

Bilag til direkte indplacering af tezepelumab i Medicinrådets af evidensgennemgang vedrørende lægemidler til svær kronisk rhinosinuitis med næsepolypyper (CRS_wNP)

Vers. 1.0



Bilagsoversigt

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

Konkurrenzsituationen

Tezspire indgår i behandlingsvejledningen for CRSwNP. De øvrige lægemidler der indgår i behandlingsvejledningen er; Dupixent (dupilumab), Exdensus (depemokimab), Nucala (mepolizumab), og Omlyclo (omalizumab). I Medicinrådets opsummering vedr. ligestillede lægemidler til CRSwNP er sammenligningsgrundlag på tre år, hvorfor tabel 2 nedenfor viser lægemiddeludgifter ved en behandlingsperiode på tre år.

Tabel 2: Lægemeddeludgifter pr. patient

Lægemiddel	Styrke (pakning)	Dosering*	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandlingsperiode** (SAIP, DKK)
Tezspire	210 mg (1 stk.)	210 mg hver 4. uge, s.c.	████████	████████
Dupixent	300 mg (2 stk.)	300 mg hver 2. uge, s.c.	████████	████████
Dupixent	300 mg (2 stk.)	300 mg hver 2. uge og dosisreduktion til hver 4. uge efter 24 uger for 90 % af patienterne, s.c.	████████	████████
Exdensur	100 mg (1 stk.)	100 mg hver 6. måned, s.c.	████████	████████
Nucala	100 mg (1 stk.)	100 mg hver 4. uge, s.c.	████████	████████
Omlyclo	150 mg (1 stk.)	300 mg hver 4. uge, s.c.	████████	████████

*Dosering jf. Opsummering af Medicinrådets evidensgennemgang vedrørende lægemidler til svær kronisk rhinosinuitis med næsepolypper (CRSwNP) tabel 3

**Behandlingsperiode på tre år

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Anbefalet	Link til vurdering
Sverige	Ikke ansøgt	
England	Under vurdering	Link til status

Opsummering

Amgros har en eksisterende aftale på Tezspire.



Application for the assessment of Tezspire (tezepelumab) by updating the treatment guideline on Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)



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Table of contents

Application for the assessment of Tezspire (tezepelumab) by updating the treatment guideline on Chronic Rhinosinusitis with Nasal Polyps (CRSwNP).....	1
Contact information	2
Tables and Figures	4
Abbreviations	5
1. Regulatory information on the pharmaceutical	6
2. Summary table	7
3. The patient population, intervention and relevant outcomes.....	8
3.1 The medical condition, patient population, current treatment options and choice of comparator(s)	8
3.2 The intervention	10
3.2.1 The intervention in relation to Danish clinical practice	11
4. Overview of literature	12
5. Clinical question 1.....	15
5.1 Efficacy of tezepelumab compared to dupilumab and mepolizumab for adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery does not provide adequate disease control.....	15
5.1.1 Relevant studies.....	15
5.1.2 Comparability of studies	15
5.1.3 Comparability of patients across studies and with Danish patients eligible for treatment	17
5.2 Comparative analyses of efficacy and safety	21
5.2.1 Efficacy and safety – results per study.....	21
5.2.2 Differences in definitions of outcomes between studies	22
5.2.3 Method of synthesis	22
5.2.4 Results from the comparative analysis	23
6. References.....	26
Appendix A. Main characteristics of studies included	29
Appendix B. Efficacy results per study	40



Appendix C. Comparative analysis of efficacy	43
Appendix D. Literature searches for the clinical assessment	47
D.1 Efficacy and safety of the intervention and comparator(s)	47
D.1.2 Search strategies.....	47
D.1.3 Systematic selection of studies.....	55
D.1.4 Quality assessment	61
D.1.5 Unpublished data.....	61
Appendix E. Additional NMA analysis requested by DMC	62
Rational and objective.....	62
Method.....	62
Results	62
Conclusion	65

Tables and Figures

Table 1 Relevant literature included in the assessment of efficacy and safety	13
Table 2 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety	18
Table 3 Results from the comparative analysis of [intervention] vs. [comparator] for [patient population] – N/A	23
Table 4 Results from the comparative analysis of tezepelumab vs. dupilumab and mepolizumab for adult patients with CRSwNP (NPS)	23
Table 5 Results from the comparative analysis of tezepelumab vs. dupilumab and mepolizumab for adult patients with CRSwNP (SNOT-22).....	24
Table 6 Results from the comparative analysis of tezepelumab vs. dupilumab and mepolizumab for adult patients with CRSwNP (UPSIT).....	25
Table 7 Main characteristic of studies included.....	29
Table 8 Results per study	40
Table 9 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]- NA	43
Table 10 Results from the comparative analysis of tezepelumab, dupilumab and mepolizumab for adult patients with CRSwNP: SNOT-22 NMA League Table at 52 weeks follow-up shown as mean difference (95% credible intervals)	45
Table 11 Results from the comparative analysis of tezepelumab, dupilumab and mepolizumab for adult patients with CRSwNP: NPS NMA League Table at 52 weeks follow-up shown as mean difference (95% credible intervals)	46
Table 12 Bibliographic databases included in the literature search	47
Table 13 Other sources included in the literature search	47
Table 14 Conference material included in the literature search - NA.....	47
Table 15 Search strategy table for OVID platform	48
Table 16 Inclusion and exclusion criteria used for assessment of studies	55
Table 17 Overview of study design for studies included in the technology assessment.....	58



Table 1E Summary of relevant RCTs for NMA <30 weeks 63

Abbreviations

CRSwNP	Chronic Rhinosinusitis with Nasal Polyps
CT	Computer tomography
DMC	Danish Medicine Council
FeNO	Fractional exhaled nitric oxide
FEV1	Forced expiratory volume 1 second
FESS	Functional Endoscopic Sinus Surgery
IgE	Immunoglobulin E
IL-4/IL-13	Interleukin 4/13
LMK	Lund MacKay score
MFNS	Mometasone furoate nasal spray
NCS	Nasal congestion score
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NOS	Nasal obstruction score
NP	Nasal polyp
NPS	Nasal polyp score
NSAID	Nonsteroid antiinflammatory drug
PCR	Polymerase chain reaction
PRESS	Peer Review of Electronic Search Strategies
Q2w	Every 2 weeks
RCT	Randomized controlled trials
SCS	Systemic corticosteroids
SD	Standard deviations
SLR	Systematic literature review
SNOT-22	Sinonasal Outcome Test total score
TSLP	Thymic stromal lymphopoietin
Th2	T helper 2 cells
V1	First on-study visit
UPSIT	University of Pennsylvania Smell Identification Test
VAS	Visual analog scale
SCS	Systemic corticosteroids



1. Regulatory information on the pharmaceutical

Overview of the pharmaceutical

Proprietary name	Tezspire
Generic name	Tezepelumab
Therapeutic indication as defined by EMA	Tezepelumab 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.
Marketing authorization holder in Denmark	AstraZeneca AB, SE 151, 85 Södertälje, Sverige
ATC code	R03DX11
Combination therapy and/or co-medication	Intranasal corticosteroids
(Expected) Date of EC approval	October 20, 2025.
Has the pharmaceutical received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	Tezepelumab is indicated as an add-on maintenance treatment in adults and adolescents 12 years and older with severe asthma who are inadequately controlled despite high dose inhaled corticosteroids plus another medicinal product for maintenance treatment.
Other indications that have been evaluated by the DMC (yes/no)	Tezepelumab is indicated as an add-on maintenance treatment in adults and adolescents 12 years and older with severe asthma who are inadequately controlled despite high dose inhaled corticosteroids plus another medicinal product for maintenance treatment.
Dispensing group	BEGR



Packaging – types, sizes/number of units and concentrations	1 syringe, 210 mg, solution 1 pen, 210 mg, solution
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2. Summary table

Summary

Therapeutic indication relevant for the assessment	Tezepelumab 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 does not provide adequate disease control.
Dosage regimen and administration:	Tezepelumab is administered by subcutaneous injection at a recommended dose of 210 mg every four weeks. No loading dose is required. The product is supplied as a ready-to-use pre-filled pen or syringe (210 mg/1.91 mL solution). Treatment is intended for long-term use, with annual reassessment of ongoing clinical benefits based on disease control.
Choice of comparator	The relevant comparators for tezepelumab in this indication, according to Danish guidelines and current clinical practice, are: • Dupixent (dupilumab) • Nucala (mepolizumab)
Most important efficacy endpoints (Difference/gain compared to comparator)	Key endpoints from the pivotal phase III studies, assessed at week 52 (network meta-analysis including WAYPOINT, SYNAPSE, SINUS-52): Mean change from baseline in total endoscopic nasal polyp score (NPS): • Tezepelumab vs placebo: -2.08 (95% Bayesian credible interval (CrI)): -2.40 to -1.76) • Tezepelumab vs mepolizumab: -1.28 (95% CrI: -1.74 to -0.82) • Tezepelumab vs dupilumab: -0.31 (95% CrI: -0.84 to 0.21) Tezepelumab showed a significantly greater reduction in NPS versus mepolizumab and placebo; efficacy was comparable to dupilumab. Mean change from baseline in sinonasal outcome test total score (SNOT-22): • Tezepelumab vs placebo: -27.44 (95% CrI: -32.51 to -22.37) • Tezepelumab vs mepolizumab: -13.726 (95% CrI: -20.636 to -6.842) • Tezepelumab vs dupilumab: -6.47 (95% CrI: -13.30 to 0.27) Tezepelumab demonstrated significantly greater improvement in SNOT-22 versus mepolizumab and placebo; efficacy was comparable to dupilumab.



Other endpoints: Significant reduction in requirement for systemic corticosteroids and nasal polyp surgery compared with placebo as well as improvements in patient-reported quality of life (i.e. SNOT-22) and symptom scores.

Most important serious adverse events for the intervention and comparator

Tezepelumab

- Serious adverse events in 4.9% of patients in WAYPOINT; similar to placebo (5.9%).
- Most common adverse events: nasopharyngitis, upper respiratory tract infection, headache, epistaxis; serious events were rare and balanced across groups.
- Hypersensitivity reactions are a potential risk but were rare.

Mepolizumab

- Serious adverse events in 6% of patients in SYNAPSE; placebo: 6%.
- Common adverse events: nasopharyngitis, headache, epistaxis, sinusitis.

Dupilumab

- Serious adverse events in 5.4% of patients in SINUS-52 group A; placebo group: 10.0%.
 - Common adverse events: nasopharyngitis, worsening nasal polyps or asthma, headache, epistaxis, injection-site reactions, conjunctivitis.
-

3. The patient population, intervention and relevant outcomes

3.1 The medical condition, patient population, current treatment options and choice of comparator(s)

Medical condition

CRSwNP is a chronic, inflammatory disease of the upper airways characterized by persistent inflammation of the nasal and paranasal sinus mucosa lasting for more than 12 weeks. CRSwNP is distinguished by the formation of benign polyps in the nasal cavity (1) which contribute to symptoms such as nasal obstruction, loss of smell (anosmia), facial pressure or pain, and rhinorrhoea. The aetiology of CRSwNP is multifactorial, involving a combination of genetic predisposition, environmental exposures, and immunological mechanisms, with type 2 (Th2) inflammation being prominent (2). CRSwNP constitutes a specific subtype of chronic rhinosinusitis, exhibiting distinct pathophysiological mechanisms and therapeutic needs compared to chronic rhinosinusitis without nasal polyps (1).



Patient population

This disease most commonly affects adults, with peak incidence between 40 and 60 years of age (3). Prevalence estimates indicate CRSwNP affect approximately 1–4% of the adult population (corresponding to 60,000–240,000 individuals in Denmark) (4). According to the Global Airway Registry per 01.01.2025 approximately 300 patients in Denmark are currently fulfilling the criteria for treatment with biologics and are thereby being treated with biologics for CRSwNP. CRSwNP patients experience significant morbidity, reduced quality of life, and a high rate of recurrence despite existing therapy (2). The disease is often more refractory to treatment compared to chronic rhinosinusitis without nasal polyps (3).

Current treatment options including current guidelines

Initial management consists of maintenance intranasal corticosteroids as first-line therapy, sometimes supplemented with short courses of systematic corticosteroids during exacerbations. For patients with persistent or severe symptoms, functional endoscopic sinus surgery (FESS) is performed. In patients with continued disease activity following surgery and/or systemic corticosteroid treatment, biologic therapies are recommended.

The current treatments options for CRSwNP in Denmark include mepolizumab, dupilumab and omalizumab. According to recommendations from the Danish Medicine Council (DMC) (5), biologic therapy is offered to patients with CRSwNP who have not achieved sufficient disease control following a FESS and/or treatment with systemic corticosteroids.

To be eligible for biologic therapy under DMC guidance, patients must fulfil all the following criteria:

- Presence of bilateral polyps in nose and sinuses
- At least one FESS operation within the last three years
- Evidence of Th2 inflammation
- Minimum three months of optimal local (intranasal steroid) therapy, defined as nasal steroid spray twice daily after nasal rinsing, without sufficient effect

In addition, at least three of following five criteria must be fulfilled:

- Use of systemic corticosteroid: at least two courses per year or low-dose treatment for more than three months
- SNOT-22 ≥ 50
- Loss of smell (Sniffin sticks identification test ≤ 8)
- NPS ≥ 2 in each nostril, minimum total score of five
- Diagnosis of asthma (treated with inhaled corticosteroids)

The efficacy of biologic therapy is evaluated at 16, 24 and 52 weeks after initiation of treatment and at least every six months.

Choice of comparators

In this application, tezepelumab is compared with the currently recommended biologics, mepolizumab and dupilumab, based on the DMC guideline and established Danish clinical practice.



3.2 The intervention

Tezepelumab is a human monoclonal antibody that targets thymic stromal lymphopoietin (TSLP) – an upstream epithelial cytokine with a key role in multiple inflammatory pathways impacted by CRSwNP (6). By inhibiting TSLP, tezepelumab interrupts the initiation of inflammation across a spectrum of immunological phenotypes, including both Th2 and non-Th2 disease. Consequently, tezepelumab works regardless of classic inflammatory biomarkers such as eosinophils or IgE, potentially benefitting patients with mixed or refractory disease profiles.

