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CADTH Reimbursement Review

# Mepolizumab (Nucala)

**Sponsor:** GlaxoSmithKline Inc.

**Therapeutic area:** Severe chronic rhinosinusitis with nasal polyps

Clinical Review
Pharmacoeconomic Review
Stakeholder Input

CADTH

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**About CADTH:** CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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## Abbreviations

| | |
|---|---|
| **AE** | adverse event |
| **BCLA** | British Columbia Lung Association |
| **CI** | confidence interval |
| **CRS** | chronic rhinosinusitis |
| **CRSwNP** | chronic rhinosinusitis with nasal polyps |
| **HRQoL** | health-related quality of life |
| **Ig** | immunoglobin |
| **IL** | interleukin |
| **INCS** | intranasal corticosteroids |
| **IQR** | interquartile range |
| **ITT** | intention to treat |
| **LTRA** | leukotriene receptor antagonist |
| **MCS** | mental component summary |
| **MID** | minimal important difference |
| **MF** | mometasone furoate |
| **OCS** | oral corticosteroids |
| **PCS** | physical component summary |
| **PnIF** | peak nasal inspiratory flow |
| **SD** | standard deviation |
| **SF-36** | Short Form (36) Health Survey |
| **SNOT-22** | Sino-Nasal Outcome Test 22 |
| **VAS** | visual analogue scale |
| **WPAI-GH** | Work Productivity and Activity Impairment — General Health |

# Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

## Introduction

Chronic rhinosinusitis (CRS) is a chronic inflammatory disease of the nasal passage linings and/or sinuses that may occur with or without nasal polyps. Nasal polyps are outgrowths of sino-nasal tissues, and those that accompany CRS are benign and typically develop bilaterally in the sino-nasal cavity.[1] The prevalence of CRS with nasal polyps (CRSwNP) is estimated to be between 1% and 4% of the US general population and between 25% and 30% of patients with CRS.[2] Currently, Canadian data on the prevalence and incidence of CRSwNP are not available. CRSwNP is more common in men and older individuals. Nasal obstruction and hyposmia or anosmia,[3] as well as rhinorrhea, severe nasal congestion, and loss of smell or taste,[4,5] are key symptoms associated with CRSwNP. The long-term symptoms associated with CRSwNP negatively impact physical and mental health-related quality of life (HRQoL).[5] Disease burden is particularly high among patients who require repeated treatment with systemic corticosteroids and/or sino-nasal surgeries to alleviate uncontrolled symptoms.[6]

The goal of therapy for CRSwNP is to reduce symptoms and complications by minimizing inflammation and controlling secondary infection if it occurs. In clinical practice in Canada, initial treatment for CRSwNP generally starts with intranasal corticosteroids (INCS) with mometasone furoate (MF) nasal spray (2 sprays each nostril twice daily or an equivalent). Antibiotics are initiated for patients with CRSwNP with a suspected bacterial infection as indicated by pain, documented purulence, or recurrent episodes of sinusitis. Other medical treatments that may be considered are oral corticosteroids (OCS), systemic corticosteroids, leukotriene receptor antagonists (LTRAs), and acetylsalicylic acid (ASA) desensitization. Endoscopic sinus surgery is reserved for patients whose CRSwNP is not responsive to medical treatment.

Mepolizumab is a targeted anti-interleukin-5 immunoglobin (Ig) G1 kappa monoclonal antibody. Mepolizumab binds to soluble interleukin-5 (IL-5) with high affinity, preventing IL-5 from binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface, thereby reducing the production and survival of eosinophils.[7] On November 5, 2021, mepolizumab received a Notice of Compliance from Health Canada as add-on maintenance

### Table 1: Submitted for Review

| Item | Description |
|---|---|
| **Drug product** | Mepolizumab (Nucala), 100 mg/mL for subcutaneous injection |
| **Indication** | As add-on maintenance treatment with INCS in adult patients with severe CRSwNP inadequately controlled by INCS alone |
| **Reimbursement request** | As per indication |
| **Health Canada approval status** | NOC |
| **Health Canada review pathway** | Standard |
| **NOC date** | November 5, 2021 |
| **Sponsor** | GlaxoSmithKline Inc. |

CRSwNP = chronic rhinosinusitis with nasal polyps; INCS = intranasal corticosteroids; NOC = Notice of Compliance.

treatment with INCS in adult patients with severe CRSwNP inadequately controlled by INCS alone. Mepolizumab is administered as a subcutaneous injection at a dose of 100 mg once every 4 weeks.

The objective of this review is to evaluate the beneficial and harmful effects of mepolizumab 100 mg/mL as add-on maintenance treatment with INCS in adult patients with severe CRSwNP inadequately controlled by INCS alone.

## Stakeholder Perspectives

The information in this section is a summary of input provided by the patient and clinician groups who responded to CADTH's call for input, from a clinical expert consulted by CADTH for the purpose of this review, and from the public drug plans.

### Patient Input

Patient input was provided by 2 groups: Asthma Canada and the Patient Lung Groups of the British Columbia Lung Association (BCLA). Survey respondents indicated that CRSwNP symptoms had had a direct negative impact on their daily lives, including decreased quality of life (90%), sleep disturbances (66%), missed time from work or school (30%), financial difficulties (20%), and hospital visits because of CRSwNP (20%). Among the survey respondents who identified as caregivers, 66% reported an impact on sleep related to nighttime symptoms and being burdened by managing frequent appointments (44%) and multiple medications (33%) for the patient they care for. Thirty-nine percent of survey respondents reported using nasal sprays to manage their CRSwNP, while 28% reported having surgery, 17% reported using OCS, and 17% reported using a biologic (e.g., dupilumab or omalizumab) to treat their nasal polyps. The side effects most commonly reported by these patients included altered sense of smell (63%), allergic reactions (36%), mental or mood changes (27%), increased risk of sinus infection (27%), headaches or dizziness (18%), and ineffectiveness (18%). Furthermore, both Asthma Canada and the BCLA expressed concern with the short- and long-term side effects associated with OCS in patients who have not experienced adequate control of their CRSwNP with previous lines of therapy, resulting in symptoms such as weight gain, cataracts, osteoporosis, increased risk of infection, and high blood sugar. Patients and caregivers have deemed the following outcomes as important for new treatment options: easier management of symptoms (63%), decreased anxiety about nasal polyps (45%), decreased reliance on OCS or other steroids (36%), reduced need for surgery (36%), and improved process for taking medication (27%). Sixty-three percent of survey respondents indicated that any potential side effects of mepolizumab would be worth tolerating in exchange for a visible improvement in CRSwNP management.

### Clinician Input

#### *Input From Clinical Expert Consulted by CADTH*

One clinical expert was consulted for the purpose of this review. According to the clinical expert consulted by CADTH, not all patients are responsive to current treatments for the management of CRSwNP. Due to the chronic and recurring nature of CRSwNP, there is a medical need for targeted treatment of nasal polyps. Recurrence of nasal polyps is most likely in the presence of high levels of local IL-5 and IgE, which drive eosinophilic inflammation. The anti-IL-5 mechanism of mepolizumab would prevent the inflammation most associated with nasal polyp recurrence. The clinical expert noted that mepolizumab would be most appropriate for use in patients who do not experience control of symptoms or cannot tolerate topical steroid treatment. According to the clinical expert consulted, patients with

eosinophilic polyps are most likely to respond to anti-IL-5 treatments. Eosinophilic polyps can be identified via pathology at the time of polyp removal. Polyps identified as being neutrophilic are less likely to respond to anti-IL-5 treatments. The clinical expert also noted that biologic treatments would likely be unnecessary among patients who respond to topical steroids. The clinical expert noted that response to treatment is determined by severity of nasal congestion. Response to treatment should typically occur within 6 months of initiating therapy. The clinical expert noted that while use of systemic steroids should be reduced during this time, more than 6 months may be needed in resistant patients to document response. The clinical expert noted that the need for prednisolone or surgery could indicate a loss of response to treatment. For those patients who require surgery, continued treatment with mepolizumab may be considered to prevent recurrence of nasal polyps.

#### *Clinician Group Input*

No input was received from any clinician groups for this submission.

### Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for mepolizumab:

- considerations related to initiation of therapy
- considerations related to continuation or renewal of therapy
- considerations related to discontinuation of therapy
- considerations related to prescribing of therapy.

## Clinical Evidence

### Pivotal Studies and Protocol-Selected Studies

#### *Description of Studies*

One sponsor-conducted study that met the CADTH review protocol criteria was included in this systematic review. SYNAPSE was a randomized, double-blind, placebo-controlled, parallel group trial assessing the clinical efficacy and safety of 100 mg mepolizumab as an add-on maintenance treatment in adults with recurrent CRSwNP. A total of 414 adult patients were randomized at 86 sites across 11 countries, including 34 patients (8.2%) across 8 sites in Canada. The study comprised a 4-week run-in period followed by a 52-week treatment period in which patients were randomized to receive either mepolizumab (n = 207) or matching placebo (n = 207). During the treatment period, patients received either mepolizumab 100 mg every 4 weeks (a total of 13 doses) or placebo delivered by subcutaneous injection. The final dose of the study treatment was administered at week 48. The first 200 patients randomized into the study entered a 6-month no-treatment follow-up period following their week 52 visit to assess maintenance of response. All patients remained on standard of care treatment for CRSwNP throughout the study. Standard of care treatment included daily MF nasal spray and, if required, saline nasal douching and/or an occasional short course of high-dose OCS and/or antibiotics. Changes in MF dosing regimen between screening and the end of the study were not permitted.

The co-primary efficacy end points were change from baseline in endoscopic nasal polyp score at week 52 and change from baseline in nasal obstruction visual analogue scale (VAS) symptom score during the 4 weeks before week 52. The key secondary end point was time

to first actual surgery for nasal polyps by week 52. Sample size determination was made to ensure sufficient power to detect meaningful changes in this key secondary end point. Other secondary end points included change from baseline in the overall VAS symptom score, change from baseline in the Sino-Nasal Outcome Test 22 (SNOT-22) score, the proportion of patients requiring systemic steroids for nasal polyps, change from baseline in the composite VAS symptom score (combining VAS scores for nasal obstruction, nasal discharge, mucus in the throat, and loss of smell), and change from baseline in the loss of smell VAS score. Multiplicity was controlled using a hierarchical closed testing approach in making inferences for the secondary end points. Analyses were adjusted for the following covariates: country region, blood eosinophil count, baseline endoscopic nasal score, number of previous surgeries, and number of courses of OCS for nasal polyps in the previous 12 months.

Overall, randomized patients were middle aged (mean = 48.8 years; standard deviation [SD] = 13.01) and generally overweight (mean body mass index = 28.16 kg/m$^2$; SD = 5.36). The mean time since onset of nasal polyps at baseline was 11.41 years (SD = 8.39). Patients presented with severe CRSwNP, as indicated by baseline total endoscopic nasal polyp score (centrally read) (mean = 5.5; SD = 1.29), nasal obstruction VAS score (mean 8.97; SD = 0.83), SNOT-22 total score (mean = 64.1; SD = 18.32), and a having had at least 1 surgery for nasal polyps in the past 10 years. While the majority of patients had a history of 1 or 2 surgeries (70%), a greater proportion of patients in the placebo group than in the mepolizumab group had had more than 1 surgery (60% versus 48%).

### *Efficacy Results*

Key efficacy results are presented in Table 2.

#### Severity of Nasal Polyps

At the end of the 52-week treatment period, the mean change in total endoscopic nasal polyp score from baseline was −0.1 (SD = 1.46) and −0.9 (SD = 1.90) in the placebo and mepolizumab groups, respectively. The median change from baseline in the placebo and mepolizumab groups was 0 (interquartile range [IQR], −1.0 to 1.0) and −1.0 (IQR, −2.0 to 0.0), respectively. The adjusted median difference in change from baseline was statistically significant in favour of mepolizumab compared to placebo (−0.73; 95% confidence interval [CI], −1.11 to −0.34; P < 0.001). In total, 28.4% and 50.5% of patients in the placebo and mepolizumab groups, respectively, demonstrated the minimal important difference (MID) of a 1-point or greater improvement in their total endoscopic nasal polyp score. According to the clinical expert consulted by CADTH for this review, the response to treatment as defined by the total endoscopic nasal polyp score is indicative of a treatment response in the clinical setting.

Exploratory subgroup analyses in patients with or without asthma and in patients with or without prior surgery for nasal polyps were conducted; however, no formal hypothesis testing was done. Therefore, whether the effect of mepolizumab differs between these subgroups is unknown.

#### Nasal Obstruction

In the 4-week period from week 49 to week 52, the mean change in total nasal obstruction VAS score from baseline was −2.45 (SD = 3.15) and −4.24 (SD = 3.42) in the placebo and mepolizumab groups, respectively. The median change from baseline to week 52 in the placebo and mepolizumab groups was −0.82 (IQR, −4.84 to 0.0) and −4.41 (IQR, −7.27 to −0.36), respectively. The adjusted median difference in change from baseline to week 52

was statistically significant in favour of mepolizumab compared to placebo (−3.14; 95% CI, −4.09 to −2.18; P < 0.001). Twenty-three percent and 44% of patients in the placebo and mepolizumab groups, respectively, demonstrated a more than 5-point improvement (suggested MID) in their nasal obstruction VAS score.

Exploratory subgroup analyses in patients with or without concurrent asthma and in patients with or without prior surgery for nasal polyps were conducted; however, no formal hypothesis testing was done. Therefore, whether the effect of mepolizumab differs between these subgroups is unknown.

The magnitude of the treatment effect for nasal obstruction VAS score was modest yet indicative of a treatment response in the clinical setting according to the clinical expert consulted by CADTH for this review. According to the clinical expert, a change in score between 20% and 50% of the baseline VAS score is considered acceptable in clinical practice. In the SYNAPSE trial, the difference in mean change from baseline across the VAS end points fell within this range.

