		–1.8	–2.43; –1.17	<0.001	–3.18 †	–4.10; –2.26†	0.0032‡	[15]
	Placebo	201	–2.5(–2.93; –2.07)								
Change from baseline in SNOT-22 total score at week 52*	Mepolizumab 100 mg q4w	206	–29.4(–32.77; –26.03)		–13.7	–18.42; –8.98	<0.001	–16.49†	–23.57;–9.42†	0.0032‡	[15]
	Placebo	201	–15.7(–19.01; –12.39)								

Results of SYNAPSE study- co-primary and secondary endpoints											
Proportion of patients requiring systemic corticosteroids (≥1 course) for nasal polyps until week 52	Mepolizumab 100 mg q4w	206		52 (25%)	NA	NA	NA	0.58¶	0.36 ;0.92¶	0.020	[15]
	Placebo	201		74 (37%)							
Change from baseline in composite** VAS score during weeks 49–52*	Mepolizumab 100 mg q4w	206	–3.8(–4.24; –3.36)		–1.6	–2.18; –1.02	<0.001	–2.68†	–3.44; –1.91†	0.020‡	[15]
	Placebo	201	–2.2(–2.59; –1.81)								
Change from baseline in loss of smell VAS symptom score during weeks 49–52*	Mepolizumab 100 mg q4w	206	–2.8(–3.29; –2.31)		–1.4	–2.01; –0.79	<0.001	–0.37†	–0.65; –0.08†	0.020‡	[15]
	Placebo	201	–1.4(–1.77; –1.03)								

White fields are published data from the SYNAPSE study[15]. Grey fields mark calculated values. Unshaded cells are published numbers. CI, confidence interval; ITT, intention-to-treat; NA, not applicable

*Patients who required nasal surgery before the visit or time period were assigned their worst observed score recorded before surgery; patients with no nasal surgery who withdrew before the visit or time period were assigned their worst observed score before study withdrawal; patients with missing data were assigned their worst observed score before the missing visit.

**Combining scores for nasal obstruction, nasal discharge, throat mucus, and loss of smell.

†Adjusted difference in medians; quantile regression with covariates of treatment group, geographic region, baseline score, and $\log_e$ baseline blood eosinophil count.

‡p value based on Wilcoxon rank-sum test. Adjusted p values for secondary endpoints, multiplicity controlled using a closed testing procedure according to a predefined hierarchy of testing.

§Hazard ratio (95% CI); Cox proportional hazards model with covariates of treatment group, baseline nasal polyp score, baseline nasal obstruction score, loge baseline blood eosinophil count, number of previous surgeries (one, two, or more than two; ordinal), and geographic region.

¶Odds ratio (95% CI); logistic regression model with covariates of treatment group, baseline nasal polyp score, baseline nasal obstruction score, loge baseline blood eosinophil count, number of systemic corticosteroid courses in previous 12 months (0, 1, >1; ordinal), and geographic region.

Responder analysis NPS – co-primary endpoint

Responder analysis was available for the co-primary endpoint NPS. The responder analysis was performed using a logistic regression model with covariates of treatment group, geographic region, baseline score and Log(e) baseline blood eosinophil count. The summary of the responder analysis is illustrated in Table 66.

Visit		Placebo (N=201)	Mepolizumab 100 mg SC (N=206)
Week 4	n	201	206
	Responder [1]	60 (30%)	73 (35%)
	Non-responder	141 (70%)	133 (65%)
	No change/worsening	137 (68%)	131 (64%)
	Nasal surgery/sinoplasty prior to visit	0	0
	Withdrawal from study prior to visit	1 (<1%)	0
	Missing visit	3 (1%)	2 (<1%)
	Odds ratio to placebo [2]		4.46
	95% CI		(0.94, 2.26)
	p-value		0.090

Week 8	n	201	206
	Responder [1]	58 (29%)	74 (36%)
	Non-responder	143 (71%)	132 (64%)
	No change/worsening	136 (68%)	125 (61%)
	Nasal surgery/sinoplasty prior to visit	2 (<1%)	1 (<1%)
	Withdrawal from study prior to visit	1 (<1%)	1 (<1%)
	Missing visit	4 (2%)	5 (2%)
	Odds ratio to placebo [2]		1.53
	95% CI		(0.99, 2.37)
	p-value		0.053
Week 12	n	201	206
	Responder [1]	51 (25%)	80 (39%)
	Non-responder	150 (75%)	126 (61%)
	No change/worsening	137 (68%)	118 (57%)
	Nasal surgery/sinoplasty prior to visit	4 (2%)	2 (<1%)
	Withdrawal from study prior to visit	1 (<1%)	2 (<1%)
	Missing visit	8 (4%)	4 (2%)
Week 16	Odds ratio to placebo [2]		2.07
	95% CI		(1.33, 3.21)

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	p-value		0.001
	n	201	206
	Responder [1]	66 (33%)	76 (37%)
	Non-responder	135 (67%)	130 (63%)
	No change/worsening	119 (59%)	117 (57%)
	Nasal surgery/sinoplasty prior to visit	7 (3%)	3 (1%)
	Withdrawal from study prior to visit	2 (<1%)	4 (2%)
	Missing visit	7 (3%)	6 (3%)
	Odds ratio to placebo [2]		1.36
	95% CI		(0.88, 2.10)
	p-value		0.163
Week 20	n	201	206
	Responder [1]	57 (28%)	89 (43%)
	Non-responder	144 (72%)	117 (57%)
	No change/worsening	125 (62%)	99 (48%)
	Nasal surgery/sinoplasty prior to visit	11 (5%)	6 (3%)
	Withdrawal from study prior to visit	3 (1%)	6 (3%)
	Missing visit	5 (2%)	6 (3%)
	Odds ratio to placebo [2]		2.28

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	95% CI		(1.47, 3.55)
	p-value		<0.001
Week 24	n	201	206
	Responder [1]	53 (26%)	88 (43%)
	Non-responder	148 (74%)	118 (57%)
	No change/worsening	122 (61%)	97 (47%)
	Nasal surgery/sinoplasty prior to visit	18 (9%)	8 (4%)
	Withdrawal from study prior to visit	4 (2%)	10 (5%)
	Missing visit	4 (2%)	3 (1%)
	Odds ratio to placebo [2]		2.55
	95% CI		(1.63, 4.01)
	p-value		<0.001
Week 32	n	201	206
	Responder [1]	54 (27%)	81 (39%)
	Non-responder	147 (73%)	125 (61%)
	No change/worsening	100 (50%)	95 (46%)
	Nasal surgery/sinoplasty prior to visit	28 (14%)	12 (6%)
	Withdrawal from study prior to visit	6 (3%)	11 (5%)
	Missing visit	13 (6%)	7 (3%)

	Odds ratio to placebo [2]		1.95
	95% CI		(1.26, 3.01)
	p-value		0.003
Week 40	n	201	206
	Responder [1]	53 (26%)	101 (49%)
	Non-responder	148 (74%)	105 (51%)
	No change/worsening	93 (46%)	72 (35%)
	Nasal surgery/sinoplasty prior to visit	37 (18%)	15 (7%)
	Withdrawal from study prior to visit	7 (3%)	14 (7%)
	Missing visit	11 (5%)	4 (2%)
	Odds ratio to placebo [2]		2.88
	95% CI		(1.88, 4.42)
	p-value		<0.001
Week 48	n	201	206
	Responder [1]	55 (27%)	106 (51%)
	Non-responder	146 (73%)	100 (49%)
	No change/worsening	80 (40%)	62 (30%)
	Nasal surgery/sinoplasty prior to visit	45 (22%)	18 (9%)
	Withdrawal from study prior to visit	13 (6%)	15 (7%)
	Missing visit	8 (4%)	5 (2%)

	Odds ratio to placebo [2]		3.20
	95% CI		(2.07, 4.93)
	p-value		<0.001
Week 52	n	201	206
	Responder [1]	57 (28%)	104 (50%)
	Non-responder	144 (72%)	102 (50%)
	No change/worsening	77 (38%)	62 (30%)
	Nasal surgery/sinoplasty prior to visit	46 (23%)	18 (9%)
	Withdrawal from study prior to visit	15 (7%)	16 (8%)
	Missing visit	6 (3%)	6 (3%)
	Odds ratio to placebo [2]		2.74
	95% CI		(1.80, 4.18)
	p-value		<0.001

[1] Defined as a subject with a >= 1-point improvement from baseline in the absence of surgery/sinuplasty prior to that visit.
[2] Analysis performed using a logistic regression model with covariates of treatment group, geographic region, baseline score and Log(e) baseline blood eosinophil count.
Note: Includes data reported up to week 52.

SNOT-22 domain

The SNOT-22 is measured through 6 domains. In each domain the patient was asked to rate their health based on different questions that was asked. The possible score range for each domain is the cumulative total of each question in that domain, each scored from 0 (no problem) to 5 (the problem is as bad as it can be). Participants were asked

"considering how severe the problem is when experience it and how often it happens, please rate each item below on how 'bad' it is. The SNOT-22 domain scores from the SYNAPSE trial are described in the following tables.

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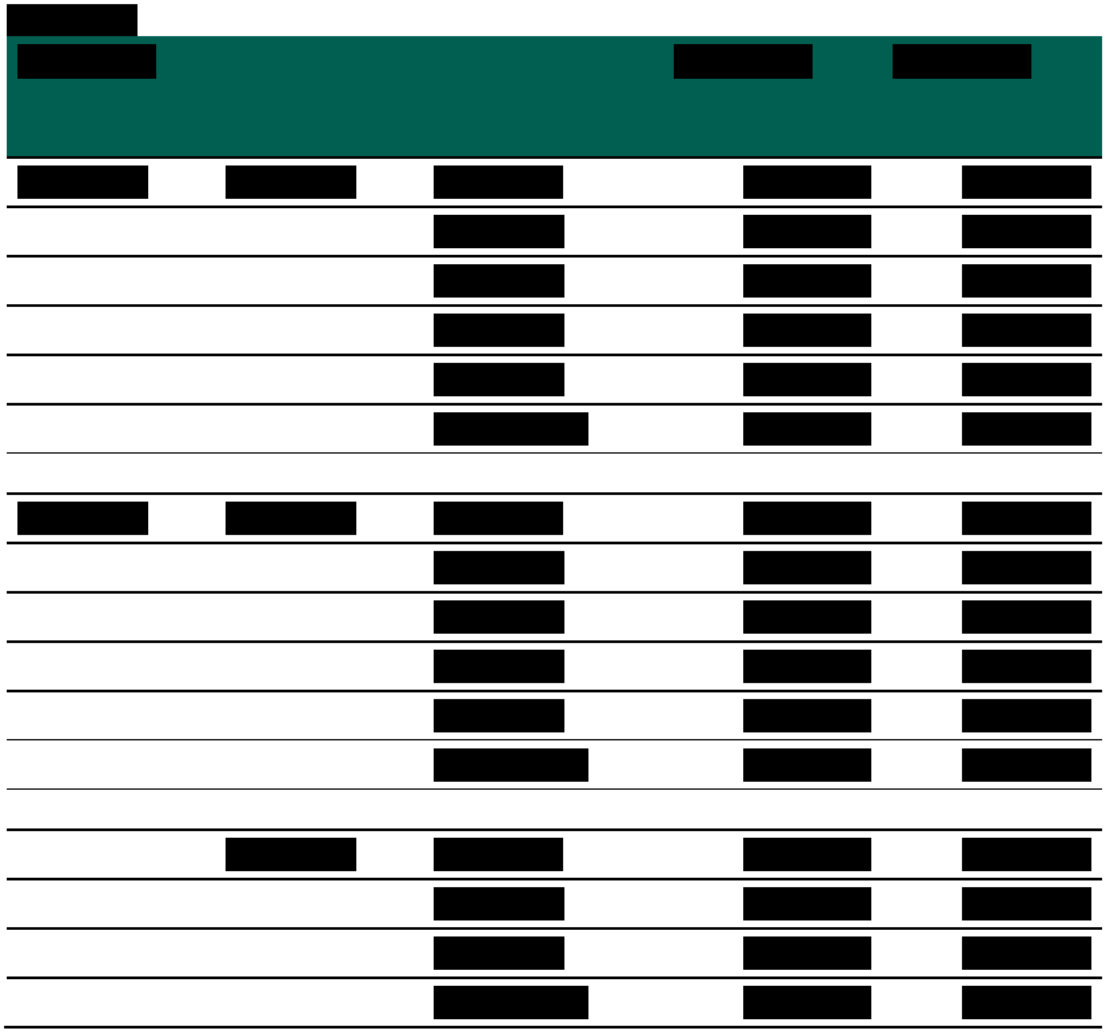

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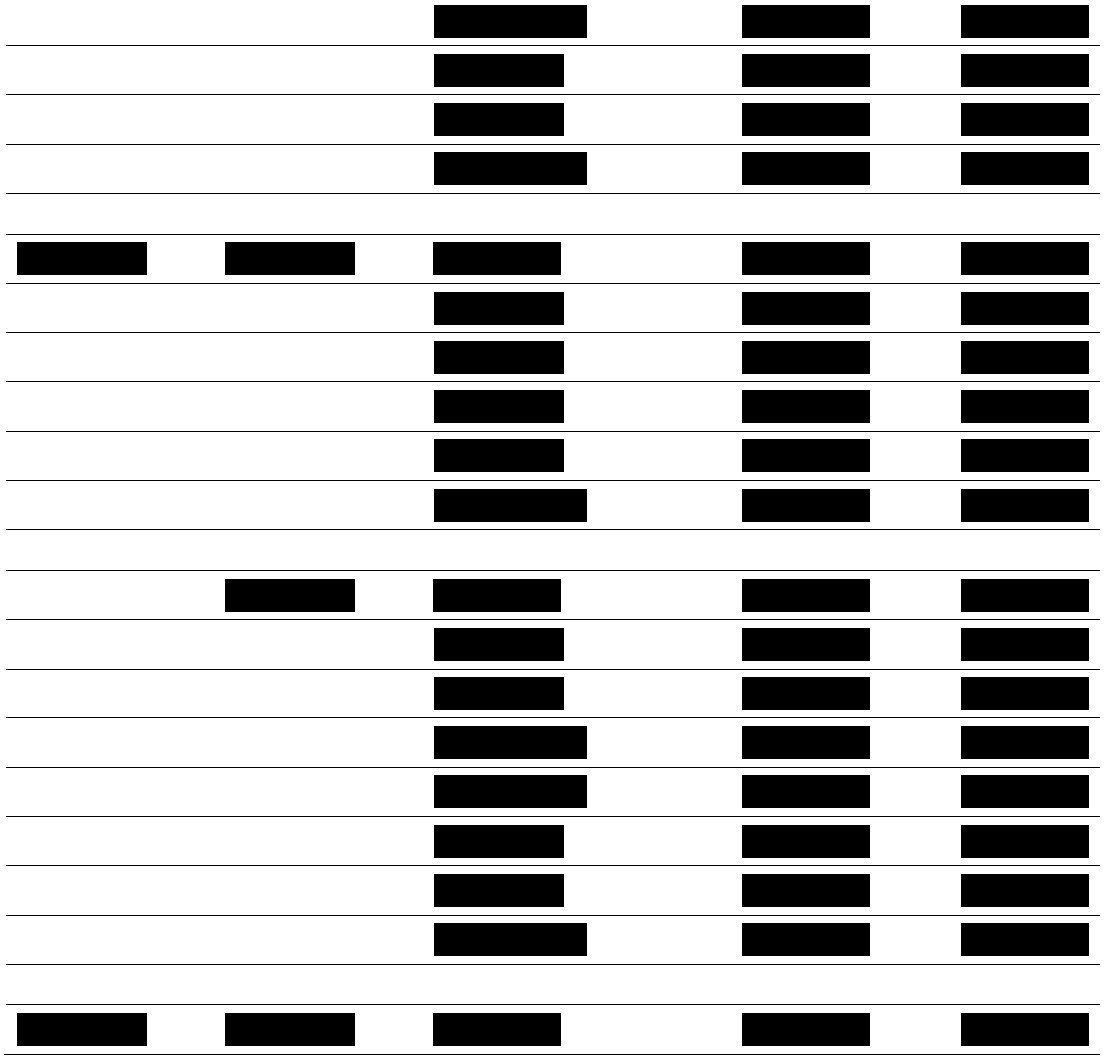

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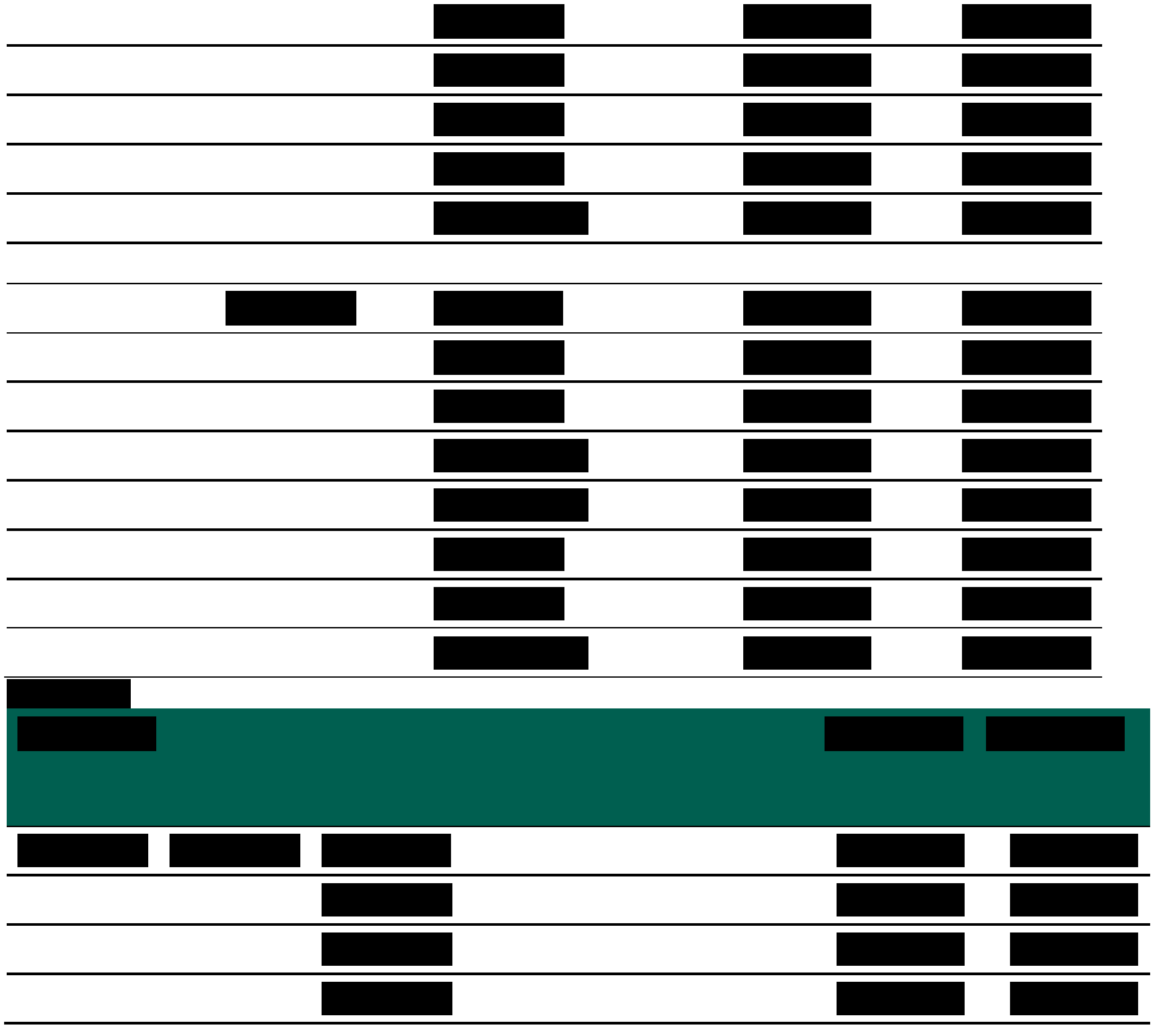