In the pivotal phase III WAYPOINT trial (7), tezepelumab (210 mg subcutaneously every four weeks) plus standard intranasal corticosteroid therapy demonstrated statistically significant and clinically meaningful improvements in key outcomes for adults with severe CRSwNP, compared to placebo, including:

- Reduction in nasal polyp size
- Significant decrease in nasal congestion severity
- Improvement in quality of life and symptom scores (SNOT-22, total symptom score)
- Reduction in requirement for rescue systemic corticosteroids and nasal polyp surgery

Tezepelumab is administered alongside intranasal corticosteroids, which remain the treatment backbone of CRSwNP management. Other relevant medications may be continued if clinically indicated; systemic corticosteroids can be tapered if symptoms are controlled. Initiation and ongoing use of tezepelumab do not require baseline or ongoing biomarker (eosinophil, IgE, FeNO) measurement – treatment selection and monitoring rely on clinical evaluation and patient-reported outcomes. The use of tezepelumab should be reassessed annually to ensure ongoing clinical benefit.

Routine monitoring is not required. Monitoring for hypersensitivity is recommended, particularly after first dose, but otherwise routine clinical evaluation and symptom assessment are sufficient. No laboratory tests or companion diagnostics are mandated at initiation or follow-up (6).

Tezepelumab is supplied as single-use prefilled syringes or pens (210 mg/1.91 mL) for subcutaneous injection, and multipacks are available as needed (6).

Overview of intervention	
Therapeutic indication relevant for the assessment	Tezepelumab 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.
Method of administration	Tezepelumab is administered as a subcutaneous injection.
Dosing	The recommended dose is 210 mg subcutaneously every four weeks; no loading dose required.
Should the pharmaceutical be administered with other medicines?	Yes. Tezepelumab is added to maintenance intranasal corticosteroids. Patients may continue other standard of care treatments (e.g., antihistamines, asthma therapies) as clinically



indicated. Systemic corticosteroids can be tapered if control is achieved.

Treatment duration / criteria for end of treatment	Intended for long-term use. Continued treatment should be evaluated at least annually based on disease control, patient-reported outcomes, and physician assessment.
Necessary monitoring, both during administration and during the treatment period	No routine laboratory or biomarker monitoring is needed. Patients should be monitored for hypersensitivity reactions following each injection (especially the initial dose), but otherwise regular clinical assessment and symptom monitoring are sufficient.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	No mandatory companion diagnostics or biomarker testing required. Diagnosis and disease severity assessment follow Danish clinical practice (history, endoscopy, imaging if relevant), aligned with criteria used in the WAYPOINT study.
Package size(s)	Supplied in pre-filled single-use pens or syringes, each containing 210 mg in 1.91mL solution.

3.2.1 The intervention in relation to Danish clinical practice

Tezepelumab is expected to be used as an add-on maintenance treatment for adult patients with severe CRSwNP who remain uncontrolled despite standard therapy. In alignment with current in [DMC recommendations for CRSwNP](#) (5), the Danish treatment algorithm (prior to potential adoption of tezepelumab) comprises:

- Initial therapy:
 - Intranasal corticosteroids (first line)
 - Short courses of systemic corticosteroids if needed
- Refractory cases:
 - Repeat systemic corticosteroids and/or functional endoscopic sinus surgery
- Further management:
 - Additional surgery or systemic steroids in patients with persistent symptoms despite above measures

Tezepelumab is positioned for use after failure of systemic corticosteroids and/or surgery, for patients not achieving adequate disease control with these interventions. In practice, tezepelumab will be added to maintenance intranasal corticosteroids, either as an alternative to further systemic corticosteroid courses or for those whose symptoms relapse post-surgery. This patient positioning mirrors the criteria employed in the WAYPOINT trial.

Patient selection for tezepelumab does not depend on diagnostic tests or biomarkers beyond those already established in Danish clinical practice. Initiation is based on:

- Confirmed diagnosis and severity of CRSwNP (assessment via clinical history, symptom severity, endoscopy and/or CT imaging)
- Documentation of inadequate disease control following conventional medical and surgical interventions



No companion diagnostic, biomarker testing (eosinophils, IgE, FeNO), or genetic assays are required to initiate tezepelumab. Tezepelumab can, therefore, be integrated into the existing Danish CRSwNP treatment pathway from DMC, without the need for additional infrastructure, diagnostics, or testing protocols.

4. Overview of literature

A global systematic literature review (SLR) was conducted to identify and critically appraise all relevant published randomized controlled trials (RCTs) of therapies used for the treatment of patients with CRSwNP. The search strategies were developed in accordance with the Peer Review of Electronic Search Strategies (PRESS) checklist (8), as recommended by the National Institute for Health and Care Excellence (NICE). Comprehensive systematic searches were performed in Embase, MEDLINE®, and Evidence-Based Medicine Reviews databases by an information specialist and independently peer-reviewed by a second senior information specialist using the PRESS checklist. Pre-defined PICO (Patient/Population, Intervention, Comparison, and Outcome) criteria were used to identify all published RCTs enrolling adult patients with CRSwNP, published from January 1, 2008, to September 2, 2025. Further detailed information on the SLR is found in Appendix D.

For this submission, the global SLR was locally adapted to be relevant for the current application by requiring that the final studies to be phase III RCTs of the selected comparators (tezepelumab, dupilumab and mepolizumab) suitable for indirect comparison with WAYPOINT. Of 177 unique RCTs identified through the global SLR, four phase III RCTs fulfilled the criteria of relevant comparators: one for tezepelumab (WAYPOINT; NCT04851964 (7)), one for mepolizumab (SYNAPSE; NCT03085797 (9)) and two for dupilumab (SINUS-52; NCT02898454 and SINUS-24; NCT02912468 (10)). Of these, SINUS-52 and SYNAPSE were identified as suitable for comparison at 52 weeks with WAYPOINT, as SINUS-24 had a shorter treatment length (24 weeks). These phase III studies—WAYPOINT, SINUS-52 and SYNAPSE—were deemed methodological comparable to generate robust and reliable estimates of comparative efficacy. High-level information regarding these RCTs, including sample size and study duration, etc. is shown in Table 1.



Table 1 Relevant literature included in the assessment of efficacy and safety

Trial name, NCT identifier and reference	Study design	Study duration	Dates of study	Patient population	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
WAYPOINT NCT04851964 Lipworth et al. 2025 (7)	Randomized, double-blind, placebo-controlled, parallel-group, phase III trial.	52 weeks	Study Start: 2021-04-22 Primary Completion: 2024-09-23 Study Completion: 2024-12-11	Adults with physician-diagnosed, symptomatic, severe CRSwNP	Tezepelumab	Placebo	1	Primary Endpoints: Change from baseline in total endoscopic NPS at week 52 (range, 0 to 8; higher scores indicate greater severity). Change from baseline in mean nasal-congestion score at week 52 (range, 0 to 3; higher scores indicate greater severity), calculated biweekly from the Nasal Polyposis Symptom Diary (NPSD). Secondary Endpoints: Change from baseline in loss-of-smell score at week 52 (NPSD; range, 0 to 3; higher scores indicate greater severity). Change from baseline in SNOT-22 total score at week 52 (22-item SNOT; range, 0 to 110; higher scores indicate greater severity). Change from baseline in Lund–Mackay score at week 52 (sinus CT opacification; range, 0 to 24; higher scores indicate greater severity). Change from baseline in NPSD total symptom score at week 52 (range, 0 to 24; higher scores indicate greater severity). Time-to-event endpoints (Kaplan–Meier and Cox analysis): Time to first decision to treat with nasal-polyp surgery for CRSwNP. Time to first use of systemic glucocorticoids for CRSwNP. Time to first of either surgery or systemic glucocorticoid use (composite endpoint).
SINUS-52 NCT02898454	Randomized, double-blind, placebo-	52 weeks	Study Start: 2016-11-28 Primary Completion:	Patients with bilateral CRSwNP and symptoms	Dupilumab	Placebo	1	Coprimary endpoints: Change from baseline in endoscopic NPS and nasal congestion/obstruction severity (based on monthly average of daily score recorded by patients) at week 24.



Bachert et al 2019 (10)	controlled, parallel-group, phase III trial.		2018-08-27 Study Completion: 2018-11-16	despite intranasal corticosteroid use, receiving systemic corticosteroids in the preceding 2 years, or having had sinonasal surgery				Secondary endpoints: Change from baseline at week 24 in opacification of sinuses measured by LMK score. Change from baseline at week 24 in TSS. Change from baseline at week 24 in the UPSIT score. Change from baseline at week 24 in severity of decreased/loss of smell as assessed by participant daily. Change from baseline at week 24 in the SNOT-22 scores. Change from baseline at week 52 in the NPS. Change from baseline at week 52 in nasal congestion/obstruction symptom severity score. Change from baseline at week 52 in SNOT-22. Rescue treatment use: estimate of percentage of participants with ≥ 1 event by week 52 obtained using the Kaplan-Meier method. Change from baseline at week 24 in FEV1 For participants with asthma.
SYNAPSE; NCT03085797 Han et al 2021 (9)	Randomised, double-blind, placebo-controlled, parallel-group, phase III trial.	52 weeks	Study Start: 2017-15-25 Primary Completion: 2019-12-11 Study Completion: 2019-12-11	Adults with recurrent, refractory, severe, bilateral CRSwNP to standard care and eligible for repeat nasal surgery.	Mepolizumab	Placebo	1	Coprimary endpoints: Change from baseline in total endoscopic NPS at week 52 and change from baseline in mean nasal obstruction visual analogue scale (VAS) score during weeks 49–52 Secondary endpoints: 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.



5. Clinical question 1

5.1 Efficacy of tezepelumab compared to dupilumab and mepolizumab for adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery does not provide adequate disease control

5.1.1 Relevant studies

All relevant studies are summarized in Table 1, with detailed study characteristics provided in Appendix A. Three phase III RCTs were included in the efficacy analysis: one for tezepelumab (WAYPOINT), one for dupilumab (SINUS-52), and one for mepolizumab (SYNAPSE).

5.1.2 Comparability of studies

The validity of network meta-analysis (NMA) results, which are based on summary-level published data, depends on the evidence meeting the exchangeability assumption (11), meaning that the studied interventions could have been included as comparators in a single clinical trial. Failure to meet this assumption can result in biased estimates of comparative effect. As such, a rigorous qualitative assessment of between-trial heterogeneity was conducted based on trial design, patient eligibility criteria, baseline patient characteristics, placebo response, and trial-specific outcome definitions, which builds upon existing recommendations regarding NMAs (12-14). Results of the feasibility assessment are provided in the sections below.

Population:

Across the included studies, the populations were similar with respect to mean age, sex, duration of nasal polyps, Lund–Mackay score, and history of prior oral corticosteroid use. The most notable heterogeneity was related to the proportion of patients with prior sinus surgery:

- SYNAPSE required prior surgery for all patients (100%); in this trial, 48% had ≥ 2 prior surgeries.
- In WAYPOINT, 71% had prior surgery and 35% had ≥ 2 prior surgeries.
- In SINUS-52, 89% had prior surgery and 53% had ≥ 2 prior surgeries.

WAYPOINT, SINUS-52 and SYNAPSE studies have different approaches to how they report the geographical regions where the patients are included from.

WAYPOINT included patients from Europe (55.4%), North America (21.1%), China (15.4%) and Japan (8.1%). In SINUS-52 the included patients are from Asia (49 pts), Latin America (136 pts), East Europe (43 pts) and Western Countries (218 pts). In the SYNAPSE



study the demographic is settled as White and European (91%/92%), East Asian (3%/3%), Black and African American (2%/2%), Arabic and North African (2%/1%), Central and South Asian (1%/1%), South East Asian (1%/1%) and multiple (1%/0%) for the placebo and active treatment arm, respectively.

Statistical considerations:

Some differences existed in the handling of rescue therapy (e.g., inclusion of post-systemic corticosteroid data in SYNAPSE vs. worst-observation-carried-forward in SINUS-52 and WAYPOINT). which may have implications for placebo response and comparative effect size. These methodological differences were considered during the heterogeneity assessment and interpreted accordingly.

The main methodological difference between WAYPOINT, SYNAPSE and SINUS-52 concerns rescue therapy and the approach used for handling patients who received systemic corticosteroid during the trials. In the SYNAPSE study, efficacy data for patients who received systemic corticosteroids during the study period were continued and incorporated into the analysis. In contrast, both the WAYPOINT and the SINUS-52 studies used the worst observation before treatment with systemic corticosteroids which was used for later data collection times.

During the trials, the following number (proportions) of patients received systemic corticosteroids in the three trials: SYNAPSE – 74 (37%) in the placebo arm, 52 (25%) in the mepolizumab arm; SINUS-52 – 88 (31%) in the placebo arm, 41 (9%) in the dupilumab arm; WAYPOINT – 40 (19%) in the placebo arm, 11 (5%) in the tezepelumab arm.

This methodological difference between the SYNAPSE study versus the SINUS-52 and WAYPOINT studies may have implications for placebo response and comparative effect size, as previously noted by the DMC in their assessment of mepolizumab for CRSwNP (15). However, it is not straightforward to interpret the impact across the treatment arms. It should also be considered that, while the short-term effect of SCS is acknowledged, recurrent courses lead to high cumulative doses which increases the risk of long-term adverse events such as osteoporosis, pneumonia, cardiovascular disease, cataracts, sleep apnoea, depression/anxiety and type 2 diabetes.(16-18) Given this, it is beneficial to offer treatment options that avoid the need for long-term SCS use and consequently limit the associated severe long-term adverse events.

Outcomes:

All studies applied the NPS score at 0 to 4 scale per nostril, with a maximum sum of 8 bilaterally, where higher scores indicate worse CRS symptoms. Definitions of NPS were consistent across studies, and baseline mean NPS was ≥ 5 in all studies, enabling for direct comparison. The NMA synthesized mean change from baseline in NPS at week 52.