### Symptoms

In the 4-week period from week 49 to week 52, the mean change in nasal symptom composite VAS score from baseline was −2.19 (SD = 2.82) and −3.81 (SD = 3.19) in the placebo and mepolizumab groups, respectively. The median change from baseline in the placebo and mepolizumab groups was −0.89 (IQR, −4.06 to 0.0) and −3.96 (IQR, −6.68 to −0.32), respectively. The adjusted median difference in change from baseline was statistically significant in favour of mepolizumab compared to placebo (−2.68; 95% CI, −3.44 to −1.91; P = 0.020). Twenty percent and 37% of patients in the placebo and mepolizumab groups, respectively, demonstrated a more than 5-point improvement in their nasal symptom composite VAS score.

In the 4-week period from week 49 to week 52, the mean change in nasal symptom and facial pain composite VAS score from baseline was −2.24 (SD = 2.88) and −3.80 (SD = 3.18) in the placebo and mepolizumab groups, respectively. The median change from baseline in the placebo and mepolizumab groups was −0.99 (IQR, −4.29 to 0.0) and −3.88 (IQR, −6.45 to −0.25), respectively. The adjusted median difference in change from baseline favoured the mepolizumab group compared to the placebo group (−2.50; 95% CI, −3.33 to −1.67). Twenty-one percent and 38% of patients in the placebo and mepolizumab groups, respectively, demonstrated a more than 5-point improvement in their nasal symptoms and facial pain composite VAS score.

In the 4-week period from week 49 to week 52, the mean change in loss of smell VAS score from baseline was −1.38 (SD = 2.65) and −2.83 (SD = 3.61) in the placebo and mepolizumab groups, respectively. The median change from baseline in the placebo and mepolizumab groups was 0 (IQR, −1.28 to 0.0) and −0.53 (IQR, −5.60 to 0.0), respectively. The adjusted median difference in change from baseline was statistically significant in favour of mepolizumab compared to placebo (−0.37; 95% CI, −0.65 to −0.08; P = 0.020). Thirteen percent and 30% of patients in the placebo and mepolizumab groups, respectively, demonstrated a 5-point or greater improvement in their loss of smell VAS score.

The magnitude of the treatment effect for the compositive VAS scores was indicative of an acceptable treatment response in the clinical setting according to the clinical expert consulted by CADTH for this review. For loss of smell, however, the magnitude of the

treatment effect was considered small. According to the clinical expert, it is difficult to regain sense of smell once lost.

### Nasal Congestion

At week 52, the mean change from baseline in peak nasal inspiratory flow (PnIF) was greater in the mepolizumab group (32.5; SD = 57.98) than in the placebo group (11.2; SD = 65.78). The median change from baseline in the placebo and mepolizumab groups was 0 (IQR, −20.0 to 50.0) and 30 (IQR, 0.0 to 60.0), respectively. The improvement in the mepolizumab group was in excess of the established 20 L/min MID.

PnIF assesses the objective improvement of nasal congestion since it is affected by both polyp size and nasal mucosa inflammation. Unfortunately, no analysis of treatment difference was conducted between the groups, and the outcome was absent from the statistical testing hierarchy. As a result, conclusions cannot be made on the efficacy of mepolizumab to improve nasal congestion. This represents a missed opportunity to demonstrate an objective treatment effect on an outcome that is considered important in the clinical setting.

### Response to Treatment

Twenty-eight percent and 50% of patients in the placebo and mepolizumab groups, respectively, demonstrated a 1-point or greater improvement in their total endoscopic nasal polyp score at the end of the 52-week treatment period. The odds ratio of being a responder in the mepolizumab group compared to the placebo group was 2.74 (95% CI, 1.80 to 4.18).

Fifty-four percent and 73% of patients in the placebo and mepolizumab groups, respectively, demonstrated a 8.9-point or greater improvement in their total SNOT-22 score at the end of the 52-week treatment period. The odds ratio of being a responder in the mepolizumab groups compared to the placebo group was 2.44 (95% CI, 1.60 to 3.73).

The SNOT-22 score is used in the clinical practice setting to determine response to treatment. Just over half the patients in the placebo group demonstrated response to treatment in terms of SNOT-22 score. The observed treatment effect in the placebo group is most likely a result of the effectiveness of MF nasal spray treatment. According to the clinical expert consulted by CADTH for this review, the benefits derived from daily MF treatment may be reflecting improvement in sinusitis, nasal turbinate edema, and secretion, leading to symptomatic and objective improvement despite polyps being resistant to steroids.

### Health-Related Quality of Life

At the end of the 52-week treatment period, the mean change in total SNOT-22 score from baseline was −15.7 (SD = 23.93) and −29.4 (SD = 24.67) in the placebo and mepolizumab groups, respectively. The median change from baseline to week 52 in the placebo and mepolizumab groups was −14.0 (IQR, −31.0 to 0.0) and −30.0 (IQR, −46.0 to −4.0), respectively. The adjusted median difference in change from baseline was statistically significant in favour of mepolizumab compared to placebo (−16.49; 95% CI, −23.57 to −9.42; P = 0.003).

At the end of the 52-week treatment period, the median change from baseline for both the physical component summary (PCS) and mental component summary (MCS) of the Short Form (36) Health Survey (SF-36) was 0.0 (IQR, −1.75 to 4.61) and 0.0 (IQR, −3.75 to 5.76), respectively, in the placebo group. The median change from baseline to week 52 for the PCS

and MCS was 6.75 (IQR, 0.0 to 12.59) and 1.20 (IQR, −2.60 to 10.08), respectively, in the mepolizumab group.

### Systemic Steroid Use for Nasal Polyps

Patient groups indicated a need for decreased reliance on OCS and other steroids.

Over the 52-week treatment period, 37% and 25% of patients in the placebo and mepolizumab groups, respectively, required at least 1 course of systemic steroid treatment for nasal polyps. By week 52, the probability of requiring an initial course of systemic steroid use for nasal polyps was 37.5% (95% CI, 31.1% to 44.6%) in the placebo group and 25.4% (95% CI, 20.0% to 32.1%) in the mepolizumab group.

### Nasal Inflammation

Nasal inflammation was not assessed in the SYNAPSE trial.

### Nasal Polyp Surgery

By week 52, 23% and 9% of patients in the placebo and mepolizumab groups, respectively, had undergone nasal surgery. The estimated risk of having surgery before week 52 was 23.6% (95% CI, 18.3% to 30.3%) in the placebo group and 9.2% (95% CI, 5.9% to 14.2%) for patients in the mepolizumab group. The probability of undergoing nasal surgery at any time before week 52 was statistically significantly lower in the mepolizumab group than in the placebo group (hazard ratio = 0.43; 95% CI, 0.25 to 0.76; P = 0.003).

A reduced need for surgery was deemed to be important by patient groups. However, the durability of the treatment effect could not be assessed due to the short duration of, and the low number of patients entering, the follow-up period.

### Work Productivity

At week 52, improvements were observed across all Work Productivity and Activity Impairment — General Health (WPAI-GH) domains, except for work time missed due to health. At week 52, impairment due to health while working was reported by 22.9% and 18.5% of patients in the placebo and mepolizumab groups, respectively. Overall work impairment due to health was reported by 27.0% and 20.6% of patients in the placebo and mepolizumab groups, respectively. Activity impairment due to health was reported by 27.1% and 19.2% of patients in the placebo and mepolizumab groups, respectively. Finally, 6.4% and 4.3% of patients reported work time missed due to health in the placebo and mepolizumab groups, respectively.

## *Harms Results*

Key harm results are summarized in Table 2.

### Adverse Events

During the 52-week study period, the proportion of patients who reported at least 1 adverse event (AE) was 84% and 82% in the placebo and mepolizumab groups, respectively. The 3 most common AEs reported in the placebo and mepolizumab groups were nasopharyngitis (23% and 25%, respectively), headache (22% and 18%), and sinusitis (11% and 5%). The following AEs were reported in less than 10% but greater than 5% of patients in either treatment group: epistaxis, asthma, nasal polyps, back pain, upper respiratory tract infection, acute sinusitis, cough, bronchitis, oropharyngeal pain, otitis media, and arthralgia.

### Serious AEs

Serious AEs were reported in 7% and 6% of patients in the placebo and mepolizumab groups, respectively. No single serious AEs were reported in more than 1% of patients in either treatment group.

### Withdrawals due to AEs

Two percent of patients in each group discontinued treatment due to any AE. The AEs contributing to withdrawal from treatment were not specified.

### Mortality

Death occurred in 1 patient in the placebo group. The 1 death was related to a fatal myocardial infarction during the follow-up period after week 52.

### Notable Harms

Potential opportunistic infections were reported by 2.48% and 1.46% of patients in the placebo and mepolizumab groups, respectively. Opportunistic infections reported by patients in the placebo group included herpes zoster, oral herpes, candida infection, and oropharyngeal candidiasis. In the mepolizumab group, herpes zoster, oral herpes, and candida infections were reported. Serious infections were reported by 2% and 0.49% of patients in the placebo and mepolizumab groups, respectively. Serious infections reported included acute sinusitis, cellulitis, and influenza in the placebo group and pneumonia in the mepolizumab group. Local injection site reactions were reported by 1.0% of patients in the placebo group and 2.43% of patients in the mepolizumab group. Systemic site reactions were reported in 0.50% and 0.97% of patients in the placebo and mepolizumab groups, respectively. No anaphylaxis events were reported in either group. In the placebo group, serious cardiac, vascular, and thromboembolic events were reported in 1.0% of patients and serious ischemic events in 0.50% of patients. In the mepolizumab group, serious cardiac disorder; serious cardiac, vascular, and thromboembolic events; and serious ischemic events were reported in 1 patient each.

### *Critical Appraisal*

The SYNAPSE trial was limited by between-group imbalances at baseline. First, a greater proportion of patients in the placebo group than in the mepolizumab group initiated therapy with LTRA before treatment with the study drug (17% versus 12%); a potential confounding effect of LTRA cannot be ruled out. Second, a greater proportion of patients in the placebo group than in the mepolizumab group had had 2 or more surgeries (60% versus 48%) at baseline. While it is unclear whether the need for more surgery was a function of disease severity or disease duration, it is a potential marker of treatment resistance. More patients in the mepolizumab group than in the placebo group experienced at least 1 asthma exacerbation in the 12 months before screening (26% versus 15%) and at least 1 asthma exacerbation requiring systemic corticosteroids but not hospitalization or an emergency room visit in the 12 months before screening (20% versus 12%). Overall, these baseline imbalances may have had an impact on the assessment of differences in treatment effects between groups, yet the magnitude and direction of the bias remain uncertain.

Other between-group imbalances — namely, greater use of concomitant medications and greater protocol deviations in the placebo group — may have influenced the treatment effect. During the treatment period, a greater proportion of patients in the placebo group than in the mepolizumab group initiated concomitant treatment with any systemic corticosteroid (46% versus 34%). Likewise, a greater proportion of patients in the placebo group than in the mepolizumab group, albeit a low percentage overall, made use of a rescue short-acting

## Table 2: Summary of Key Results From the SYNAPSE Trial — ITT Population

| Outcome | SYNAPSE | |
|---|---|---|
| | Placebo (n = 201) | Mepolizumab (n = 206) |
| **Severity of nasal polyps** | | |
| Change in total endoscopic nasal polyp score from baseline | | |
| Mean (SD) | −0.1 (1.46) | −0.9 (1.90) |
| Median | 0 | −1.0 |
| IQR | −1.0 to 1.0 | −2.0 to 0.0 |
| Analysis of change from baseline | | |
| Adjusted median difference (95% CI)[a] | — | −0.73 (−1.11 to −0.34) |
| P value[b] | — | < 0.001 |
| **Nasal obstruction** | | |
| Change in nasal obstruction VAS score from baseline to week 52 | | |
| Mean (SD) | −2.45 (3.15) | −4.24 (3.42) |
| Median | −0.82 | −4.41 |
| IQR | −4.84 to 0.0 | −7.27 to −0.36 |
| Analysis of change from baseline | | |
| Adjusted median difference (95% CI)[a] | — | −3.14 (−4.09 to −2.18) |
| P value[b] | — | < 0.001 |
| **Symptoms** | | |
| Nasal symptom composite VAS score[c] (ITT) | | |
| Change from baseline to week 52 | | |
| Mean (SD) | −2.19 (2.82) | −3.81 (3.19) |
| Median | −0.89 | −3.96 |
| IQR | −4.06 to 0.0 | −6.68 to −0.32 |
| Analysis of change from baseline | | |
| Adjusted median difference (95% CI)[a] | — | −2.68 (−3.44 to −1.91) |
| Multiplicity-adjusted P value[b,d] | — | 0.020 |
| Nasal symptoms and facial pain composite VAS score[e] | | |
| Change from baseline to week 52 | | |
| Mean (SD) | −2.24 (2.88) | −3.80 (3.18) |
| Median | −0.99 | −3.88 |
| IQR | −4.29 to 0.0 | −6.45 to −0.25 |
| Analysis of change from baseline | | |

| Outcome | SYNAPSE | |
|---|---|---|
| | Placebo (n = 201) | Mepolizumab (n = 206) |
| Adjusted median difference (95% CI)[a] | — | −2.50 (−3.33 to −1.67) |
| P value[b] | — | < 0.001 |
| Loss of smell VAS score | | |
| Change from baseline to week 52 | | |
| Mean (SD) | −1.38 (2.65) | −2.83 (3.61) |
| Median | 0.0 | −0.53 |
| IQR | −1.28 to 0.0 | −5.60 to 0.0 |
| Analysis of change from baseline | | |
| Adjusted median treatment (95% CI)[a] | — | −0.37 (−0.65 to −0.08) |
| Multiplicity-adjusted P value[b,d] | — | 0.020 |
| **Nasal congestion** | | |
| Change in PnIF from baseline to week 52[i] | | |
| Mean (SD) | 11.2 (65.78) | 32.5 (57.98) |
| Median | 0.0 | 30.0 |
| IQR | −20.0 to 50.0 | 0.0 to 60.0 |
| **Response to treatment** | | |
| Response based on total endoscopic nasal polyp score[f] | | |
| Responders, n (%) | 57 (28) | 104 (50) |
| Nonresponders, n (%) | 144 (72) | 102 (50) |
| No change or worsening | 77 (38) | 62 (30) |
| Analysis of group difference | | |
| Odds ratio (95% CI) to placebo[g] | — | 2.74 (1.80 to 4.18) |
| P value | — | < 0.001 |
| Response based on SNOT-22[h] | | |
| n | 198 | 205 |
| Responders, n (%) | 106 (54) | 150 (73) |
| Nonresponders, n (%) | 92 (46) | 55 (27) |
| ≥ 1-point to < 8.9-point improvement | 13 (7) | 8 (4) |
| No change or worsening | 15 (8) | 9 (4) |
| Analysis of group difference | | |
| Odds ratio (95% CI) to placebo[g] | — | 2.44 (1.60 to 3.73) |
| P value | — | < 0.001 |