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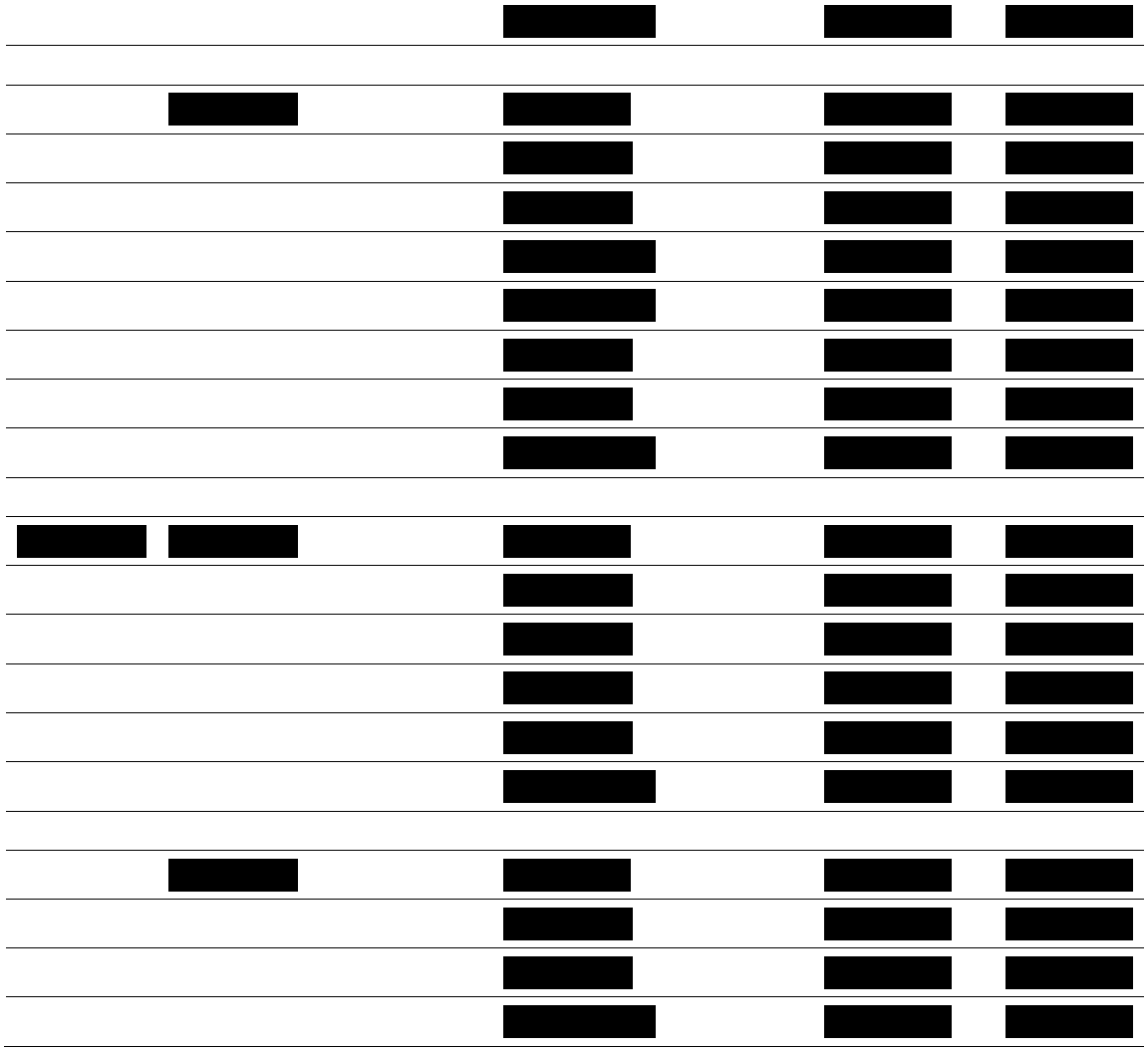

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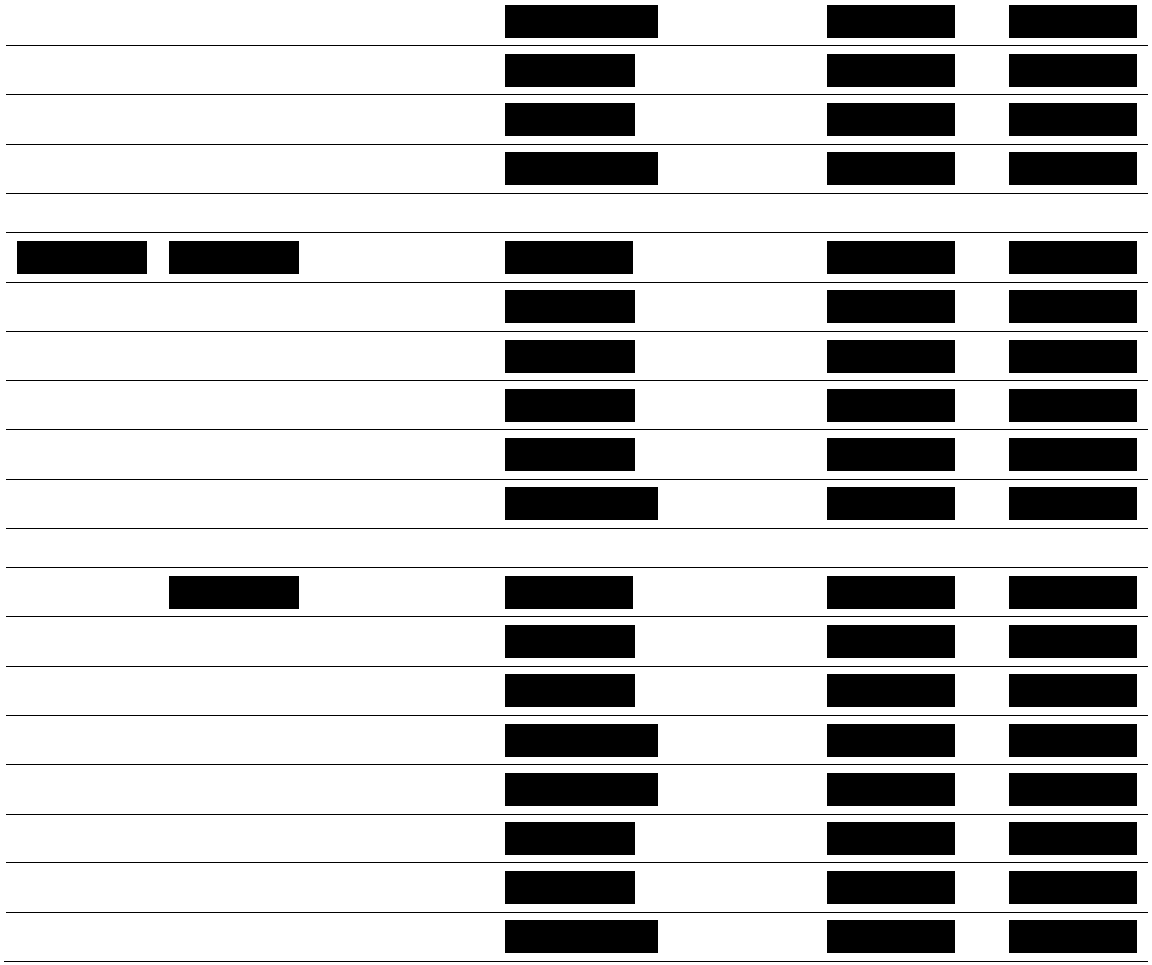

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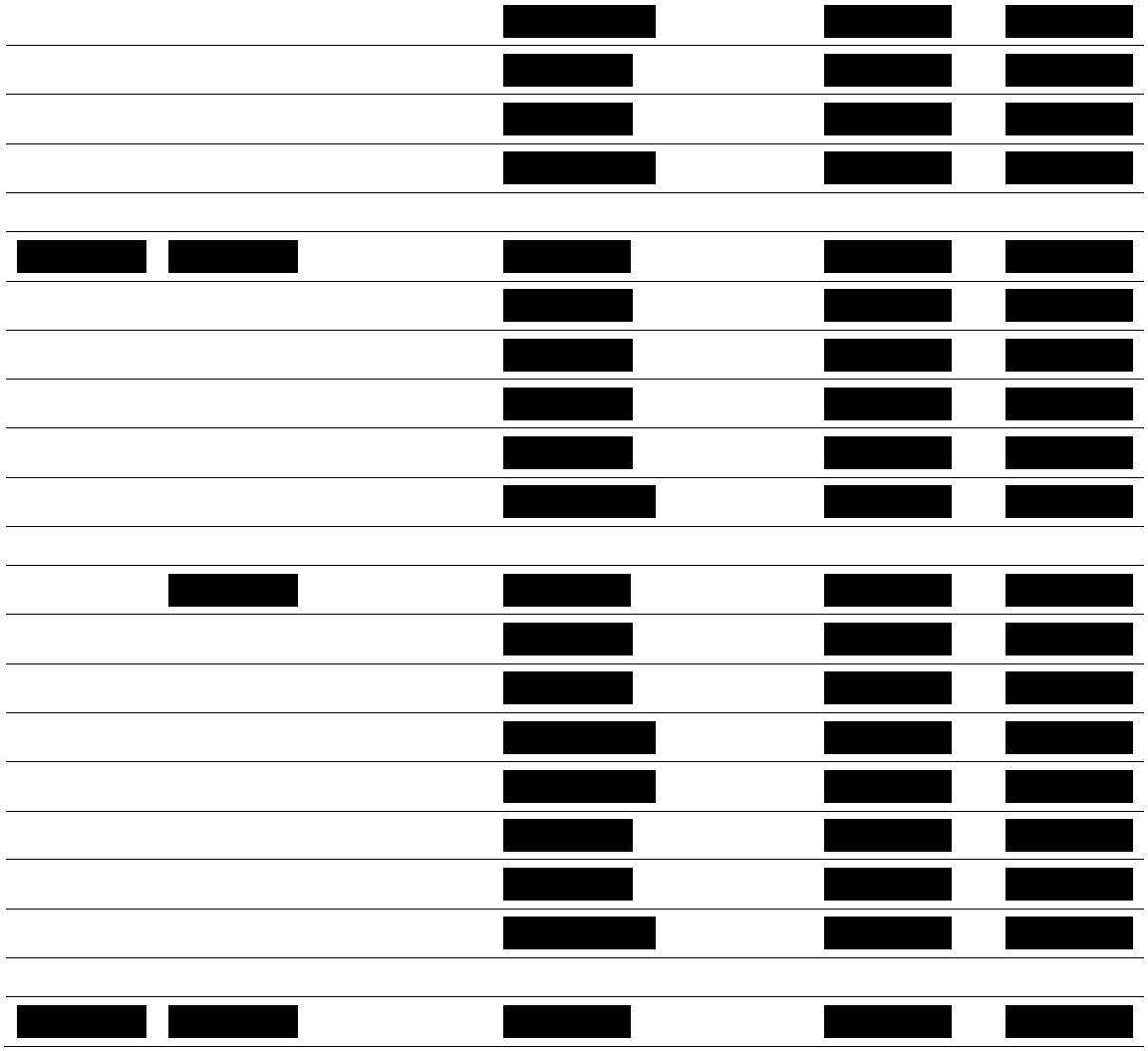

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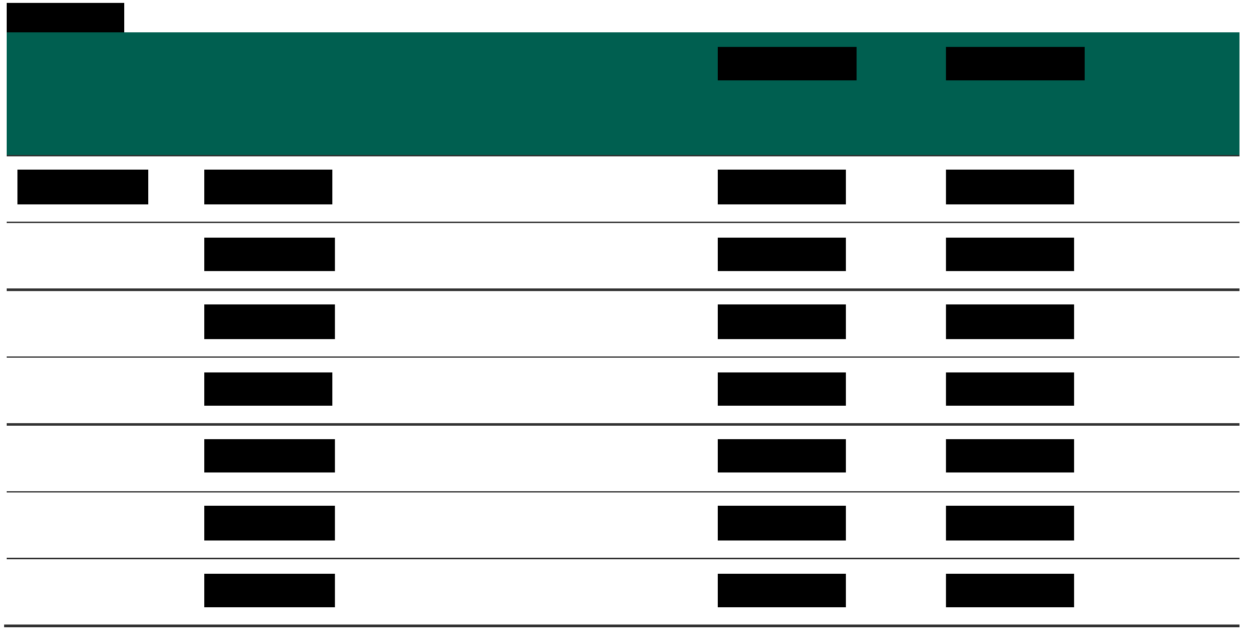

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Appendix E Safety data for intervention and comparators

This appendix contains the following information on safety data:

- Adverse events and Serious adverse events by study (Table 67)
- Extract from the Summary of Product Characteristics (Table 68)

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Adverse Events and Serious Adverse Events by study

Table 67: Serious adverse events (SAE), adverse events (AE), discontinuation and withdrawal by study

Study ID	Outcome	Assessment day	Treatment group	N	Mean (95% CI)	Estimated absolute difference in effect (in percentages (%))			Estimated relative difference in effect			References
						Difference	95% CI	*P* value	Difference	95% CI	*P* value	
NCT03085797 ITT population	SAE, proportion	52 weeks	Mepolizumab 100mg q4w	206	5.8 (2.6; 9.0)	-0.64*	-5.31; 4.03	0.7874	RR: 0.901**	0.42; 1.93	0.7874	[15]
			Placebo	201	6.5 (3.1; 9.9)							
	AE, proportion	52 weeks	Mepolizumab 100mg q4w	206	82 (76.8; 87.3)	-1.54*	-8.87; 5.79	0.6799	RR: 0.982**	0.90; 1.07	0.6799	[15]
			Placebo	201	83.6 (78.5; 88.7)							
	Treatment discontinuation due to AE	52 weeks	Mepolizumab 100mg q4w	206	1.9 (0.1; 3.8)	-0.05*	-2.75; 2.65	0.9720	RR:0.976**	0.25; 3.85	0.9720	[15]
			Placebo	201	2 (0.1; 3.9)							
	Study withdrawal due to AE	52 weeks	Mepolizumab 100mg q4w	206	0 (0.0; 1.5)	-0.05*	-2.16; 1.15	0.5567	RR:0.488**	0.04; 5.34	0.5567	[15]
			Placebo	201	0.5 (0.0; 1.5)							

Grey fields mark calculated values. **Unshaded cells are published numbers.** CI, confidence interval; **ITT, intention-to-treat**; RR, relative risk

*Absolute difference estimated by subtracting the mean estimates between the groups. ** The relative risk provides a measure of the overall association between the type of treatment and the outcome. Proportions with the corresponding 'exact' 95% Clopper-Pearson intervals were derived and relative (RR) and absolute risk differences were estimated with approximative Wald confidence intervals. The p-value corresponding to the asymptotic test of RR=1 was used as a common p-value for relative and absolute risk differences.

Extract from the Summary of Product Characteristics

Table 68: Extract from the Summary of Product Characteristics

	Mepolizumab
Posology, special populations	**Elderly** No dose adjustment is needed for elderly patients. **Hepatic impairment** No dose adjustment is required in patients with hepatic impairment (see section 5.2). **Renal impairment** No dose adjustment is required in patients with hepatic impairment (see section 5.2). Nucala® is intended for long-term treatment. The need for continued therapy should be considered at least on an annual basis as determined by physician assessment of the patient's disease severity and level of control of exacerbations.
Contraindications	Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Special warnings and precautions for use	**Traceability** In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. **Allergic reactions** General allergic reactions, including pruritus, as well as rare and sometimes serious allergic reactions such as hypersensitivity injection site reactions have been reported in clinical studies. If signs or symptoms of serious allergic reactions occur, treatment with mepolizumab must be discontinued and appropriate symptomatic treatment initiated. **Renal impairment** No formal studies have been conducted to investigate the effect of renal impairment on the pharmacokinetics of mepolizumab. Based on population pharmacokinetic analyses, no dose adjustment is required in patients with creatinine clearance values between 50-80 mL/min. There are limited data available in patients with creatinine clearance values <50 mL/min. **Hepatic impairment** No formal studies have been conducted to investigate the effect of hepatic impairment on the pharmacokinetics of mepolizumab. Since mepolizumab is degraded by widely distributed proteolytic enzymes, not restricted to hepatic tissue, changes in hepatic function are unlikely to have any effect on the elimination of mepolizumab.
Interaction with other medicinal products and other forms of interaction	No interaction studies have been performed. Cytochrome P450 enzymes, efflux pumps and protein-binding mechanisms are not involved in the clearance of mepolizumab. Increased levels of pro-inflammatory cytokines (e.g., IL-6), via interaction with their cognate receptors on hepatocytes, have been shown to suppress the formation of CYP450 enzymes and drug transporters, however, elevation of systemic pro-inflammatory markers in severe refractory eosinophilic asthma is minimal and there is no evidence of IL-5 receptor alpha expression on hepatocytes. The potential for interactions with mepolizumab is therefore considered low.

Undesirable effects

CRSwNP

In placebo-controlled clinical studies in subjects-adult and adolescent patients with severe refractory eosinophilic asthma, the most commonly reported adverse reactions during treatment were headache (20%), injection site reactions (8%) and back pain (6%). In a placebo-controlled study in patients with CRSwNP, the most commonly reported adverse reactions during treatment were nasopharyngitis (25%) and headache (18%).

Tabulated list of adverse reactions

The table below presents the adverse reactions from placebo-controlled studies with frequencies from patients receiving mepolizumab 100 mg subcutaneously (SC) (n=263), and from spontaneous post-marketing reports. Safety data is available from open-label extension studies in severe refractory eosinophilic asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years).

In a randomised, double-blind placebo-controlled 52-week study in patients with CRSwNP receiving mepolizumab 100 mg SC (n=206), no additional adverse reactions were identified to those reported in the severe eosinophilic asthma studies.

The frequency of adverse reactions is defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	Adverse reactions	Frequency
Infections and infestations	Lower respiratory tract infection Urinary tract infection Pharyngitis	Common
Immune system disorders	Hypersensitivity reactions (systemic allergic)* Anaphylaxis**	Common Rare
Nervous system disorders	Headache	Very common
Respiratory, thoracic and mediastinal disorders	Nasal congestion	Common
Gastrointestinal disorders	Abdominal pain upper	Common
Skin and subcutaneous tissue disorders	Eczema	Common
Musculoskeletal and connective tissue disorders	Back pain	Common
General disorders and administration site conditions	Administration-related reactions (systemic non allergic)*** Local injection site reactions Pyrexia	Common

* Systemic reactions including hypersensitivity have been reported at an overall incidence comparable to that of placebo in the severe eosinophilic asthma studies. For examples of the associated manifestations reported and a description of the time to onset, see section 4.4.

**From spontaneous post marketing reporting.

*** The most common manifestations associated with reports of systemic non-allergic administration-related reactions from patients in the severe eosinophilic asthma studies were rash, flushing and myalgia; these manifestations were reported infrequently and in <1% of subjects receiving mepolizumab 100 mg subcutaneously.