The SNOT-22 is a 22-item patient-reported questionnaire that can range from 0 to 110 with higher scores indicating worse symptoms (each item can be scored from 0 (no problem at all) to 5 (worst possible symptom)). Definitions for SNOT-22 were consistent across studies and baseline SNOT-22 was comparable across the studies (mean 50.2-68.2). The NMA synthesized mean change from baseline in SNOT-22 at week 52.

**Conclusion:**

Based on assessments of heterogeneity in trial design, eligibility criteria, baseline characteristics, and outcome definitions, the three identified studies were deemed suitable for comparison and sufficiently similar to support reliable estimates of comparative efficacy via NMA.

5.1.3 Comparability of patients across studies and with Danish patients eligible for treatment

The baseline characteristics of patients in the included trials are summarized in Table 2. As noted above, the patients were similar across the studies with certain heterogeneity, e.g. proportions with prior sinus surgery. In comparison with Danish patients, the study populations were similar to patients from a population-based Danish register study in terms of expected age and female/male ratio (i). The WAYPOINT study population is comparable to the Danish patients eligible for treatment according to the recommendation and guideline treatment (5).



Table 2 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	WAYPOINT Study		SYNAPSE Study		SINUS-52 Study	
	Placebo	Tezepelumab	Placebo	Mepolizumab	Placebo	Dupilumab
Age (SD)	49.4 (13.7)	50.1 (13.6)	48.9 (12.5)	48.6 (13.6)	53 (44–61)	51 (42–61)
Sex						
Male	140 (68.3%)	126 (62.1%)	125 (62%)	139 (67%)	95 (62%)	97 (65%)
Female	65 (31.7%)	77 (37.9%)	76 (38%)	67 (33%)	58 (38%)	53 (35%)
Body mass index, kg/m ² (SD)	27.31 (4.62)	26.60 (4.47)	28.2 (5.5)	28.2 (5.3)	27.9 (5.5)	27.9 (5.6)
Race						
White	149 (72.7%)	150 (73.9%)	190 (92%)	183 (91%)	-	-
Asian	51 (24.9%)	46 (22.7%)	9 (4%)	9 (4%)	-	-
Black	3 (1.5%)	3 (1.5%)	5 (2%)	4 (2%)	-	-
Other	2 (1.0%)	4 (2.0%)	2 (1%)	5 (3%)	-	-
Time since diagnosis of nasal polyps, years (SD)	12.80 (10.34)	12.71 (10.43)	11.5 (8.3)	11.4 (8.5)	10.9 (9.4)	11.3 (10.4)
Prior Nasal Polyp Surgery						
0	58 (28.3%)	59 (29.1%)	0 (0%)	0 (0%)	47 (30%)	40 (26%)



≥1	77 (37.6%)	73 (36.0%)	201 (100%)	206 (100%)	88 (58%)	88 (59%)
≥2	70 (34.1%)	71 (35.0%)	120 (60%)	98 (48%)	-	-
≥3	-	-	73 (36%)	51 (25%)	18 (12%)	22 (15%)
≥4	-	-	38 (19%)	24 (12%)	-	-
≥5	-	-	26 (13%)	11 (5%)	-	-
Time since last FESS surgery, years (SD)	7.68 (6.24)	7.71 (6.54)	3.8 (2.7)	4.2 (2.7)	8.8 (7.2)	7.5 (7.0)
Number of treatments with systemic corticosteroids, within the last 12 months						
0	90 (43.9%)	83 (40.9%)	110 (55%)	100 (49%)	-	-
≥1	90 (43.9%)	101 (49.8%)	91 (45%)	106 (51%)	-	-
≥2	25 (12.2%)	19 (9.4%)	45 (23%)	42 (20%)	-	-
Number of treatments with systemic corticosteroids, within the last 24 months	-	-	-	-	122 (80%)	121 (81%)
Total endoscopic score, scale 0–8 (SD)	6.1 (1.3)	6.1 (1.2)	5.6 (1.4)	5.4 (1.2)	6.9 (1.2)	6.1 (1.2)
Nasal obstruction VAS score, scale 0–10 (SD)	-	-	9.0 (0.8)	8.9 (0.8)	8.2 (0.8)	8.2 (0.8)
Symptom VAS score, scale 0–10 (SD)	-	-	9.1 (0.7)	9.0 (0.8)	8.9 (0.6)	8.9 (0.7)
Loss of smell, VAS score, scale 0–10 (SD)	-	-	9.7 (0.6)	9.6 (0.6)	9.6 (0.6)	9.6 (0.7)



UPSIT score (SD)	11.9 (5.9)	13.1 (7.3)	13.4 (7.45)*	13,0 (6.81) *	13.8 (13.3)	13.1 (13.1)
SNOT-22 total score (SD)	69.2 (18.4)	68.2 (18.4)	64.4 (19.0)	63.7 (17.6)	53.5 (21.9)	50.2 (19.7)
Asthma	126 (61.5%)	122 (60.1%)	149 (74%)	146 (71%)	59 (59%)	61 (62%)
Patients with NSAID/acetylcysteine intolerance	37 (18%)	34 (16.7%)	63 (31%)	45 (22%)	44 (29%)	35 (23%)
Blood eosinophil granulocytes, cells per μL	359 $\pm$ 248	357 $\pm$ 229	400 (0.9)	390 (0.9)	-	-

*In SYNAPSE, UPSIT was assessed in a subset in three countries (Canada, the UK, and the USA), n = 54 per treatment arm.



5.2 Comparative analyses of efficacy and safety

5.2.1 Efficacy and safety – results per study

Key efficacy and safety findings for the three studies included in the comparative analysis are summarized below, with full details provided in Appendix B.

Key efficacy outcomes

The key efficacy outcomes, consistent with the endpoints recommended in the treatment guidelines (5), were defined as change from baseline in NPS and SNOT-22 at week 52.

NPS

For tezepelumab, data from the WAYPOINT study showed that after 52 weeks of treatment, the least-squares mean change (SE) from baseline in NPS was -2.46 (0.11) in the tezepelumab group and -0.38 (0.12) for the placebo group, a statistically significant difference of -2.08 (95% CI -2.40 to -1.76 ; $p < 0.001$) in favour of tezepelumab (7).

For mepolizumab, data from the SYNAPSE study showed that after 52 weeks of treatment, the mean (SD) change from baseline was -0.9 (1.90) in the mepolizumab group and -0.1 (1.46) for the placebo group (9). The estimated absolute difference in effect is -0.8 (95% CI -1.13 to -0.47 ; $p < 0.001$), as reported in the application to DMC for mepolizumab in CRSwNP ((15), table 65).

For dupilumab, data from SINUS-52 showed that after 52 weeks of treatment, the least-squares mean change (SE) from baseline in NPS was -2.24 (0.15) in the dupilumab group and 0.15 (0.15) for the placebo group, a statistically significant difference of -2.40 (95% CI -2.77 to -2.02 ; $p < 0.001$) in favour of dupilumab (10).

SNOT-22

For tezepelumab, data from the WAYPOINT study showed that after 52 weeks of treatment, the least-squares mean change (SE) from baseline in SNOT-22 was -45.02 (1.81) in the tezepelumab group and -17.58 (1.84) for the placebo group, a statistically significant difference of -27.44 (95% CI -35.51 to -22.37 ; $p < 0.001$) in favour of tezepelumab (7).

For mepolizumab, data from the SYNAPSE study showed that after 52 weeks of treatment, the mean change (SD) from baseline in SNOT-22 was -29.4 (25.67) in the mepolizumab group and -15.7 (23.93) for the placebo group. The estimated absolute difference in effect is -13.7 (95% CI -18.42 to -8.98 ; $p < 0.001$), as reported in the application to DMC for mepolizumab in CRSwNP ((15), table 65).

For dupilumab, data from SINUS-52 showed that after 52 weeks of treatment, the least-squares mean change (SE) from baseline in SNOT-22 was -29.84 (1.63) in the dupilumab group and -8.88 (1.61) for the placebo group, a statistically significant difference of -20.96 (95% CI -25.03 to -16.89 ; $p < 0.001$) in favour of dupilumab (10).



Safety data

In the WAYPOINT study, adverse events occurred in 78.3% of patients in the tezepelumab group (159 of 203 patients) and 77.1% of those in the placebo group (158 of 205 patients). The most frequently reported adverse events were coronavirus disease (covid-19), nasopharyngitis, upper respiratory tract infection, headache, epistaxis, and worsening of CRSwNP (which was observed more frequently in the placebo group than the tezepelumab group [22.9% vs. 5.4%]). Serious adverse events occurred in 10 patients (4.9%) in the tezepelumab group and 12 patients (5.9%) in the placebo group (7).

In the SYNAPSE study, 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). The most frequently reported adverse events were nasopharyngitis, headache, epistaxis, and sinusitis. On-treatment serious adverse events occurred in 12 (6%) patients receiving mepolizumab and 13 (6%) receiving placebo (9).

In the SINUS-52 study, adverse events occurred in 83.2% of patients in the dupilumab 300 mg q2w group (124 of 149 patients) and 90.7% of those in the placebo group (136 of 150 patients). The most common adverse events were nasopharyngitis, worsening of nasal polyps and asthma, headache, epistaxis, and injection-site erythema. Serious adverse events occurred in eight patients (5.4%) in the dupilumab 300 mg q2w group and 15 patients (10.0%) in the placebo group (10).

5.2.2 Differences in definitions of outcomes between studies

The key efficacy outcomes (NPS and SNOT-22) were defined in the same way across the three studies and measured as mean change from baseline at week 52.

5.2.3 Method of synthesis

To derive comparisons of tezepelumab with several relevant therapies simultaneously, NMAs were performed. NMA is a widely used approach to derive comparisons of treatment effects between interventions that may not have been compared directly in clinical trials, or for which both direct and indirect evidence is available for synthesis. NMA methodology uses summary or aggregate data from published studies and has been used broadly in recent years by health technology assessment agencies worldwide, including Canada's Drug Agency (CDA-AMC), NICE, and EUnetHTA in the context of evaluating therapies for indications where multiple active comparators exist.

Bayesian NMAs were conducted using fixed-effect models. A detailed description of the methodology is found in Appendix C.

NMAs were performed to compare tezepelumab with dupilumab and mepolizumab respectively for the treatment of CRSwNP for the following outcomes at week 52:

- Mean change from baseline in NPS – continuous
- Mean change from baseline in SNOT-22 – continuous

The network of the identified studies consisted of 1,263 patients (WAYPOINT, SINUS-52, SYNAPSE).



5.2.4 Results from the comparative analysis

Table 3 Results from the comparative analysis of [intervention] vs. [comparator] for [patient population] – N/A

Outcome measure	[Intervention] (N=x)	[Comparator] (N=x)	Result
[Outcome measure 1], time point	N/A	N/A	N/A
[Outcome measure 2], time point	N/A	N/A	N/A
[Outcome measure 3], time point	N/A	N/A	N/A

NPS

The NMA results demonstrate that tezepelumab showed significantly lower NPS than mepolizumab and placebo. Tezepelumab was not statistically different from dupilumab for NPS. A league table summarizing all pairwise comparisons between treatments in terms of mean differences and Bayesian 95% credible intervals is presented in Table 4, per standard practice of reporting results from NMA (19-21). League tables are recognized by methodological guidelines (such as NICE guidelines (22)) as a standard method to summarize pairwise comparisons in NMA.

Table 4 Results from the comparative analysis of tezepelumab vs. dupilumab and mepolizumab for adult patients with CRSwNP (NPS)

Dupilumab			
-0.311 (-0.835 to -0.214)	Tezepelumab		
-1.586* (-2.115 to -1.056)	-1.277* (-1.737 to -0.817)	Mepolizumab	
-2.390* (-2.801 to -1.971)	-2.077* (-2.400 to -1.755)	-0.801* (-1.129 to -0.473)	Placebo

Note: Pairwise comparisons are shown in terms of mean differences and Bayesian 95% credible intervals; each value reflects a comparison between treatments belonging to the intersecting column and row, with additional benefit indicated for the treatment in the column. * = Statistically significant results

SNOT-22

The primary NMA results demonstrate that tezepelumab showed significantly lower SNOT-22 scores than mepolizumab and placebo. Tezepelumab was positioned as the most favourable treatment, though not statistically different from dupilumab. A league table summarizing all pairwise comparisons between treatments in terms of mean differences and Bayesian 95% credible intervals is presented in Table 5, per standard practice of



reporting results from NMA (19-21). League tables are recognized by methodological guidelines (such as NICE guidelines(22)) as a standard method to summarize pairwise comparisons in NMA.

Table 5 Results from the comparative analysis of tezepelumab vs. dupilumab and mepolizumab for adult patients with CRSwNP (SNOT-22)

Tezepelumab			
-6.474 (-13.297 to 0.265)	Dupilumab		
-13.726* (-20.636 to -6.842)	-7.264* (-13.722 to -0.741)	Mepolizumab	
-27.420* (-32.514 to -22.358)	-20.940* (-25.441 to -16.424)	-13.680* (-18.349 to -8.997)	Placebo

Note: Pairwise comparisons are shown in terms of mean differences and Bayesian 95% credible intervals; each value reflects a comparison between treatments belonging to the intersecting column and row, with additional benefit indicated for the treatment in the column. * = Statistically significant results

Other results from the NMA

The focus in this application has been on the main endpoints NPS and SNOT-22, consistent with the endpoints recommended in the treatment guidelines (5). Additional endpoints from the performed NMA across the three comparators were the following: University of Pennsylvania Smell Identification Test (UPSIT), proportion of systemic corticosteroids use, as well as proportion of ESS (Endoscopic Sinus Surgery), time to first ESS and time to ESS decision.

Across these endpoints, tezepelumab had statistically significant better results than mepolizumab. For the proportion of ESS and time to first ESS endpoint, tezepelumab was significantly favoured over dupilumab and was comparable to dupilumab for the other endpoints.

As requested by the DMC, the results of the NMA for the UPSIT outcome is found below.