| Outcome | SYNAPSE | |
|---|---|---|
| | Placebo (n = 201) | Mepolizumab (n = 206) |
| **Health-related quality of life** | | |
| **SNOT-22** | | |
| Change from baseline to week 52 | | |
| n | 198 | 205 |
| Mean (SD) | −15.7 (23.93) | −29.4 (24.67) |
| Median | −14.0 | −30.0 |
| IQR | −31.0 to 0.0 | −46.0 to −4.0 |
| Analysis of change from baseline | | |
| Adjusted median difference (95% CI)[a] | — | −16.49 (−23.57 to −9.42) |
| Multiplicity-adjusted P value[b,d] | — | 0.003 |
| **SF-36** | | |
| Change in PCS from baseline to week 52[i] | | |
| n | 198 | 205 |
| Mean (SD) | 1.89 (7.65) | 6.99 (8.35) |
| Median | 0.0 | 6.75 |
| IQR | −1.75 to 4.61 | 0.0 to 12.59 |
| Change in MCS from baseline to week 52[i] | | |
| n | 198 | 205 |
| Mean (SD) | 1.04 (10.23) | 4.0 (10.45) |
| Median | 0.0 | 1.20 |
| IQR | −3.75 to 5.76 | −2.60 to 10.08 |
| **Systemic steroid use for nasal polyps** | | |
| At end of week 52 | | |
| Patients with at least 1 course, n (%) | 74 (37) | 52 (25) |
| Analysis of group difference[i] | | |
| Odds ratio to placebo (95% CI)[j] | — | 0.58 (0.36 to 0.92) |
| Multiplicity-adjusted P value[d,j] | — | 0.02 |
| **Time to first nasal polyp surgery** | | |
| Time to surgery by week 24 | | |
| Patients with at least 1 surgery, n (%) | 18 (9) | 8 (4) |
| Probability of surgery (95% CI)[k] | 9.1 (5.8 to 14.0) | 4.0 (2.0 to 7.8) |
| Time to surgery at end of week 52 | | |

| Outcome | SYNAPSE | |
|---|---|---|
| | Placebo (n = 201) | Mepolizumab (n = 206) |
| Patients with at least 1 surgery, n (%) | 46 (23) | 18 (9) |
| Probability of surgery (95% CI)[k] | 23.6 (18.3 to 30.3) | 9.2 (5.9 to 14.2) |
| Analysis of group difference | | |
| Hazard ratio (95% CI)[l] | — | 0.43 (0.25 to 0.76) |
| Multiplicity-adjusted P value[d,l] | — | 0.003 |
| **Work productivity** | | |
| WPAI-GH at week 52 | | |
| Work time missed due to health | | |
| n | 115 | 130 |
| Mean, % of patients (SD) | 6.4 (17.59) | 4.3 (12.63) |
| Median, % of patients | 0 | 0 |
| Impairment while working due to health | | |
| n | 113 | 128 |
| Mean, % of patients (SD) | 22.9 (25.45) | 18.5 (23.71) |
| Median, % of patients | 10.0 | 10.0 |
| Overall work impairment due to health | | |
| n | 115 | 130 |
| Mean, % of patients (SD) | 27.0 (28.69) | 20.6 (26.4) |
| Median, % of patients | 20.0 | 10.0 |
| Activity impairment due to health | | |
| n | 176 | 185 |
| Mean, % of patients (SD) | 27.1 (28.14) | 19.2 (24.09) |
| Median, % of patients | 20.0 | 10.0 |
| **Summary of harms: safety population** | | |
| Patients with ≥ 1 AE, n (%) | 168 (84) | 169 (82) |
| Patients with ≥ 1 SAE, n (%) | 14 (7) | 12 (6) |
| Patients who discontinued treatment due to AEs, n (%) | 4 (2) | 4 (2) |
| Death | 1 (0.50) | 0 |
| Notable harms, n (%) | | |
| Systemic site reactions | 1 (0.50) | 2 (0.97) |
| Local injection site reactions | 2 (1.0) | 5 (2.43) |
| Serious infection | 4 (2) | 1 (0.49) |
| Potential opportunistic infections | 7 (3.48) | 3 (1.46) |

| Outcome | SYNAPSE | |
|---|---|---|
| | Placebo (n = 201) | Mepolizumab (n = 206) |
| Serious cardiac disorders | 0 (0) | 1 (0.49) |
| Serious CVT events | 2 (1.0) | 1 (0.49) |
| Serious ischemic events | 1 (0.50) | 1 (0.49) |

AE = adverse event; CI = confidence interval; CVT = cardiac, vascular, and thromboembolic; IQR = interquartile range; ITT = intention to treat; MCS = mental component summary; PCS = physical component summary; PnIF = peak nasal inspiratory flow; SAE = serious adverse event; SD = standard deviation; SF-36 = Short Form (36) Health Survey; SNOT-22 = Sino-Nasal Outcome Test 22; VAS = visual analogue scale; WPAI-GH = Work Productivity and Activity Impairment — General Health.

Note: Patients with nasal surgery or sinuplasty who withdrew from study before visit were assigned their worst observed score before nasal surgery or sinuplasty. Patients with no nasal surgery or sinuplasty who withdrew from study before visit were assigned their worst observed score before study withdrawal. Patients with missing visit data were assigned their worst observed score before the missing visit.

[a]Quantile regression with covariates of treatment group, geographic region, baseline score, and log(e) baseline blood eosinophil count.

[b]Based on Wilcoxon rank sum test.

[c]Composed of the individual VAS scores of nasal obstruction, nasal discharge, mucus in the throat, and loss of smell.

[d]Multiplicity controlled through testing end points following a predefined hierarchy.

[e]Composed of the individual VAS scores of nasal obstruction, nasal discharge, mucus in the throat, loss of smell, and facial pain.

[f]Defined as a patient with a 1-point or greater improvement from baseline in the endoscopic nasal polyp score and the absence of surgery or sinuplasty before that visit.

[g]Analysis performed using a logistic regression model with covariates of treatment group, geographic region, baseline score, and log(e) baseline blood eosinophil count.

[h]Defined as a patient with a greater than 8.9-point improvement (decrease) from baseline at a given time point in the absence of surgery or sinuplasty before that visit.

[i]Difference in change from baseline between placebo and mepolizumab groups was not available in the Clinical Study Report for SYNAPSE.

[j]Analysis using logistic regression model with covariates of treatment group, geographic region, number of oral corticosteroid courses for nasal polyps in last 12 months (0, 1, > 1 as ordinal), baseline total endoscopic score (centrally read), baseline nasal obstruction VAS score, and log(e) baseline blood eosinophil count.

[k]Estimated using Kaplan-Meier.

[l]Estimated from a Cox proportional hazard model with covariates of treatment group, geographic region, baseline total endoscopic score (centrally read), baseline nasal obstruction VAS score, log(e) baseline blood eosinophil count, and number of previous surgeries (1, 2, > 2 as ordinal).

Source: SYNAPSE Clinical Study Report.[8]

beta2-agonist inhaler (9% versus 1%). According to the clinical expert consulted by CADTH, the use of systemic corticosteroids for any reason or the use of rescue corticosteroid (but not short-acting beta2-agonist) medication for asthma may improve nasal polyp symptoms, thereby potentially introducing bias against mepolizumab into the results. While the impact of these additional interventions could not be assessed due to the small percentage of patients requiring their use during the study period, it is possible that that the placebo group benefited from the additional therapies.

A greater proportion of patients in the placebo group than in the mepolizumab group discontinued treatment (17% versus 11%), and a substantial proportion of patients were documented with an incomplete (42% versus 31%) or missing (6% versus 4%) end point assessment. The majority of missed or incomplete assessments were due to missing clinical chemistry, hematology, and/or urinalysis due to spoiled samples; however, missed visits or phone calls related to patient diary, health-related quality of life (HRQoL), and work productivity occurred in 10% and 5% of patients in the placebo and mepolizumab groups, respectively. To mitigate discontinuation and missed assessments, patients were assigned their worst observed score before withdrawal or missed assessment. However, the high percentage of major protocol violations (65% in the placebo group versus 55% in the mepolizumab group) may have compromised the quality of the data from this trial, which may have had an impact on the assessment of efficacy outcomes.

Overall, the study population represented the patients who were more likely to adhere to the long-term use of the study drug. The 4-week run-in period further excluded those patients who met the study eligibility criteria (severe CRSwNP with at least 1 surgery for recurrent nasal

polyps and refractory to standard of care) but who were intolerant or poorly adherent to the study drug or procedures (21% did not meet the continuation criteria). An enrichment design tends to overestimate the treatment effectiveness in the clinical practice setting. Clinical improvements noted in the placebo group during the treatment period raised the question of how much of the maintained treatment effect observed during the follow-up period in the mepolizumab group was due to mepolizumab versus standard of care with INCS, given that full onset of action of intranasal steroids may be delayed for some patients.[9] As noted by the clinical expert, adherence to persistent daily INCS may have led to the placebo group maintaining the modest improvement experienced during the treatment period. Consequently, uncertainty exists in how much of the treatment effect observed in the mepolizumab group was due to the efficacy of mepolizumab versus the effectiveness of MF therapy, although both groups were on INCS therapy. All these factors contributed to the difficulty in interpreting and assessing the generalizability of the efficacy results.

### Indirect Comparisons

No indirect treatment comparisons were included in the sponsor's submission to CADTH or identified in the literature search.

### Other Relevant Evidence

No long-term extension studies or other relevant studies were included in the sponsor's submission to CADTH or identified in the literature search.

## Conclusions

Based on the SYNAPSE trial, mepolizumab as an add-on maintenance therapy in combination with standard of care was efficacious in achieving endoscopic improvement and relief of nasal obstruction as measured by the VAS in patients with severe recurrent CRSwNP inadequately controlled by inhaled nasal corticosteroids alone. Moreover, mepolizumab was found to be efficacious in prolonging time to nasal surgery, reducing the need for systemic corticosteroids for nasal polyps, and improving CRSwNP symptoms. However, the magnitude of the treatment effect was modest. Based on the response observed in the placebo group and on input from the clinical expert consulted by CADTH for this review, the extent to which these improvements were due to treatment with mepolizumab remains uncertain. Mepolizumab appeared to be well tolerated. However, due to the lack of head-to-head trials or availability of indirect treatment comparisons, it remains unknown how mepolizumab compares in efficacy and safety to other similar maintenance therapy for severe recurrent CRSwNP. Despite these limitations, mepolizumab fills an unmet need for more treatment options for patients with severe CRSwNP inadequately controlled with standard of care.

# Introduction

## Disease Background

CRS is a chronic inflammatory disease of the nasal passage linings and/or sinuses. CRS is defined by the presence of anterior or posterior rhinorrhea, nasal congestion, hyposmia, and/or facial pressure or pain lasting for more than 12 weeks.[10] CRS may be subcategorized as CRSwNP or CRS without nasal polyps.[2] Nasal polyps are outgrowths of sino-nasal tissues,

and those that accompany CRS are benign. These nasal polyps typically develop bilaterally in the sino-nasal cavity.[1] Currently, Canadian data on the prevalence and incidence of CRSwNP are not available. The prevalence of CRSwNP is estimated to be between 1% and 4% of the general US population and between 25% and 30% of patients with CRS.[1,10] CRSwNP is more common in men and older individuals.[11] Symptoms of CRSwNP tend to be more severe than those associated with CRS without nasal polyps.[12,13] Key symptoms of CRSwNP include nasal obstruction and hyposmia or anosmia,[3] as well as rhinorrhea, severe nasal congestion, and loss of smell or taste.[4,5] The long-term symptoms associated with CRSwNP (i.e., prominent nasal obstruction, postnasal drip, loss of smell, and discharge) negatively impact physical and mental HRQoL.[1,6] Disease burden is particularly high among patients who require repeated treatment with corticosteroids and/or sino-nasal surgeries to alleviate uncontrolled symptoms.[14] Some studies suggest that the impact of CRSwNP on HRQoL is comparable with other chronic diseases such as chronic obstructive pulmonary disease, asthma, and diabetes.[15,16]

Symptomatic assessment of CRSwNP, as defined by the European Position Paper on Rhinosinusitis and Nasal Polyps guidelines,[10] is as follows: inflammation of the nose and the paranasal sinuses characterized by 2 or more symptoms, 1 of which should either be nasal blockage, obstruction, or congestion or nasal discharge (anterior or posterior nasal drip) with or without facial pain or pressure and with or without reduction or loss of smell for 12 weeks or more. Diagnosis is confirmed upon evidence of sino-nasal inflammation and nasal polyps on sinus via CT scan and/or nasal endoscopy. Currently, there are no single validated biomarkers to distinguish CRSwNP from CRS without nasal polyps, acute sinusitis, or no sinus disease at all.