	Mepolizumab
	Description of selected adverse reactions *Systemic reactions, including hypersensitivity reactions in CRSwNP* In the 52-week placebo-controlled study, systemic allergic (type I hypersensitivity) reactions were reported in 2 patients (<1%) in the group receiving mepolizumab 100 mg and in no patients in the placebo group. Other systemic reactions were reported by no patients in the group receiving mepolizumab 100 mg and in 1 patient (<1%) in the placebo group. *Local injection site reactions* CRSwNP In the placebo-controlled study, injection site reactions (e.g., erythema, pruritus) occurred in 2% of patients receiving mepolizumab 100 mg compared with <1% in patients receiving placebo.
Undesirable effects (cont.)	**Immunogenicity** *Severe eosinophilic asthma and CRSwNP* Consistent with the potentially immunogenic properties of protein and peptide therapeutics, patients may develop antibodies to mepolizumab following treatment. In the placebo-controlled trials, 15/260 (6%) of adults and adolescents with severe eosinophilic asthma treated with 100 mg dose and 6/196 (3%) of adults with CRSwNP treated with 100 mg dose, subcutaneously had detectable anti-mepolizumab antibodies after having received at least one dose of mepolizumab. The immunogenicity profile of mepolizumab in severe refractory eosinophilic asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years) in open-label extension studies was similar to that observed in the placebo-controlled studies. In children aged 6 to 11 years old with severe refractory eosinophilic asthma following either 40 mg subcutaneously (for a weight < 40kg) or 100 mg subcutaneously (for a weight ≥ 40 kg), 2/35 (6%) had detectable anti-mepolizumab antibodies after having received at least one dose of mepolizumab during the initial short phase of the study. No children had detectable anti-mepolizumab antibodies during the long-term phase of the study. Neutralising antibodies were detected in one adult subject with severe eosinophilic asthma and in no patients with CRSwNP. Anti-mepolizumab antibodies did not discernibly impact the pharmacokinetics and pharmacodynamics of mepolizumab in the majority of patients and there was no evidence of a correlation between antibody titres and change in blood eosinophil level.

Appendix F Comparative analysis of efficacy and safety

Not applicable as only one study was included in this application

Appendix G – Extrapolation

Not applicable.

Appendix H – Literature search for HRQoL data

INTRODUCTION

To support Health Technology Assessment (HTA) submissions to extend of mepolizumab's license to include the indication of CRSwNP, a systematic literature review (SLR) was performed with respect to the clinical and economic impact of available therapies on patients with CRSwNP, as well as to identify published evidence about the economic burden of CRSwNP.

1. RESEARCH QUESTIONS

2.1 Research Objectives

The objectives of this SLR were to comprehensively identify 1) clinical efficacy and safety studies of mepolizumab and relevant comparators in treating CRSwNP, and 2) existing economic analyses, health utility studies, and healthcare resource use and cost studies. This report is focused on the second objective.

2.2 Research Questions

Specifically, this report focuses on the following research questions:

1. What economic models have been published for CRSwNP?
2. What is the cost and health care resource use associated CRSwNP and related comorbid conditions?
3. What health state utility values are available for CRSwNP?

STUDY ELIGIBILITY

The overarching SLR included phase 2 and 3 randomized controlled trials that assessed the efficacy and safety of treatments for CRSwNP, as well as observational studies reporting economic assessments, healthcare resource use and costs, or health utility data related to CRSwNP. Note: Data extracted for this report is specific to economic models, healthcare resource use and costs, and health utility values.

Potentially eligible studies were identified via structured search terms. For specific search strings and keywords, please refer to **Table 3-1** and **Table 3-2** in section **6.1 Search Results**. Abstracts and full text articles were reviewed by two independent reviewers for inclusion and exclusion criteria, which are outlined below in **Table 0-1** and **Table 0-4.** Data was extracted by one reviewer, with a second reviewer validating the extracted data against the source material.

The SLR was conducted in accordance with accepted guidelines for high quality SLRs such as the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the National Institute for Health and Care Excellence (NICE) Decision Support Unit guidance for evidence synthesis and decision-making (Moher 2009, Dias 2013). Published economic analyses were assessed for quality the British Medical Journal (BMJ) Checklist (Drummond 1996).

3.1 Inclusion and Exclusion Criteria

The study eligibility criteria for this review are described in Table 0-1 through Table 0-4.

Table 0-1. Inclusion Criteria for Economic Models

Category	Inclusion Criteria
Population	CRSwNP or NP
Interventions	Any
Outcomes	Cost-effectiveness and cost-minimization • Total costs • Total quality-adjusted life years • Cost per outcome (i.e., ICER) Budget impact • Total costs • Incremental costs (i.e., PMPM costs)
Study designs	• Cost-effectiveness/cost-utility models • Budget impact models
Language	English language
Date of publication	• No temporal limit applied to electronic database searches • Scientific meeting proceedings from 2015 to 2021

Key: CRSwNP – chronic rhinosinusitis with nasal polyps; ICER – incremental cost-effectiveness ratio; NP – nasal polyps; PMPM – per member per month.

Table 0-2. Inclusion Criteria for Utility Studies

Category	Inclusion Criteria
Population	CRSwNP or NP
Interventions	Any, including non-interventional studies
Outcomes	Utility scores, including (but not limited to): • EQ-5D-3L • EQ-5D-5L • SF-6D
Study designs	• RCTs • Cost-effectiveness/cost-utility models • Observational studies
Language	English language
Date of publication	• No temporal limit applied to electronic database searches • Scientific meeting proceedings from 2015 to 2021

Key: CRSwNP – chronic rhinosinusitis with nasal polyps; NP – nasal polyps; PMPM – per member per month; RCT – randomized controlled trial.

Table 0-3. Inclusion Criteria for Resource Use and Cost Studies

Category	Inclusion Criteria
Population	CRSwNP or NP
Interventions	Any, including non-interventional studies
Outcomes	• Health care resource use • Direct costs (total, medical, medication) • Indirect resource use (e.g., work productivity, absenteeism/presenteeism) • Indirect costs
Study designs	• Systematic reviews • Economic models • Observational studies
Language	English language articles/conference abstracts
Date of publication	• No temporal limit applied to electronic database searches • Scientific meeting proceedings from 2015 to 2021

Key: CRSwNP – chronic rhinosinusitis with nasal polyps.

Category	Exclusion Criteria
Population	• Chronic rhinosinusitis without nasal polyps (CRSsNP) • Unilateral NPs • NPs associated with another chronic condition (e.g., cerebral palsy, granulomatosis with polyangiitis) • CRS not specific to the subgroup with NPs • Exclusively pediatric population (<18 years of age)
Intervention	No exclusion
Outcomes	No outcomes listed in Table 0-1, Table 0-2 or Table 0-3
Study design	• Letters, comments, non-systematic reviews

Key: CRS – chronic rhinosinusitis; CRSsNP – chronic rhinosinusitis without nasal polyps; NP – nasal polyps.

2. SEARCH STRATEGY

2.3 Databases

Searches were conducted for articles published in English at any time until the search date in the following databases:

1. EMBASE and MEDLINE (via PubMed)
2. Cochrane Database of Systematic Reviews (Cochrane Reviews)
3. Database of Abstracts of Reviews of Effects (DARE) and NHS EED (National Health System Economic Evaluation Database)
4. Cochrane Central Register of Controlled Trials (CENTRAL)
5. Center for the Evaluation of Value and Risk in Health (CEVR) at Tufts Medical Center
6. Australian New Zealand Clinical Trials Registry (ANZCTR)

The search strategies included a combination of controlled vocabulary terms (medical subject headings [MeSH] terms in MEDLINE/CENTRAL Hand EMTREE terms in Embase), as well as free-text search terms, as recommended by the Cochrane Collaboration in alignment with guidance from NICE (NICE 2012). For specific search strings and keywords, refer to Table 3-1 and Table 3-2 in Section 3.1.

2.4 Scientific Conferences

Proceedings the years 2015 to 2021 of the following conferences were reviewed for relevant abstracts:

1. American Academy of Allergy, Asthma & Immunology (AAAAI)
2. American Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS)
3. American College of Allergy, Asthma & Immunology (ACAAI)
4. American Thoracic Society (ATS)
5. European Respiratory Society (ERS)
6. European Academy of Allergy and Clinical Immunology (EAACI)
7. European Congress of Immunology (ECI)
8. European Otolaryngology-ENT Surgery
9. European Rhinologic Society
10. International Society of Pharmacoeconomics and Outcomes Research (ISPOR)

Conference abstracts were screened through a combination of database indexing by topic and hand-searching. For conferences without such searchable indexing, relevant articles were identified using broad keywords such as "nasal polyp*" and "CRSwNP".

2.5 HTA Websites

Submissions and appraisals available in English and published from 2015 to 2021 of the following HTA websites were reviewed for relevant outcomes:

1. National Institute for Health and Care Excellence (NICE)
2. Haute Autorité de Santé (HAS)
3. Institute for Quality and Efficiency in Health Care (IQWiG)
4. Scottish Medicines Consortium (SMC)
5. Australia Pharmaceutical Benefit Scheme (PBS)
6. Canadian Agency for Drugs & Technologies in Health (CADTH)
7. The Institute for Clinical and Economic Review (ICER)

HTA submissions were queried for broad disease-related terms such as "nasal polyp*" or "CRSwNP" to capture articles of interest.

DATA EXTRACTION

2.1 Screening and Data Extraction

Title/abstract and full-text screening were conducted by two investigators to determine whether the inclusion criteria were met. A third investigator was consulted when consensus was not reached. Data were extracted by one investigator with quality assurance against the original source publication of all data done by another independent investigator.

2.2 Subgroups of Interest

Where available, data were collected and noted for the following subpopulations:

1. **Comorbid asthma**

   Patients with concomitant asthma and NPs. Some studies enrolled a CRSwNP population with a subgroup analysis of patients with comorbid asthma while other studies enrolled an asthmatic population with a subgroup analysis of patients with comorbid NPs.

2. **Comorbid aspirin or nonsteroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (AERD/N-ERD)**

   Some patients with CRSwNP have a hypersensitivity reaction to NSAIDs (including aspirin) that leads to an exacerbation of symptoms such as nasal congestion, coughing, and shortness of breath. Originally referred to as AERD, the condition has been expanded broadly to N-ERD to include NSAIDs as an entire drug class.

3. **Eosinophilia**

   Patients with CRSwNP who also exhibit a high level of eosinophils as confirmed by histopathologic examination or blood eosinophil count. The threshold and criteria for eosinophilia varies by study; these criteria were captured where available.

4. **Prior surgery**

   Patients with a history of prior NP surgery, with the number of prior surgeries noted, if available.

2.3 Quality Assessment

Economic model publications were assessed for quality using the BMJ Checklist (Drummond 1996). The BMJ Economic Checklist is comprised of 35 questions that aids reviewers in qualitatively evaluating an economic analysis. These questions address the study quality across three domains: study design, data collection, and analysis and interpretation of results (Drummond 2016).

3. RESULTS

3.1 Search Results

Based on the search criteria implemented for the MEDLINE and EMBASE databases, a total of 3,931 citations were identified. An additional 739 citations were identified through hand-searching of conferences and HTA websites. **Tables 6-1** through **6-5** detail the search results yielded from each source. After removal of 1,718 duplicate citations, 2,952 citations were screened based on title and abstract. Exclusions in the title abstract screening phase

were primarily studies not related to either CRSwNP or NPs or studies that did not report an outcome of interest. After title and abstract screening, 496 citations were selected to undergo full text screening.

Of the 496 citations that underwent full text review, 136 were identified as potentially providing information related to economic models, utility values, health care resource use, or cost for patients with CRSwNP. Three additional citations were added by hand-searching of grey literature and two studies were identified for extraction based on bibliographic review of SLRs. The PRISMA diagram summarizes the literature review process from the number of citations identified through to the number of citations included for data extraction (Error! Reference s ource not found.). In total, 38 publications were selected for data extraction representing 35 unique studies. Of these, 12 were published economic models, 9 reported utility values, 25 reported health care resource use and/or cost (categories not mutually exclusive) (**Table 3-6**).

Table 3-1. MEDLINE search (Conducted April 13, 2021)

Search	Terms	Number of Citations
1	"CRSwNP"[tiab] OR "nasal polyp*"[tiab] OR nasal polyps[mesh] OR ((nasal[tiab] OR nose[tiab]) AND (polyp[tiab] OR polyps[tiab] OR polyposis[tiab])) NOT ("antrochoanal"[tiab])	9,844
2	clinical trial[publication type] OR clinical trials as topic[mesh] OR control groups[mesh] OR "controlled clinical trial"[tiab] OR "controlled clinical trials"[tiab] OR "randomised controlled trial*"[tiab] OR "randomized controlled trial*"[tiab] OR "randomised controlled trials"[tiab] OR "randomized controlled trials"[tiab] OR randomized controlled trial[publication type] OR random allocation[mesh] OR double-blind method[majr] OR cross-over studies[majr] OR placebo*[tiab] OR controlled clinical trial[pt] OR controlled clinical trials as topic[mesh] OR placebo effect[mesh] OR rct[tiab] OR "random allocation"[tiab] OR "randomly allocated"[tiab] OR "allocated randomly"[tiab] OR random*[tiab] OR ((single[tiab] OR double[tiab] OR triple[tiab] OR treble[tiab]) AND (blind*[tiab] OR mask*[tiab])) OR ((allocated[tiab] OR assign*[tiab]) AND random[tiab]))	1,977,841
3	#1 AND #2	912
4	Economics[mesh] OR cost-benefit analysis[mesh] OR decision trees[mesh] OR models, economic[mesh] OR "cost minimi*"[tiab] OR cost-utilit*[tiab] OR "economic evaluation"[tiab] OR "budget impact"[tiab] OR economics[tiab] OR cost-effective*[tiab]	738,411
5	#1 AND #4	85
6	Health care costs[mesh] OR costs and cost analysis[mesh] OR budgets[mesh] OR "economic burden"[tiab] OR cost*[tiab] OR cost of illness[mesh] OR productivity[tiab] OR "indirect cost"[tiab] OR employer[tiab] OR workplace[tiab] OR health utilit*[tiab] OR "quality of life"[mesh] OR "quality of life"[tiab] OR "EQ-5D"[tiab] OR QoL[tiab] OR HRQoL[tiab] OR patient reported outcome*[tiab] OR patient reported outcomes[mesh]	1,204,114
7	#1 AND #6	784
8	#3 OR #5 OR #7	1,535
9	Limit: Remove study designs/publication types not of interest #8 NOT (comment[pt] OR editorial[pt] OR letter[pt] OR "case reports"[pt])	1,487
10	Limit: Remove narrative reviews (retain SLRs) #9 NOT (review[pt] NOT (systematic review[pt])) Filters: Humans	1,282

Search	Terms	Number of Citations
1	(crswnp:ab,ti OR 'nose polyp'/exp OR 'nasal polyp*':ab,ti) OR ((nasal:ab,ti OR nose:ab,ti) AND (polyp:ab,ti OR polyps:ab,ti OR polyposis:ab,ti)) NOT 'antrochoanal':ab,ti	14,355
2	'clinical trial'/exp OR 'controlled study'/exp OR 'major clinical study'/exp OR 'phase 2 clinical trial'/exp OR 'phase 3 clinical trial'/exp OR 'controlled clinical trial*':ab,ti 'randomised controlled trial*':ab,ti OR 'randomized controlled trial*':ab,ti OR 'random allocation':ab,ti OR 'randomly allocated':ab,ti OR 'allocated randomly':ab,ti OR random*:ab,ti OR ((single:ab,ti OR double:ab,ti OR triple:ab,ti) AND (blind*:ab,ti OR mask*:ab,ti) OR ((allocated:ab,ti OR assign*:ab,ti) AND random:ab,ti))	1,731,896
3	#1 AND #2	832
4	'economics'/exp OR 'cost benefit analysis'/exp OR 'decision tree'/exp OR 'economic model'/exp OR 'cost minimi*':ab,ti OR 'cost utilit*':ab,ti OR 'economic evaluation':ab,ti OR 'health utilit*':ab,ti OR 'budget impact':ab,ti OR economics:ab,ti OR 'cost effective*':ab,ti	535,902
5	#1 AND #4	87
6	'health care cost'/exp OR (costs AND 'cost analysis'/exp) OR 'budgets'/exp OR 'economic burden':ab,ti OR cost*:ab,ti OR 'cost of illness':ab,ti OR productivity:ab,ti OR 'indirect cost':ab,ti OR employer:ab,ti OR workplace:ab,ti OR 'quality of life'/exp OR 'quality of life':ab,ti OR 'eq-5d':ab,ti OR qol:ab,ti OR hrqol:ab,ti OR 'patient-reported outcome':ab,ti OR 'patient-reported outcome'/exp	1,737,435
7	#1 AND #6	1,585
8	#3 OR #5 OR #7	2,714
9	Limit: Remove study designs/publication types not of interest#8 NOT ([editorial]/lim OR [letter]/lim OR [note]/lim OR [short survey]/lim)	2,054
10	Limit: Remove narrative reviews (retain SLRs) #9 NOT [review]/lim NOT systematic:ab,ti	1,636
11	Limit: Humans #10 AND [humans]/lim	1,589

Table 3-3. Results of Other Database Searches

Database	Number of Citations Selected for Screening	
	Initial Search June 2020	Supplemental Search April 2021
Cochrane Reviews	15	1
Database of Abstracts of Reviews of Effects (DARE) and NHS EED (NHS Economic Evaluation Database)	26	0
Cochrane Central Register of Controlled Trials (CENTRAL)	873	131

*Added during April 2021 SLR update

Table 3-4. Results of Conference Searches

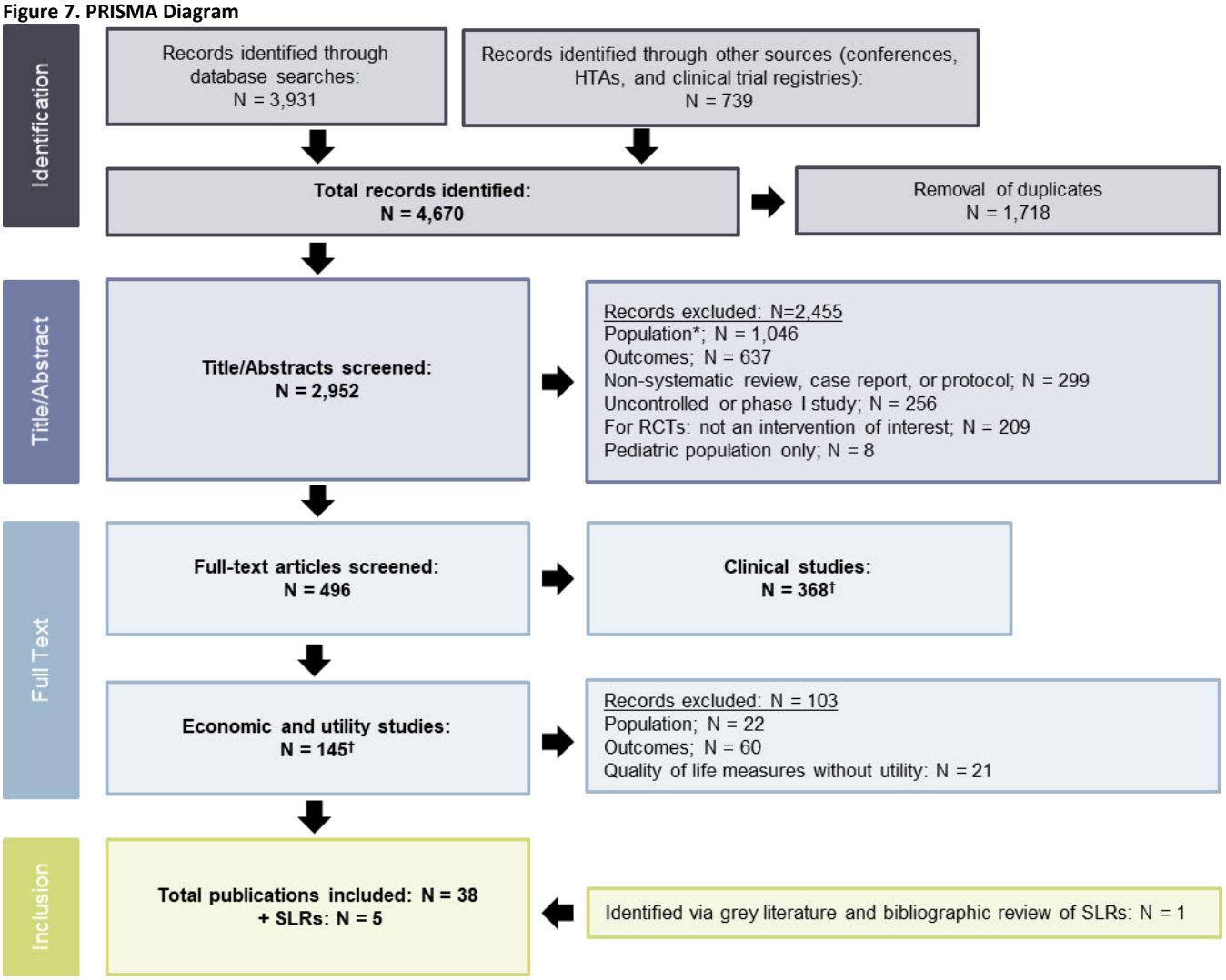
	Number of Citations Selected for Screening	
Conference	Initial Search June 2020	Supplemental Search April 2021
American Academy of Allergy, Asthma and Immunology (AAAAI)	43	7

American Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS)	21	4
American College of Allergy, Asthma and Immunology (ACAAI)	41	7
American Thoracic Society (ATS)	5	0
European Respiratory Society (ERS)	76	3
European Academy of Allergy and Clinical Immunology (EAACI)	171	8
European Congress of Immunology (ECI)	1	0
European Otolaryngology-ENT Surgery	1	0
European Rhinologic Society	227	0
American Rhinologic Society	60	14
International Society of Pharmacoeconomics and Outcomes Research (ISPOR)	7	1

Table 3-5. Results of HTA Website Searches

	Number of Citations Selected for Screening	
Website	**Initial Search June 2020**	**Supplemental Search April 2021**
National Institute for Health and Care Excellence (NICE)	18	20
Haute Autorité de Santé (HAS)	0	0
Institute for Quality and Efficiency in Health Care (IQWiG)	1	0
Scottish Medicines Consortium (SMC)	0	0
Australia Pharmaceutical Benefit Scheme (PBS)	1	0
Canadian Agency for Drugs and Technologies in Health (CADTH)	1	1
The Institute for Clinical and Economic Review (ICER)	0	0

Figure 7. PRISMA Diagram



Key: CRSwNP – chronic rhinosinusitis with nasal polyps, HTA – health technology assessments, RCT – randomized controlled trial; SLR – systematic literature review.