UPSIT

The NMA results demonstrate that tezepelumab showed significantly higher UPSIT scores than mepolizumab and placebo. Tezepelumab was not statistically different from dupilumab for UPSIT. A league table summarizing all pairwise comparisons between treatments in terms of mean differences and Bayesian 95% credible intervals is presented in Table 6, per standard practice of reporting results from NMA (19-21). League tables are recognized by methodological guidelines (such as NICE guidelines (22)) as a standard method to summarize pairwise comparisons in NMA.



Table 6 Results from the comparative analysis of tezepelumab vs. dupilumab and mepolizumab for adult patients with CRSwNP (UPSIT)

Dupilumab			
1.009 (-1.629 to 3.621)	Tezepelumab		
9.187* (4.993 to 13.400)	8.190* (4.148 to 12.229)	Mepolizumab	
10.502* (8.477 to 12.548)	9.493* (7.865 to 11.160)	1.308 (-2.355 to 5.002)	Placebo

Note: Pairwise comparisons are shown in terms of mean differences and Bayesian 95% credible intervals; each value reflects a comparison between treatments belonging to the intersecting column and row, with additional benefit indicated for the treatment in the column. * = Statistically significant results

Conclusion

Based on evidence from the WAYPOINT trial and robust comparative analyses, tezepelumab demonstrates statistically significant and clinically meaningful benefits as an add-on maintenance therapy for adult patients with CRSwNP inadequately controlled by systemic corticosteroids and/or surgery.

The NMA indicate that tezepelumab provides a significantly greater reduction in NPS and improvements in SNOT-22, compared to both placebo and mepolizumab, and offers efficacy comparable to dupilumab for these measures. Furthermore, tezepelumab is associated with significant reductions in the requirement for systemic corticosteroids and further sinus surgery, underscoring its impact on reducing disease burden and healthcare utilization.

The safety profile of tezepelumab is favourable and comparable to that of currently available biologics, with serious adverse events occurring at similar or lower rates to both comparator biologics and placebo arms in clinical studies. The most common adverse events—such as nasopharyngitis, headache, and upper respiratory tract infection—were generally mild or moderate, and hypersensitivity reactions were rare. Tezepelumab requires no routine laboratory or biomarker monitoring for selection or follow-up, facilitating straightforward integration into current Danish clinical practice and existing DMC patient selection criteria.

In conclusion, tezepelumab represents a beneficial therapeutic addition for the management of CRSwNP, addressing an unmet need in patients with persistent disease despite conventional medical and surgical interventions. Based on the results from the comparative analysis presented in this application, it is justified that tezepelumab should be included in the DMC treatment guidelines on CRSwNP.



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Appendix A. Main characteristics of studies included

Table 7 Main characteristic of studies included

Trial name:	NCT number:
WAYPOINT	NCT04851964
Objective	Evaluate the efficacy and safety of tezepelumab in adults with severe, uncontrolled CRSwNP.
Publications – title, author, journal, year	Tezepelumab in Adults with Severe CRSwNP. Lipworth et al, New England Journal of Medicine, 2025.
Study type and design	Double-blind, randomized, placebo-controlled phase III study. Adults with severe, uncontrolled CRSwNP were randomly assigned in a 1:1 ratio to received either tezepelumab 210 mg or placebo, administered subcutaneously every 4 weeks for 52 weeks, alongside standard care. Randomization was stratified by geographic region, history of previous nasal-polyp surgery, and coexisting asthma or NSAID-exacerbated respiratory disease. No crossover was permitted. Treatment assignment was masked for investigators, patients, and the sponsor throughout the study period.
Sample size (n)	408 were included in the efficacy and safety end-point analyses — 203 patients who received tezepelumab and 205 who received placebo
Main inclusion criteria	From clinicaltrials.gov: 1. Participants with physician-diagnosed CRSwNP for at least 12 months prior to Visit 1 that have: 1. Severity consistent with need for surgery as defined by total NPS ≥ 5 (≥ 2 for each nostril) at screening, as determined by the central reader 2. Nasal Congestion Score (NCS) ≥ 2 at Visit 1 3. Ongoing documented NP symptoms over > 8 weeks prior to screening such as rhinorrhoea and/or reduction/loss of smell 2. SNOT-22 total score ≥ 30 at screening (Visit 1) 3. Any standard of care for treatment of CRSwNP provided the participant is stable on that treatment for 30 days prior to Visit 1 4. Documented treatment of nasal polyposis exacerbation with SCS for at least 3 consecutive days or one IM depo-injectable dose (or contraindications/intolerance to) within the past 12 months prior to Visit 1 but not within the last 3 months prior to Visit 1 and/or any history of NP surgery (or contraindications/intolerance to)



Main exclusion criteria	From clinicaltrials.gov: 1. Any clinically important comorbidities other than asthma (e.g. active lung infection, bronchiectasis, pulmonary fibrosis, cystic fibrosis, primary ciliary dyskinesia, allergic bronchopulmonary mycosis, hyper eosinophilic syndromes, etc.) that could confound interpretation of clinical efficacy results. 2. Sinus surgery within 6 months of screening visit OR any sinus surgery in the past which changed the lateral wall of the nose making NPS evaluation impossible. 3. Positive COVID-19 PCR test (or COVID-19 rapid test) or COVID-19 entry screening questionnaire during the screening visit. Evaluation will be based on local SoC as determined by current local guidelines. 4. Regular use of decongestants (topical or systematic) at enrolment is not allowed unless used for endoscopic procedure. 5. Use of immunosuppressive medication (including but not limited to methotrexate, troleandomycin, cyclosporine, azathioprine, mycophenolate, tacrolimus, gold, penicillamine, sulfasalazine, hydroxychloroquine, systemic corticosteroids or any experimental anti-inflammatory therapy) within 3 months prior to Visit 1 and during the study period. Systemic corticosteroid use is defined as treatment with a burst of systemic corticosteroids for at least 3 consecutive days or a single IM depo-injectable dose of corticosteroids (considered equivalent to a 3-day burst of systemic corticosteroids). 6. Receipt of COVID-19 vaccine (regardless of vaccine delivery platform) 28 days prior to date of IP administration at Visit 3 (randomization visit).
Intervention	The intervention was tezepelumab, a human monoclonal antibody that blocks TSLP. It was administered at a dose of 210 mg subcutaneously every 4 weeks for a total of 52 weeks, alongside SoC treatment with intranasal glucocorticoids. A total of 203 patients received the tezepelumab intervention in the WAYPOINT study.
Comparator(s)	The comparator was placebo, administered subcutaneously every 4 weeks for 52 weeks along with standard-care treatment (intranasal glucocorticoids). A total of 205 patients received the placebo comparator in the WAYPOINT study.
Follow-up time	The follow-up time in the WAYPOINT study consisted of a 52-week treatment period, after which patients who completed the treatment entered a post-treatment follow-up period of either 12 weeks or 24 weeks to assess durability of effect and safety.
Primary, secondary and exploratory endpoints	Co-Primary Endpoints



- **Change from baseline in total endoscopic NPS** at week 52 (range, 0 to 8; higher scores indicate greater severity).
- **Change from baseline in mean NCS** at week 52 (range, 0 to 3; higher scores indicate greater severity), calculated biweekly from the NPSD.

Key Secondary Endpoints

Key secondary endpoints, assessed in the overall study population:

- **Change from baseline in loss-of-smell score** at week 52 (NPSD; range, 0 to 3; higher scores indicate greater severity).
- **Change from baseline in SNOT-22 total score** at week 52 (22-item SNOT; range, 0 to 110; higher scores indicate greater severity).
- **Change from baseline in Lund–Mackay score** at week 52 (sinus CT opacification; range, 0 to 24; higher scores indicate greater severity).
- **Change from baseline in NPSD total symptom score** at week 52 (range, 0 to 24; higher scores indicate greater severity).
- **Time-to-event endpoints (Kaplan–Meier and Cox analysis):**
 - Time to first decision to treat with nasal-polyp surgery for CRSwNP.
 - Time to first use of systemic glucocorticoids for CRSwNP.
 - Time to first of either surgery or systemic glucocorticoid use (composite endpoint).
- **For the subset of patients with comorbid asthma:**
 - Change from baseline in prebronchodilator forced expiratory volume in 1 second (FEV1) at week 52.
 - Change from baseline in Asthma Control Questionnaire-6 (ACQ-6) score at week 52.
- **Change from baseline in University of Pennsylvania Smell Identification Test (UPSIT) score** at week 52 (in all patients; range, 0 to 40; lower scores indicate greater severity).

Method of analysis

Efficacy analyses were performed on data from all the patients who had received at least one dose of tezepelumab or placebo. Both coprimary efficacy end points were analysed with the use of a covariance model with the baseline value as a covariate and trial group, baseline coexisting asthma status, status regarding previous nasal-polyp surgery, and geographic region as factors. Data obtained after nasal-polyp surgery were replaced with the worst possible score. Data after treatment with systemic glucocorticoids were replaced with the worst observation before the rescue treatment. Data after treatment discontinuation without rescue treatment were included in the analysis. Multiple imputation was used to handle data that were assumed to be missing at random.

Subgroup analyses

NA



Other relevant information N/A

Trial name:

LIBERTY SINUS-52

NCT number:

NCT02898454

Objective

Assess the efficacy and safety of dupilumab (IL-4/IL-13 pathway inhibitor) added to intranasal corticosteroids in adults with severe, uncontrolled CRSwNP, including those with prior systemic corticosteroid use and/or prior sinus surgery, and with or without comorbid asthma or NSAID-exacerbated respiratory disease.

Publications – title, author, journal, year

Efficacy and safety of dupilumab in patients with severe CRSwNP (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase III trials.

Bachert et al; The Lancet, 2019;394: 1638-50.

Study type and design

Phase 3, multinational, multicentre, randomised, double blind, placebo-controlled, parallel-group studies assessing the efficacy and safety of dupilumab in patients with severe uncontrolled CRSwNP.

The trials consisted of a 4-week run-in period, a treatment period (24 weeks in SINUS-24 and 52 weeks in SINUS-52).

In SINUS-52, patients were randomly assigned (1:1:1) to dupilumab 300 mg every 2 weeks for 52 weeks (group A), the same schedule for the first 24 weeks followed by dupilumab 300 mg every 4 weeks (group B), or placebo (group C).

Sample size (n)

276 randomized patients in SINUS-24.

448 randomized patients in SINUS-52.

In total 724 patients in the overall population.

Main inclusion criteria

From clinicaltrials.gov:

- Participants with bilateral sino-nasal polyposis that despite prior treatment with SCS anytime within the past two years; and/or had a medical contraindication/intolerance to SCS; and/or had prior surgery for NP at the screening visit, had:
- An endoscopic bilateral NPS at Visit 1 (V1) of at least five out of a maximum score of eight (with a minimum score of two in each nasal cavity).
- Ongoing symptoms (for at least eight weeks before V1) of NC/blockage/obstruction with moderate or severe symptom severity (score 2 or 3) at V1 and a weekly average severity of greater than 1 at time of randomization (V2), and another symptom such as loss of smell, rhinorrhoea (anterior/posterior).
- Signed written informed consent.



Main exclusion criteria

From clinicaltrials.gov:

- Participants <18 years of age.
- Participant who had been previously treated in dupilumab studies.
- Participant who had taken:
 - Biologic therapy/ systemic immunosuppressant to treat inflammatory disease or autoimmune disease (e.g., rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis, etc.) within two months before V1 or five half-lives, whichever was longer.
 - Any experimental monoclonal antibody within five half-lives or within six months before V1 if the half-life was unknown.
 - Anti-immunoglobulin E therapy (omalizumab) within 130 days prior to V1.
 - Participants who received leukotriene antagonists/modifiers at V1 unless they were on a continuous treatment for at least 30 days prior to V1.
- Initiation of allergen immunotherapy within three months prior to V1 or a plan to begin therapy or change its dose during the run-in period or the randomized treatment period.
- Participants who underwent any and/or sinus surgery (including polypectomy) within six months before V1.
- Participants who had a sino-nasal or sinus surgery changing the lateral wall structure of the nose making impossible the evaluation of NPS.
- Participants with conditions/concomitant diseases making them non evaluable at V1 or for the primary efficacy endpoint

Intervention

- Dupilumab 300 mg subcutaneous:
 - SINUS-52 Group A: every two weeks for 52 weeks (n= 150 patients)
 - SINUS-52 Group B: every two weeks for 24 weeks then every four weeks until week 52 (n= 145 patients)
- All arms continued daily mometasone furoate nasal spray (MFNS) background therapy

Comparator(s)

Placebo subcutaneous every two weeks for 52 weeks (SINUS-52), with MFNS background therapy, n= 153 patients.

Follow-up time

Up to 68 weeks (4 weeks run-in + 52 weeks treatment + 12 weeks follow-up).

Primary, secondary and exploratory endpoints

Co-Primary endpoints (assessed at week 24)

- Change from baseline in endoscopic bilateral NPS
- Change from baseline in NCS/NOS

Secondary endpoints

- Change from baseline at week 42 in opacification of sinuses measured by LMK score
- Change from baseline at week 24 in TSS



- Change from baseline at week 24 in the UPSIT score
- Change from baseline at week 24 in severity of decreased/loss of smell
- Change from baseline at week 52 in NPS
- Change from baseline at week 52 in NCS/NOS
- Change from baseline at week 52 in SNOT-22
- Rescue treatment use
- Change from baseline at week 24 in FEV1 for participants with asthma.