The exact etiology of nasal polyps is unknown, although allergies, asthma,[17-19] and gene polymorphism[20-22] have been implicated in nasal polyp occurrence in adults.[1] Inflammatory mediators may also play a role in the development of nasal polyps, including the cytokines IL-4, IL-5, and IL-13 and the C-C motif chemokines ligands 24 and 26. In Western countries, CRSwNP is often associated with eosinophilic inflammation. Those who show evidence of type 2 airway inflammation also present with comorbid asthma and/or nonsteroidal anti-inflammatory drug-exacerbated respiratory disease. Additional contributors to nasal polyps include microbial colonization such as the *Alternaria* species and *Staphylococcus aureus*.[23]

## Standards of Therapy

The goal of therapy for CRSwNP is to reduce symptoms and complications by minimizing inflammation and controlling secondary infection from CRS. However, treatment options for patients with CRSwNP are limited.[6] Initial treatment for CRSwNP generally starts with an INCS, such as mometasone. The European Position Paper on Rhinosinusitis and Nasal Polyps reported that there is high-quality evidence indicating that treatment with nasal corticosteroids improves symptomatology, reduces nasal polyp size, and improves PnIF.[24] When administered after endoscopic sinus surgery, INCS have shown to prevent polyp recurrence.[9] Antibiotics are initiated for patients with CRSwNP suspected to have a bacterial infection as indicated by pain, documented purulence, or recurrent episodes of sinusitis. Long-term use of antibiotics, however, is not recommended due to potential increased risk of AEs.

Other medical treatments that may be considered are oral steroids, systemic and topical steroids, LTRAs, and ASA desensitization. Monoclonal antibodies, such as dupilumab, are also approved for the treatment of CRSwNP by Health Canada, but use of dupilumab in clinical practice in Canada is currently limited due to the lack of insurance coverage.

Endoscopic sinus surgery is reserved for patients whose CRSwNP is not responsive to medical treatment. Surgery has been shown to reduce disease burden and prevent or prolong the time to polyp recurrence. However, nasal polyps may still recur post-surgery.[25] Indeed, 10% to 30% of patients with CRSwNP require revision surgery within 5 years.[26]

### Drug

Mepolizumab is a targeted anti-IL-5 IgG1 kappa monoclonal antibody.[7] Mepolizumab binds to soluble IL-5 with high affinity, preventing IL-5 from binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface, thereby reducing the production and survival of eosinophils. Inflammation is an important component in the pathogenesis of asthma, CRSwNP, and eosinophilic granulomatosis with polyangiitis. The reduction of eosinophilic inflammation may play an important role in eliciting a therapeutic effect in the treatment of the aforementioned conditions; however, the precise mechanism of mepolizumab action has not been definitively established.

On November 5, 2021, mepolizumab received a Notice of Compliance from Health Canada as add-on maintenance treatment with INCS in adult patients with severe CRSwNP inadequately controlled by INCS alone.[27] Health Canada recommends that mepolizumab be administered as a subcutaneous injection at a dose of 100 mg/mL once every 4 weeks.

Mepolizumab was approved by the European Medicines Agency in December 2021as add-on maintenance therapy with INCS for the treatment of adult patients with severe CRSwNP for whom therapy with systemic corticosteroid and/or surgery do not provide adequate control;[28] this indication is the same as approved by Health Canada and the subject of the current CADTH review. Mepolizumab received approval from the FDA in July 2021 as add-on maintenance treatment for CRSwNP in adult patients 18 years and older who experience inadequate response to nasal corticosteroids.[29]

## Stakeholder Perspectives

### Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups. The full original patient input(s) received by CADTH have been included in the Stakeholder Input section at the end of this report.

Patient input was provided by 2 groups: Asthma Canada and the Patient Lung Groups of the BCLA. Asthma Canada conducted an online survey of patients with severe CRSwNP and caregivers residing across 7 Canadian provinces between April and May 2022 (n = 17). Two survey respondents reported experience with mepolizumab; patients did not specify how they received access to mepolizumab. The BCLA summarized its collective knowledge and experience gained through research, practice guidelines, and the direct care of patients with asthma and other respiratory diseases.

Survey respondents indicated that CRSwNP symptoms had had a direct negative impact on their daily lives, including decreased quality of life (90%), sleep disturbances (66%), missed time from work or school (30%), financial difficulties (20%), and hospital visits because of CRSwNP (20%). Among the survey respondents who identified as caregivers, 66% reported

an impact on sleep (related to sleep loss due to nighttime symptoms) and being burdened by managing frequent appointments (44%) and managing multiple medications (33%) for the patient they care for. Thirty-nine percent of survey respondents reported using nasal sprays to manage their CRSwNP, while 28% reported having surgery, 17% reported using OCS, and 17% reported using a biologic (e.g., dupilumab or omalizumab) to treat their nasal polyps. The side effects most reported by these patients included altered sense of smell (63%), allergic reactions (36%), mental or mood changes (27%), increased risk of sinus infection (27%), headaches or dizziness (18%), and ineffectiveness (18%). Of the 2 survey respondents with experience using mepolizumab, 1 reported improvement in quality of life and no side effects and the other reported improvement in nasal polyps and no exacerbations. From the information collected by the BCLA, reaction at injection site was reported as a common but minor side effect of mepolizumab, while some patients experienced blood eosinophilia after use of mepolizumab.

Patients and caregivers have deemed the following outcomes as important for new treatment options: easier management of symptoms (63%), decreased anxiety about nasal polyps (45%), decreased reliance on OCS or steroids (36%), reduced need for surgery (36%), and improved process for taking medication (27%). Other unmet needs that should be targeted by any new treatment options, as identified by the BCLA, included reduction or cessation of disease progression, improvement in lung function, reduction in lung attacks, and the prevention of subsequent hospitalizations.

## Clinician Input

### Input From Clinical Expert Consulted by CADTH

All CADTH review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol; assisting in the critical appraisal of clinical evidence; interpreting the clinical relevance of the results; and providing guidance on the potential place in therapy). The following input was provided by 1 clinical specialist with expertise in the diagnosis and management of CRSwNP.

#### *Unmet Needs*

According to the clinical expert consulted by CADTH, not all patients are responsive to current treatments for the management of CRSwNP. Patients with severe CRSwNP tend to be particularly resistant to treatment. Due to the chronic and recurring nature of CRSwNP, there is a medical need for targeted treatment of nasal polyps.

#### *Place in Therapy*

Recurrence of nasal polyps is most likely in the presence of high local levels of IL-5 and IgE, which drive eosinophilic inflammation. The anti-IL-5 mechanism of mepolizumab is anticipated to prevent the inflammation most associated with nasal polyp persistence and recurrence. According to the clinical expert, mepolizumab would be most appropriate for use in patients who do not experience control of symptoms or cannot tolerate topical steroid treatment.

#### *Patient Population*

According to the clinical expert consulted, patients with eosinophilic polyps are most likely to respond to anti-IL-5 treatments. Eosinophilic polyps can be identified via pathology at the time

of polyp removal. Neutrophilic polyps are less likely to respond to anti-IL-5 treatments. The clinical expert also noted that biologics would be considered unnecessary among patients who respond to topical steroids.

*Assessing Response to Treatment*

Based on clinical expert input, response to treatment is based on the severity of nasal congestion, usually with SNOT-22. Response to treatment should typically occur within 6 months of initiating therapy. The clinical expert noted that while use of systemic steroids should be reduced during this time, more than 6 months may be needed in resistant patients to document response.

*Discontinuing Treatment*

According to the clinical expert consulted, the need for prednisolone or surgery would indicate a loss of response to treatment. For those patients who require surgery, continued treatment with mepolizumab may be considered to prevent recurrence.

*Prescribing Conditions*

According to the clinical expert consulted, ear, nose, and throat specialists or allergists should diagnose, treat, and monitor patients who may receive mepolizumab.

### Clinician Group Input

No input was received from any clinician groups for this submission.

## Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's reimbursement review processes by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical expert consulted by CADTH are summarized in Table 3.

## Table 3: Summary of Drug Plan Input and Clinical Expert Response

| Drug program implementation questions | Clinical expert response |
|---|---|
| **Consideration for initiation of therapy** | |
| Are VAS scores and endoscopic bilateral NPSs routinely used in clinical practice? | VAS scores are not routinely used in clinical practice. |
| Is nasal endoscopy typically done by a specialist other than an ENT (e.g., allergists or respirologists), or would these specialists refer to an ENT for the procedures? | Endoscopic bilateral nasal polyp surgery is performed by an ENT and by some allergists. |
| When would nasal polyp surgery be contraindicated? | Nasal polyp surgery is considered contraindicated in patients who cannot undergo general anesthetic. |
| Would patients who have not had prior nasal polyp surgery or do not have bilateral disease still quality for coverage? | Patients who do not have bilateral disease should first undergo biopsy. If biopsy reveals benign eosinophilic polyps k, anti-IL-5 may be considered beneficial. If the patient has bilateral nasal polyps and cannot tolerate surgery, anti-IL-5 could be considered. |

| Drug program implementation questions | Clinical expert response |
|---|---|
| Can nasal polyps occur unilaterally? | Nasal polyps may occur unilaterally. In these cases, malignancy must be ruled out. Eosinophilic polyps, however, rarely occur unilaterally. However, such patients were not entered into the SYNAPSE trial. |
| Would LTRAs be trialled before mepolizumab in "appropriate patients"? Who would qualify as an "appropriate patient"? | While LTRAs target eosinophilic inflammation, the evidence regarding the efficacy of LTRAs in nasal polyps is weak and not as strong as for intranasal corticosteroids. |
| Should the criteria or implementation advice specify use of intranasal steroids at the Health Canada–approved dose for nasal polyps for at least 8 weeks? | Biologics would be considered unnecessary among patients who respond to topical steroids. |
| **Considerations for continuation or renewal of therapy** | |
| Would nasal endoscopy be used in clinical practice to assess response to treatment? | Nasal endoscopy is performed in clinical practice by an ENT or by allergists who are trained to perform nasal endoscopy. |
| Is 1 year an appropriate time frame for the initial assessment of therapeutic response vs. 6 months initially and annually thereafter? | While it is acceptable to change therapy if patients have not responded to treatment by 6 months, it may be best to assess initial response to therapy at 8 months to 12 months, since 6 months is required to reach a steady state. |
| How would response to treatment be defined in terms of improvement in the various scores (i.e., VAS, NPS, SNOT-22)? | An improved response to treatment as assessed by NPS and SNOT-22 may be defined by the established MID for the assessment tool. For the NPS, response to treatment is defined by an improvement (decrease in score) of at least 1, whereas for SNOT-22, response is defined by an improvement (decrease in score) of greater than 8.9. Response to treatment as assessed by VAS has not been definitively established. Generally, an improvement (decrease in score) between 2 and 5 indicates response to treatment when assessed by VAS. |
| **Consideration for discontinuation of therapy** | |
| How would loss of response or disease progression be defined? | The need for prednisolone or surgery would indicate a loss of response to treatment. For those patients who require surgery, continued treatment with mepolizumab may be considered to prevent recurrence. |
| **Consideration for prescribing of therapy** | |
| Is there potential for dose escalation for the CRSwNP indication? | Current studies have not been able to demonstrate a clinical difference of mepolizumab at higher doses, but there are not many studies published that have assessed this. |
| Would use of mepolizumab be a lifelong treatment? | While it is possible that treatment may be gradually withdrawn or even stopped in the case of clinical remission, for patients with large polyps that recur post-surgery, treatment may be lifelong. |

CRSwNP = chronic rhinosinusitis with nasal polyps; ENT = ear, nose, and throat specialist; IL = interleukin; LTRA = leukotriene receptor antagonist; MID = minimal important difference; NPS = nasal polyp score; SNOT-22 = Sino-Nasal Outcome Test 22; VAS = visual analogue scale.

# Clinical Evidence

The clinical evidence included in the review of mepolizumab is presented in only 1 section. The systemic review section includes pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those studies that were selected according to an a priori protocol. The other 2 sections that usually accompany the CADTH review are not applicable to the review of mepolizumab as no indirect evidence was identified from the literature, nor were any sponsor-submitted long-term extension studies or additional relevant studies submitted.

## Systematic Review: Pivotal and Protocol-Selected Studies

### Objectives

To perform a systematic review of the beneficial and harmful effects of mepolizumab 100 mg/mL as add-on maintenance treatment with INCS for the treatment of severe CRSwNP in adult patients inadequately controlled with INCS alone.

### Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those meeting the selection criteria presented in Table 4. Outcomes included in the CADTH review protocol reflect outcomes considered to be important to patients, clinicians, and drug plans.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the PRESS (Peer Review of Electronic Search Strategies) checklist.

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid and Embase (1974–) via Ovid. All Ovid searches were run simultaneously as a multifile search. Duplicates were removed using Ovid deduplication for multifile searches, followed by manual deduplication in Endnote. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were mepolizumab and chronic rhinosinusitis with nasal polyps. Clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, WHO's International Clinical Trials Registry Platform search portal, Health Canada's Clinical Trials Database, and the European Union Clinical Trials Register.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. Refer to Appendix 1 for the detailed search strategies.

The initial search was completed on June 6, 2022. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee on May 16, 2020.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the *Grey Matters: A Practical Tool for Searching Health-Related Grey Literature* checklist. Included in this search were the websites of regulatory agencies (the FDA and the European Medicines Agency). Google was used to search for additional

## Table 4: Inclusion Criteria for the Systematic Review

| Criteria | Description |
|---|---|
| **Population** | Adult patients 18 years and older with severe CRSwNP inadequately controlled by intranasal corticosteroids alone<br>**Subgroups:**<br>• Asthma diagnosis (yes/no)<br>• Prior surgery (yes/no) |
| **Intervention** | Mepolizumab, 100 mg administered by SC injection once every 4 weeks, used in combination with intranasal corticosteroids and/or saline irrigation |
| **Comparator** | Intranasal corticosteroids and/or saline irrigation |
| **Outcomes** | **Efficacy outcomes:**<br>• Nasal obstruction<br>  ◦ VAS for nasal obstruction<br>• Symptoms[a]<br>  ◦ composite VAS symptom score for nasal discharge, feeling of mucus in the throat, loss of smell, facial pain, and nasal polyp symptoms<br>  ◦ sense of smell<br>• Response to treatment<br>  ◦ change in nasal polyp size<br>• Severity of nasal polyps and nasal obstruction<br>  ◦ endoscopic nasal polyp score<br>• Nasal congestion<br>  ◦ PnIF<br>• HRQoL[a]<br>  ◦ SNOT-22<br>• Systemic steroid use for nasal polyps[a]<br>• Nasal inflammation<br>  ◦ CT imaging<br>• Nasal polyp surgery[a]<br>  ◦ need for nasal surgery<br>  ◦ time to first nasal surgery<br>  ◦ nasal surgery at 24 weeks<br>• Work productivity<br>  ◦ WPAI-GH<br>**Harms outcomes:**<br>AEs, SAEs, WDAEs, mortality, and notable harms of special interest, including systemic and local injection site reactions; serious and opportunistic infection; serious cardiac, vascular, and thromboembolic events; and serious ischemic events. |
| **Study designs** | Published and unpublished phase III and IV RCTs |

AE = adverse event; CRSwNP = chronic rhinosinusitis with nasal polyps; HRQoL = health-related quality of life; PnIF = peak nasal inspiratory flow; RCT = randomized controlled trial; SAE = serious adverse event; SC = subcutaneous; SNOT-22 = Sino-Nasal Outcome Test 22; VAS = visual analogue scale; WDAE = withdrawal due to adverse event; WPAI-GH = Work Productivity and Activity Impairment — General Health.