Table 3-6. List of Included Economic Models, Cost and HCRU, and Utility Studies CRSwNP

Economic Models	Cost and HCRU	Utility Values
Berggren 2003*	Bachert 2020	Alobid 2011
Ernst 2019*	• Bachert 2016 as earlier abstract presentation	Ference 2015
Kumar 2020*	Berggren 2003*	Kumar 2020*
Jommi 2020	Bhattacharyya 2009	Luk 2019
Rizzo 2016*	Bhattacharyya 2019	Rudmik 2014
Rudmik 2016a*	Davis 2020	Rudmik 2016b*
Scangas 2017a*	Ernst 2019*	Scangas 2018*
Scangas 2017b*	• Ernst 2018 as earlier abstract presentation	Smith 2019
Scangas 2018*	Hopkins 2019	Soler 2011
Scangas 2021*	Hunter 2018	Lloyd 2007
Velez 2018a	• Hunter 2017 as earlier abstract presentation	Shavit 2017
Velez 2018c	Kumar 2020*	
	Leung 2014	
	Lourijsen 2020	
	Palmer 2019	
	Peters 2020	
	Rizzo 2016*	
	Rondón 2015	
	Rudmik 2016a*	
	Rudmik 2016b*	
	Sahlstrand-Johnson 2017	
	Scangas 2017a*	
	Scangas 2017b*	
	Scangas 2018*	
	Scangas 2021*	
	Schladweiler 2020	
	Velez 2018b	
	Velez 2019	

* Contributes data to multiple categories.
Key: HCRU – health care resource use

List of Studies Excluded During Full Text Review

1072	Epperson M, McCann A, Phillips KM, et al. Unbiased Measure of General Quality of Life in Chronic Rhinosinusitis Reveals Disease Modifiers. *Laryngoscope.* 2021;131(6):1206-1211.	QoL measure without utility
1157	Maspero J.,Philpott C, Hellings P, et al. Health-Related Quality of Life Impairment Among Patients With Severe Chronic Rhinosinusitis With Nasal Polyps in the SINUS-24 Trial. *Journal of Allergy and Clinical Immunology.* 2021(147):AB133	QoL measure without utility
1189	Philpott C, Ta Ngan Hong, Hopkins C. Socioeconomic, comorbidity, lifestyle, and quality of life comparisons between chronic rhinosinusitis phenotypes. Laryngoscope Published online ahead of print March 26, 2021.	QoL measure without utility
6008	Mehta, Mitesh. Radiographic Disease Severity in Chronic Rhinosinusitis Patients and Health Care Utilization. AAO-HNS 2020(163);1	Population (CRS not specific to NP)
10400843	Radenne F, Lamblin C, Vandezande LM, et al. Quality of life in nasal polyposis. *JACI.* 1999;104(1):79-84.	No outcomes of interest
11770963	Durr DG, Desrosiers MY, Dassa C. Impact of rhinosinusitis in health care delivery: the Quebec experience. *Otolaryngol Head Neck Surg.* 2001;30(2):93.	Population (CRS not specific to NP)
12866594	Durr DG, Desrosiers M. Evidence-based endoscopic sinus surgery. *J Otolaryngol.* 2003;32(2).	QoL measure without utility
14699246	Akarçay M, Kizilay A, Miman MC, Çokkeser Y, Ozturan O. The effect of endoscopic sinus surgery on quality of life. *Kulak burun bogaz ihtisas dergisi*: *KBB= Journal of ear, nose, and throat*. 2003;11(3):65.	Population (CRS not specific to NP)
15224637	Salhab M, Matai V, Salam MA. The impact of functional endoscopic sinus surgery on health status. *Rhinology.* 2004;42(2):98-102.	No outcomes of interest
16022071	Alobid I, Benítez P, Bernal-Sprekelsen M, Guilemany JM, Picado C, Mullol J. The impact of asthma and aspirin sensitivity on quality of life of patients with nasal polyposis. *Quality of life research.* 2005;14(3):789-93.	No outcomes of interest
16175980	Serrano E, Neukirch F, Pribil C, Jankowski R. Nasal polyposis in France: impact on sleep and quality of life. *JLO.* 2005;119(7):543.	No outcomes of interest
16369166	Smith TL, Mendolia-Loffredo S, Loehrl TA, Sparapani R, Laud PW, Nattinger AB. Predictive factors and outcomes in endoscopic sinus surgery for chronic rhinosinusitis. *Laryngoscope.* 2005;115(12):2199-205.	QoL measure without utility
16564382	Alobid I, Benítez P, Valero A, Berenguer J, Bernal-Sprekelsen M, Picado C, Mullol J. The impact of atopy, sinus opacification, and nasal patency on quality of life in patients with severe nasal polyposis. *Otolaryngol Head and Neck Surg*. 2006;134(4):609-12.	No outcomes of interest
17190421	Zuo KJ, Xu G, Shi JB, Wen WP, Fan YP. Quality of life survey on patients with chronic rhinosinusitis and nasal polyps. *Zhonghua er bi yan hou tou jing wai ke za zhi.* 2006;41(10):748-52.	No outcomes of interest
17364348	Brämerson A, Nordin S, Bende M. Clinical experience with patients with olfactory complaints, and their quality of life. *Acta Oto-Laryngologica*. 2007;127(2):167-74.	No outcomes of interest
17592662	Newton JR, Shakeel M, Ram B. Evaluation of endoscopic sinus surgery by Glasgow benefit inventory. *JLO.* 2008;122(4):357.	No outcomes of interest
17891047	JR Litvack, S Griest, KE James, TL Smith. Endoscopic and quality-of-life outcomes after revision endoscopic sinus surgery. *Laryngoscope*. 2007;117(12):2233-8.	No outcomes of interest
17903570	Hopkins C, Browne JP, Slack R, Lund V, Brown P. The Lund-Mackay staging system for chronic rhinosinusitis: how is it used and what does it predict? *Otolaryngol Head Neck Surg.* 2007;137(4):555-61.	No outcomes of interest
18187985	AKGÜN S, ÇAKMAK Ö. Reliability and validity of the Turkish version of the Rhinosinusitis Disability Index. *Kulak Burun Bogaz Ihtis Derg*. 2007;17(5):265-71.	Population (CRS not specific to NP)
18260370	Ji X, Li H, Cao Z. Evaluation to the quality of life of patients with chronic sinusitis and polyps and analysis of influential factors. *Clin Otolaryngol Head Neck Surg.* 2007;21(23):1060-3.	No outcomes of interest
19034825	Holzmüller A, Gudziol H, Müller A. Quality of life after functional endoscopic sinus surgery (a long-term study). *Laryngo-Rhino-Otologie*. 2008;88(3):174-80.	No outcomes of interest

19068102	FC Valera, R Queiroz, C Scrideli, LG Tone, WT Anselmo-Lima. Evaluating budesonide efficacy in nasal polyposis and predicting the resistance to treatment. Clin Exp Allergy. 2009;39(1):81-8.	No outcomes of interest
19086309	D Marchioni, M Alicandri-Ciufelli, F Mattioli, A Marchetti, G Jovic, F Massone, L Presutti. Middle turbinate preservation versus middle turbinate resection in endoscopic surgical treatment of nasal polyposis. *Acta Otolaryngol.* 2008;128(9):1019-26.	No outcomes of interest
19493385	JA Eloy, TJ Walker, RR Casiano, JW Ruiz. Effect of coblation polypectomy on estimated blood loss in endoscopic sinus surgery. *Am J Rhinol Allergy.* 2009;23(5):535-9.	No outcomes of interest
19772517	Guilemany JM, Angrill J, Alobid I, Centellas S, Prades E, Roca J, Pujols L, Bernal-Sprekelsen M, Picado C, Mullol J. United airways: the impact of chronic rhinosinusitis and nasal polyps in bronchiectasic patient's quality of life. *Allergy.* 2009;64(10):1524-9.	Population (not CRSwNP)
19786212	Soler ZM, Sauer DA, Mace J, Smith TL. Relationship between clinical measures and histopathologic findings in chronic rhinosinusitis. *Otolaryngol Head Neck Surg.* 2009;141(4):454-61.	QoL measure without utility
20096225	Soler ZM, Sauer D, Mace J, Smith TL. Impact of mucosal eosinophilia and nasal polyposis on quality-of-life outcomes after sinus surgery. *Otolaryngol Head Neck Surg*. 2010;142(1):64-71.	QoL measure without utility
20109323	Zheng Y, Zhao Y, Lv D, Liu Y, Qiao X, An P, Wang D. Correlation between computed tomography staging and quality of life instruments in patients with chronic rhinosinusitis. *AM J Rhinol Allergy.* 2010;24(1):e41-5.	QoL measure without utility
20826121	Mortuaire G, Vandeville S, Chevalier D. Psychometric evaluation of the SinoNasal Outcome Test-16 for quality of life in chronic rhinosinusitis with nasal polyps. *Eur Ann Otorhinolaryngol* 2010;127(3):91-6.	QoL measure without utility
20974329	Soler ZM, Smith TL. Quality-of-life outcomes after endoscopic sinus surgery: how long is long enough? *Otolaryngol Head Neck Surg.* 2010;143(5):621-5.	QoL measure without utility
21595508	Nordin S, Hedén Blomqvist E, Olsson P, Stjärne P, Ehnhage A, NAF2S2 Study Group. Effects of smell loss on daily life and adopted coping strategies in patients with nasal polyposis with asthma. *Acta oto-laryngologica.* 2011;131(8):826-32.	No outcomes of interest
21991567	Sahlstrand-Johnson P, Ohlsson B, von Buchwald C, Jannert M, Ahlner-Elmqvist M. A multi-centre study on quality of life and absenteeism in patients with CRS referred for endoscopic surgery. *Rhinology*. 2011;49(4):420.	QoL measure without utility
22696512	JD Clinger, JC Mace, TL Smith. Quality-of-life outcomes following multiple revision endoscopic sinus surgery. *Int Forum Allergy Rhinol.* 2012;2(6):444-52	No outcomes of interest
22708279	Rózańska-Kudelska M, Szulc A, Matulka M, Simonienko K, Rogowski M. Quality of life, depression and anxiety symptoms in patients with chronic rhinosinusitis with polyps treated by endoscopic sinus surgery. *Polski merkuriusz lekarski: organ Polskiego Towarzystwa Lekarskiego*. 2012;32(190):228-31.	No outcomes of interest
23135235	Dudvarski Z, Djukic V, Janosevic L, Tomanovic N, Soldatovic I. Influence of asthma on quality of life and clinical characteristics of patients with nasal polyposis. *Eur Archives Oto-Rhino-L.* 2013;270(4):1379-83.	QoL measure without utility
23168143	Dávila I, Rondón C, Navarro A, Antón E, Colás C, Dordal MT, Ibáñez MD, Fernández-Parra B, Lluch-Bernal M, Matheu V, Montoro J. Aeroallergen sensitization influences quality of life and comorbidities in patients with nasal polyposis. *Am J Rhinol Allergy.* 2012;26(5):e126-31.	No outcomes of interest
23317561	ME Fraire, MV Sanchez-Vallecillo, ME Zernotti, OA Paoletti. Effect of premedication with systemic steroids on surgical field bleeding and visibility during nasosinusal endoscopic surgery. *Acta Otorrinolaringol Esp*. 2013;64(2):133-9.	No outcomes of interest
23371324	Han JK. Subclassification of chronic rhinosinusitis. Laryngoscope. 2013;123:S15-27.	No outcomes of interest
23842603	Katotomichelakis M, Simopoulos E, Tripsianis G, Balatsouras D, Danielides G, Kourousis C, Livaditis M, Danielides V. Predictors of quality of life outcomes in chronic rhinosinusitis after sinus surgery. *Eur Archives Oto-Rhino-L*. 2014;271(4):733-41.	No outcomes of interest
23883800	Hsu CY, Wang YP, Shen PH, Weitzel EK, Lai JT, Wormald PJ. Objective olfactory outcomes after revision endoscopic sinus surgery. *Am J Rhinol Allergy.* 2013;27(4):e96-100.	No outcomes of interest

24131818	Lange B, Holst R, Thilsing T, Baelum J, Kjeldsen A. Quality of life and associated factors in persons with chronic rhinosinusitis in the general population: a prospective questionnaire and clinical cross-sectional study. *Clin Otolaryngol.* 2013;38(6):474-80.	Population (CRS not specific to NP)
24260765	ME Cornet, C Georgalas, SM Reinartz, WJ Fokkens. Long-term results of functional endoscopic sinus surgery in children with chronic rhinosinusitis with nasal polyps. *Rhinology.* 2013;51(4):328-34.	Population (pediatric)
24431279	DeConde AS, Mace JC, Smith TL. The impact of comorbid migraine on quality-of-life outcomes after endoscopic sinus surgery. *Laryngoscope.* 2014;124(8):1750-5.	No outcomes of interest
24717866	Topal O, Kulaksızoglu S, Erbek SS. Oxidative stress and nasal polyposis: does it affect the severity of the disease? *Am J Rhinol Allergy.* 2014;28(1):e1-4.	No outcomes of interest
24760309	Djukic V, Dudvarski Z, Arsovic N, Dimitrijevic M, Janosevic L. Clinical outcomes and quality of life in patients with nasal polyposis after functional endoscopic sinus surgery. *Eur Archives Oto-Rhino-L.* 2015;272(1):83-9.	QoL measure without utility
24765830	Saedi B, Sadeghi M, Akhavan-Khaleghi N, Seifmanesh H. Impact of endoscopic sinus surgery on the quality of life of patients with nasal polyposis. *B-ENT*. 2014;10(1):59-65.	No outcomes of interest
25813521	Lange B, Thilsing T, Baelum J, Pedersen OF, Holst R, Kjeldsen AD. Do patients with chronic rhinosinusitis benefit from consultation with an ENT-doctor? *Acta Oto-laryngologica*. 2015;135(7):706-12.	Population (CRS not specific to NP)
25858054	Ta V, White AA. Survey-defined patient experiences with aspirin-exacerbated respiratory disease. *JACI.* 2015;3(5):711-8.	Population (AERD)
27277358	T Rahman, MM Alam, S Ahmed, MA Karim, M Rahman, M Wahiduzzaman. Outcome of Endoscopic Sinus Surgery in the Treatment of Chronic Rhinosinusitis. Mymensingh Med J. 2016;25(2):261-70	No outcomes of interest
27384037	Alt JA, Mace JC, Smith TL, Soler ZM. Endoscopic sinus surgery improves cognitive dysfunction in patients with chronic rhinosinusitis. *Int Forum Allergy Rhinol*. 2016;6(12):1264-1272.	No outcomes of interest
28160430	ST Gray, LP Hoehle, KM Phillips, DS Caradonna, AR Sedaghat. Patient-reported control of chronic rhinosinusitis symptoms is positively associated with general health-related quality of life. Clin Otolaryngol. 2017;42(6):1161-1166.	Population (CRS not specific to NP)
28247540	Whitcroft KL, Andrews PJ, Randhawa PS. Peak nasal inspiratory flow correlates with quality of life in functional endoscopic sinus surgery. *Clin Otolaryngol.* 2017;42(6):1187-92.	QoL measure without utility
28434016	Erskine SE, Hopkins C, Clark A, Anari S, Robertson A, Sunkaraneni S, Wilson JA, Beezhold J, Philpott CM. Chronic rhinosinusitis and mood disturbance. *Rhinology.* 2017;55(2):113-9.	QoL measure without utility
29103995	Song J, Wang H, Zhang YN, Cao PP, Liao B, Wang ZZ, Shi LL, Yao Y, Zhai GT, Wang ZC, Liu LM. Ectopic lymphoid tissues support local immunoglobulin production in patients with chronic rhinosinusitis with nasal polyps. *JACI.* 2018;141(3):927-37.	No outcomes of interest
29531195	Khairuddin NK, Salina H, Gendeh BS, Wan Hamizan AK, Lund VJ. Quality of life and recurrence of disease in patients with eosinophilic and non-eosinophilic 1 chronic rhinosinusitis with nasal polyposis. *Med J Malaysia*. 2018;73(1):1.	No outcomes of interest
30629853	Chowdhury NI, Chandra RK, Li P, Ely K, Turner JH. Investigating the correlation between mucus cytokine levels, inflammatory cell counts, and baseline quality-of-life measures in chronic rhinosinusitis. *Int Forum Allergy* Rhinol. 2019;9(5):538-544.	No outcomes of interest
31668870	Chowdhury N. Sino-nasal outcome Test-22 predicts SF-6D-R2 in medically treated patients with nasal polyps. Presented at 2018 Annual Meeting of the American Academy of Otolaryngology-Head and Neck Surgery Foundation; October 7-10, 2018; Atlanta, GA.	No outcomes of interest
31668945	Bachert C, Gevaert P, Corren J, Mullol J, Han J, Ow R, Hussain I, Islam L, Fogel R, Kaufman D, Omachi T. Baseline characteristics of phase 3 randomized controlled trials of omalizumab in chronic rhinosinusitis with nasal polyps. EAACI. 2019;74(106): 329-330.	No outcomes of interest
31669314	Eitenmüller A, Piano L, Böhm M, Shah-Hosseini K, Glowania A, Pfaar O, Mösges R, Klimek L. Liposomal nasal spray versus guideline-recommended steroid nasal spray in patients with chronic rhinosinusitis: a comparison of tolerability and quality of life. *J Allergy*. 2014.	Population (CRS not specific to NP)