Method of analysis	Efficacy analyses were done in the intention-to-treat population, defined as all patients who were randomly assigned. Primary and key secondary endpoints were prospectively defined, multiplicity-adjusted, and analysed using a hybrid of the worst observation carried forward, followed by an ANCOVA model with the baseline value of the corresponding endpoint, treatment, asthma or NSAID-exacerbated respiratory disease status, surgery history and study region as co-variables. Statistical inference, including the least squares means obtained from all 40 imputed data were combined by use of Rubins rule. For patients who underwent nasal polyps surgery or received systemic corticosteroids for any reason, data collected post-surgery (actual date) or post-systemic corticosteroid treatment were set to missing in the WOCF-multiple imputation approach, and the worst post-baseline value on or before the time of surgery or systemic corticosteroid treatment was used to impute missing week 24 or 52 values (depending on the study; baseline values were used for patients whose post-baseline values were all missing). For patients who discontinued treatment without rescue by surgery or systemic corticosteroids, we used a multiple imputation approach to impute missing values, using all patients who had not been rescued by surgery or were not receiving systemic corticosteroids.
Subgroup analyses	N/A
Other relevant information	N/A

Trial name:	NCT number:
SYNAPSE	NCT03085797
Objective	To assess the efficacy and safety of mepolizumab in adults with recurrent, refractory, severe, bilateral CRSwNP who were eligible for repeat surgery.
Publications – title, author, journal, year	Mepolizumab for CRSwNP (SYNAPSE): a randomized, double-blind, placebo-controlled, phase III trial. Han KH et al; Lancet Respiratory Medicine, October 2021
Study type and design	SYNAPSE was a randomised, double-blind, parallel group phase III study.



Han JK et al, Lancet Repir Med, 2021.

Sample size (n)	Population: 407 patients were included in the ITT population. This population was divided into: • 206 patients who received mepolizumab. • 201 patients who received placebo.
Main inclusion criteria	From clinicaltrials.gov: • 18 years of age and older inclusive, at the time of signing the informed consent. • Body weight greater or equal to 40 kilograms (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 ten years for the removal of 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 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: 1. Participants with an overall VAS symptom score >7, 2. Participants with an endoscopic bilateral NP score of at least five out of a maximum score of eight (with a minimum score of two in each nasal cavity). • Treatment with intranasal corticosteroids (INCS) for at least eight weeks prior to screening. • Capable of giving signed informed consent
Main exclusion criteria	From cliricaltrials.gov: • 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 (URTI) at screening or in two weeks prior to screening
- Ongoing rhinitis medicamentosa (rebound or chemical induced rhinitis)
- Participants who have had an asthma exacerbation requiring admission to hospital within four weeks of Screening.
- Participants who have undergone any intranasal and/or sinus surgery (for example polypectomy, balloon dilatation or nasal stent insertion) within six months prior V1.
- 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 six months prior to V1.
- Participants who are currently receiving or have received within three months (or five 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 four weeks prior to screening or planned use of such medications during the double-blind period.
- INCS dose changes within one month prior to screening.
- Treatments with biological or immunosuppressive treatment (other than omalizumab) treatment within five terminal phase half-lives of V1.
- Omalizumab treatment in the 130 days prior to V1.
- Commencement of leukotriene antagonist treatment less than 30 days prior to V1.
- Allergen immunotherapy within the previous three 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 six 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, haematological or any other system abnormalities that are uncontrolled with standard treatment.
- Immunocompromised, other than that explained using 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 (except for 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 V1.
- A known or suspected history of alcohol or drug abuse within two years prior to screening (V1) 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	Patients received 100 mg mepolizumab subcutaneously once every four weeks, in addition to standard of care for 52 weeks. 206 patients received mepolizumab.
Comparator(s)	Patients received subcutaneously placebo once every four weeks, in addition to standard of care for 52 weeks. 201 patients received placebo.
Follow-up time	The follow-up time for the study was primarily 52 weeks for the main treatment period and assessment of primary and most secondary endpoints. A subset of patients had an extended follow-up: The study was designed to follow up to the first 200 randomly assigned patients for six months after stopping treatment. For these specific patients, the follow-up extended to approximately 76 weeks (52 weeks of treatment + 24 weeks of post-treatment follow-up).
Primary, secondary and exploratory endpoints	Coprimary Endpoints • Change from baseline in total endoscopic NPS at week 52.



- Change from baseline in mean NOS measured using VAS during weeks 49–52.

Secondary Endpoints

- Time-to-first nasal surgery until week 52.
- Change from baseline in mean overall symptom VAS 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.

Exploratory Endpoints

- Proportion of patients with a decrease of one or more points from baseline in nasal polyps score at week 52 in the absence of surgery.
- Number of courses of systemic corticosteroids up to week 52.
- Antibiotics up to week 52.
- Proportion of patients with a decrease of 8.9 points or more from baseline in SNOT-22 total score in the absence of surgery.
- 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 University of Pennsylvania Smell Identification Test (UPSIT) (maximum score 40).
- On-treatment blood eosinophil count.
- Additional pre-specified analyses (outside of the original analysis plan):
 - Change from baseline in loss of smell VAS score by the number of previous surgeries (one, two, or more than two) at weeks 49–52.
 - Peak nasal inspiratory flow at week 52.
- Post-hoc analyses:
 - Exacerbation rates in patients with comorbid asthma.
 - Asthma Control Questionnaire-5 scores at week 52 in patients with comorbid asthma.

Method of analysis

The study was designed to continue to collect data for patients who prematurely discontinued treatment; all data reported up to week 52 were included in the analysis, regardless of treatment discontinuation. Occurrence of nasal surgery at any time following randomization was an anticipated intercurrent event (ie, expected to affect evaluation of subsequent scores) for the coprimary and symptom and health-related quality of life-based secondary endpoints. Patients who underwent nasal



surgery before week 52 were assigned their worst observed score, recorded before the surgery, for all subsequent visits. Patients who withdrew early from the study without having undergone nasal surgery or who had missing data for any other reason were assigned their worst observed score, recorded before study withdrawal or the missing visit. Use of systemic corticosteroids during the treatment period was considered part of standard of care; therefore, observed scores following systemic corticosteroids use were included in the analyses.

For coprimary endpoints, VAS scores, SNOT-22 score, peak nasal inspiratory flow, and UPSIT, 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 (country for UPSIT analysis), baseline score, and $\log_e$ baseline blood eosinophil count were presented as a difference in medians between treatment groups based on a quantile regression model using the bootstrap approach with 1 000 000 replicates.

For the post-hoc analysis of the coprimary endpoints to show differences in means (as opposed to medians), the analysis was conducted with a mixed model for repeated measures with estimates of the treatment effect; covariates of treatment group, geographic region, baseline score and $\log_e$ baseline blood eosinophil count, visit/time period, interaction terms for visit/time period by baseline and visit/time period by treatment. Estimates based on weighting applied to each level of class variable from observed proportions. Missing data imputed as though patients continued to receive their randomised treatment. Imputations made stepwise by visit/time period and conditioned on data from previous visits/time periods with the same covariates used in the analysis model. Estimates combined using Rubin's rule based on 2000 imputations. In this analysis, patients with nasal surgery prior to the visit/time period were assigned the worst possible score.

Subgroup analyses	N/A
Other relevant information	N/A



Appendix B. Efficacy results per study

Table 8 Results per study

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	
Outcome	Study arm	n	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value		
WAYPOINT study			Least-squares mean change from baseline (SE); (95% CI)								
Change from baseline in total endoscopic NPS at week 52	Tezepelumab	203	−2.46 (0.11); (−2.68, −2.24)	−2.08	(−2.40, −1.76)	p<0.001	N/A	N/A	N/A	ANCOVA model, full analysis set, multiple imputation for missing data	
	Placebo	205	−0.38 (0.12); (−0.62, −0.14)								
Change from baseline in SNOT-22 score at week 52	Tezepelumab	203	−45.02 (1.81); (−48.57, −41.47)	−27.44	(−32.51, −22.37)	p<0.001	N/A	N/A	N/A	ANCOVA model, full analysis set, multiple imputation for missing data	
	Placebo	205	−17.58 (1.84); (−21.19, −13.97)								
SYNAPSE study			Mean change from baseline (SE); (95% CI)								
Change from baseline in total	Mepolizumab	206	−0.9; (−1.16, −0.64)	−0.8	(−1.13, −0.47)	p<0.001	N/A	N/A	N/A	Mixed model repeated measures,	



Outcome	Study arm	n	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
				Difference	95% CI	P value	Difference	95% CI	P value	
endoscopic NPS at week 52	Placebo	201	−0.1(−0.30, 0.10)							intention-to-treat, multiple imputation for missing data
Change from baseline in SNOT-22 score at week 52	Mepolizumab	206	−29.4 (24.67); (−32.77, −26.03)	−13.7	(−18.42, −8.98)	p<0.001	N/A	N/A	N/A	Quantile regression, intention-to-treat, multiple imputation for missing data
	Placebo	201	−15.7 (23.93); (−19.01, −12.39)							
SINUS-52 study			Least-squares mean change from baseline (SE); (95% CI)							
Change from baseline in total endoscopic NPS at week 52	Dupilumab, q2w	150	−2.24 (0.15); (−2.53, −1.95)	−2.40	(−2.77, −2.02)	p<0.001	N/A	N/A	N/A	ANCOVA model, intention-to-treat, hybrid of the worst observation carried forward (WOCF) and multiple imputation methods
	Placebo	153	0.15 (0.15); (−0.14, 0.44)							



Outcome	Study arm	n	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
				Difference	95% CI	P value	Difference	95% CI	P value	
Change from baseline in SNOT-22 score at week 52	Dupilumab, q2w	150	−29.84 (1.63); (−33.03; −26.65)	−20.96	(−25.03, −16.89)	p<0.001	N/A	N/A	N/A	ANCOVA model, intention-to-treat, hybrid of the worst observation carried forward (WOCF) and multiple imputation methods
	Placebo	153	−8.88 (1.61); (−12.04, −5.72)							



Appendix C. Comparative analysis of efficacy

Table 9 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]- NA

Outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
		Difference	CI	P value	Difference	CI	P value		
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A



To derive comparisons of tezepelumab with several relevant therapies simultaneously, NMAs were performed. NMA is a widely used approach to derive comparisons of treatment effects between interventions that may not have been compared directly in clinical trials, or for which both direct and indirect evidence is available for synthesis. NMA methodology uses summary or aggregate data from published studies and has been used broadly in recent years by health technology assessment agencies worldwide, including CDA-AMC, NICE, and EUnetHTA in the context of evaluating therapies for indications where multiple active comparators exist.

NMAs were performed to compare tezepelumab with dupilumab and mepolizumab respectively for the treatment of CRSwNP for the following outcomes at week 52:

- Change from baseline in SNOT-22 – continuous
- Change from baseline in NPS – continuous

The network of the identified studies consisted of 1,263 patients (WAYPOINT, SINUS-52, SYNAPSE).

Statistical Analysis

For each outcome, Bayesian NMAs were performed. Standard ITC methodology based on NICE Decision Support Unit Technical Support Document 2 was followed (23). Analyses were performed using R statistical software (version 3.5.3) with R package 'rjags' (version 4-8) to interface with JAGS software (version 4.3.0). The 'rjags' code was adapted from the WinBUGS code provided by the NICE TSU 2 and 3 with some minor modifications to address the difference in syntax between JAGS and WinBUGS. Markov Chain Monte Carlo sampling process used to construct the posterior distribution for all model parameters. The chosen reference treatment for all analyses was placebo, given that all RCTs included in the ITC were placebo controlled. Primary analyses used the full analysis set for the study populations.

Bayesian Network Meta-Analysis

Bayesian network meta-analyses were conducted using JAGS (24). All NMA models are based on code outlined in NICE DSU TSD (25). An NMA model with a binomial likelihood and logit link was used for binary outcomes with treatment effects modelled on the log odds ratio scale. An NMA model with a normal likelihood and identity link was used for continuous outcomes with treatments effects modelled as mean difference. An NMA model with a normal likelihood and identity link was used for time-to-event outcomes with treatment effects modelled on the log hazard ratio scale.

All analyses were performed using four unique sets of starting values and were based on 20,000 iterations with a burn-in of 20,000 iterations, per chain. Convergence was monitored quantitatively using the latest implementation Gelman-Rubin diagnostic (Rhat) based on four chains (26). Samples were considered to have converged if Rhat is equal to or less than 1.05. If convergence was not reached, the iterations and burn-in were adjusted until sufficient convergence is observed.



Model Selection and Performance Assessment

Fixed and random effects models were analysed. Random effects models assumed a shared estimate of the between trial heterogeneity. For random effects models, the estimated degree of between trial heterogeneity was used to describe the standard deviation of the random effect on the scale of the linear predictor. This was compared to the scale of the basic parameters (comparisons vs the reference treatment).

The relative fit between the two models was compared with deviance information criteria (DIC) where a difference of five points or more was considered evidence to prefer one model over another. If no meaningful difference existed, the fixed effect model was preferred. Due to no meaningful differences existing between the model types, there being a lack of studies (single study connections) for most random effects models, the fixed effects models were the preferred models and are presented as the primary analysis.

SNOT-22

The primary NMA results demonstrate that tezepelumab showed significantly lower SNOT-22 scores than mepolizumab and placebo. Tezepelumab was positioned as the most favourable treatment, though not statistically different from dupilumab. A league table summarizing all pairwise comparisons between treatments in terms of mean differences and 95% credible intervals is presented in Table 10.

Table 10 Results from the comparative analysis of tezepelumab, dupilumab and mepolizumab for adult patients with CRSwNP: SNOT-22 NMA League Table at 52 weeks follow-up shown as mean difference (95% credible intervals)

Tezepelumab			
-6.474 (-13.297 to 0.265)	Dupilumab		
-13.726* (-20.636 to -6.842)	-7.264* (-13.722 to -0.741)	Mepolizumab	
-27.420* (-32.514 to -22.358)	-20.940* (-25.441 to -16.424)	-13.680* (-18.349 to -8.997)	Placebo

Pairwise comparisons are shown in terms of mean differences and 95% credible intervals; each value reflects a comparison between treatments belonging to the intersecting column and row, with additional benefit indicated for the treatment in the column. * = Statistically significant results

NPS

The NMA results demonstrate that tezepelumab showed significantly lower NPS than mepolizumab and placebo. Tezepelumab was not statistically different from dupilumab for NPS. A league table summarizing all pairwise comparisons between treatments in terms of mean differences and 95% credible intervals is presented in Table 11.