[a]These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

internet-based materials. Refer to Appendix 1 for more information on the grey literature search strategy.

These searches were supplemented through the review of bibliographies of key papers and through contacts with appropriate experts. In addition, the sponsor was contacted for information regarding unpublished studies.

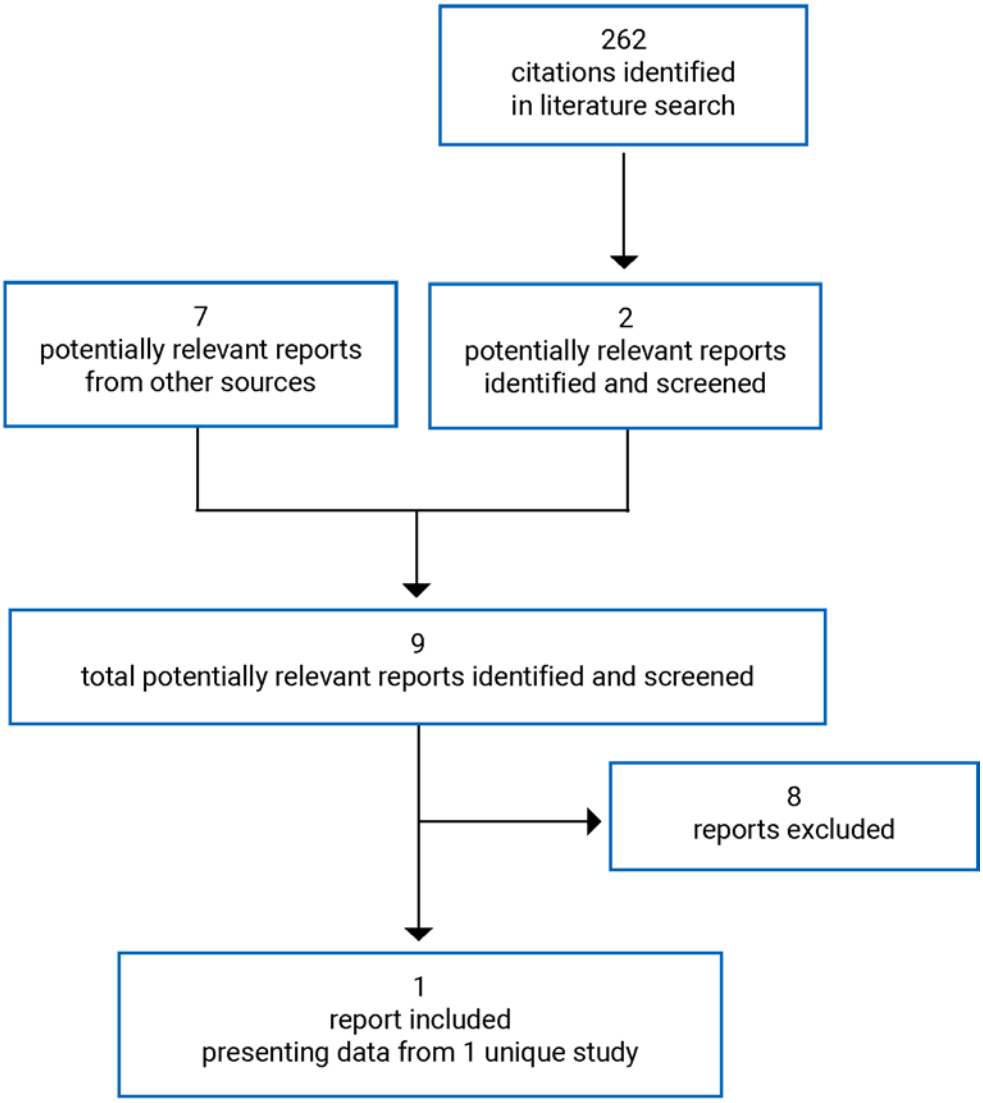
Two CADTH clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least 1 reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

A focused literature search for indirect treatment comparisons dealing with CRSwNP was run in MEDLINE All (1946–) via Ovid and Embase (1974) via Ovid on June 6, 2022. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results.

## Findings From the Literature

One study was identified from the literature for inclusion in the systematic review (Figure 1). The included study is summarized in Table 5. A list of excluded studies is presented in Appendix 2.

## Figure 1: Flow Diagram for Inclusion and Exclusion of Studies




## Table 5: Details of Included Study

| Detail | Description |
|---|---|
| **Design and population** | |
| **Study design** | Phase III, multicentre, double-blind, placebo-controlled, parallel group RCT |
| **Locations** | Study conducted across 86 sites in 11 countries (US, Argentina, Germany, Russian Federation, UK, Canada, Sweden, Australia, Republic of Korea, Romania, Netherlands) |
| **Patient enrolment dates** | December 11, 2010, to May 25, 2017 |
| **Randomized (N)** | 414 |

| Detail | Description |
|---|---|
| **Inclusion criteria** | • Male and non-pregnant female patients 18 years of age or older<br>• Had bilateral NPs as diagnosed by endoscopy or historical CT scan<br>• Had at least 1 surgery for removal of NPs within previous 10 years, with surgery defined as any procedure involving instruments resulting in incision and removal of NP tissue from the nasal cavity (polypectomy); not included are procedures limited to instrumentation in the nasal cavity resulting in dilation of the nasal passage (i.e., balloon sinuplasty, insertion of coated stents, or direct injection of steroids or other medication without any removal of NP tissue)<br>**Prior to screening:**<br>• Had treatment with INCS, including INCS via intranasal liquid steroid wash or douching, for at least 8 weeks before screening<br>• Showed symptoms of CRS, defined as the presence for at least 12 weeks before screening of nasal blockage, obstruction, or congestion, or nasal discharge (anterior or posterior nasal drip), and at least 1 of the following:<br>◦ nasal discharge (anterior or posterior nasal drip)<br>◦ facial pain or pressure<br>◦ reduction or loss of sense of smell<br>**At screening:**<br>• Had severe NP symptoms, defined as an obstruction VAS symptom score of > 5 out of a maximum of 10 and severity consistent with a need for surgery as described by an overall VAS symptom score of 7 out of a maximum of 10 and an endoscopic bilateral NP score of ≥ 5 out of a maximum of 8 (with a minimum score of 2 in each nasal cavity)<br>**At randomization (end of 4-week run-in period):**<br>• Have an endoscopic NP score of at least 3 in one nostril and 2 in the other as per read from central lab taken at visit 1 (screening)<br>• Have a mean overall symptom VAS score > 7 over the 7 days preceding visit 2 (randomization)<br>• Have a mean nasal obstruction VAS score > 5 over the 7 days preceding visit 2<br>• Not had any NP surgery or placed on a waiting list for NP surgery between visit 1 and visit 2<br>• Agree to be removed from waiting list and/or cancel surgery if included on a waiting list for NP surgery or had a preplanned NP surgery date<br>• Show electronic diary compliance for VAS (at least 4 out of the 7 days preceding visit 2)<br>• No evidence of a clinically significant abnormality in the hematological, biochemical, or urinalysis screen from visit 1, as judged by the investigators, or in liver function test values from visit 1 |
| **Exclusion criteria** | • Had antrochoanal polyps, nasal septal deviation occluding 1 nostril, or rhinitis medicamentosa within 6 months before visit 1<br>• Had undergone any intranasal and/or sinus surgery (e.g., polypectomy, balloon dilatation, or nasal stent insertion) within 6 months before visit 1<br>• NP surgery was contraindicated in the opinion of the investigator<br>• Had confounding conditions including cystic fibrosis, eosinophilic granulomatosis with polyangiitis (also known as Churg-Strauss syndrome), Young syndrome, Kartagener syndrome, dyskinetic ciliary syndrome, medical history of HIV infection, or a known, pre-existing parasitic infestation within 6 months before visit 1<br>• For patients who had asthma:<br>◦ had an asthma exacerbation requiring admission to hospital within the 4 weeks before screening |

| Detail | Description |
|---|---|
| | ◦ had used systemic corticosteroid, including OCS, within the 4 weeks before screening<br>◦ were planning to use systemic corticosteroids during the double-blind period<br>◦ had INCS dose changes within the 1 month before screening<br>**At randomization (end of 4-week run-in period):**<br>• Had changes in CRSwNP maintenance therapy during the run-in period, including change in or addition of an INCS, a course of systemic corticosteroids such as OCS, leukotriene receptor antagonist, or allergen immunotherapy<br>• For patients with asthma:<br>◦ had an asthma exacerbation during the run-in period, defined as worsening of asthma requiring systemic corticosteroids (IV or oral steroid) for at least 3 days, or a single IM dose and/or emergency department visit, or hospitalization |
| **Drugs** | |
| **Intervention** | Mepolizumab, 100 mg/mL, administered by SC injection every 4 weeks for 52 weeks in combination with SoC<br>**SoC:**<br>INCS (MF) and OCS (prednisolone, prednisone, or methylprednisolone for Republic of Korea only) |
| **Comparator(s)** | Matching placebo administered by SC injection every 4 weeks for 52 weeks in combination with SoC<br>**SoC:**<br>INCS (MF) and OCS (prednisolone, prednisone, or methylprednisolone for Republic of Korea only) |
| **Duration** | |
| **Phase** | |
| Run-in | 4 weeks |
| Double-blind | 52 weeks |
| Follow-up | 24 weeks for up to the first 200 patients |
| **Outcomes** | |
| **Primary end point** | **Co-primary end points:**<br>• Change from baseline in endoscopic NP score at week 52<br>• Change from baseline in nasal obstruction VAS symptom score during the 4 weeks before week 52 |
| **Secondary and exploratory end points** | **Key secondary:**<br>• Time to first actual surgery for NP by week 52<br>**Other secondary:**<br>• Change from baseline in mean overall VAS symptom score during the 4 weeks before week 52<br>• Change from baseline in SNOT-22 total score at week 52<br>• Proportion of participants requiring systemic steroids for NPs for week 52<br>• Change from baseline in the mean composite VAS symptom score (combining VAS score for nasal obstruction, nasal discharge, mucus in the throat, and loss of smell) during the 4 weeks before week 52 |

| Detail | Description |
|---|---|
| | • Change from baseline in mean individual VAS symptom score for loss of smell during the 4 weeks before week 52<br>**Exploratory:**<br>• Percentage of participants classified as responder according to a 1-point or greater decrease from baseline NP score at week 52<br>• Change from baseline in mean individual VAS symptom score for nasal discharge, mucus in the throat, and facial pain during the 4 weeks before week 52<br>• Change from baseline in mean compositive VAS score (combining VAS score for nasal discharge, mucus in the throat, loss of smell, and facial pain) during the 4 weeks before week 52<br>• Change from baseline in UPSIT at week 52<br>• Change from baseline in PnIF at week 52<br>• Percentage of participants classified at week 52 as responders according to an 8.9-point or greater decrease from baseline in SNOT-22 total score<br>• Change from baseline in SNOT-22 domain scores at week 52<br>• Rate of nasal surgery up to week 52<br>• Time to first inclusion on waiting list for NP surgery up to week 52<br>• Percentage of participants classified as "need for surgery"' responders according to NP score and overall VAS symptom score<br>• Presence of exploratory blood biomarkers, including blood eosinophils, on response to mepolizumab<br>• Change from baseline SF-36 MCS, PCS, and 8-dimension summary score at week 52<br>• Change from baseline WPAI questionnaire at week 52<br>• Number of courses of systemic steroid therapy up to week 52<br>• Number of milligrams per year of prednisolone-equivalent OCS dose up to week 52<br>• Number of days on systemic steroid therapy up to week 52<br>• Time to first course of OCS up to week 52<br>• Time to first course of OCS up to week 52<br>• Number of courses of antibiotic up to week 52<br>• Change from baseline in ACQ-5 at week 52<br>• Number of clinically significant asthma exacerbations, defined as worsening of asthma requiring systemic corticosteroids (IV or oral steroid) for at least 3 days or a single IM<br>• Corticosteroid dose and/or emergency department visit and/or hospitalization for asthma up to week 52<br>**For all patients who entered post-treatment follow-up period:**<br>• Change from baseline in total endoscopic NP score<br>• Change from baseline in mean nasal obstruction VAS score<br>• Change from baseline in mean individual VAS symptoms score for nasal discharge, mucus in throat, loss of smell, facial pain, and overall VAS symptom score during the 4 weeks before week 76<br>• Number of milligrams per year of prednisolone-equivalent OCS dose<br>• Change from baseline SF-36 MCS, PCS, and 8-dimension summary scores<br>• Change from baseline in WPAI questionnaire<br>• Time to first nasal surgery, including off-treatment period, from randomization to week 76 |

| Detail | Description |
|---|---|
| | • Time to first inclusion on waiting list for NP surgery up to week 76<br>**Safety:**<br>• AEs and SAEs<br>• Vital signs<br>• Hematological and clinical chemistry parameters<br>• 12-lead ECG derived end points<br>• Presence of anti-mepolizumab antibodies<br>**PKs:**<br>• PK concentration and population PK parameters<br>• PK/PD (blood eosinophil count) analysis |
| **Notes** | |
| Publications | Han et al. (2021)[30] |

ACQ-5 = Asthma Control Questionnaire 5; AE = adverse event; aka = also known as; CRS = chronic rhinosinusitis; CRSwNP = chronic rhinosinusitis with nasal polyps; ECG = electrocardiogram; IM = intramuscular; INCS = intranasal corticosteroids; MCS = mental component summary; MF = mometasone furoate; NP = nasal polyp; OCS = oral corticosteroids; PCS = physical component summary; PD = pharmacodynamic; PK = pharmacokinetic; PnIF = peak nasal inspiratory flow; RCT = randomized controlled trial; SAE = serious adverse event; SF-36 = Short Form (36) Health Survey; SC = subcutaneous; SoC = standard of care; SNOT-22 = Sino-Nasal Outcome Test 22; UPSIT = University of Pennsylvania Smell Identification Test; VAS = visual analogue scale; WPAI = Work Productivity and Activity Impairment.