31669401	Castro M, Rabe KF, Brusselle G, Rice MS, Rowe P, Deniz Y, Kamat S, Khan A. Dupilumab effect on asthma control and health-related quality of life in patients with oral corticosteroid-dependent severe asthma with comorbid chronic rhinosinusitis with and without nasal polyps. *EAACI.* 2019;(74):27.	Population (CRS not specific to NP)
31669731	Vennik J, Eyles C, Thomas M, et al. Chronic rhinosinusitis: a qualitative study of patient views and experiences of current management in primary and secondary care. *BMJ*. 2019;9(4):e022644.	No outcomes of interest
55500061	Penezić A, Paić M, Gregurić T, Grgić MV, Baudoin T, Kalogjera L. The impact of asthma on quality of life and symptoms in patients with chronic rhinosinusitis. *Cur Med Res Opin*. 2020:1-6.	No outcomes of interest
55500102	Nilsen AH, Helvik AS, Thorstensen WM, Salvesen Ø, Bugten V. General health, vitality, and social function after sinus surgery in chronic rhinosinusitis. *Laryngoscope Investig Otolaryngol.* 2019;4(5):476-83.	QoL measure without utility
55500106	Khan A, Huynh TM, Vandeplas G, et al. The GALEN rhinosinusitis cohort: chronic rhinosinusitis with nasal polyps affects health-related quality of life. *Rhinology.* 2019;57(5):343-51.	QoL measure without utility
55500180	Laababsi R, Elkrimi Z, Allouane A, Rouadi S, Abada R, Roubal M, Mahtar M. Quality of life outcomes of patients with chronic rhinosinusitis after functional endoscopic sinus surgery, prospective cohort study. *Ann Med Surg.* 2019;40:9-13.	No outcomes of interest
55500186	Draf J, Menzel S, Draf C, Hummel T, Zahnert T, Cuevas M. Improvement of quality of life after septoplasties and endonasal sinus surgery. *Laryngo-Rhino-Otologie.* 2019;98(S02):11465.	No outcomes of interest
55500255	Ylitalo-Heikkilä M, Virkkula P, Sintonen H, Lundberg M, Roine RP, Hytönen M. Different rhinologic diseases cause a similar multidimensional decrease in generic health-related quality of life*. Clin Otolaryngol.* 2018;43(6):1487-93.	Population (CRS not specific to NP)
55500256	Sedaghat AR, Hoehle LP, Gray ST. Chronic rhinosinusitis control from the patient and physician perspectives. *Laryngoscope Investigative Otolaryngol.* 2018;3(6):419-33.	Population (CRS not specific to NP)
55500268	Khan A, Huynh T, Kamat S, Mannent L, Tomassen P, Van Zele T, Cardell L, Arebro J, Olze H, Foerster-Ruhrmann U, Kowalski M. Impact of chronic rhinosinusitis with nasal polyposis on quality of life by sino-nasal surgery history. *Ann Allergy Asthma Immunol*. 2018;121(5):S20.	No outcomes of interest
55500439	van der Veen J, Seys SF, Timmermans M, et al. Real-life study showing uncontrolled rhinosinusitis after sinus surgery in a tertiary referral centre. *Allergy*. 2017;72(2):282-290.	QoL measure without utility
55500522	Kim SW, Kim DH. Quality of life of chronic rhinosinusitis patients with or without nasal polyps in Korea. *World Allergy Organ J.* 2016;9(1)14.	No outcomes of interest
55500539	Gregurić T, Trkulja V, Baudoin T, Grgić M, Šmigovec I, Kalogera L. Differences in the Sino-Nasal Outcome Test 22 and visual analog scale symptom scores in chronic rhinosinusitis with and without nasal polyps. *Am J Rhinol Allergy.* 2016;30(2):107-12.	No outcomes of interest
55500663	DeConde AS, Mace JC, Alt JA, Soler ZM, Orlandi RR, Smith TL. Investigation of change in cardinal symptoms of chronic rhinosinusitis after surgical or ongoing medical management. *Int Forum Allergy Rhinol.* 2015;5(1):36-45.	No outcomes of interest
55500674	Kumar K, Shah A. Effect of nasal polyposis on nocturnal sleep disturbances, daytime sleepiness, and sleep specific quality of life disturbances in patients presenting with allergic rhinitis. *Ann Allergy Asthma Immunol.* 2014;113(5):A17.	No outcomes of interest
55500755	Harugop A. Subjective outcome of Endoscopic Sinus Surgery in patients of chronic rhinosinusitis without nasal polyposis and chronic rhinosinusitis with nasal polyposis. Biomedicine (India). 2014;34(3):348-355.	No outcomes of interest
55500788	Soy FK, Pinar E, Imre A, Calli C, Calli A, Oncel S. Histopathologic parameters in chronic rhinosinusitis with nasal polyposis: impact on quality of life outcomes. *Int Forum Allergy Rhinol*. 2013;3(10, pp. 828-833.	QoL measure without utility
55500842	Behera S. Health outcomes, education, healthcare delivery and quality–3040. Occurrence and effects of nasal polyps in patients with bronchial asthma and/or allergic rhinitis. *World Allergy Organ* J. 2013;6(1):P213-P213.	No outcomes of interest
55501259	Dereköylü L, Canakçioğlu S, Mamak A, Güvenç MG, Banitahmaseb A. Quality of life assessment with the use of the SF-36 in patients with nasal polyposis: correlations	No outcomes of interest

	with clinical and laboratory findings. Kulak burun bogaz ihtisas dergisi: *J Ear Nose Throat*. 2003;11(3):72-9.	
55501322	Weiss KB. Cost implications of upper respiratory allergic diseases. *J Allergy Clin Immunol.* 1998;101(2):S383-5.	No outcomes of interest
55501372	Corren J, Bachert C, Gevaert P, Mullol J, Han J, Ow R, Toppila-Salmi S, Alobid I, Kaufman D, Braid J, Howard M. Omalizumab improves quality of life in patients with chronic rhinosinusitis with nasal polyps and comorbid asthma. *JACI.* 2020;145(2):AB250.	No outcomes of interest
55501400	R Mahmoud. Healthcare for Chronic Rhinosinusitis (CRS) Symptoms - A Cross-Sectional Population-Based Survey of U.S. Adults Meeting Symptom Criteria for CRS. Poster presented at AAAAI 2017.	No outcomes of interest
55501510	Khan A, VANDEPLAS G, Huynh T, Mannent L, Tomassen P, Van Zele T, Cardell LO, Arebro J, Olze H, Foerster U, Kowalski M. The GALEN sinusitis cohort: impact on quality of life in patients with chronic rhinosinusitis with nasal polyps (CRSwNP). *EAACI.* 2015;70(101):282-283.	No outcomes of interest
55501560	Ylitalo-Heikkila M, Roine RP, Sintonen H, Lundberg M, Virkkula P, Hytonen M. Rhinologic disease is a burden for a patient. *Allergy.* 2017;72:788-788.	Population (not CRSwNP)
55501636	Seys SF, De Bont S, Bousquet J, Bachert C, Fokkens WJ, Agache I, Bernal-Sprekelsen M, Callebaut I, Cardell L, Carrie S, Castelnuovo P. Real-life assessment of chronic rhinosinusitis patients using mobile technology. *EAACI.* 2019;74(106):54.	No outcomes of interest
55501684	Dietz de Loos DA, Hopkins C, Fokkens WJ. Symptoms in chronic rhinosinusitis with and without nasal polyps. *Laryngoscope*. 2013;123(1):57-63.	No outcomes of interest
55501772	Smith R, Erskine S, Philpott C. Preliminary results of a survey to identify the socio-economic costs of chronic rhinosinusitis (crs) to patients and the NHS in the United Kingdom. Presented at: 26th Congress of the European Rhinologic Society in conjunction with 35th International Symposium of Infection & Allergy of the Nose; July 3-7, 2016; Stockholm, Sweden.	Population (CRS not specific to NP)
55501776	R. Lakhani. A SYSTEMATIC REVIEW OF OUTCOMES IN CHRONIC RHINOSINUSITIS. Presented at 26th Congress of the European Rhinologic Society; July 3-7, 2016; Stockholm, Sweden.	No outcomes of interest
55501797	M. Setzen. SYMPOSIUM 42: IMPACT OF NASAL INFLAMMATION ON HEALTH ECONOMICS. Presented at 26th Congress of the European Rhinologic Society; July 3-7, 2016; Stockholm, Sweden.	Population (CRS not specific to NP)
55501800	Lundberg M, Ylitalo-Heikkilä M, Roine RP, Sintonen H, Virkkula P, HytönenHan M. The burden of rhinologic disease. Presented at 26th Congress of the European Rhinologic Society; July 3-7, 2016; Stockholm, Sweden.	Population (CRS not specific to NP)
55501817	S Kilty. CASE- CONTROL STUDY OF ENDOSCOPIC POLYPECTOMY IN CLINIC (EPIC) VERSUS ENDOSCOPIC SINUS SURGERY FOR CHRONIC RHINOSINUSITIS WITH NASAL POLYPS. Presented at: 27th Congress of the European Rhinologic Society; June 2018; London, UK.	No outcomes of interest
55501822	Brunet-Garcia A, Paya XM, Gimeno JC, Armegot M. Clinical, morphological, molecular and quality of life correlations in patients with chronic rhinosinusitis with nasal polyps. Presented at: 27th Congress of the European Rhinologic Society; June 2018; London, UK.	QoL measure without utility
55501841	E Lourijsen. CLINICAL BENEFIT AND COST-EFFECTIVENESS OF ENDOSCOPIC SINUS SURGERY IN ADULT PATIENTS WITH CHRONIC RHINOSINUSITIS WITH NASAL POLYPS – POLYPESS TRIAL. Presented at: 27th Congress of the European Rhinologic Society; June 2018; London, UK.	No outcomes of interest
55501881	M Speth. CHANGES IN CHRONIC RHINOSINUSITIS DIFFERENTIALLY ASSOCIATE WITH IMPROVEMENT IN GENERAL HEALTH-RELATED QUALITY OF LIFE. Presented at: 27th Congress of the European Rhinologic Society; June 2018; London, UK.	Population (CRS not specific to NP)
55501884	Clarke C, Williamson E, Denaxas S, et al. Cost analysis of chronic rhinosinusitis in England: regression analysis using linked CPRD and HES data. *Rhinology*. 2018;56(27):629.	No outcomes of interest
55501892	Yin T. Sinonasal outcome test-22 domain scores in a New Zealand chronic rhinosinusitis cohort. *Rhinology.* 2020.	QoL measure without utility

55501899	Ryu G, Lee JJ, Hong SD, et al. Predict postoperative subjective outcomes in patients with chronic rhinosinusitis using cluster analysis. Presented at: 92nd Annual Congress of Korean Society of Otorhinolaryngology-Head & Neck Surgery; April 27-29, 2018; Seoul, Korea.	No outcomes of interest
55501924	Characteristics of patients enrolled in two identical trials of Omalizumab in chronic rhinosinusitis with nasal polyps. Presented at: American Rhinologic Society 65th Annual Meeting. September 13-14, 2019. New Orleans, LA.	No outcomes of interest
55501936	Khaku A. Cost analysis of endoscopic sinus surgery for chronic rhinosinusitis: In-office based procedures versus traditional operating room endoscopic sinus surgery. *ARS* 2020.	Population (CRS not specific to NP)
55501993	Carr T, Griffin N, Yang M, Rosén K, Casale T. CLINICALLY SIGNIFICANT IMPROVEMENT IN MINI-RQLQ SCORES IN PATIENTS WITH NASAL POLYPS AFTER OMALIZUMAB INITIATION. *Ann Allergy Asthma Immunol*. 2017;119(5):S88-S89.	No outcomes of interest
55501971	Khanna R, Holy CE, Romano A. Prevalence and health care use burden associated with rhinosinusitis in a united states commercially insured population. *Value Health* 2017;20(5):A349-A349.	Population (CRS not specific to NP)
55501973	Battaglia S, Annoni E, Hodge D, Barnett G. The under-recognised human and economic impact of chronic rhinosinusitis. *Value Health*. 2015;18(7):A516.	Population (CRS not specific to NP)
55502005	Wong M, Keith P. P457 ASSESSING RESPONSIVENESS OF QUALITY OF LIFE INSTRUMENTS FOR PATIENTS WITH NASAL POLYPOSIS: A SYSTEMATIC REVIEW. *Ann Allergy Asthma Immunol*. 2019;123(5):S60.	No outcomes of interest
55502006	Zhang H, Ye F, Chuang C, Kamat S. P454 PREVALENCE AND TREATMENT OF DIAGNOSED CHRONIC RHINOSINUSITIS WITH NASAL POLYPS (CRSWNP) IN THE UNITED STATES. *Ann Allergy Asthma Immunol*. 2019;123(5):S59.	No outcomes of interest

Appendix I Mapping of HRQoL data

Establishing utility values for the 22-item Sino-Nasal Outcome Test (SNOT-22) using a crosswalk to the Euro-Qol-five-dimensional questionnaire-three-level version (EQ-5D-3L) by R. Trafford Crump [40] was used to map the SNOT-22 data to utilities by the defined mapping algorithm. Model 2 was used for mapping in our study. In Model 2, responses to individual SNOT-22 items were used to predict the EQ-5D-3L utility, and the regression coefficients for each item were listed in Table 3. Validation of the programming was conducted using extreme SNOT-22 values (i.e., 0 and 110) and the predicted utility value is consistent with the numbers reported in the publication. In addition, out of all 6,967 mapping records (multiple SNOT-22 measures per patient), we found only one record with mapped EQ-5D value out of the range of 0-1. Actual value was 1.0288 and was set at 1.

Appendix J Probabilistic sensitivity analyses

Appendix K – Statistical methods

Statistical methods: mepolizumab versus placebo (in addition to standard-of-care).

The endpoints considered were of two types:

- binary (fractions)
- continuous outcomes

There were two treatment arms involved (mepolizumab and placebo).
Direct comparison was only possible for mepolizumab versus placebo. Absolute difference between both groups was estimated by subtracting the mean estimates between the groups.

In general, some simple pre-processing imputation was done on published data in cases where no doubt existed as to the relevant procedure: missing standard errors were derived from reported standard deviations and the number of patients, and missing proportions (and 95% CI') were derived from the number of events and patients. For fractions, a missing risk-ratio could then be derived in almost every case, including a confidence interval.

For the within study analyses of fractions, the incidences and 95% confidence intervals were found as exact Clopper-Pearson intervals, whereas risk differences were derived directly as Newcombe intervals, since the general principle of finding the absolute difference as $(RR - 1)*P_0$ where RR is the risk/effect ratio and P_0 is the normal comparator level in Danish setting for the given endpoint, could not be used in the present setup. It has not been possible for the applicant to establish the P_0 values.

Published data from the SYNAPSE study were included in Table 65 regarding relative treatment effects between mepolizumab and placebo. For coprimary endpoints, VAS scores, SNOT-22 score, the non-parametric Wilcoxon rank-sum test was used to assess the difference in change from baseline scores between treatment groups. Estimates of the treatment effect accounting for covariates of treatment group, geographical region, baseline score, and $\log_e$ baseline blood
eosinophil count was presented as a difference in medians between treatment groups based on a quantile regression model using the bootstrap approach with1,000,000 replicates.
Time-to-nasal surgery was analysed using a Cox proportional hazards model with covariates of treatment group, baseline nasal polyp score (centrally read), baseline nasal obstruction VAS score, loge baseline blood eosinophil count, number of previous surgeries (one, two, or more than two; ordinal), and geographical region.
The proportion of patients requiring systemic corticosteroids for nasal polyps was analysed using a logistic regression model with covariates of treatment group, baseline nasal polyp score (centrally read), baseline nasal obstruction VAS score, $\log_e$ baseline blood eosinophil count, number of systemic corticosteroids courses in previous 12 months (none, one, or more than one; ordinal), and geographic region[15].

Anchor-based analysis

Ability to detect change (responsiveness)

Ability to detect change was assessed for each individual symptom VAS, overall symptom VAS and both composite VAS scores (nasal symptoms composite VAS and nasal symptoms and facial pain composite VAS). Change over time was evaluated in participants believed to have experienced change (improvement or worsening) versus those who remained stable in their condition. Changes were assessed from baseline to Week 52 and within-group effect sizes (ES) were calculated.

Results from the ability to detect change analysis for each anchor used are presented in Table 1. Notably, for each VAS and composite score, sample sizes in the worsened group were small, limiting the interpretation of the results. No participants were classified as having worsened according to Overall Symptom VAS and SNOT-22 Loss of smell and taste anchors, thus only improved and stable groups are presented.

Statistically significant differences were observed between improved, stable and worsened groups across each anchor used for nasal discharge VAS, mucus in throat VAS, facial pain VAS, overall symptom VAS ($p<0.05$), as well as the nasal symptoms composite VAS and nasal symptoms and facial pain composite VAS scores ($p<0.001$). For nasal obstruction VAS and loss of smell VAS, all anchors showed statistically significant differences between groups ($p<0.001$), with the exception of PnIF ($p=0.091$-0.155). This finding is not surprising in light of prior observations of weak correlations between PnIF (an objective measure) and patient-reported symptoms of nasal obstruction.

Effect sizes reported using all anchors indicated very large changes in the improved groups across all VAS and both composite scores. Effect sizes were also large for stable groups, likely due to the low standard deviation at baseline due to the inclusion criteria of the SYNAPSE study. However, these were substantially smaller than the improved groups for all VAS and composite scores.

Anchor	Mean Change (SD)		Effect size [1]		Between groups p-value [2]
	Improved	Stable	Improved	Stable	
Nasal obstruction VAS					
ENP	-5.2 (3.09)	-4.3 (3.07)	-6.47	-5.04	<.001
PnIF	-4.8 (3.04)	-4.3 (3.28)	-5.65	-4.84	0.155
Overall VAS Symptom score	-6.0 (2.21)	-0.4 (0.85)	-7.24	-0.52	<.001
SNOT-22 Total Score	-5.0 (2.98)	-1.8 (2.56)	-6.12	-1.78	<.001
SNOT-22 Nasal Obstruction item	-5.7 (2.83)	-2.6 (2.67)	-6.85	-3.06	<.001
Nasal discharge VAS					
Endoscopic NP score	-5.2 (3.09)	-4.4 (3.06)	-4.55	-3.40	<.001
Overall VAS Symptom score	-6.0 (2.31)	-0.5 (1.49)	-5.01	-0.47	<.001
SNOT-22 Total Score	-5.0 (2.99)	-1.8 (2.54)	-4.68	-1.16	<.001
SNOT-22 Thick Nasal Discharge item	-5.7 (2.93)	-2.8 (2.78)	-5.52	-1.92	<.001
Mucus in throat VAS					
Endoscopic NP score	-4.8 (3.17)	-4.3 (3.08)	-3.30	-2.67	0.002
Overall VAS Symptom score	-5.7 (2.54)	-0.5 (1.74)	-3.97	-0.32	<.001
SNOT-22 Total Score	-4.8 (3.13)	-2.1 (2.63)	-3.42	-1.29	<.001
SNOT-22 Post-nasal Discharge item	-5.6 (2.92)	-3.0 (3.06)	-5.51	-1.54	<.001
Loss of smell VAS					

Endoscopic NP score	-3.4 (3.66)	-3.0 (3.45)	-3.61	-5.02	<.001
PnIF	-3.2 (3.50)	-2.6 (3.39)	-4.97	-1.97	0.091
Overall VAS Symptom score	-3.8 (3.60)	-0.3 (0.78)	-4.60	-0.48	<.001
SNOT-22 Total Score	-3.2 (3.54)	-1.1 (2.38)	-4.01	-1.46	<.001
SNOT-22 Loss of Taste or Smell item	-5.9 (3.24)	-1.0 (2.03)	-8.84	-1.23	<.001
Facial pain VAS					
Endoscopic NP score	-4.6 (3.26)	-4.1 (3.28)	-1.93	-1.50	0.006
Overall VAS Symptom score	-5.5 (2.74)	-0.5 (1.79)	-2.20	-0.21	<.001
SNOT-22 Total Score	-4.7 (3.18)	-1.6 (2.80)	-2.03	-0.55	<.001
SNOT-22 Facial Pain/Pressure	-5.5 (2.97)	-2.7 (3.03)	-3.47	-0.91	<.001
Overall symptom VAS					
Endoscopic NP score	-5.1 (3.04)	-4.4 (3.06)	-7.09	-5.67	<.001
SNOT-22 Total Score	-5.0 (2.95)	-1.8 (2.59)	-6.73	-2.46	<.001
Nasal symptoms composite VAS					
Endoscopic NP score	-4.6 (2.90)	-4.0 (2.79)	-5.92	-4.61	<.001
Overall VAS Symptom score	-5.5 (2.74)	0.5 (1.79)	-6.67	-0.56	<.001
SNOT-22 Total Score	-4.5 (2.80)	-1.7 (2.17)	-5.69	-2.04	<.001
Nasal symptoms and facial pain composite VAS					
Endoscopic NP score	-4.6 (2.85)	-4.0 (2.80)	-4.81	-3.71	<.001

Overall VAS Symptom score	-5.4 (2.18)	-0.5 (1.00)	-5.46	-0.46	<.001
SNOT-22 Total Score	-4.5 (2.78)	-1.7 (2.18)	-4.79	-1.48	<.001

SD = Standard Deviation
[1] The within-group effect size is calculated as the mean change score divided by the standard deviation of the score at baseline.
[2] Between-group p-values are derived from ANOVA F-test to evaluate the statistical significance of differences in change scores between groups
ENP: improved (n=160), stable (n=86); PnIF: improved (n=200), stable (n=57); Overall VAS: improved (n=223), stable (n=85); SNOT-22 Total Score: stable (n=256), stable (n=113); SNOT-22 Nasal Obstruction: improved (n=186), stable (n=113).