Table 11 Results from the comparative analysis of tezepelumab, dupilumab and mepolizumab for adult patients with CRSwNP: NPS NMA League Table at 52 weeks follow-up shown as mean difference (95% credible intervals)

Dupilumab			
-0.311 (-0.835 to 0.214)	Tezepelumab		
-1.586* (-2.115 to -1.056)	-1.277* (-1.737 to -0.817)	Mepolizumab	
-2.390* (-2.801 to -1.971)	-2.077* (-2.400 to -1.755)	-0.801* (-1.129 to -0.473)	Placebo

Pairwise comparisons are shown in terms of mean differences and 95% credible intervals; each value reflects a comparison between treatments belonging to the intersecting column and row, with additional benefit indicated for the treatment in the column. * = Statistically significant results



Appendix D. Literature searches for the clinical assessment

D.1 Efficacy and safety of the intervention and comparator(s)

The selection of studies included for the clinical assessment is based on a study with the objective to conduct a global SLR of RCTs used for the treatment of patients with CRSwNP. For this application, the global SLR was locally adapted by adding further inclusion criteria as relevant for the current application, requiring the final selected studies to be phase III RCTs of the determined relevant comparators (tezepelumab, dupilumab and mepolizumab) suitable for comparison with WAYPOINT.

Table 12 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of completion	search
Embase	OVID platform	1974 to 2025	02.09.2025	
Medline	OVID platform	1946 to 2025	02.09.2025	
EBMR	OVID platform	1974 to 2025	02.09.2025	

Abbreviations: EBRM: Evidence-Based Medicine Reviews

Table 13 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
Clinical Trials Register	Clinical Trials Register	Manual search	02.09.2025

Table 14 Conference material included in the literature search - NA

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	N/A	N/A	N/A	N/A

D.1.2 Search strategies

An experienced medical information specialist developed and tested the search strategies through an iterative process in consultation with the review team. Another senior information specialist peer reviewed the strategies prior to execution using the PRESS checklist(27), which is recommended by the NICE.



Using the OVID platform, Ovid MEDLINE® was searched, including Epub Ahead of Print and In-Process & Other Non-Indexed Citations, Embase, and the Evidence-Based Medicine Reviews (EBMR) databases (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, Health Technology Assessment Database, Cochrane Central Register of Controlled Trials). A single database search was conducted to identify relevant RCT. All searches were performed on February 16, 2019, and updated on October 23, 2023, and again on September 2, 2025.

Strategies utilized a combination of controlled vocabulary (e.g., “Sinusitis”, “Nasal Polyps”, “Chronic Disease”) and keywords (e.g., “rhinosinusitis”, “CRSwNP”, “chronic sinusitis”). Filter was applied for RCTs. There were no language or date restrictions on any of the searches. When possible, animal-only and opinion pieces, and all but the most recent two years of conference abstracts were removed from the results. The results of the database searches were validated and supplemented by searching the United States (US) National Libraries of Medicine’s ClinicalTrials.gov. In addition, findings from published literature were validated against targeted literature searches and bibliographies of select review articles.

Table 15 Search strategy table for OVID platform

No.	Query	Results
0	exp Sinusitis/	86325
2	exp Rhinitis/	176737
3	(sinusit* or rhinit* or nasal catarrh*).tw,kf.	144196
4	(rhinosinus* or rhino-sinus*).tw,kf.	37451
5	or/1-4 [SINUSITIS/RHINITIS/RHINOSINUSITIS]	271851
6	exp Chronic Disease/	988472
7	Nasal Polyps/	26513
8	((nose? or nasal* or nasi or paranasal* or para-nasal* or sino-nasal* or sino-nasal*) adj2 (polyp? or polypos#s or papilloma*)).tw,kf.	27498
9	or/6-8 [CHRONIC OR POLYPS]	1017659
10	5 and 9 [SINUSITIS/RHINITIS/RHINOSINUSITIS - CHRONIC OR WITH POLYPS]	34743
11	CRSwNP.tw,kf.	6737
12	(CRS adj5 polyp*).tw,kf.	2842
13	((ceaseless* or chronic* or constant* or continual* or continuous* or incessant* or intractable or non-remit* or ongoing or persist* or prolong* or recur* or refractory or sustain* or unremit*) adj2 (sino-nasal* or sinus* or rhino* or rhini*)).tw,kf.	54277
14	or/10-13 [SINUSITIS/RHINITIS/RHINOSINUSITIS - CHRONIC OR WITH POLYPS]	65656
15	exp Animals/ not Humans/	11347400
16	14 not 15 [ANIMAL-ONLY REMOVED]	64096
17	(comment or editorial or news or newspaper article).pt.	2653564



18	(letter not (letter and randomized controlled trial)).pt.	2686834
19	16 not (17 or 18) [OPINION PIECES REMOVED]	61994
20	(controlled clinical trial or randomized controlled trial or pragmatic clinical trial or equivalence trial).pt.	737361
21	clinical trials as topic.sh.	245965
22	Randomized Controlled Trials as Topic/	536076
23	(randomi#ed or randomi#ation? or randomly or RCT or placebo*).tw,kf.	5024400
24	((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kf.	945781
25	trial.ti.	1377841
26	or/20-25 [RCT FILTER]	5887113
27	19 and 26 [SINUSITIS/RHINITIS/RHINOSINUSITIS - CHRONIC OR WITH POLYPS - RCTS]	8108
28	27 use ppezv [MEDLINE results]	2375
29	rhinosinusitis/	7469
30	rhinitis/	41135
31	sinusitis/ or paranasal sinusitis/	52428
32	(sinusit* or rhinit* or nasal catarrh*).tw,kw.	142071
33	(rhinosinus* or rhino-sinus*).tw,kw.	36343
34	or/29-33 [SINUSITIS/RHINITIS/RHINOSINUSITIS]	199825
35	exp chronic disease/	988472
36	nose polyp/	17175
37	((nose? or nasal* or nasi or paranasal* or para-nasal* or sinonasal* or sino-nasal*) adj2 (polyp? or polypos#s or papilloma*)).tw,kw.	26510
38	or/35-37 [CHRONIC OR POLYPS]	1015515
39	34 and 38 [SINUSITIS/RHINITIS/RHINOSINUSITIS - CHRONIC OR WITH POLYPS]	30986
40	CRSwNP.tw,kw.	6708
41	(CRS adj5 polyp*).tw,kw.	2832
42	chronic rhinosinusitis/	12479
43	chronic sinusitis/	5955
44	((ceaseless* or chronic* or constant* or continual* or continuous* or incessant* or intractable or non-remit* or ongoing or persist* or prolong* or recur* or refractory or sustain* or unremit*) adj2 (sinonasal* or sino-nasal* or sinus* or rhino* or rhini*)).tw,kw.	54459
45	or/39-44 [SINUSITIS/RHINITIS/RHINOSINUSITIS - CHRONIC OR WITH POLYPS]	67131
46	exp animal/ or animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/	66014580



47	exp human/ or exp human experimentation/ or exp human exper- iment/	52782673
48	46 not 47	13234600
49	45 not 48 [ANIMAL-ONLY REMOVED]	65352
50	editorial.pt.	1582799
51	letter.pt. not (letter.pt. and randomized controlled trial/)	2679901
52	49 not (50 or 51) [OPINION PIECES REMOVED]	63087
53	exp randomized controlled trial/	1746747
54	controlled clinical trial/	555811
55	"clinical trial (topic)"/	137378
56	"randomized controlled trial (topic)"/	299158
57	(randomi#ed or randomi#ation? or randomly or RCT or pla- cebo*).tw,kw.	5077611
58	((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*).tw,kw.	979480
59	trial.ti.	1377841
60	or/53-59 [RCT FILTER]	6100701
61	52 and 60 [SINUSITIS/RHINITIS/RHINOSINUSITIS - CHRONIC OR WITH POLYPS - RCTS]	8645
62	conference abstract.pt.	5591266
63	61 not 62	8083
64	61 and 62	562
65	limit 64 to yr="2022-current"	124
66	63 or 65 [SINUSITIS/RHINITIS/RHINOSINUSITIS - CHRONIC OR WITH POLYPS - RCTS - MOST RECENT 2 YRS CONF ABSTRACTS RE- TAINED]	8207
67	66 use oomezd [Embase results]	3564
68	exp Sinusitis/	86325
69	exp Rhinitis/	176737
70	(sinusit* or rhinit* or nasal catarrh*).ti,ab,kw.	142071
71	(rhinosinus* or rhino-sinus*).ti,ab,kw.	36342
72	or/68-71 [SINUSITIS/RHINITIS/RHINOSINUSITIS]	271209
73	exp Chronic Disease/	988472
74	Nasal Polyps/	26513
75	((nose? or nasal* or nasi or paranasal* or para-nasal* or sinona- sal* or sino-nasal*) adj2 (polyp? or polypos#s or papil- loma*).ti,ab,kw.	26510
76	or/73-75 [CHRONIC OR POLYPS]	1017344
77	72 and 76 [SINUSITIS/RHINITIS/RHINOSINUSITIS - CHRONIC OR WITH POLYPS]	34349
78	CRSwNP.ti,ab,kw.	6708
79	(CRS adj5 polyp*).ti,ab,kw.	2832



80	((ceaseless* or chronic* or constant* or continual* or continuous* or incessant* or intractable or non-remit* or ongoing or persist* or prolong* or recur* or refractory or sustain* or unremit*) adj2 (sino-nasal* or sinus* or rhino* or rhini*)).ti,ab,kw.	53871
81	or/77-80 [SINUSITIS/RHINITIS/RHINOSINUSITIS - CHRONIC OR WITH POLYPS]	65466
82	conference abstract.pt.	5591266
83	81 not 82	59111
84	81 and 82	6355
85	limit 84 to yr="2022-current"	1315
86	83 or 85 [SINUSITIS/RHINITIS/RHINOSINUSITIS - CHRONIC OR WITH POLYPS - MOST RECENT 2 YRS CONF ABSTRACTS RETAINED]	60426
87	86 use cctr [CENTRAL results]	3452
88	exp Sinusitis/	86325
89	exp Rhinitis/	176737
90	(sinusit* or rhinit* or nasal catarrh*).tw,kf.	144196
91	(rhinosinus* or rhino-sinus*).tw,kf.	37451
92	or/88-91 [SINUSITIS/RHINITIS/RHINOSINUSITIS]	271851
93	exp Chronic Disease/	988472
94	92 and 93 [CHRONIC SINUSITIS/RHINITIS/RHINOSINUSITIS]	17677
95	((ceaseless* or chronic* or constant* or continual* or continuous* or incessant* or intractable or non-remit* or ongoing or persist* or prolong* or recur* or refractory or sustain* or unremit*) adj2 (sino-nasal* or sinus* or rhino* or rhini*)).tw,kf.	54277
96	94 or 95 [CHRONIC SINUSITIS/RHINITIS/RHINOSINUSITIS]	59690
97	Nasal Polyps/	26513
98	((nose? or nasal* or nasi or paranasal* or para-nasal* or sinonasal* or sino-nasal*) adj2 (polyp? or polypos#s or papilloma*)).tw,kf.	27498
99	97 or 98 [POLYPS]	34801
100	96 and 99	16843
101	CRSwNP.tw,kf.	6737
102	(CRS adj5 polyp*).tw,kf.	2842
103	or/100-102 [CRSwNP]	17346
104	exp Animals/ not Humans/	11347400
105	103 not 104 [ANIMAL-ONLY REMOVED]	17220
106	(comment or editorial or news or newspaper article).pt.	2653564
107	(letter not (letter and randomized controlled trial)).pt.	2686834
108	105 not (106 or 107)	16717
109	controlled clinical trial.pt.	95729
110	Controlled Clinical Trial/ or Controlled Clinical Trials as Topic/	575393
111	(control* adj2 trial*).tw,kf.	1502317



112	Non-Randomized Controlled Trials as Topic/	15179
113	(nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw,kf.	227745
114	(nRCT or nRCTs or non-RCT?).tw,kf.	4655
115	Controlled Before-After Studies/	327443
116	(control* adj3 ("before and after" or "before after")).tw,kf.	15761
117	Interrupted Time Series Analysis/	329245
118	time series.tw,kf.	122538
119	(pre- adj3 post-).tw,kf.	439185
120	(pretest adj3 posttest).tw,kf.	23780
121	Historically Controlled Study/	326847
122	(control* adj2 stud\$3).tw,kf.	916229
123	Control Groups/	112001
124	(control* adj2 group?).tw,kf.	2108800
125	or/109-124	5364925
126	108 and 125 [NON-RCTs]	2871
127	exp Cohort Studies/	4430429
128	cohort?.tw,kf.	2995472
129	Retrospective Studies/	3222072
130	(longitudinal or prospective or retrospective).tw,kf.	5502541
131	((followup or follow-up) adj (study or studies)).tw,kf.	160100
132	Observational study.pt.	181786
133	(observation\$2 adj (study or studies)).tw,kf.	570309
134	((population or population-based) adj (study or studies or analys#s)).tw,kf.	58999
135	((multidimensional or multi-dimensional) adj (study or studies)).tw,kf.	410
136	Comparative Study.pt.	1958385
137	((comparative or comparison) adj (study or studies)).tw,kf.	371409
138	exp Case-Control Studies/	1919756
139	((case-control* or case-based or case-comparison) adj (study or studies)).tw,kf.	353136
140	or/127-139	11895462
141	108 and 140 [OBSERVATIONAL STUDIES]	5325
142	126 or 141 [NON-RCTS/OBSERVATIONAL STUDIES]	6993
143	142 use ppezv [MEDLINE results - Non-RCTs]	2915
144	rhinosinusitis/	7469
145	rhinitis/	41135
146	sinusitis/ or paranasal sinusitis/	52428
147	(sinusit* or rhinit* or nasal catarrh*).tw,kw.	142071