Note: Two additional reports were included.[27,29]

Source: SYNAPSE Clinical Study Report.[8]

## Description of Studies

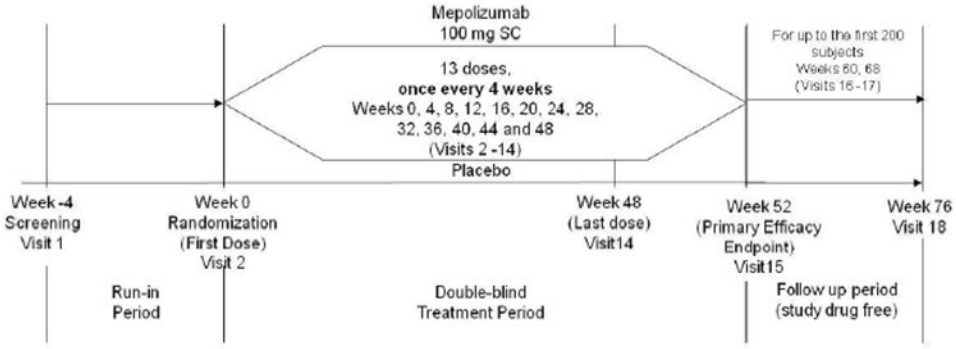
One sponsor-conducted study that met the CADTH review protocol criteria was included in this systematic review. SYNAPSE was a randomized, double-blind, placebo-controlled, parallel group trial assessing the clinical efficacy and safety of 100 mg/mL mepolizumab as an add-on maintenance treatment in adults with recurrent CRSwNP that was not adequately controlled with optimized medical treatment. A total of 414 adult patients were randomized at 86 sites across 11 countries, including 34 (8.2%) patients across 8 sites in Canada. The study comprised a 4-week run-in period to allow assessment for tolerability of INCS at its maximum dose, followed by a 52-week treatment period in which patients were randomized to receive either mepolizumab or matching placebo in addition to standard of care with INCS. During the treatment period, patients who completed the full treatment regimen received a total of 13 doses of mepolizumab 100 mg/mL or placebo delivered by subcutaneous injection using a prefilled safety syringe. The final dose of the study treatment was administered at week 48. Patients who withdrew from the study treatment prematurely were encouraged to remain in the study per protocol until week 52. Patients who completed the week 52 assessment were considered to have completed the study. The first 200 patients randomized into the study also entered a 6-month no-treatment follow-up period following their week 52 visit to assess maintenance of response. The final visit for the no-treatment follow-up period occurred on week 76. All patients remained on standard of care treatment for CRSwNP throughout the study. Standard of care treatment included daily MF and, if required, saline nasal douching and/or an occasional short course of high-dose OCS and/or antibiotics. A schematic of the SYNAPSE trial is presented in Figure 2.

The randomization schedule was generated using the validated randomization software RandAll NG and was stratified by country. Countries were grouped into regions with consideration for standard of care, medical practice, number of patients enrolled, and regulatory considerations. Treatment allocation was done via an interactive response

technology, the Registration and Medication Ordering System Next Generation, per the randomization schedule. Treatment assignment was kept blind to all persons (i.e., physician, nurse, and patients) involved in the study. Post-randomization, the site staff and central study team were blinded to patients' eosinophil count, including white blood count differential. Treatment codes could be unblinded by the investigator or treating physician only in the case of a medical emergency or in the event of a serious medical condition in which knowledge of the investigational product was essential for clinical management or patient welfare.

The co-primary efficacy end points were change from baseline in endoscopic nasal polyp score at week 52 and change from baseline in nasal obstruction VAS symptom score during the 4 weeks before week 52. The key secondary end point was time to first actual surgery for nasal polyps by week 52. Other secondary end points included change from baseline in the overall VAS symptom score, change from baseline in SNOT-22 score, the proportion of patients requiring systemic steroids for nasal polyps, change from baseline composite VAS symptom score (combining VAS scores for nasal obstruction, nasal discharge, mucus in the throat, and loss of smell), and change from baseline in loss of smell VAS score.

## Figure 2: Study Schema for the SYNAPSE Trial




SC = subcutaneous.

Source: SYNAPSE Clinical Study Report.[8]

### *Protocol Amendments*

The original study protocol (dated December 8, 2016) was amended 4 times. Protocol amendment 1 (May 15, 2017) was made before the first patient final visit (May 25, 2017) and applied only to study sites in the Republic of Korea to support country-specific requirements. Protocol amendments 2 (July 14, 2017) and 3 (February 20, 2018) were made after the first patient final visit and applied to all sites. Protocol amendment 2 reflected comments from the investigator to clarify protocol points and reflected the removal of CT scan and exit interviews as well as simplifying the end point related to reduction of endoscopic nasal polyp score. Protocol amendment 3 clarified that screen failures could also be re-screened. Protocol amendment 4 (February 13, 2020) was made after the last patient's last visit (December 11, 2019) but before unblinding and was related to the data analysis. Protocol amendment 4 reflected regulatory authority feedback to update the analysis methodology for the co-primary end points, including imputation rules; limit the definition of surgery for the key secondary end point to include only events involving polypectomy in the nasal cavity; update the OCS end point; and include 2 additional secondary end points of composite nasal symptom score and loss of smell VAS score, which were previously included as "other" end points.

## Populations

### *Inclusion and Exclusion Criteria*

The key inclusion and exclusion criteria for the SYNAPSE trial are summarized in Table 5. Patients eligible for inclusion were male and non-pregnant female adults 18 years or older with bilateral nasal polyps and recurrent CRSwNP that was not adequately controlled with optimized medical treatment. Eligible patients were required to have had at least 1 surgery for the removal of nasal polyps within the previous 10 years and treatment with INCS for at least 8 weeks before screening. Patients were also required to show symptoms of CRS. At screening, participants were required to have severe nasal polyp symptoms, defined as an obstruction VAS symptom score of greater than 5 out of a maximum of 10 and severity consistent with need for surgery as described by an overall VAS symptom score greater than 7 out of a maximum of 10, and an endoscopic bilateral nasal polyp score of 5 or greater out of a maximum of 8.

Patients were excluded from the trial if they had antrochoanal polyps, nasal septal deviation occluding 1 nostril, or rhinitis medicamentosa; had undergone any intranasal and/or sinus surgery within the 6 months before visit 1; or had a confounding medical condition. They were also excluded if nasal polyp surgery was contraindicated for them in the opinion of the investigator. Patients with asthma who had an asthma exacerbation requiring admission to hospital within 4 weeks of screening, had used systemic corticosteroid within 4 weeks before screening, or were planning to use such medications during trials were excluded from the trial.

### *Baseline Characteristics*

Baseline characteristics, demographics, and disease history are summarized in Table 6.

Overall, randomized patients had a mean age of 48.8 years (SD = 13.01) and a mean body mass index of 28.16 kg/m$^2$ (SD = 5.36). The majority of patients were between 40 and 64 years old (58%), male (65%), and white (93%). The mean time since onset of nasal polyps at baseline was 11.41 years (SD = 8.39). All patients had had at least 1 surgery for nasal polyps in the past 10 years. While the majority of patients had a history of 1 or 2 surgeries (70%), a greater proportion of patients in the placebo group than the mepolizumab group had had more than 1 surgery (60% versus 48%). Approximately half the patients had received at least 1 course of OCS for nasal polyps in the 12 months before screening. At baseline, the overall mean total endoscopic score, nasal obstruction VAS score, overall symptom VAS scores, and SNOT-22 total scores were 5.5 (SD = 1.29), 8.97 (SD = 0.83), 9.07 (SD = 0.74), and 64.1 (SD = 18.32), respectively. All were similar between the treatment groups.

Seventy-one percent of patients had a diagnosis of asthma at screening. Of these, some patients had experienced an asthma exacerbation (20%) or required systemic corticosteroid for an asthma exacerbation that did not require hospitalization or an emergency room visit (16%) in the 12 months before screening.

## Table 6: Summary of Baseline Demographic and Disease Characteristics — ITT Population

| Characteristic | SYNAPSE (N = 407) | |
|---|---|---|
| | Placebo (n = 201) | Mepolizumab (n = 206) |
| **Demographics** | | |
| Male sex, n (%) | 125 (62.2) | 139 (67.5) |
| Age, years | | |
| Mean (SD) | 48.9 (12.46) | 48.6 (13.55) |
| Min to max | 20 to 82 | 18 to 79 |
| Age group, years, n (%) | | |
| 18 to < 40 | 52 (26) | 64 (31) |
| 40 to < 65 | 122 (61) | 113 (55) |
| ≥ 65 | 27 (13) | 29 (14) |
| Race, n (%) | | |
| White — White/Caucasia/European heritage | 183 (91) | 190 (92) |
| Asian — East Asian heritage | 7 (3) | 6 (3) |
| Black or African American | 4 (2) | 5 (2) |
| White — Arabic/North African heritage | 4 (2) | 2 |
| Asian — Central/South Asian heritage | 1 | 2 |
| Asian — South-East Asian heritage | 1 | 1 |
| Multiple | 1 | 0 |
| Body mass index, $kg/m^2$ | | |
| Mean (SD) | 28.17 (5.45) | 28.15 (5.26) |
| Min to max | 17.34 to 49.29 | 18.59 to 44.71 |
| **Disease history and characteristics** | | |
| Duration of nasal polyps, years | | |
| Mean (SD) | 11.46 (8.27) | 11.36 (8.52) |
| Min to max | 0.6 to 48.0 | 1.0 to 42.0 |
| Duration of nasal polyps, years, n (%) | | |
| < 1 | 4 (2) | 0 |
| ≥ 1 to < 5 | 35 (17) | 47 (23) |
| ≥ 5 to < 10 | 61 (30) | 60 (29) |
| ≥ 10 to < 15 | 40 (20) | 42 (20) |
| ≥ 15 to < 20 | 35 (17) | 27 (13) |
| ≥ 20 to < 25 | 13 (6) | 11 (5) |
| ≥ 25 | 13 (6) | 19 (9) |

| Characteristic | SYNAPSE (N = 407) | |
|---|---|---|
| | Placebo (n = 201) | Mepolizumab (n = 206) |
| Previous surgeries for nasal polyps in past 10 years, n (%) | | |
| 0 | 0 | 0 |
| 1 | 81 (40) | 108 (52) |
| 2 | 47 (23) | 47 (23) |
| 3 | 35 (17) | 27 (13) |
| 4 | 12 (6) | 13 (6) |
| 5 | 15 (7) | 4 (2) |
| > 5 | 11 (5) | 7 (3) |
| Number of courses of OCS for nasal polyps in the previous 12 months, n (%) | | |
| 0 | 110 (55) | 100 (49) |
| 1 | 47 (23) | 64 (31) |
| 2 | 18 (9) | 17 (8) |
| > 2 | 26 (13) | 25 (12) |
| Screening total endoscopic score[a] | | |
| n | 200 | 206 |
| Mean (SD) | 5.9 (0.94) | 5.9 (0.86) |
| Min to max | 4 to 8 | 4 to 8 |
| Baseline total endoscopic score[a] | | |
| Mean (SD) | 5.6 (1.41) | 5.4 (1.17) |
| Min to max | 0 to 8 | 2 to 8 |
| Baseline nasal obstructive VAS score[a] | | |
| Mean (SD) | 9.02 (0.83) | 8.92 (0.83) |
| Min to max | 5.31 to 10.0 | 6.54 to 10.0 |
| Baseline overall symptoms VAS score | | |
| Mean (SD) | 9.10 (0.72) | 9.04 (0.77) |
| Min to max | 7.21 to 10.0 | 7.17 to 10.0 |
| Baseline SNOT-22 total score[b] | | |
| n | 198 | 205 |
| Mean (SD) | 64.4 (19.04) | 63.7 (17.64) |
| Min to max | 19 to 110 | 17 to 105 |
| **Asthma history in the 12 months before screening** | | |
| Patients with asthma, n (%) | 149 (74.1) | 140 (68.0) |

| Characteristic | SYNAPSE (N = 407) | |
|---|---|---|
| | Placebo (n = 201) | Mepolizumab (n = 206) |
| Total number of asthma exacerbations,[c] n (%) | | |
| 0 | 127 (85) | 104 (74) |
| 1 | 12 (8) | 23 (16) |
| 2 | 6 (4) | 5 (4) |
| 3 | 0 | 5 (4) |
| ≥ 4 | 4 (3) | 3 (2) |
| Asthma exacerbations requiring systemic corticosteroids but not requiring hospitalization or emergency room visit,[c] n (%) | | |
| 0 | 131 (88) | 112 (80) |
| 1 | 10 (7) | 18 (13) |
| 2 | 4 (3) | 5 (4) |
| 3 | 1 | 4 (3) |
| ≥ 4 | 3 (2) | 1 |

ITT = intention to treat; OCS = oral corticosteroids; SD = standard deviation; SNOT-22 = Sino-Nasal Outcome Test 22; VAS = visual analogue scale.