Meaningful within-patient change

The anchor-based analysis was conducted to establish thresholds for clinically meaningful change. In line with regulatory guidelines, thresholds for meaningful within-patient change were established primarily using anchor-based methods and supplemented by consideration of Cumulative Distribution Function (CDF) and Probability Density Function (PDF) plots. All analyses were conducted using an independent blinded version of the SYNAPSE study data at baseline Week 52. Given that very few participants worsened during the trial period, anchor-based estimates focused on minimal improvement only.
Anchor-based analyses were only performed for those anchors which correlated at ≥0.30 with the change in individual and composite VAS scores between baseline and Week 52 reports the recommended thresholds for meaningful within-patient change for the individual VAS scores and composite VAS scores used to support primary, secondary and exploratory endpoints in the SYNAPSE study. Recommended thresholds for the five individual symptom VAS and overall symptoms VAS ranged from -2.5 to -3. Thresholds for both composite VAS scores (nasal symptoms composite VAS and nasal symptoms and facial pain composite VAS) were both -2. These recommendations are in line with previous research, with a change of 2-3 points typically considered meaningful to individual patients on a 0-10 VAS.
Evidence generated to inform the establishment of thresholds for meaningful within-patient change definitions for primary and secondary endpoints is summarized below.

Table 2. Recommended thresholds for meaningful within-patient change for the individual VAS and composite VAS scores

Primary endpoint	
Nasal Obstruction VAS	-3
Secondary endpoints	
Loss of Smell VAS	-3
Overall Symptom VAS	-2.5

Nasal Symptoms Composite VAS Score	-2
Exploratory endpoints	
Nasal Discharge VAS	-2.5
Mucus in Throat VAS	-3
Facial Pain VAS	-2.5
Nasal Symptoms and Facial Pain Composite VAS Score	-2

In addition to anchor-based approaches, distribution-based estimates (half of standard deviation [SD] and the standard error of measurement [SEM]) of meaningful within-patient change were also produced as supportive evidence. Half SD estimates ranged from 1.28 to 1.65, and SEM estimates ranged from 0.36 to 0.77, across all single-item and composite VAS scores. This provides confidence that changes surpassing all recommend thresholds are unlikely to be a result of measurement error.

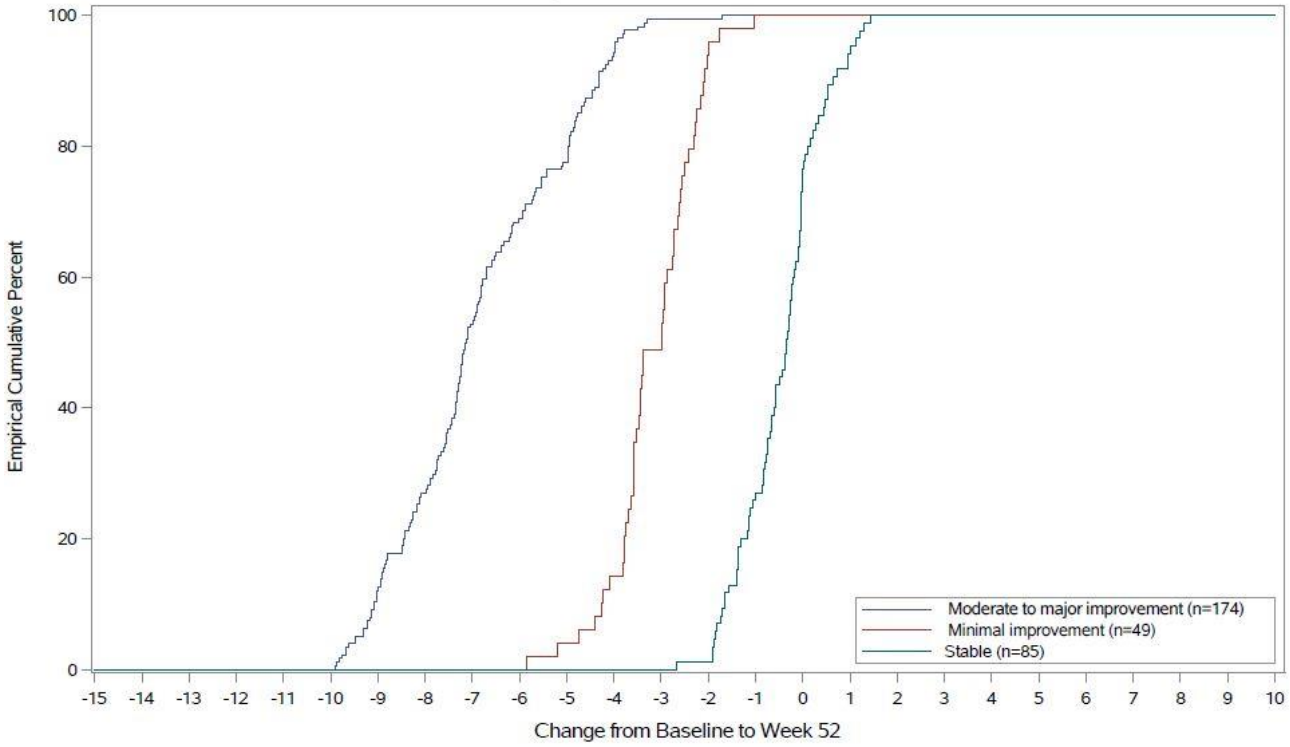
Nasal Obstruction VAS - Recommended threshold for meaningful within-patient change (-3 points).

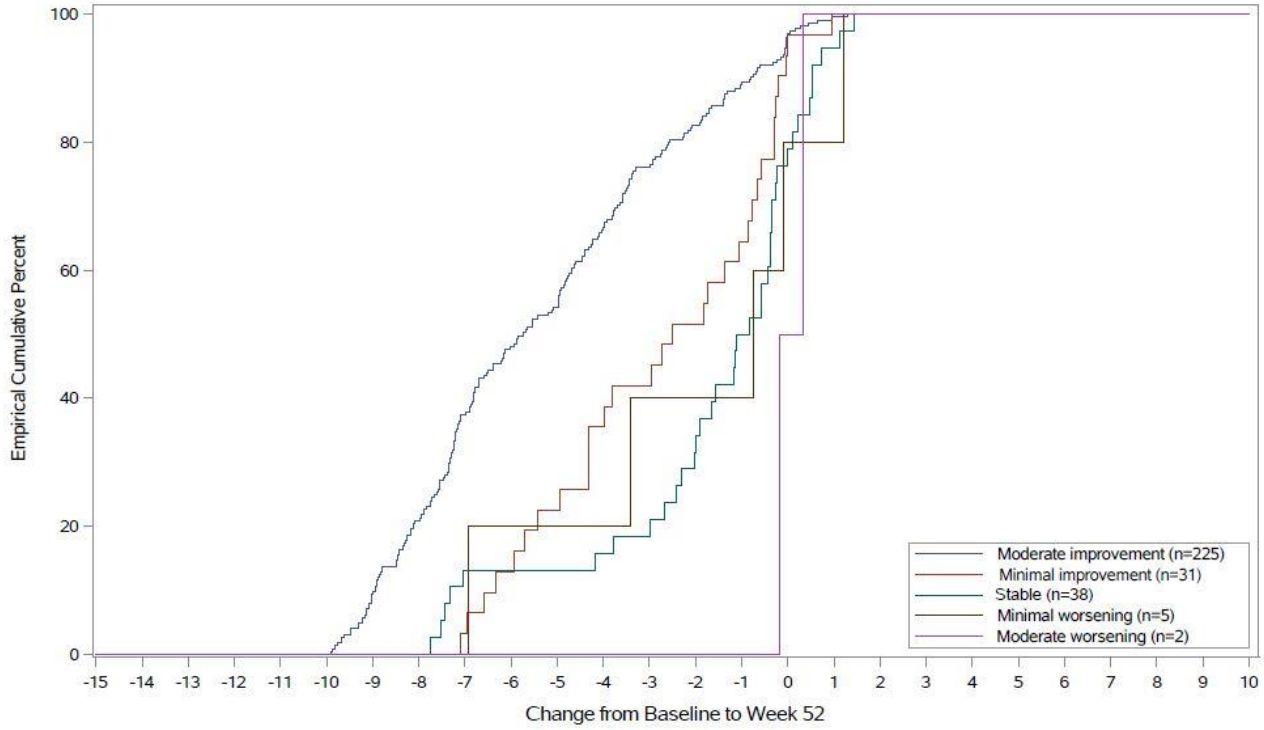
Changes in Nasal Obstruction VAS scores between baseline and Week 52 were examined among participants classified as stable and minimally improved according to the following anchors: Overall Symptom VAS, SNOT-22 Total Score and SNOT-22 Nasal Obstruction. The mean change for patients in the minimally improved group ranged from -2.80 (for overall VAS) to -3.16 (for Overall Symptom VAS and SNOT-22 Nasal Obstruction).

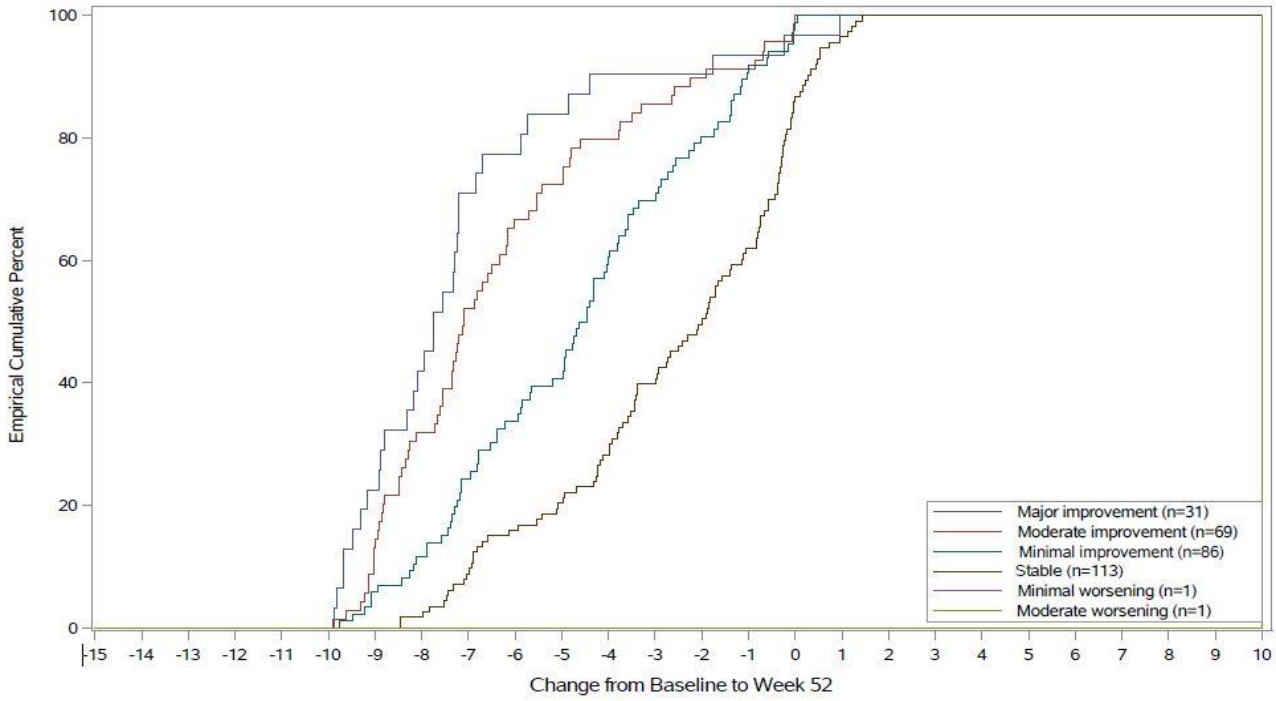
			95% CIs			25th		75th	
Anchor	N	Mean	Lower	Upper	Min	Percentile	Median	Percentile	Max
Overall Symptom VAS anchor	49	-3.16	-3.42	-2.90	-5.84	-3.63	-2.99	-2.56	-1.04
Minimal improvement	85	-0.45	-0.63	-0.26	-2.67	-1.06	-0.34	0.00	1.45
Stable									
SNOT-22 Total Score Anchor									
Minimal improvement	31	-2.80	-3.70	-1.90	-7.10	-4.94	-2.50	-0.58	0.96
Stable	38	-1.77	-2.61	-0.93	-7.74	-2.42	-0.97	-0.24	1.45
SNOT-22 Nasal Obstruction Anchor	86	-4.66	-5.23	-4.09	-9.75	-6.96	-4.55	-2.61	0.04
Minimal improvement	113	-2.62	-3.12	-2.13	-8.47	-4.22	-2.00	-0.33	1.45
Stable									

Cumulative Distribution Function (CDF) and Probability Density Function (PDF) plots aided the comparison of all possible thresholds for meaningful within-patient change when presented by anchor category, based on changes from baseline to Week 52. CDF plots are presented below for anchors Overall Symptom VAS. SNOT-22 Total Score and SNOT-22 Nasal Obstruction.

Generally, the CDF plots suggested setting a threshold for within-patient meaningful change between -2 and -3 (inclusive). Setting the threshold at -3 was deemed optimal to correctly classify a sizeable proportion of improved patients while limiting the proportion of stable patients that would be incorrectly classified as improved.


Empirical Cumulative Percent
100
80
60
40
20
0
-15 -14 -13 -12 -11 -10 -9 -8 -7 -6 -5 -4 -3 -2 -1 0 1 2 3 4 5 6 7 8 9 10
Change from Baseline to Week 52
Moderate to major improvement (n=174)
Minimal improvement (n=49)
Stable (n=85)


Empirical Cumulative Percent
100
80
60
40
20
0
-15 -14 -13 -12 -11 -10 -9 -8 -7 -6 -5 -4 -3 -2 -1 0 1 2 3 4 5 6 7 8 9 10
Change from Baseline to Week 52
Moderate improvement (n=225)
Minimal improvement (n=31)
Stable (n=38)
Minimal worsening (n=5)
Moderate worsening (n=2)


Empirical Cumulative Percent
100
80
60
40
20
0
-15 -14 -13 -12 -11 -10 -9 -8 -7 -6 -5 -4 -3 -2 -1 0 1 2 3 4 5 6 7 8 9 10
Change from Baseline to Week 52
Major improvement (n=31)
Moderate improvement (n=69)
Minimal improvement (n=86)
Stable (n=113)
Minimal worsening (n=1)
Moderate worsening (n=1)

Appendix L – subpopulation data included in the economic model

Response

NPS ≥1 or NCS ≥3, Comorbid Asthma

	Value	95% CI	SE	Distribution	Source
Response at Week 24					
Mepolizumab	72.9%	(69.1%, 76.6%)	1.9%	beta	SYNAPSE
Standard of Care	45.6%	(41.6%, 49.7%)	2.1%	beta	SYNAPSE
Proportion of Responders at Week 24 with Response at Week 52					
Mepolizumab	85.3%	(81.8%, 88.8%)	1.8%	beta	SYNAPSE
Standard of Care	69.1%	(63.5%, 74.7%)	2.9%	beta	SYNAPSE

CI – confidence interval; NCS – nasal congestion score; NPS – nasal polyp score; SE – standard error.

NPS ≥1 or NCS ≥3, Eosinophil Count

	Value	95% CI	SE	Distribution	Source
Response at Week 24					
Mepolizumab	69.4%	(66.0%, 72.7%)	1.7%	beta	SYNAPSE
Standard of Care	46.5%	(42.8%, 50.2%)	1.9%	beta	SYNAPSE
Proportion of Responders at Week 24 with Response at Week 52					
Mepolizumab	86.8%	(83.8%, 89.8%)	1.5%	beta	SYNAPSE
Standard of Care	67.4%	(62.4%, 72.5%)	2.6%	beta	SYNAPSE

CI – confidence interval; NCS – nasal congestion score; NPS – nasal polyp score; SE – standard error.

NPS ≥1 or NCS ≥3, Eosinophil Count

	Value	95% CI	SE	Distribution	Source
Response at Week 24					
Mepolizumab	72.7%	(68.9%, 76.4%)	1.9%	beta	SYNAPSE
Standard of Care	47.5%	(43.2%, 51.7%)	2.2%	beta	SYNAPSE
Proportion of Responders at Week 24 with Response at Week 52					
Mepolizumab	85.1%	(81.6%, 88.7%)	1.8%	beta	SYNAPSE
Standard of Care	66.7%	(60.9%, 72.5%)	3.0%	beta	SYNAPSE

CI – confidence interval; NCS – nasal congestion score; NPS – nasal polyp score; SE – standard error.

NPS ≥1 or NCS ≥3, Comorbid AERD

	Value	95% CI	SE	Distribution	Source
Response at Week 24					
Mepolizumab	77.8%	(71.6%, 84.0%)	3.2%	beta	SYNAPSE

Standard of Care	47.6%	(41.3%, 53.9%)	3.2%	beta	SYNAPSE
Proportion of Responders at Week 24 with Response at Week 52					
Mepolizumab	88.6%	(83.2%, 93.9%)	2.7%	beta	SYNAPSE
Standard of Care	60.0%	(51.1%, 68.9%)	4.6%	beta	SYNAPSE

AERD – aspirin-associated respiratory disease; CI – confidence interval; NCS – nasal congestion score; NPS – nasal polyp score; SE – standard error.

NPS ≥1 or NCS ≥3, Eosinophil Count

	Value	95% CI	SE	Distribution	Source
Response at Week 24					
Mepolizumab	72.9%	(68.6%, 77.2%)	2.2%	beta	SYNAPSE
Standard of Care	46.3%	(41.5%, 51.1%)	2.4%	beta	SYNAPSE
Proportion of Responders at Week 24 with Response at Week 52					
Mepolizumab	83.3%	(79.1%, 87.6%)	2.2%	beta	SYNAPSE
Standard of Care	70.0%	(63.5%, 76.5%)	3.3%	beta	SYNAPSE

CI – confidence interval; NCS – nasal congestion score; NPS – nasal polyp score; SE – standard error.

Surgery – probability

Probability of Surgery, Comorbid Asthma

	Value	95% CI	SE	Distribution	Source
Surgery at Week 24					
Mepolizumab	4.3%	(2.6%, 6.0%)	0.9%	beta	SYNAPSE
Standard of Care	7.4%	(5.2%, 9.5%)	1.1%	beta	SYNAPSE
Surgery at Week 52					
Mepolizumab	10.7%	(8.1%, 13.3%)	1.3%	beta	SYNAPSE
Standard of Care	21.5%	(18.1%, 24.8%)	1.7%	beta	SYNAPSE
Proportion of Responders at Week 24 Needing Surgery by Week 52					
Mepolizumab	4.9%	(2.8%, 7.0%)	1.1%	beta	SYNAPSE
Standard of Care	17.6%	(13.0%, 22.3%)	2.4%	beta	SYNAPSE
Proportion of Non-Responders at Week 24 Needing Surgery by Week 52	12.9%	(8.9%, 16.9%)	2.0%	beta	SYNAPSE

CI – confidence interval; SE – standard error.

Table 0-1 Probability of Surgery, Eosinophil Count ≥150 cells/µL

	Value	95% CI	SE	Distribution	Source
Surgery at Week 24					
Mepolizumab	4.3%	(2.8%, 5.8%)	0.8%	beta	SYNAPSE
Standard of Care	9.7%	(7.6%, 11.9%)	1.1%	beta	SYNAPSE
Surgery at Week 52					
Mepolizumab	9.1%	(7.0%, 11.3%)	1.1%	beta	SYNAPSE
Standard of Care	23.8%	(20.7%, 26.9%)	1.6%	beta	SYNAPSE
Proportion of Responders at Week 24 Needing Surgery by Week 52					
Mepolizumab	3.9%	(2.2%, 5.6%)	0.9%	beta	SYNAPSE
Standard of Care	17.4%	(13.3%, 21.5%)	2.1%	beta	SYNAPSE
Proportion of Non-Responders at Week 24 Needing Surgery by Week 52	13.6%	(9.8%, 17.4%)	1.9%	beta	SYNAPSE

CI – confidence interval; SE – standard error.