148	(rhinosinus* or rhino-sinus*).tw,kw.	36343
149	or/144-148 [SINUSITIS/RHINITIS/RHINOSINUSITIS]	199825
150	exp chronic disease/	988472
151	149 and 150	16475
152	chronic rhinosinusitis/	12479
153	chronic sinusitis/	5955
154	((ceaseless* or chronic* or constant* or continual* or continuous* or incessant* or intractable or non-remit* or ongoing or persist* or prolong* or recur* or refractory or sustain* or unremit*) adj2 (sinonasal* or sino-nasal* or sinus* or rhino* or rhini*)).tw,kw.	54459
155	or/151-154 [CHRONIC SINUSITIS/RHINITIS/RHINOSINUSITIS]	63317
156	nose polyp/	17175
157	((nose? or nasal* or nasi or paranasal* or para-nasal* or sinonasal* or sino-nasal*) adj2 (polyp? or polypos#s or papilloma*)).tw,kw.	26510
158	156 or 157 [POLYPS]	31920
159	155 and 158	16832
160	CRSwNP.tw,kw.	6708
161	(CRS adj5 polyp*).tw,kw.	2832
162	or/159-161 [CRSwNP]	17442
163	exp animal/ or animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/	66014580
164	exp human/ or exp human experimentation/ or exp human experiment/	52782673
165	163 not 164	13234600
166	162 not 165 [ANIMAL-ONLY REMOVED]	17306
167	editorial.pt.	1582799
168	letter.pt. not (letter.pt. and randomized controlled trial/)	2679901
169	166 not (167 or 168) [OPINION PIECES REMOVED]	16598
170	exp controlled clinical trial/	2027818
171	exp "controlled clinical trial (topic)"/	308860
172	(control* adj2 trial*).tw,kw.	1869974
173	(nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw,kw.	229874
174	(nRCT or nRCTs or non-RCT?).tw,kw.	4653
175	(control* adj3 ("before and after" or "before after")).tw,kw.	15700
176	time series analysis/	47677
177	time series.tw,kw.	120181
178	pretest posttest control group design/	788
179	(pre- adj3 post-).tw,kw.	438791
180	(pretest adj3 posttest).tw,kw.	31798



181	controlled study/	11742325
182	(control* adj2 stud\$3).tw,kw.	1423162
183	control group/	112001
184	(control* adj2 group?).tw,kw.	2110316
185	or/170-184	16031347
186	169 and 185 [NON-RCTS]	6410
187	cohort analysis/	1810922
188	cohort?.tw,kw.	2989196
189	longitudinal study/	450702
190	prospective study/	1857211
191	retrospective study/	3222072
192	(longitudinal or prospective or retrospective).tw,kw.	5500435
193	follow up/	2505042
194	((followup or follow-up) adj (study or studies)).tw,kw.	153532
195	observational study/	665380
196	(observation\$2 adj (study or studies)).tw,kw.	566412
197	population research/	147347
198	((population or population-based) adj (study or studies or analys#s)).tw,kw.	62248
199	((multidimensional or multi-dimensional) adj (study or stud- ies)).tw,kw.	409
200	exp comparative study/	3812412
201	((comparative or comparison) adj (study or studies)).tw,kw.	388260
202	exp case control study/	1919756
203	((case-control* or case-based or case-comparison) adj (study or studies)).tw,kw.	350931
204	or/187-203	14542928
205	169 and 204 [OBSERVATIONAL STUDIES]	6206
206	186 or 205 [NON-RCTS, OBSERVATIONAL STUDIES]	9736
207	conference abstract.pt.	5591266
208	206 not 207	8642
209	206 and 207	1094
210	limit 209 to yr="2022-current"	395
211	208 or 210 [NON-RCTS/OBSERVATIONAL STUDIES - MOST RECENT 2 YRS CONF ABSTRACTS RETAINED]	9037
212	211 use oemzd [Embase results - Non-RCTs]	5718
213	28 or 143 [MEDLINE results: RCTs & Non-RCTs]	4788
214	67 or 212 [Embase results: RCTs & Non-RCTs]	8192
215	limit 213 to dt="20231001-20251231" [MEDLINE results: RCTs & Non-RCTs Limited to Update Date span: Sept/Oct 2023 - Current]	683



216	limit 214 to dc="20231001-20251231" [Embase results: RCTs & Non-RCTs Limited to Update Date span: Sept/Oct 2023 - Current]	2155
217	87 and (202309\$ or 202310\$ or 202311\$ or 202312\$ or 2024\$ or 2025\$).up. [CENTRAL results: Limited to Update Date span: Sept/Oct 2023 - Current]	1248
218	215 or 216 or 217	4086
219	limit 218 to yr="2023-current"	2848

D.1.3 Systematic selection of studies

Study screening was performed using the systematic review software DistillerSR (Evidence Partners, Ontario, Canada) for the original SLR conducted in 2019 and the 2023 SLR update. Systematic review software Nested Knowledge (Nested Knowledge Version 1.0, 2025, St. Paul, Minnesota, USA) was used for the 2025 SLR update. Screening was conducted by two reviewers who independently reviewed the citation titles and abstracts identified in the literature search to assess study eligibility based on the pre-defined PICO criteria. Citations considered to describe potentially eligible articles were independently reviewed by two reviewers in full-text form to determine formal inclusion in the final review. Reasons for exclusion were documented at the full-text stage. Any disagreements during study screening were resolved by discussion or by a third independent reviewer.

Table 16 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Patients aged ≥ 18 years old with CRSwNP	Only patients aged < 18 years old
Intervention	Any treatment for CRSwNP	Treatments not for CRSwNP
Comparators	Any treatment for CRSwNP	Treatments not for CRSwNP
Outcomes	Lund Mackay CT score Nasal obstruction score SNOT-22 Total symptom score VAS Endoscopic polyp score University of Pennsylvania Smell Identification Test (UPSIT) Need for surgery Adverse events	Outcomes not related to the efficacy or safety of CRSwNP treatments
Study design/publication type	RCTs Published articles (January 1, 2008 to September 2, 2025)	Animal studies, in vitro studies, case reports, expert opinion articles, commentaries, letters



	Conference abstracts (January 1, 2021 to September 2, 2025)	Non-randomized studies Single-arm studies Pilot studies Articles published prior to 2008 Conference abstracts published prior to January 1, 2021
Language restrictions	Articles in English*	All non-English articles

Abbreviations: CRSwNP = chronic rhinosinusitis with nasal polyps; CT = computed tomography; RCTs = randomized controlled trials; RWE = real world evidence; SNOT-22 = Sino-nasal Outcome Test; UPSIT = University of Pennsylvania Smell Identification Test; VAS = visual analogue scale.

*Citation retrieval was not limited by language. Records were categorized based on language during title and abstract screening stage, and non-English abstracts were excluded. English abstracts with non-English articles were excluded at the full-text screening stage.

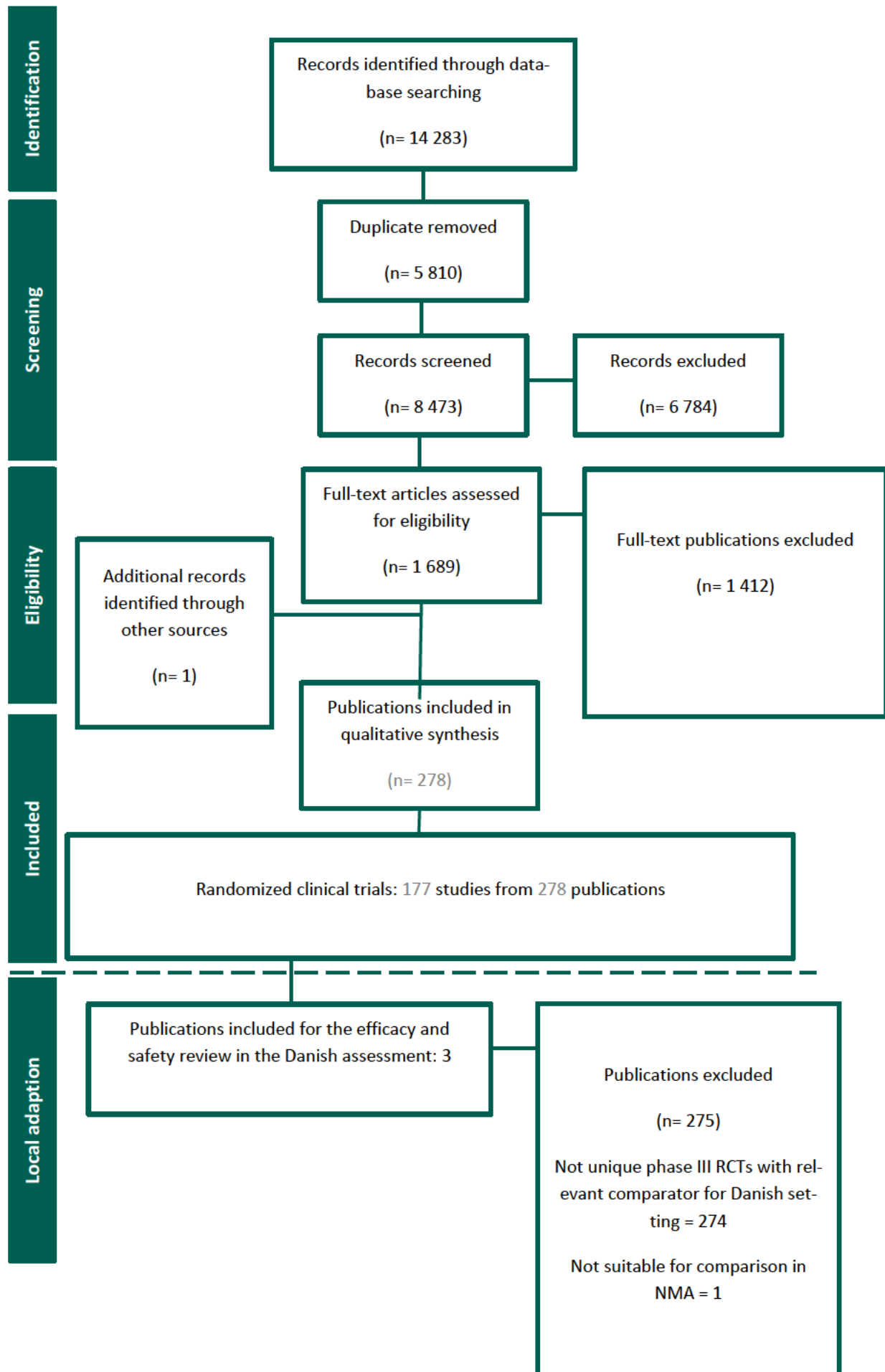




Table 17 Overview of study design for studies included in the technology assessment

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
WAYPOINT NCT04851964 Lipworth et al. 2025 (7)	Evaluate the efficacy and safety of tezepelumab in adults with severe, uncontrolled CRSwNP.	Randomized, double-blind, placebo-controlled, parallel-group, phase III trial.	Adults with severe, uncontrolled CRSwNP	tezepelumab 210 mg or placebo (408 pts)	Co-Primary Endpoints •Change from baseline in total endoscopic NPS at week 52 (range, 0 to 8; higher scores indicate greater severity). •Change from baseline in mean NCS at week 52 (range, 0 to 3; higher scores indicate greater severity), calculated bi-weekly from the NPSD.	Key secondary endpoints, assessed in the overall study population: •Change from baseline in loss-of-smell score at week 52 (NPSD; range, 0 to 3; higher scores indicate greater severity). •Change from baseline in SNOT-22 total score at week 52 (22-item Sinonasal Outcome Test; range, 0 to 110; higher scores indicate greater severity). •Change from baseline in Lund–Mackay score at



week 52 (sinus CT opacification; range, 0 to 24; higher scores indicate greater severity).

•Change from baseline in NPSD total symptom score at week 52 (range, 0 to 24; higher scores indicate greater severity).

SINUS-52 NCT02898454 Bachert et al 2019 (10)	Assess the efficacy and safety of dupilumab (IL-4/IL-13 pathway inhibitor) added to intranasal corticosteroids in adults with severe, uncontrolled CRSwNP, including those with prior systemic corticosteroid use and/or prior sinus surgery, and with or without comorbid asthma or NSAID-exacerbated	Randomised, double-blind, placebo-controlled, parallel-group, phase III trial.	Patients with bilateral CRSwNP and symptoms despite intranasal corticosteroid use, receiving systemic corticosteroids in the preceding two years, or having had sinonasal surgery.	Dupilumab 300 mg subcutaneous Placebo subcutaneous (448 pts)	Co-Primary endpoints (assessed at week 24): •Change from baseline in endoscopic bilateral NPS (0-8) •Change from baseline in NCS/NOS (patient-reported daily, monthly average, 0-3)	Secondary endpoints (key, multiplicity-controlled at week 24; plus selected at week 52 for SINUS-52 Group A): •Lund-Mackay CT total score (0–24) at week 24 •Patient-reported total symptom score (sum of daily nasal congestion, loss of smell, rhinorrhoea; 0–9)
--	--	--	--	--	---	--



respiratory
disease.

- Daily loss-of-smell severity
- SNOT-22 total score (0–110)
- UPSIT smell test score (0–40)
- For SINUS-52 Group A at week 52: change in NPS, NCS, SNOT-22

SYNAPSE NCT030857 97 Han et al 2021 (9)	To assess the efficacy and safety of mepolizumab in adults with recurrent, refractory, severe, bilateral CRSwNP who were eligible for repeat surgery.	Randomised, double-blind, placebo-controlled, parallel-group, phase III trial.	Adults with recurrent, refractory, severe, bilateral CRSwNP to standard care and eligible for repeat nasal surgery.	mepolizumab 100 mg subcutaneously Placebo subcutaneously (407 pts)	Coprimary Endpoints •Change from baseline in total endoscopic NPS at week 52. •Change from baseline in mean NOS measured using VAS during weeks 49–52.	Secondary Endpoints •Time-to-first nasal surgery until week 52. •Change from baseline in mean overall symptom VAS 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
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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

D.1.4 Quality assessment

A major strength of the SLR is that it adheres to best practices for the conduct and reporting of systematic reviews. Notably, the literature search was performed and peer-reviewed by experienced information specialists. A detailed search strategy, a PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flow diagram, and full included and excluded study lists have been developed, as per PRISMA Guidelines.