[a]Higher score indicates greater disease severity.

[b]Higher scores indicate worse quality of life.

[c]Denominator of percentages is the number of patients with asthma.

Source: SYNAPSE Clinical Study Report.[8]

## Interventions

### *Intervention*

Patients were randomized to receive either mepolizumab 100 mg/mL or matching placebo during a 52-week treatment period. Both treatments were administered in combination with standard of care. Mepolizumab and placebo were identical in appearance and provided as solution for injection in a blinded prefilled syringe, assembled as a safety syringe device for subcutaneous administration in the thigh, abdomen, or upper arm every 4 weeks by a health care professional. The last dose of the investigational product was administered at week 48.

### *Standard of Care*

Patients received standard of care treatments for CRSwNP throughout the study (run-in, treatment, and no-treatment follow-up periods). Standard of care medication for CRSwNP was provided by the study site. Standard of care treatment included daily MF and, if required, saline nasal douching and/or occasional short courses of high-dose OCS (prednisolone, prednisone, or methyl-prednisolone for Republic of Korea only) for CRSwNP and/or antibiotics for CRSwNP. Patients with a concurrent asthma diagnosis maintained their baseline standard of care asthma treatment. The use of rescue medications, such as OCS, was allowed at any time during the study.

At the start of the run-in period and throughout the study, patients were placed on MF at the maximum prescribed dose (if not already) according to the local label, if available, or in line with local standard of care. The maximum dose was 2 actuations (50 mcg per actuation) in each nostril twice daily, which equalled a total daily dose of 400 mcg. For patients who were intolerant to this dose, a lower dose of 200 mcg could be used (2 actuations [50 mcg per

actuation] in each nostril once daily). Changes in dosing regimen between screening and end of the study were not allowed.

*Concomitant Therapy*

Concomitant use of LTRAs and allergen immunotherapies was permitted, but their use could not be initiated, nor the dosing regimen changed, between screening and end of the study. Change in the dosing regimens of inhaled corticosteroids from screening to end of the study was also not permitted.

The following medications were not permitted during the study period: investigational monoclonal antibodies, omalizumab, or other monoclonal antibodies; experimental anti-inflammatory drugs; and immunosuppressive medications, including regular systemic corticosteroids, methotrexate, troleandomycin, cyclosporin, azathioprine, oral gold, chemotherapy used for conditions other than asthma; insertion of any non-drug or drug eluting nasal stents (e.g., propel stents), and direct steroid injections into nasal polyps.

## Outcomes

A list of efficacy end points identified in the CADTH review protocol that were assessed in the clinical trial is provided in Table 7. These end points are further summarized below. Detailed discussion and critical appraisal of the outcome measures are provided in Appendix 4.

### Table 7: Summary of Outcomes of Interest Identified in the CADTH Review Protocol

| Outcome measure | SYNAPSE |
|---|---|
| Nasal obstruction VAS score | Co-primary |
| Severity of nasal polyps and nasal obstruction<br>• Endoscopic nasal polyp score | Co-primary |
| Symptoms<br>• Composite VAS symptom score<br>• Loss of smell VAS score | Secondary |
| Response to treatment<br>• Improvement in total endoscopic nasal polyp score from baseline<br>• Improvement in SNOT-22 from baseline | Exploratory |
| Nasal congestion<br>• PnIF | Exploratory |
| HRQoL<br>• SNOT-22 | Secondary |
| • SF-36 MCS and PSC | Exploratory |
| Systemic steroid use for nasal polyps | Secondary |
| Time to surgery for nasal polyps | Key Secondary |
| Work productivity<br>• WPAI questionnaire | Exploratory |
| Frequency of AEs, SAEs, and notable harms | Safety |

AE = adverse event; HRQoL = health-related quality of life; MCS = mental component summary; PCS = physical component summary; PnIF = peak nasal inspiratory flow;

SAE = serious adverse event; SF-36 = Short Form (36) Health Survey; SNOT-22 = Sino-Nasal Outcome Test 22; VAS = visual analogue scale; WPAI = Work Productivity and Activity Impairment.

Source: SYNAPSE Clinical Study Report.[8]

*Severity of Nasal Polyps and Nasal Obstruction*

Endoscopic nasal polyp score was a co-primary end point in the SYNAPSE trial. Endoscopic nasal polyp score was determined using predefined parameters, as summarized in Table 8 and Figure 3.

Endoscopic nasal polyp assessment was performed on site by a trained health care professional, usually an ear, nose, and throat surgeon. Endoscopies were performed at baseline and then within a 3-day window before dosing for each study visit. The image recordings of the nasal endoscopies were sent to a central lab for blinded assessment. Endoscopies conducted at screening, randomization (baseline), and week 52 were assessed by 2 independent members of the centralized team. For all other visits, the blinded central read was conducted by a single assessor, and whenever possible by the same individual.

The total endoscopic nasal polyp score was the sum of the right and left nostril score. Scores ranged from 0 to 8, with higher scores indicating worse status. Using an anchor-based method, a 1-point or greater improvement (decrease) in total endoscopic nasal polyp score is considered a clinically MID in adult patients with CRSwNP that is medically managed.[31]

## Table 8: Description of Nasal Polyp Score

| Polyp score | Polyp size |
|---|---|
| 0 | No polyps |
| 1 | Small polyps in the middle meatus not reaching below the inferior border of the middle concha |
| 2 | Polyps reaching below the lower border of the middle turbinate |
| 3 | Large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle concha |
| 4 | Large polyps causing complete congestion or obstruction of the inferior meatus |

Source: SYNAPSE Clinical Study Report.[8]

*Nasal Obstruction*

Nasal obstruction was a co-primary end point in the SYNAPSE trial. Nasal obstruction was assessed using a VAS. The VAS was presented as an electronic diary (eDiary) and collected daily in the morning from screening to the end of the study period. Each day, patients were asked to indicate on the VAS the severity of their nasal obstruction, with the prompt, "Please rate your nasal obstruction at its worst over the previous 24 hours." The VAS was presented as a measurement scale from 0 to 100, which was pixelated to allow patients to select all integers within the scales. The scale was anchored on the left-hand side with 0 representing "none" and on the right-hand side with 100 representing "as bad as you can imagine." The method of data collection employed was demonstrated to be equivalent to the 10 cm VAS typically used for paper data collection.[32-35] Values for the VAS collected on the eDiary were divided by 10 and reported to 1 decimal place across the range 0 (none) to 10 (as bad as you can imagine). Currently, there is no established MID for nasal obstruction VAS score. According to the clinical expert consulted by CADTH, a change of score between 2 and 5 is considered clinically meaningful for VAS scores in the CRSwNP population.

*Symptoms*

The SYNAPSE trial assessed symptoms related to CRSwNP via VAS score, including the composite nasal symptom score (secondary end point) and the individual symptom of loss of smell.

Each day, patients were asked to indicate on a VAS the severity of their nasal obstruction, nasal discharge, mucus in the throat, loss of smell, and facial pain. Patients were presented with 1 VAS for each of the symptoms. VAS scores for each symptom were collected and scored as described above for nasal obstruction. The nasal symptom composite score combined the individual scores of nasal obstruction, nasal discharge, mucus in the throat, and loss of smell. The nasal symptom and facial pain composite score combined the individual scores of nasal obstructions, nasal discharge, mucus in the throat, loss of smell, and facial pain. Loss of smell alone was also recorded.

*Nasal Congestion*

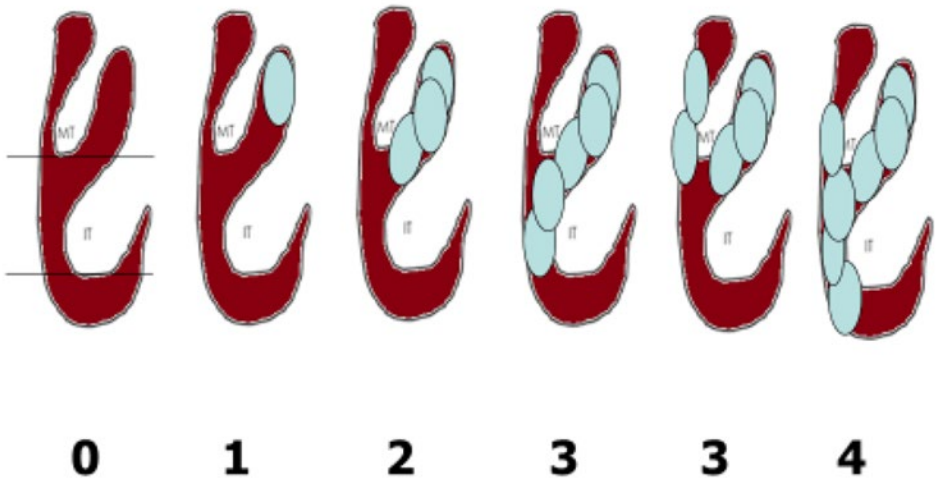
Nasal congestion was assessed via PnIF, which was measured using an In-Check flow meter. Patients were instructed to blow their nose and then inspire forcefully from the residual volume to total lung capacity with their mouth closed. All measurements were made in the sitting position. The highest value of 3 consecutive (maximal) readings was recorded. The MID in PnIF is a change of more than 20 L/min.[36]

*Health-Related Quality of Life*

HRQoL was assessed using SNOT-22[37] and the SF-36, version 2,[38] in the SYNAPSE trial.

SNOT-22 was designated as a secondary end point. SNOT-22 is a 22-item self-reported questionnaire used to assess symptoms and impacts related to CRS. The 22 items are categorized into the following 5 domains: nasal, non-nasal, ear and facial, sleep and fatigue, and emotional consequences. Questions are self-completed by patients based on their recall of their symptoms over the past 2 weeks. Patients are asked, "Considering how severe the

## Figure 3: Diagrammatic Representation of Nasal Polyp Score




IT = Inferior turbinate; MT = middle turbinate.
Source: SYNAPSE Clinical Study Report.[8]

problem is when you experience it and how often it happens, please rate each item below on how 'bad' it is." The response to each question ranges from 0 (no problem) to 5 (the problem is as bad as it can be). The final score is the sum of the individual scores from each question and ranges from 0 to 110. Higher scores indicate a greater negative impact of CRS on HRQoL. The MID for SNOT-22 is an improvement (decrease) in score of **at least** 8.9.[37]

The SF-36, version 2, is a generic self-reported health assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on HRQoL. The SF-36 consists of 8 domains: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional health problems, and mental health. The SF-36 also provides 2 component summaries: the PCS and the MCS, which are scores created by aggregating the 8 domains.[39] The PCS, MCS, and individual domains are each measured on a scale of 0 to 100, with an increasing score indicating improvement in health status.[39] Currently, there is no established MID for the CRSwNP population.

### *Response to Treatment*

Response to treatment was designated as an exploratory end point in the SYNAPSE trial and assessed using the endoscopic nasal polyp score and SNOT-22. Both outcome measures have been described above. Response to treatment as assessed by each of the instruments was matched to the appropriate MID.[31,37] A response to treatment as indicated by change in endoscopic nasal polyp score was defined as a 1-point or greater decrease in total baseline endoscopic nasal polyp score based on centrally read data at a given time point in the absence of surgery or sinuplasty.[31] Response to treatment as indicated by SNOT-22 was defined as an 8.9-point or greater decrease from baseline at week 52.[37]

### *Nasal Polyp Surgery*

Time to nasal polyp surgery was a key secondary outcome in the SYNAPSE trial. Nasal polyp surgery was defined as any procedure involving instruments resulting in incision and removal of tissue (polypectomy) in the nasal cavity. Dilation of the air passage in the nasal cavity (e.g., balloon sinuplasty) was not considered a surgical event.

### *Work Productivity*

Work productivity was designated as an exploratory end point in the SYNAPSE trial and measured using the WPAI-GH. The WPAI-GH is a self-administered 6-item questionnaire with a 7-day recall period that measures the impact of health problems on absenteeism (percentage of work time missed), presenteeism (percentage of impairment while working), percentage of overall work impairment due to health (combined absenteeism and presenteeism), and percentage of daily activity impairment. Patients completed the WPAI-GH using the eDiary at randomization and at each subsequent visit until study completion or early withdrawal. WPAI-GH outcomes are scored as impairment percentages (0% to 100%), with higher percentages indicating greater impairment of work productivity and daily activity.

## Statistical Analysis

The statistical analysis of efficacy end points conducted in the SYNAPSE trial is summarized in Table 9.

### *Sample Size Determination*

Sample size calculations were based on the co-primary efficacy end points of total endoscopic nasal polyp score and nasal obstruction VAS score at week 52 and on the key

secondary end point of time to actual surgery. A sample size of 200 patents per treatment arm was estimated to provide the study more than 90% power to observe statistical significance at a 2-sided 5% level for both the co-primary end points and for the key secondary end point of time to actual surgery. Calculations were based on the analysis of study MPP111782,[40] which demonstrated the following:

- 27% of patients in the placebo group experienced a 1-point improvement in nasal polyp score compared to 52% of patients in the mepolizumab group.
- For nasal blockage, 39% of patients in the placebo group experienced a 1-point improvement in nasal polyp score compared to 70% of patients in the mepolizumab group.
- For surgery, 20% of patients in the placebo group and 9% of patients in the mepolizumab group received surgery; a greater proportion of patients receiving surgery was expected in SYNAPSE.

*Primary Efficacy Analysis*

For each of the co-primary efficacy end points, the P value for comparing the treatment groups was based on the non-parametric Wilcoxon rank sum test. The difference in median change from baseline with a 95% CI was estimated by quantile regression using the bootstrap approach.[41,42] Covariates included in the statistical analysis models of the co-primary efficacy end points included randomized treatment group, region, baseline total nasal polyp score, and baseline $\log_e$ blood eosinophil count.