Probability of Surgery, Eosinophil Count ≥300 cells/µL

	Value	95% CI	SE	Distribution	Source
Surgery at Week 24					
Mepolizumab	2.9%	(1.5%, 4.3%)	0.7%	beta	SYNAPSE
Standard of Care	9.4%	(6.9%, 11.8%)	1.3%	beta	SYNAPSE
Surgery at Week 52					
Mepolizumab	7.2%	(5.0%, 9.4%)	1.1%	beta	SYNAPSE
Standard of Care	25.2%	(21.5%, 28.9%)	1.9%	beta	SYNAPSE
Proportion of Responders at Week 24 Needing Surgery by Week 52					
Mepolizumab	4.0%	(2.0%, 5.9%)	1.0%	beta	SYNAPSE
Standard of Care	18.2%	(13.4%, 22.9%)	2.4%	beta	SYNAPSE
Proportion of Non-Responders at Week 24 Needing Surgery by Week 52	16.7%	(11.9%, 21.5%)	2.5%	beta	SYNAPSE

CI – confidence interval; SE – standard error.

Probability of Surgery, Comorbid AERD

	Value	95% CI	SE	Distribution	Source
Surgery at Week 24					
Mepolizumab	6.7%	(2.9%, 10.4%)	1.9%	beta	SYNAPSE
Standard of Care	7.9%	(4.5%, 11.3%)	1.7%	beta	SYNAPSE
Surgery at Week 52					

	Value	95% CI	SE	Distribution	Source
Surgery at Week 24					
Mepolizumab	6.7%	(2.9%, 10.4%)	1.9%	beta	SYNAPSE
Mepolizumab	11.1%	(6.4%, 15.8%)	2.4%	beta	SYNAPSE
Standard of Care	28.6%	(22.9%, 34.3%)	2.9%	beta	SYNAPSE
Proportion of Responders at Week 24 Needing Surgery by Week 52					
Mepolizumab	2.9%	(0.0%, 5.7%)	1.4%	beta	SYNAPSE
Standard of Care	23.3%	(15.6%, 31.1%)	3.9%	beta	SYNAPSE
Proportion of Non-Responders at Week 24 Needing Surgery by Week 52	21.4%	(13.7%, 29.2%)	4.0%	beta	SYNAPSE

AERD – aspirin-associated respiratory disease; CI – confidence interval; SE – standard error.

Probability of Surgery, Eosinophil Count ≥300 cells/µL & Comorbid Asthma

	Value	95% CI	SE	Distribution	Source
Surgery at Week 24					
Mepolizumab	3.7%	(1.9%, 5.6%)	0.9%	beta	SYNAPSE
Standard of Care	7.4%	(4.9%, 9.9%)	1.3%	beta	SYNAPSE
Surgery at Week 52					
Mepolizumab	8.4%	(5.7%, 11.1%)	1.4%	beta	SYNAPSE
Standard of Care	25.0%	(20.8%, 29.2%)	2.1%	beta	SYNAPSE
Proportion of Responders at Week 24 Needing Surgery by Week 52					
Mepolizumab	3.8%	(1.7%, 6.0%)	0.8%	beta	SYNAPSE
Standard of Care	20.0%	(14.3%, 25.7%)	2.9%	beta	SYNAPSE
Proportion of Non-Responders at Week 24 Needing Surgery by Week 52	18.0%	(12.6%, 23.4%)	2.8%	beta	SYNAPSE

CI – confidence interval; SE – standard error.

Asthma exacerbation rate

Asthma Exacerbation Rate, Comorbid Asthma

	Value	95% CI	Log(SE)	Distribution	Source
In-Trial (24 weeks) Annual Rate					
Mepolizumab	0.03	N/A	0.75	lognormal	SYNAPSE
Standard of Care	0.10	N/A	0.53	lognormal	SYNAPSE
Responder Annual Rate (Weeks 24-52)					
Mepolizumab	0.02	N/A	1.08	lognormal	SYNAPSE
Standard of Care	0.15	N/A	0.74	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 24-52)	0.09	N/A	0.58	lognormal	SYNAPSE
Responder Annual Rate (Weeks 52+)					
Mepolizumab	0.02	N/A	1.22	lognormal	SYNAPSE
Standard of Care	0.05	N/A	1.30	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 52+)	0.14	N/A	0.50	lognormal	SYNAPSE

CI – confidence interval; SE – standard error.

Asthma Exacerbation Rate, Eosinophil Count ≥150 cells/µL

	Value	95% CI	Log(SE)	Distribution	Source
In-Trial (24 weeks) Annual Rate					
Mepolizumab	0.03	N/A	0.74	lognormal	SYNAPSE
Standard of Care	0.08	N/A	0.53	lognormal	SYNAPSE
Responder Annual Rate (Weeks 24-52)					
Mepolizumab	0.01	N/A	1.07	lognormal	SYNAPSE
Standard of Care	0.16	N/A	0.63	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 24-52)	0.08	N/A	0.58	lognormal	SYNAPSE
Responder Annual Rate (Weeks 52+)					
Mepolizumab	0.01	N/A	1.18	lognormal	SYNAPSE
Standard of Care	0.08	N/A	0.96	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 52+)	0.12	N/A	0.50	lognormal	SYNAPSE

CI – confidence interval; SE – standard error.

Asthma Exacerbation Rate, Eosinophil Count ≥300 cells/µL

	Value	95% CI	Log(SE)	Distribution	Source
In-Trial (24 weeks) Annual Rate					
Mepolizumab	0.04	N/A	0.71	lognormal	SYNAPSE
Standard of Care	0.07	N/A	0.64	lognormal	SYNAPSE
Responder Annual Rate (Weeks 24-52)					
Mepolizumab	0.02	N/A	1.06	lognormal	SYNAPSE
Standard of Care	0.21	N/A	0.62	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 24-52)	0.11	N/A	0.58	lognormal	SYNAPSE
Responder Annual Rate (Weeks 52+)					
Mepolizumab	0.02	N/A	1.06	lognormal	SYNAPSE
Standard of Care	0.14	N/A	0.91	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 52+)	0.16	N/A	0.50	lognormal	SYNAPSE

CI – confidence interval; SE – standard error.

Asthma Exacerbation Rate, Comorbid AERD

	Value	95% CI	Log(SE)	Distribution	Source
In-Trial (24 weeks) Annual Rate					
Mepolizumab	0.03	N/A	1.39	lognormal	SYNAPSE
Standard of Care	0.06	N/A	1.18	lognormal	SYNAPSE
Responder Annual Rate (Weeks 24-52)					
Mepolizumab	0.02	N/A	1.08	lognormal	SYNAPSE
Standard of Care	0.27	N/A	0.94	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 24-52)	0.08	N/A	1.00	lognormal	SYNAPSE
Responder Annual Rate (Weeks 52+)					
Mepolizumab	0.02	N/A	1.22	lognormal	SYNAPSE
Standard of Care	0.05	N/A	1.30	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 52+)	0.14	N/A	0.50	lognormal	SYNAPSE

AERD – aspirin-associated respiratory disease; CI – confidence interval; SE – standard error.

Asthma Exacerbation Rate, Eosinophil Count ≥300 cells/

	Value	95% CI	Log(SE)	Distribution	Source
In-Trial (24 weeks) Annual Rate					
Mepolizumab	0.05	N/A	0.70	lognormal	SYNAPSE
Standard of Care	0.10	N/A	0.59	lognormal	SYNAPSE
Responder Annual Rate (Weeks 24-52)					
Mepolizumab	0.02	N/A	1.07	lognormal	SYNAPSE
Standard of Care	0.20	N/A	0.73	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 24-52)	0.14	N/A	0.58	lognormal	SYNAPSE
Responder Annual Rate (Weeks 52+)					
Mepolizumab	0.03	N/A	1.24	lognormal	SYNAPSE
Standard of Care	0.11	N/A	1.24	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 52+)	0.21	N/A	0.50	lognormal	SYNAPSE

CI – confidence interval; SE – standard error.

Oral corticosteroid courses

OCS Use, Comorbid Asthma

	Value	95% CI	Log(SE)	Distribution	Source
In-Trial (24 weeks) Annual Rate					
Mepolizumab	0.48	N/A	0.19	lognormal	SYNAPSE
Standard of Care	0.53	N/A	0.19	lognormal	SYNAPSE
Responder Annual Rate (Weeks 24-52)					
Mepolizumab	0.18	N/A	0.35	lognormal	SYNAPSE
Standard of Care	0.54	N/A	0.28	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 24-52)	0.58	N/A	0.26	lognormal	SYNAPSE
Responder Annual Rate (Weeks 52+)					
Mepolizumab	0.13	N/A	0.44	lognormal	SYNAPSE
Standard of Care	0.39	N/A	0.38	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 52+)	0.79	N/A	0.27	lognormal	SYNAPSE

CI – confidence interval; OCS – oral corticosteroids; SE – standard error.

OCS Use, Eosinophil Count ≥150 cells/µL

	Value	95% CI	Log(SE)	Distribution	Source
In-Trial (24 weeks) Annual Rate					
Mepolizumab	0.43	N/A	0.18	lognormal	SYNAPSE
Standard of Care	0.46	N/A	0.18	lognormal	SYNAPSE
Responder Annual Rate (Weeks 24-52)					
Mepolizumab	0.26	N/A	0.25	lognormal	SYNAPSE
Standard of Care	0.52	N/A	0.24	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 24-52)	0.57	N/A	0.25	lognormal	SYNAPSE
Responder Annual Rate (Weeks 52+)					
Mepolizumab	0.16	N/A	0.33	lognormal	SYNAPSE
Standard of Care	0.37	N/A	0.30	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 52+)	0.78	N/A	0.24	lognormal	SYNAPSE

CI – confidence interval; OCS – oral corticosteroids; SE – standard error.

OCS Use, Eosinophil Count ≥300 cells/µL

	Value	95% CI	Log(SE)	Distribution	Source
In-Trial (24 weeks) Annual Rate					
Mepolizumab	0.43	N/A	0.20	lognormal	SYNAPSE
Standard of Care	0.55	N/A	0.19	lognormal	SYNAPSE
Responder Annual Rate (Weeks 24-52)					
Mepolizumab	0.24	N/A	0.30	lognormal	SYNAPSE
Standard of Care	0.54	N/A	0.27	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 24-52)	0.74	N/A	0.25	lognormal	SYNAPSE
Responder Annual Rate (Weeks 52+)					

	Value	95% CI	Log(SE)	Distribution	Source
In-Trial (24 weeks) Annual Rate					
Mepolizumab	0.43	N/A	0.20	lognormal	SYNAPSE
Mepolizumab	0.26	N/A	0.33	lognormal	SYNAPSE
Standard of Care	0.46	N/A	0.37	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 52+)	0.94	N/A	0.23	lognormal	SYNAPSE

OCS Use, Comorbid AERD

	Value	95% CI	Log(SE)	Distribution	Source
In-Trial (24 weeks) Annual Rate					
Mepolizumab	0.29	N/A	0.41	lognormal	SYNAPSE
Standard of Care	0.60	N/A	0.28	lognormal	SYNAPSE
Responder Annual Rate (Weeks 24-52)					
Mepolizumab	0.23	N/A	0.50	lognormal	SYNAPSE
Standard of Care	0.46	N/A	0.43	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 24-52)	1.21	N/A	0.31	lognormal	SYNAPSE
Responder Annual Rate (Weeks 52+)					
Mepolizumab	0.18	N/A	0.62	lognormal	SYNAPSE
Standard of Care	0.48	N/A	0.63	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 52+)	1.33	N/A	0.30	lognormal	SYNAPSE

AERD – aspirin-associated respiratory disease; CI – confidence interval; OCS – oral corticosteroids; SE – standard error.

OCS Use, Eosinophil Count ≥300 cells/µL & Comorbid Asthma

	Value	95% CI	Log(SE)	Distribution	Source
In-Trial (24 weeks) Annual Rate					
Mepolizumab	0.49	N/A	0.22	lognormal	SYNAPSE
Standard of Care	0.58	N/A	0.21	lognormal	SYNAPSE
Responder Annual Rate (Weeks 24-52)					
Mepolizumab	0.15	N/A	0.48	lognormal	SYNAPSE
Standard of Care	0.58	N/A	0.38	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 24-52)	0.66	N/A	0.30	lognormal	SYNAPSE
Responder Annual Rate (Weeks 52+)					
Mepolizumab	0.09	N/A	0.58	lognormal	SYNAPSE
Standard of Care	0.27	N/A	0.42	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 52+)	1.15	N/A	0.27	lognormal	SYNAPSE

CI – confidence interval; OCS – oral corticosteroids; SE – standard error.

Antibiotic courses

Antibiotic Use, Comorbid Asthma

	Value	95% CI	Log(SE)	Distribution	Source
In-Trial (24 weeks) Annual Rate					
Mepolizumab	0.33	N/A	0.23	lognormal	SYNAPSE
Standard of Care	0.32	N/A	0.23	lognormal	SYNAPSE
Responder Annual Rate (Weeks 24-52)					
Mepolizumab	0.15	N/A	0.38	lognormal	SYNAPSE
Standard of Care	0.54	N/A	0.29	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 24-52)	0.37	N/A	0.33	lognormal	SYNAPSE
Responder Annual Rate (Weeks 52+)					
Mepolizumab	0.11	N/A	0.45	lognormal	SYNAPSE
Standard of Care	0.46	N/A	0.30	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 52+)	0.55	N/A	0.34	lognormal	SYNAPSE

CI – confidence interval; SE – standard error.

Antibiotic Use, Eosinophil Count ≥150 cells/µL

	Value	95% CI	Log(SE)	Distribution	Source
In-Trial (24 weeks) Annual Rate					
Mepolizumab	0.25	N/A	0.21	lognormal	SYNAPSE
Standard of Care	0.27	N/A	0.21	lognormal	SYNAPSE
Responder Annual Rate (Weeks 24-52)					
Mepolizumab	0.15	N/A	0.33	lognormal	SYNAPSE
Standard of Care	0.56	N/A	0.24	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 24-52)	0.31	N/A	0.34	lognormal	SYNAPSE
Responder Annual Rate (Weeks 52+)					
Mepolizumab	0.09	N/A	0.43	lognormal	SYNAPSE
Standard of Care	0.39	N/A	0.29	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 52+)	0.59	N/A	0.28	lognormal	SYNAPSE

CI – confidence interval; SE – standard error.

Antibiotic Use, Eosinophil Count ≥300 cells/µL

	Value	95% CI	Log(SE)	Distribution	Source
In-Trial (24 weeks) Annual Rate					
Mepolizumab	0.20	N/A	0.28	lognormal	SYNAPSE
Standard of Care	0.26	N/A	0.25	lognormal	SYNAPSE
Responder Annual Rate (Weeks 24-52)					
Mepolizumab	0.15	N/A	0.36	lognormal	SYNAPSE
Standard of Care	0.61	N/A	0.25	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 24-52)	0.35	N/A	0.41	lognormal	SYNAPSE
Responder Annual Rate (Weeks 52+)					
Mepolizumab	0.12	N/A	0.42	lognormal	SYNAPSE
Standard of Care	0.49	N/A	0.30	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 52+)	0.49	N/A	0.34	lognormal	SYNAPSE

CI – confidence interval; SE – standard error.

Antibiotic Use, Comorbid AERD

	Value	95% CI	Log(SE)	Distribution	Source
In-Trial (24 weeks) Annual Rate					
Mepolizumab	0.25	N/A	0.51	lognormal	SYNAPSE
Standard of Care	0.37	N/A	0.38	lognormal	SYNAPSE
Responder Annual Rate (Weeks 24-52)					
Mepolizumab	0.09	N/A	0.78	lognormal	SYNAPSE
Standard of Care	0.58	N/A	0.47	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 24-52)	0.69	N/A	0.41	lognormal	SYNAPSE
Responder Annual Rate (Weeks 52+)					
Mepolizumab	0.05	N/A	1.04	lognormal	SYNAPSE
Standard of Care	0.64	N/A	0.51	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 52+)	0.81	N/A	0.36	lognormal	SYNAPSE

CI – confidence interval; SE – standard error.

Antibiotic Use, Eosinophil Count ≥300 cells/µL & Comorbid Asthma

	Value	95% CI	Log(SE)	Distribution	Source
In-Trial (24 weeks) Annual Rate					
Mepolizumab	0.25	N/A	0.28	lognormal	SYNAPSE
Standard of Care	0.31	N/A	0.26	lognormal	SYNAPSE
Responder Annual Rate (Weeks 24-52)					
Mepolizumab	0.12	N/A	0.48	lognormal	SYNAPSE
Standard of Care	0.76	N/A	0.29	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 24-52)	0.29	N/A	0.50	lognormal	SYNAPSE
Responder Annual Rate (Weeks 52+)					
Mepolizumab	0.10	N/A	0.56	lognormal	SYNAPSE
Standard of Care	0.55	N/A	0.33	lognormal	SYNAPSE
Non-Responder Annual Rate (Weeks 52+)	0.46	N/A	0.44	lognormal	SYNAPSE

CI – confidence interval; SE – standard error.

Utility

Treatment Independent Utilities, Comorbid Asthma

	Value	95% CI	SE	Distribution	Source
Baseline	0.514	(0.494, 0.534)	0.010	lognormal	SYNAPSE
CFB Week 52+ Non-Responder	0.034	(-0.015, 0.083)	0.025	normal	SYNAPSE
Utility Gain from Surgery	0.107	(0.044, 0.170)	0.032	normal	SYNAPSE
CFB Post Surgery in Non-responders to Surgery (not used in base-case)	0.000	N/A	N/A	N/A	Assumption

CFB – change from baseline; CI – confidence interval; N/A – not applicable; SE – standard error.

	Value	95% CI	SE	Distribution	Source
Baseline	0.534	(0.516, 0.552)	0.009	lognormal	SYNAPSE
CFB Week 52+ Non-Responder	0.032	(-0.011, 0.075)	0.022	normal	SYNAPSE
Utility Gain from Surgery	0.107	(0.044, 0.170)	0.032	normal	SYNAPSE
CFB Post Surgery in Non-responders to Surgery (not used in base-case)	0.000	N/A	N/A	N/A	Assumption

CFB – change from baseline; CI – confidence interval; N/A – not applicable; SE – standard error.

Treatment Independent Utilities, Eosinophil Count ≥300 cells/µL

	Value	95% CI	SE	Distribution	Source
Baseline	0.526	(0.506, 0.546)	0.010	lognormal	SYNAPSE
CFB Week 52+ Non-Responder	0.036	(-0.015, 0.087)	0.026	normal	SYNAPSE
Utility Gain from Surgery	0.107	(0.044, 0.170)	0.032	normal	SYNAPSE
CFB Post Surgery in Non-responders to Surgery (not used in base-case)	0.000	N/A	N/A	N/A	Assumption

CFB – change from baseline; CI – confidence interval; N/A – not applicable; SE – standard error.

Treatment Independent Utilities, Comorbid AERD

	Value	95% CI	SE	Distribution	Source
Baseline	0.495	(0.464, 0.526)	0.016	lognormal	SYNAPSE
CFB Week 52+ Non-Responder	0.013	(-0.046, 0.072)	0.030	normal	SYNAPSE
Utility Gain from Surgery	0.107	(0.044, 0.170)	0.032	normal	SYNAPSE
CFB Post Surgery in Non-responders to Surgery (not used in base-case)	0.000	N/A	N/A	N/A	Assumption

AERD – aspirin-associated respiratory disease; CFB – change from baseline; CI – confidence interval; N/A – not applicable; SE – standard error.

Treatment Independent Utilities, Eosinophil Count ≥300 cells/µL & Comorbid Asthma

	Value	95% CI	SE	Distribution	Source
Baseline	0.509	(0.487, 0.531)	0.011	lognormal	SYNAPSE
CFB Week 52+ Non-Responder	0.049	(-0.016, 0.114)	0.033	normal	SYNAPSE
Utility Gain from Surgery	0.107	(0.044, 0.170)	0.032	normal	SYNAPSE
CFB Post Surgery in Non-responders to Surgery (not used in base-case)	0.000	N/A	N/A	N/A	Assumption

CFB – change from baseline; CI – confidence interval; N/A – not applicable; SE – standard error.