A limitation of the systematic review is that the included studies were restricted to the English language at the study selection stage. This is likely a minor limitation, since the majority of studies are published in English journals. Of note, the search itself was not restricted to English-only articles; therefore, regions for which non-English studies are of interest could use the same search as was used for this systematic review.

D.1.5 Unpublished data

N/A



Appendix E. Additional NMA analysis requested by DMC

Rational and objective

Per request from DMC, an additional NMA analysis with omalizumab as a comparator is included as an appendix.

Method

The phase III RCTs for omalizumab in CRSwNP (POLYP1 and POLYP2(28)) had study durations of 24 weeks. As follow-up time is to be considered as an important source of heterogeneity, a separate NMA was conducted considering study results at <30 weeks follow-up. The same method was used as described in Appendix C.

Results

Out of RCTs identified in the global SLR (described in Appendix D) nine studies were identified for the NPS outcome and seven studies for the SNOT-22 endpoint. Data for WAY-POINT results <30 weeks were obtained from a high-level summary of results and a clinical study report provided by AstraZeneca. High level information (number of randomized patients, study duration, etc.) for the total ten RCTs of interest are presented in Table 1E.



Table 1E Summary of relevant RCTs for NMA <30 weeks

Trial; NCT	Phase	Treatment arms	N random-ized	Study Du-ration (weeks)
Tezepelumab				
WAYPOINT; NCT04851964 (7)	3	Tezepelumab + intranasal corticosteroid	400	52
		Placebo + intranasal corticosteroid		
		Placebo		
Dupilumab				
SINUS-52; NCT02898454 (10)	3	Dupilumab + mometasone furoate	448	52
		Placebo + mometasone furoate		
SINUS-24; NCT02912468 (10)	3	Dupilumab + mometasone furoate	276	24
		Placebo + mometasone furoate		
NCT01920893 (29)	2	Dupilumab + mometasone furoate	60	16
		Placebo + mometasone furoate		
Mepolizumab				
SYNAPSE; NCT03085797 (9)	3	Mepolizumab + mometasone furoate	407	52
		Placebo + mometasone furoate		
NCT01362244 (30)	2	Mepolizumab + fluticasone propionate	107	25
		Placebo + fluticasone propionate		
Gevaert et al 2011 (31)	NR	Mepolizumab	30	48
		Placebo		
Omalizumab				
POLYP 1; NCT03280550 (28)	3	Omalizumab + mometasone	138	24
		Placebo + mometasone		
POLYP 2; NCT03280537 (28)	3	Omalizumab + mometasone	127	24
		Placebo + mometasone		
Gevaert et al 2013 (32)	NR	Omalizumab	24	16
		Placebo		
		Medical therapy		

NPS

A total of 10 relevant studies reporting NPS at less than 30 weeks were identified, which resulted in a network consisting of 1,679 patients (WAYPOINT, SINUS-24, SINUS-52, NCT01920893, NCT01362244, SYNAPSE, POLYP1, POLYP2, Gevaert et al. 2011, Gevaert et al. 2013).

[REDACTED]

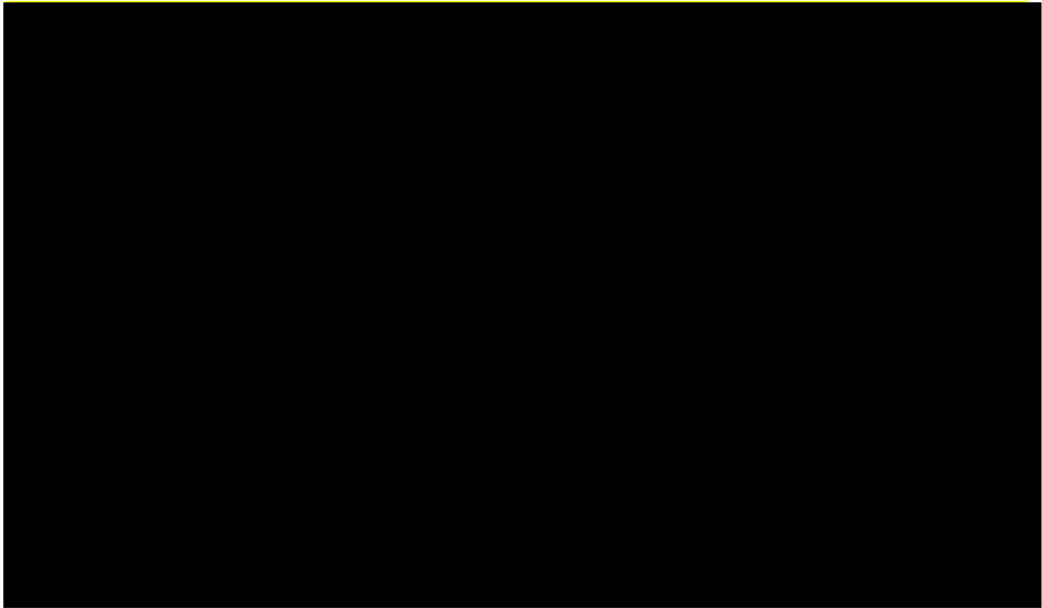
[REDACTED]

[REDACTED] A

league table summarizing all pairwise comparisons between treatments in terms of mean differences and Bayesian 95% credible intervals is presented in Figure 1E.



[REDACTED]



[REDACTED]

SNOT-22

A total of 8 relevant studies reporting the SNOT-22 at less than 30 weeks were identified, which resulted in a network consisting of 1,598 patients (WAYPOINT, SINUS-24, SINUS-52, NCT01920893, NCT01362244, SYNAPSE, POLYP1, POLYP2).

[REDACTED]

A league table summarizing all pairwise comparisons between treatments in terms of mean differences and Bayesian 95% credible intervals is presented in Figure 2E.



Figure 2E SNOT-22 NMA League Table (<30 weeks)



Conclusion

Per request from DMC to include an additional NMA with omalizumab as comparator and as no omalizumab trials reported outcomes at ≥ 30 weeks, an additional NMA over results for outcomes reported at <30 week was conducted.

According to the DMC protocol for the dupilumab application for CRSwNP (33), assessments should be based on data with the longest possible follow-up. For this reason, the assessment of comparative analysis should be based on the results of the NMA of end-points at 52 weeks presented in the main application (section 5.2), when available.

Medicinrådet
Dampfærgevej 21-23, 3. sal
2100 København Ø

04.09.2026

Bemærkninger til MR's udkast til vurderingsrapport om Tezspire (tezepelumab) ved CRSwNP

AstraZeneca takker MR for vurderingen af Tezspire til behandling af CRSwNP og for muligheden for at kommentere udkastet til Evidensgennemgang og Sammenfatning. Vi værdsætter anerkendelsen af at tezepelumab og dupilumab er de mest effektive behandlingsmuligheder til patienter med svær CRSwNP. Desuden ser vi positivt på ændringerne i kriterierne for opstart af behandling med biologiske lægemidler mod CRSwNP. Vores kommentarer vedrører følgende:

1. Inkludering af et forlænget doseringsinterval for dupilumab
2. Risiko for manglende konsistens mellem den kliniske vurdering og efterfølgende anbefaling

1) Inkludering af et forlænget doseringsinterval for dupilumab

Det fremgår af dokumenterne, at den EMA-godkendte dosis af dupilumab er 300 mg hver 2. uge. Samtidig foreslås et scenarie i omkostningsanalysen, hvor 90 % af patienterne efter uge 24 overgår til dosering hver 4. uge. AstraZeneca er af flere grunde bekymret for, at dette indebærer, at effektdokumentation fra det EMA godkendte doseringsregime kombineres med omkostninger baseret på et forlænget off-label-doseringsinterval:

- **Usikkerhed om vedvarende effekt ved forlængelse af dosisintervallet**

Den kliniske sammenligning er baseret på de EMA-godkendte doseringsregimer. Hvis dosisintervallet forlænges for dupilumab, kan det imidlertid ikke uden videre antages, at effekten forbliver uændret. AstraZeneca bemærker, at dokumentationen for forlænget doseringsinterval med dupilumab primært stammer fra et hollandsk, ikke-randomiseret observationsstudie fra ét enkelt center [1]. Studiet havde ingen komparatorarm og omfattede en stærkt selekteret patientpopulation. Ifølge GRADE-systemet vil evidensen fra et sådant studie blive vurderet som værende af meget lav kvalitet. Studiet kan derfor ikke dokumentere, at tilsvarende resultater ville være opnået sammenlignet med en gruppe af respondenter, der fortsatte dosering hver 2. uge, eller i en ikke-selekteret patientpopulation.

I en nylig systematisk litteraturgennemgang og metaanalyse [2] af forlænget doseringsinterval for dupilumab konkludere forfatterne på baggrund af betydelig heterogenitet, selektionsbias og mangel på prospektiv, kontrolleret evidens, at randomiserede, kontrollerede studier er nødvendige for at validere dosisforlængelses-strategier og identificere egnede kriterier for patientudvælgelse.

- **Mangel på ækvivalente antagelser for andre terapier i omkostningsanalysen**

Da der ikke foreligger tilstrækkelig robust evidens for vedvarende effekt ved forlænget doseringsinterval, skaber det usikkerhed at kombinere den observerede effekt ved dosering af dupilumab hver 2. uge med de lavere omkostninger forbundet med off-label-dosering hver 4. uge. Dette kan uberettiget favorisere dupilumab i den økonomiske sammenligning, fordi tilsvarende antagelser ikke anvendes for tezepelumab eller andre biologiske behandlinger. Sammenligningen bliver dermed asymmetrisk: En behandling får fordel af en ikke-godkendt reduktion i lægemiddelforbruget, mens de øvrige behandlinger vurderes ud fra deres godkendte doseringsregimer. Sammenligningen afspejler derfor ikke længere de relative omkostninger ved de godkendte behandlingsregimer, som indgår i evidensgennemgangen.

Desuden er antagelsen om, at 90 % af patienterne efter uge 24 vil blive doseret hver 4. uge, ikke direkte underbygget af den citerede evidens. Det hollandske studie beskriver en individuelt monitoreret, trinvis forlængelse af dosisintervallet hos udvalgte respondenter – ikke et fast doseringsmønster, der anvendes på hele behandlingspopulationen. Analysen nævnt i sammenfatningen tager ligeledes ikke højde for patienter, som efter nedsat behandlingseffekt må vende tilbage til dosering hver 2. uge, selv om ekspertudvalget udtrykkeligt anerkender, at en sådan optrapning igen kan blive nødvendig.

AstraZeneca stiller sig desuden kritisk overfor, at tidshorisonten i omkostningsanalysen er udvidet fra to til tre år, da der ikke foreligger evidens, som understøtter denne forlængelse. En længere tidshorisont øger usikkerheden om, hvorvidt effekten opretholdes, fordi det er uvist, hvor mange patienter, der som følge af nedsat behandlingseffekt vil have behov for at vende tilbage til det godkendte doseringsregime, som ekspertudvalget også bemærker. Jo længere tidshorisont der anvendes i omkostningsanalysen, desto større vil denne asymmetri blive.

Potentiel indvirkning på anbefalingen og den foreslåede revision

Det fremgår udtrykkeligt af MR's opsummering, at det vil blive nævnt i anbefalingen, hvis rangeringen afhænger af et forlænget doseringsinterval af dupilumab. Da dupilumab og tezepelumab er vurderet som klinisk ligeværdige ved de godkendte doseringsregimer, kan antagelser om doseringshyppighed blive afgørende for anbefalingen. Hvis effekten for dupilumab derfor baseres på dosering hver 2. uge, mens omkostningerne beregnes ud fra dosering hver 4. uge, opstår der en uoverensstemmelse mellem de kliniske og økonomiske antagelser, som systematisk kan favorisere dupilumab. AstraZeneca finder det derfor særligt vigtigt, at den økonomiske sammenligning baseres på behandlingsregimer, der er godkendte og evidensbaserede, og som anvendes konsekvent på tværs af behandlingerne.

På baggrund af ovenstående foreslår AstraZeneca, at det EMA-godkendte doseringsregime for dupilumab anvendes som det primære grundlag for både den kliniske sammenligning og omkostningsanalysen. Det vil sikre en retvisende og metodisk konsistent sammenligning baseret på studier med høj intern validitet.

Hvis det mod forventning har interesse at undersøge andre doseringsregimer bør dette undersøges i følsomhedsanalyser som supplement til selve omkostningsanalysen, **men bør ikke danne basis for den endelige rekommandering.**

2) Risiko for manglende konsistens mellem klinisk vurdering og efterfølgende anbefaling

AstraZeneca hilser MR's konklusion velkommen om, at dupilumab og tezepelumab er de mest effektive behandlingsmuligheder og derfor bør placeres i kategorien "Anvend", mens omalizumab og mepolizumab placeres i kategorien "Overvej" på grund af en lavere samlet behandlingseffekt.

Vi er derfor bekymrede over formuleringen i MR's Udkast til Sammenfatning om, at et biosimilært lægemiddel i kategorien "Overvej" kan vælges før behandlinger i kategorien "Anvend", hvis økonomiske hensyn taler for det. Forskellen mellem "Anvend" og "Overvej" bygger på klinisk relevante forskelle i effekt, som MR har identificeret. AstraZeneca mener derfor, at den efterfølgende anbefaling bør være i overensstemmelse med konklusionerne i den kliniske vurdering og ikke føre til, at patienter rutinemæssigt påbegynder en behandling, der er vurderet som mindre effektiv end de foretrukne behandlingsalternativer. MR opfordres derfor til at præcisere, at omkostningsanalysen skal fortolkes inden for det fastlagte kliniske hierarki, og at behandlinger i kategorien "Anvend" fortsat bør være førstvalg for de fleste patienter.

På basis af ovenstående vil vi derfor opfordre MR til at lade disse kommentarer indgå i den endelige Evidensgennemgang og i Sammenfatningen. Det vil bidrage til at sikre, at den endelige anbefaling og de tilhørende sundhedsøkonomiske sammenligninger, herunder antagelser om behandlingsvarighed, er tilstrækkeligt evidensbaserede og i overensstemmelse med de godkendte produktinformationer.

Venlig hilsen,

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