Standard of Care EQ-5D Utilities, Comorbid Asthma

All Trial Population, Standard of Care	Value	95% CI	SE	Distribution	Source
CFB Week 4	0.070	(0.050, 0.090)	0.010	normal	SYNAPSE
CFB Week 8	0.095	(0.073, 0.117)	0.011	normal	SYNAPSE
CFB Week 12	0.104	(0.080, 0.128)	0.012	normal	SYNAPSE
CFB Week 16	0.112	(0.088, 0.136)	0.012	normal	SYNAPSE
CFB Week 20	0.117	(0.092, 0.142)	0.013	normal	SYNAPSE
CFB Week 24 Responder	0.160	(0.125, 0.195)	0.018	normal	SYNAPSE
CFB Week 28 Responder	0.142	(0.105, 0.179)	0.019	normal	SYNAPSE
CFB Week 32 Responder	0.151	(0.110, 0.192)	0.021	normal	SYNAPSE
CFB Week 36 Responder	0.133	(0.096, 0.170)	0.019	normal	SYNAPSE
CFB Week 40 Responder	0.162	(0.121, 0.203)	0.021	normal	SYNAPSE
CFB Week 44 Responder	0.154	(0.109, 0.199)	0.023	normal	SYNAPSE
CFB Week 48 Responder	0.140	(0.101, 0.179)	0.020	normal	SYNAPSE
CFB Week 52+ Responder	0.156	(0.113, 0.199)	0.022	normal	SYNAPSE
CFB Week 24 Non-Responder	0.065	(0.020, 0.110)	0.023	normal	SYNAPSE
CFB Week 28 Non-Responder	0.094	(0.047, 0.141)	0.024	normal	SYNAPSE
CFB Week 32 Non-Responder	0.088	(0.041, 0.135)	0.024	normal	SYNAPSE
CFB Week 36 Non-Responder	0.121	(0.074, 0.168)	0.024	normal	SYNAPSE
CFB Week 40 Non-Responder	0.085	(0.040, 0.130)	0.023	normal	SYNAPSE
CFB Week 44 Non-Responder	0.096	(0.047, 0.145)	0.025	normal	SYNAPSE
CFB Week 48 Non-Responder	0.106	(0.059, 0.153)	0.024	normal	SYNAPSE
CFB Week 52+ Non-Responder	0.034	(-0.015, 0.083)	0.025	normal	SYNAPSE

CFB – change from baseline; CI – confidence interval; SE – standard error.

Mepolizumab EQ-5D Utilities, Comorbid Asthma

All Trial Population, Mepolizumab	Value	95% CI	SE	Distribution	Source
Difference from SOC in CFB Week 4	0.024	(-0.005, 0.053)	0.015	normal	SYNAPSE
Difference from SOC in CFB Week 8	0.030	(-0.001, 0.061)	0.016	normal	SYNAPSE
Difference from SOC in CFB Week 12	0.042	(0.008, 0.076)	0.017	normal	SYNAPSE
Difference from SOC in CFB Week 16	0.047	(0.013, 0.082)	0.018	normal	SYNAPSE
Difference from SOC in CFB Week 20	0.049	(0.013, 0.085)	0.018	normal	SYNAPSE
CFB Week 24 Responder	0.198	(0.163, 0.233)	0.018	normal	SYNAPSE
CFB Week 28 Responder	0.195	(0.160, 0.230)	0.018	normal	SYNAPSE
CFB Week 32 Responder	0.206	(0.169, 0.243)	0.019	normal	SYNAPSE
CFB Week 36 Responder	0.202	(0.165, 0.239)	0.019	normal	SYNAPSE
CFB Week 40 Responder	0.193	(0.154, 0.232)	0.020	normal	SYNAPSE
CFB Week 44 Responder	0.196	(0.157, 0.235)	0.020	normal	SYNAPSE
CFB Week 48 Responder	0.202	(0.163, 0.241)	0.020	normal	SYNAPSE
CFB Week 52+ Responder	0.214	(0.175, 0.253)	0.020	normal	SYNAPSE

CFB – change from baseline; CI – confidence interval; SE – standard error; SOC – standard of care.

Standard of Care EQ-5D Utilities, Eosinophil Count ≥150 cells/µL

All Trial Population, Standard of Care	Value	95% CI	SE	Distribution	Source
CFB Week 4	0.070	(0.050, 0.090)	0.010	normal	SYNAPSE
CFB Week 8	0.090	(0.070, 0.110)	0.010	normal	SYNAPSE
CFB Week 12	0.102	(0.082, 0.122)	0.010	normal	SYNAPSE
CFB Week 16	0.121	(0.099, 0.143)	0.011	normal	SYNAPSE
CFB Week 20	0.118	(0.096, 0.140)	0.011	normal	SYNAPSE
CFB Week 24 Responder	0.153	(0.120, 0.186)	0.017	normal	SYNAPSE
CFB Week 28 Responder	0.151	(0.116, 0.186)	0.018	normal	SYNAPSE
CFB Week 32 Responder	0.158	(0.119, 0.197)	0.020	normal	SYNAPSE
CFB Week 36 Responder	0.140	(0.105, 0.175)	0.018	normal	SYNAPSE
CFB Week 40 Responder	0.168	(0.131, 0.205)	0.019	normal	SYNAPSE
CFB Week 44 Responder	0.154	(0.113, 0.195)	0.021	normal	SYNAPSE
CFB Week 48 Responder	0.145	(0.106, 0.184)	0.020	normal	SYNAPSE
CFB Week 52+ Responder	0.170	(0.129, 0.211)	0.021	normal	SYNAPSE
CFB Week 24 Non-Responder	0.066	(0.027, 0.105)	0.020	normal	SYNAPSE
CFB Week 28 Non-Responder	0.095	(0.054, 0.136)	0.021	normal	SYNAPSE
CFB Week 32 Non-Responder	0.083	(0.042, 0.124)	0.021	normal	SYNAPSE
CFB Week 36 Non-Responder	0.118	(0.077, 0.159)	0.021	normal	SYNAPSE
CFB Week 40 Non-Responder	0.084	(0.045, 0.123)	0.020	normal	SYNAPSE
CFB Week 44 Non-Responder	0.096	(0.055, 0.137)	0.021	normal	SYNAPSE
CFB Week 48 Non-Responder	0.103	(0.062, 0.144)	0.021	normal	SYNAPSE
CFB Week 52+ Non-Responder	0.032	(-0.011, 0.075)	0.022	normal	SYNAPSE

CFB – change from baseline; CI – confidence interval; SE – standard error.

Mepolizumab EQ-5D Utilities, Eosinophil Count ≥150 cells/µL

All Trial Population, Mepolizumab	Value	95% CI	SE	Distribution	Source
Difference from SOC in CFB Week 4	0.024	(-0.003, 0.051)	0.014	normal	SYNAPSE
Difference from SOC in CFB Week 8	0.032	(0.005, 0.060)	0.014	normal	SYNAPSE
Difference from SOC in CFB Week 12	0.038	(0.009, 0.067)	0.015	normal	SYNAPSE
Difference from SOC in CFB Week 16	0.029	(0.000, 0.059)	0.015	normal	SYNAPSE
Difference from SOC in CFB Week 20	0.040	(0.009, 0.071)	0.016	normal	SYNAPSE
CFB Week 24 Responder	0.187	(0.156, 0.218)	0.016	normal	SYNAPSE
CFB Week 28 Responder	0.186	(0.155, 0.217)	0.016	normal	SYNAPSE
CFB Week 32 Responder	0.191	(0.160, 0.222)	0.016	normal	SYNAPSE
CFB Week 36 Responder	0.182	(0.149, 0.215)	0.017	normal	SYNAPSE
CFB Week 40 Responder	0.183	(0.150, 0.216)	0.017	normal	SYNAPSE
CFB Week 44 Responder	0.183	(0.150, 0.216)	0.017	normal	SYNAPSE
CFB Week 48 Responder	0.190	(0.157, 0.223)	0.017	normal	SYNAPSE
CFB Week 52+ Responder	0.208	(0.175, 0.241)	0.017	normal	SYNAPSE

CFB – change from baseline; CI – confidence interval; SE – standard error; SOC – standard of care.

Standard of Care EQ-5D Utilities, Eosinophil Count ≥300 cells/µL

All Trial Population, Standard of Care	Value	95% CI	SE	Distribution	Source
CFB Week 4	0.070	(0.048, 0.092)	0.011	normal	SYNAPSE
CFB Week 8	0.092	(0.072, 0.112)	0.010	normal	SYNAPSE
CFB Week 12	0.103	(0.078, 0.128)	0.013	normal	SYNAPSE
CFB Week 16	0.115	(0.090, 0.140)	0.013	normal	SYNAPSE
CFB Week 20	0.116	(0.091, 0.141)	0.013	normal	SYNAPSE
CFB Week 24 Responder	0.144	(0.107, 0.181)	0.019	normal	SYNAPSE
CFB Week 28 Responder	0.137	(0.096, 0.178)	0.021	normal	SYNAPSE
CFB Week 32 Responder	0.141	(0.096, 0.186)	0.023	normal	SYNAPSE
CFB Week 36 Responder	0.128	(0.089, 0.167)	0.020	normal	SYNAPSE
CFB Week 40 Responder	0.165	(0.122, 0.208)	0.022	normal	SYNAPSE
CFB Week 44 Responder	0.138	(0.089, 0.187)	0.025	normal	SYNAPSE
CFB Week 48 Responder	0.129	(0.086, 0.172)	0.022	normal	SYNAPSE
CFB Week 52+ Responder	0.159	(0.112, 0.206)	0.024	normal	SYNAPSE
CFB Week 24 Non-Responder	0.067	(0.018, 0.116)	0.025	normal	SYNAPSE
CFB Week 28 Non-Responder	0.094	(0.043, 0.145)	0.026	normal	SYNAPSE
CFB Week 32 Non-Responder	0.091	(0.040, 0.142)	0.026	normal	SYNAPSE
CFB Week 36 Non-Responder	0.125	(0.074, 0.176)	0.026	normal	SYNAPSE
CFB Week 40 Non-Responder	0.100	(0.055, 0.145)	0.023	normal	SYNAPSE
CFB Week 44 Non-Responder	0.107	(0.058, 0.156)	0.025	normal	SYNAPSE
CFB Week 48 Non-Responder	0.106	(0.057, 0.155)	0.025	normal	SYNAPSE
CFB Week 52+ Non-Responder	0.036	(-0.015, 0.087)	0.026	normal	SYNAPSE

CFB – change from baseline; CI – confidence interval; SE – standard error.

Mepolizumab EQ-5D Utilities, Eosinophil Count ≥300 cells/µL

All Trial Population, Mepolizumab	Value	95% CI	SE	Distribution	Source
Difference from SOC in CFB Week 4	0.028	(-0.003, 0.058)	0.016	normal	SYNAPSE
Difference from SOC in CFB Week 8	0.036	(0.004, 0.069)	0.017	normal	SYNAPSE
Difference from SOC in CFB Week 12	0.041	(0.006, 0.076)	0.018	normal	SYNAPSE
Difference from SOC in CFB Week 16	0.036	(0.001, 0.071)	0.018	normal	SYNAPSE
Difference from SOC in CFB Week 20	0.043	(0.006, 0.079)	0.019	normal	SYNAPSE
CFB Week 24 Responder	0.191	(0.156, 0.226)	0.018	normal	SYNAPSE
CFB Week 28 Responder	0.184	(0.149, 0.219)	0.018	normal	SYNAPSE
CFB Week 32 Responder	0.192	(0.155, 0.229)	0.019	normal	SYNAPSE
CFB Week 36 Responder	0.180	(0.141, 0.219)	0.020	normal	SYNAPSE
CFB Week 40 Responder	0.188	(0.149, 0.227)	0.020	normal	SYNAPSE
CFB Week 44 Responder	0.181	(0.142, 0.220)	0.020	normal	SYNAPSE
CFB Week 48 Responder	0.191	(0.152, 0.230)	0.020	normal	SYNAPSE
CFB Week 52+ Responder	0.207	(0.170, 0.244)	0.019	normal	SYNAPSE

CFB – change from baseline; CI – confidence interval; SE – standard error; SOC – standard of care.

Standard of Care EQ-5D Utilities, Comorbid AERD

All Trial Population, Standard of Care	Value	95% CI	SE	Distribution	Source
CFB Week 4	0.049	(0.018, 0.080)	0.016	normal	SYNAPSE
CFB Week 8	0.124	(0.095, 0.153)	0.015	normal	SYNAPSE
CFB Week 12	0.124	(0.089, 0.159)	0.018	normal	SYNAPSE
CFB Week 16	0.114	(0.075, 0.153)	0.020	normal	SYNAPSE
CFB Week 20	0.100	(0.057, 0.143)	0.022	normal	SYNAPSE
CFB Week 24 Responder	0.178	(0.125, 0.231)	0.027	normal	SYNAPSE
CFB Week 28 Responder	0.156	(0.101, 0.211)	0.028	normal	SYNAPSE
CFB Week 32 Responder	0.138	(0.077, 0.199)	0.031	normal	SYNAPSE
CFB Week 36 Responder	0.139	(0.078, 0.200)	0.031	normal	SYNAPSE
CFB Week 40 Responder	0.162	(0.103, 0.221)	0.030	normal	SYNAPSE
CFB Week 44 Responder	0.161	(0.102, 0.220)	0.030	normal	SYNAPSE
CFB Week 48 Responder	0.129	(0.072, 0.186)	0.029	normal	SYNAPSE
CFB Week 52+ Responder	0.199	(0.144, 0.254)	0.028	normal	SYNAPSE
CFB Week 24 Non-Responder	0.022	(-0.035, 0.079)	0.029	normal	SYNAPSE
CFB Week 28 Non-Responder	0.079	(0.014, 0.144)	0.033	normal	SYNAPSE
CFB Week 32 Non-Responder	0.055	(-0.014, 0.124)	0.035	normal	SYNAPSE
CFB Week 36 Non-Responder	0.104	(0.028, 0.180)	0.039	normal	SYNAPSE
CFB Week 40 Non-Responder	0.068	(-0.001, 0.137)	0.035	normal	SYNAPSE
CFB Week 44 Non-Responder	0.063	(-0.015, 0.141)	0.040	normal	SYNAPSE
CFB Week 48 Non-Responder	0.073	(-0.003, 0.149)	0.039	normal	SYNAPSE
CFB Week 52+ Non-Responder	0.013	(-0.046, 0.072)	0.030	normal	SYNAPSE

AERD – aspirin-associated respiratory disease; CFB – change from baseline; CI – confidence interval; SE – standard error.

Mepolizumab EQ-5D Utilities, Comorbid AERD

All Trial Population, Mepolizumab	Value	95% CI	SE	Distribution	Source
Difference from SOC in CFB Week 4	0.069	(0.020, 0.117)	0.025	normal	SYNAPSE
Difference from SOC in CFB Week 8	0.039	(-0.008, 0.085)	0.024	normal	SYNAPSE
Difference from SOC in CFB Week 12	0.040	(-0.015, 0.096)	0.028	normal	SYNAPSE
Difference from SOC in CFB Week 16	0.056	(-0.004, 0.116)	0.031	normal	SYNAPSE
Difference from SOC in CFB Week 20	0.067	(0.001, 0.132)	0.033	normal	SYNAPSE
CFB Week 24 Responder	0.201	(0.134, 0.268)	0.034	normal	SYNAPSE
CFB Week 28 Responder	0.194	(0.129, 0.259)	0.033	normal	SYNAPSE
CFB Week 32 Responder	0.199	(0.128, 0.270)	0.036	normal	SYNAPSE
CFB Week 36 Responder	0.197	(0.126, 0.268)	0.036	normal	SYNAPSE
CFB Week 40 Responder	0.189	(0.113, 0.265)	0.039	normal	SYNAPSE
CFB Week 44 Responder	0.186	(0.112, 0.260)	0.038	normal	SYNAPSE
CFB Week 48 Responder	0.195	(0.122, 0.268)	0.037	normal	SYNAPSE
CFB Week 52+ Responder	0.207	(0.134, 0.280)	0.037	normal	SYNAPSE

AERD – aspirin-associated respiratory disease; CFB – change from baseline; CI – confidence interval; SE – standard error; SOC – standard of care.

Standard of Care EQ-5D Utilities, Eosinophil Count ≥300 cells/µL & Comorbid Asthma

All Trial Population, Standard of Care	Value	95% CI	SE	Distribution	Source
CFB Week 4	0.069	(0.045, 0.093)	0.012	normal	SYNAPSE
CFB Week 8	0.089	(0.064, 0.114)	0.013	normal	SYNAPSE
CFB Week 12	0.097	(0.068, 0.126)	0.015	normal	SYNAPSE
CFB Week 16	0.105	(0.076, 0.134)	0.015	normal	SYNAPSE
CFB Week 20	0.109	(0.080, 0.138)	0.015	normal	SYNAPSE
CFB Week 24 Responder	0.148	(0.107, 0.189)	0.021	normal	SYNAPSE
CFB Week 28 Responder	0.127	(0.084, 0.170)	0.022	normal	SYNAPSE
CFB Week 32 Responder	0.131	(0.082, 0.180)	0.025	normal	SYNAPSE
CFB Week 36 Responder	0.122	(0.077, 0.167)	0.023	normal	SYNAPSE
CFB Week 40 Responder	0.168	(0.119, 0.217)	0.025	normal	SYNAPSE
CFB Week 44 Responder	0.139	(0.080, 0.198)	0.030	normal	SYNAPSE
CFB Week 48 Responder	0.132	(0.083, 0.181)	0.025	normal	SYNAPSE
CFB Week 52+ Responder	0.144	(0.093, 0.195)	0.026	normal	SYNAPSE
CFB Week 24 Non-Responder	0.062	(0.005, 0.119)	0.029	normal	SYNAPSE
CFB Week 28 Non-Responder	0.092	(0.033, 0.151)	0.030	normal	SYNAPSE
CFB Week 32 Non-Responder	0.087	(0.030, 0.144)	0.029	normal	SYNAPSE
CFB Week 36 Non-Responder	0.129	(0.070, 0.188)	0.030	normal	SYNAPSE
CFB Week 40 Non-Responder	0.093	(0.042, 0.144)	0.026	normal	SYNAPSE
CFB Week 44 Non-Responder	0.098	(0.041, 0.155)	0.029	normal	SYNAPSE
CFB Week 48 Non-Responder	0.101	(0.044, 0.158)	0.029	normal	SYNAPSE
CFB Week 52+ Non-Responder	0.049	(-0.016, 0.114)	0.033	normal	SYNAPSE

CFB – change from baseline; CI – confidence interval; SE – standard error.

Mepolizumab EQ-5D Utilities, Eosinophil Count ≥300 cells/µL & Comorbid Asthma

All Trial Population, Mepolizumab	Value	95% CI	SE	Distribution	Source
Difference from SOC in CFB Week 4	0.029	(-0.006, 0.063)	0.018	normal	SYNAPSE
Difference from SOC in CFB Week 8	0.039	(0.003, 0.075)	0.018	normal	SYNAPSE
Difference from SOC in CFB Week 12	0.050	(0.009, 0.091)	0.021	normal	SYNAPSE
Difference from SOC in CFB Week 16	0.049	(0.008, 0.089)	0.021	normal	SYNAPSE
Difference from SOC in CFB Week 20	0.052	(0.009, 0.094)	0.022	normal	SYNAPSE
CFB Week 24 Responder	0.197	(0.156, 0.238)	0.021	normal	SYNAPSE
CFB Week 28 Responder	0.188	(0.147, 0.229)	0.021	normal	SYNAPSE
CFB Week 32 Responder	0.201	(0.158, 0.244)	0.022	normal	SYNAPSE
CFB Week 36 Responder	0.190	(0.145, 0.235)	0.023	normal	SYNAPSE
CFB Week 40 Responder	0.188	(0.141, 0.235)	0.024	normal	SYNAPSE
CFB Week 44 Responder	0.185	(0.140, 0.230)	0.023	normal	SYNAPSE
CFB Week 48 Responder	0.197	(0.152, 0.242)	0.023	normal	SYNAPSE
CFB Week 52+ Responder	0.209	(0.164, 0.254)	0.023	normal	SYNAPSE

CFB – change from baseline; CI – confidence interval; SE – standard error; SOC – standard of care.