*Key Secondary Efficacy Analysis*

Time to first nasal surgery was analyzed by a Cox proportional hazard model. Hazard represented the probability of nasal surgery for a patient at a given point in time following the first dose of the investigational product, given the patient had not experienced the event before that time. Nasal surgery times were included in the analysis regardless of whether the surgery occurred before or after discontinuation of the investigational product. The nasal surgery time event was censored at the time of study withdrawal if a patient withdrew from the study before week 52 and before experiencing nasal surgery. Covariates included in the statistical analysis model of time to first nasal surgery were randomized treatment group, region, baseline total endoscopic nasal polyp score, baseline nasal obstruction VAS, baseline $\log_e$ blood eosinophil count, and number of previous surgeries (1, 2, > 2 as an ordinal variable).

*Secondary Efficacy Analysis*

Analysis for change from baseline VAS symptom scores, including overall VAS symptom score, mean composite VAS score, mean loss of smell, and SNOT-22 total score, was based on the non-parametric Wilcoxon rank sum test. The difference in median change from baseline with 95% CI was estimated by quantile regression using a bootstrap approach with adjusted covariates as detailed for the co-primary end point of change from baseline in mean nasal obstruction VAS score.

A logistic regression model was used to compare the proportion of patients requiring systemic steroids for nasal polyps. The odds ratio comparing treatment groups was estimated using the observed marginal distribution of the sample covariates. Covariates included randomized treatment group, region, baseline total nasal polyp score, baseline nasal obstruction VAS, baseline $\log_e$ blood eosinophil count, and number of OCS courses for nasal polyps in the previous 12 months (0, 1, > 1 as an ordinal variable).

*Multiple Comparison and Multiplicity*

Statistical significance for the first secondary end point in the hierarchy was dependent on statistical significance having been achieved for the 2 co-primary end points. Statistical significance for all other subsequent secondary end points was dependent on statistical significance having been achieved for the previous end point in the hierarchy. A closed testing procedure was used to control multiplicity according to the following predefined hierarchy:

1. Time to first nasal surgery
2. Change from baseline in overall VAS symptom score
3. Change from baseline SNOT-22 total score
4. Proportion of patients requiring systemic steroids for nasal polyps
5. Change from baseline in the mean composite VAS symptom score (nasal obstruction, nasal discharge, mucus in the throat, and loss of smell)
6. Change from baseline in mean individual VAS symptom score for loss of smell

*Subgroup Analysis*

For each co-primary end point, exploratory subgroup analyses were performed within the following subgroups: concurrent asthma and number of previous surgeries for nasal polyps. No formal hypothesis testing in the subgroups was performed.

*Analysis Populations*

Seven populations were defined for the purpose of data analysis. Definitions of the populations are summarized in Table 10.

## Table 9: Statistical Analysis of Efficacy End Points

| End point | Statistical model | Adjustment factors | Sensitivity analyses |
|---|---|---|---|
| Change from baseline in total endoscopic NP score at week 52<br>Change from baseline in mean nasal obstruction VAS score during the 4 weeks before week 52 | • Wilcoxon rank sum test with 95% CI estimated by quantile regression using a bootstrap approach<br>• 95% CI estimated by quantile regression using the bootstrap approach | Randomized treatment group, region, baseline score, baseline $\log_e$ blood eosinophil count | • Sensitivity analysis for impact of missing data, including MI and tipping point analysis<br>• Subgroup analysis within the subgroups, defined as concurrent asthma and number of previous surgeries for NPs |
| Time to first nasal surgery up to week 52 | Cox proportional hazard model | • Randomized treatment group, region, baseline total endoscopic NP score, baseline nasal obstruction VAS, baseline $\log_e$ blood eosinophil count, number of previous surgeries (1, 2, > 2 as an ordinal variable)<br>• Hierarchical closed testing procedure to control multiplicity | • Sensitivity analysis for impact of missing data, including MI and tipping point analysis<br>• Subgroup analysis within the subgroups, defined as concurrent asthma and number of previous surgeries for NPs |

| End point | Statistical model | Adjustment factors | Sensitivity analyses |
|---|---|---|---|
| Change from baseline in mean overall VAS symptom score during the 4 weeks before week 52<br>Change from baseline in SNOT-22 total score at week 52 | • Wilcoxon rank sum test with 95% CI estimated by quantile regression using a bootstrap approach<br>• 95% CI estimated by quantile regression using the bootstrap approach | • Randomized treatment group, region, baseline score, baseline $\log_e$ blood eosinophil count<br>• Hierarchical closed testing procedure to control multiplicity | None conducted |
| Proportion of patients requiring systemic steroids for NPs up to week 52 | • Logistic regression model<br>• Odds ratio estimated using the observed marginal distribution of the sample covariates | • Randomized treatment group, region, baseline total NP score, baseline nasal obstruction VAS, baseline $\log_e$ blood eosinophil count, number of oral corticosteroid courses for NPs in the previous 12 months (0, 1, > 1 as an ordinal variable)<br>• Hierarchical closed testing procedure to control multiplicity | None conducted |
| Change from baseline in the mean composite VAS symptom score during the 4 weeks before week 52<br>Change from baseline in mean individual VAS symptom score of loss of smell during the 4 weeks before week 52 | • Wilcoxon rank sum test with 95% CI estimated by quantile regression using a bootstrap approach<br>• 95% CI estimated by quantile regression using the bootstrap approach | • Randomized treatment group, region, baseline score, baseline $\log_e$ blood eosinophil count<br>• Hierarchical closed testing procedure to control multiplicity | None conducted |
| Change from baseline mean individual VAS symptom scores for nasal discharge, mucus in the throat, and facial pain during the 4 weeks before week 52 | • Wilcoxon rank sum test with 95% CI estimated by quantile regression using a bootstrap approach<br>• 95% CI was estimated by quantile regression using the bootstrap approach | Randomized treatment group, region, baseline score, baseline $\log_e$ blood eosinophil count | None conducted |
| Percentage of patients classified as responders based on change from baseline in | NR | NR | NR |

| End point | Statistical model | Adjustment factors | Sensitivity analyses |
|---|---|---|---|
| NP scores at week 52 | | | |
| Change from baseline in PnIF at week 52 | NR | NR | NR |
| Percentage of patients classified as responders based on change from baseline in SNOT-22 total score | NR | NR | NR |
| Percentage of patients classified as needing surgery based on NP score and overall VAS score | NR | NR | NR |
| Change from baseline SF-36 MCS and PCS | NR | NR | NR |
| Change from baseline WPAI questionnaire at week 52 | NR | NR | NR |

CI = confidence interval; MCS = mental component summary; MI = myocardial infarction; NP = nasal polyp; NR = not reported; PCS = physical component summary; PnIF = peak nasal inspiratory flow; SF-36 = Short Form (36) Health Survey; SNOT-22 = Sino-Nasal Outcome Test 22; VAS = visual analogue scale; WPAI = Work Productivity and Activity Impairment.

## Table 10: Summary of Analysis Populations

| Population | Definition | Analyses evaluated |
|---|---|---|
| ITT | • All randomized patients who had at least 1 dose of study treatment<br>• Data were analyzed according to randomized treatment arm | • Patient population<br>• Efficacy end points |
| Safety | • All randomized patients who had at least 1 dose of study treatment<br>• Data were analyzed according to actual treatment received for more than 50% of treatment administrations | Safety end point |
| PP | • All patients in the ITT population who were not identified as protocol deviators with respect to criteria that were considered to impact the primary efficacy analysis<br>• Protocol deviations that excluded participants from the PP population are defined in the SAP | Supplementary analyses of co-primary end points |
| Follow-up after week 52 | • All patients in the ITT population who participated in the no-treatment follow-up period after visit 15<br>• Data were summarized according to randomized treatment arms | Efficacy and safety end points |

ITT = intention to treat; PP = per protocol; SAP = statistical analysis plan.

## Results

### Patient Disposition

Patient disposition is summarized in Table 11.

Of the 854 patients who signed an informed consent form, 30 did not attend the screening visit (pre-screen failures) and 432 were withdrawn before randomization because they did not meet the entry criteria (27%) or did not meet the continuation criteria at the end of the run-in period (21%). Of the 414 patients randomized, 7 were randomized in error and did not receive any study treatment. Accordingly, 407 patients were included in the intention-to-treat (ITT) population, with 201 patients randomized to receive placebo and 206 randomized to receive mepolizumab. Patients were encouraged to remain in the study even if they discontinued the study treatment protocol; 92% completed the study to week 52 as scheduled. Withdrawal from the study treatment before week 52 was greater in the placebo group (16.9%) than in the mepolizumab group (11.2%). More patients in the mepolizumab group self-withdrew from the study treatment (52.2% versus 44.1%), and more patients in the placebo group discontinued treatment due to lack of efficacy (32.3% versus 21.7%).

### Table 11: Patient Disposition

| Disposition details | SYNAPSE | |
|---|---|---|
| | Placebo | Mepolizumab |
| **Screened, N** | 854 | |
| **Randomized, N** | 207 | 207 |
| **Discontinued treatment, N (%)** | 34 (16.9) | 23 (11.2) |
| **Reason for discontinuation, n (%)** | | |
| Adverse events | 4 (11.8) | 4 (17.4) |
| Lack of efficacy | 11 (32.3) | 5 (21.7) |
| Protocol deviation | 1 (2.9) | 0 (0) |
| Protocol-specific withdrawal[a] | 1 (2.9) | 1 (4.3) |
| Lost to follow-up | 0 (0) | 0 (0) |
| Withdrawal by physician | 2 (5.9) | 1 (4.3) |
| Withdrawal by patient[b] | 15 (44.1) | 12 (52.2) |
| **Completed to week 52, N (%) (even if IP discontinued)** | 184 (91.5) | 189 (91.7) |
| Completed study treatment as scheduled, n (%) | 167 (83.1) | 183 (88.8) |
| Withdrew before week 52, n (%) | 17 (8.5) | 17 (8.3) |
| Entered no-treatment phase, n | 65 | 69 |
| Completed no-treatment phase, n | 65 | 68 |
| **ITT, N[c]** | 201 | 206 |
| **PP, N** | 187 | 194 |
| **Follow-up after week 52, N** | 65 | 69 |

| Disposition details | SYNAPSE | |
|---|---|---|
| | Placebo | Mepolizumab |
| **Safety, N[c]** | 201 | 206 |

IP = investigational product; ITT = intention to treat; PP = per protocol.

[a]Protocol-specific withdrawal included patient meeting GlaxoSmithKline-defined liver chemistry stopping criteria, pregnancy, and meeting QT corrected for heart rate withdrawal criteria.

[b]Withdrawal by patient included the following reasons: relocation, frequency of visits, burden of procedures, and withdrawal due to serious adverse event (placebo).

[c]Excludes randomized patients who did not receive any dose of the IP.

Source: SYNAPSE Clinical Study Report.[8]

### Protocol Deviations

Protocol deviations are summarized in Table 12.

Major protocol deviations were documented for 65% and 55% of patients in the placebo and mepolizumab groups, respectively. The most frequently reported protocol deviations were related to assessment or time point completion and were mainly attributable to missing clinical chemistry, hematology, and/or urinalysis due to spoiled samples. Other frequently reported categories of protocol deviations were visit completion (17%); study procedures (14%); and wrong study, treatment, administration, or dose (9%).

After unblinding it was found that 4 patients (< 5%) had received a single dose of treatment that did not correspond to their randomization treatment: Two patients in the mepolizumab group received a single dose of placebo each; 2 patients in the placebo group received a single dose of mepolizumab each.

## Table 12: Protocol Deviations

| Protocol deviations | SYNAPSE | |
|---|---|---|
| | Placebo (n = 201) | Mepolizumab (n = 206) |
| **Any major protocol deviations, n (%)** | 130 (65) | 114 (55) |
| **Reasons for protocol deviations, n (%)** | | |
| Informed consent | 3 (1) | 4 (2) |
| Not signed or dated by site staff | 2 (1) | 0 |
| Wrong version signed | 0 | 2 (1) |
| Not signed or dated by patient | 0 | 2 (1) |
| Eligibility criteria not met | 5 (2) | 7 (3) |
| Medication excluded by the protocol was administered | 4 (2) | 4 (2) |
| Visit completion | 38 (19) | 31 (15) |
| Missed visit or phone contact | 20 (10) | 10 (5) |
| Out of window visit or phone contact | 25 (12) | 23 (11) |
| Assessment or time point completion | 91 (45) | 69 (33) |
| Missed assessment | 13 (6) | 9 (4) |
| Incomplete assessment | 85 (42) | 64 (31) |

| Protocol deviations | SYNAPSE | |
|---|---|---|
| | Placebo (n = 201) | Mepolizumab (n = 206) |
| Assessment not properly performed | 2 (1) | 0 |
| Wrong study treatment, administration, or dose | 17 (8) | 19 (9) |
| Study treatment not administered per protocol | 1 (< 1) | 1 (< 1) |
| Study treatment administered during contraindication | 0 | 0 |
| Wrong study treatment or assignment administered | 9 (4) | 11 (5) |
| Expired study treatment administered | 0 | 3 (1) |
| Use of study treatment impacted by temperature excursion (not reported/approved/disapproved for further use) | 5 (2) | 2 (1) |
| Other deviations related to wrong treatment, administration, or dose | 2 (1) | 3 (1) |
| Study procedure | 25 (12) | 30 (15) |
| Study blinding or unblinding procedures | 11 (5) | 11 (5) |
| Diary procedures | 11 (5) | 9 (4) |
| Equipment procedures | 1 (< 1) | 5 (2) |
| Post–study treatment observation not done | 3 (1) | 9 (4) |
| Biological sample specimen procedures | 3 (1) | 4 (2) |
| Failure to report safety events per protocol | 8 (4) | 3 (1) |
| SAE not reported within the expected time frame | 2 (1) | 1 (< 1) |
| Failure to confirm causality assessment within the expected time frame | 6 (3) | 2 (1) |

SAE = serious adverse event.

Note: Patients can have more than 1 important protocol deviation.

Source: SYNAPSE Clinical Study Report.[8]

## Exposure to Study Treatments

### *Extent of Exposure*

Mean exposure to study treatment was 11.2 months (SD = 2.33 months) and 11.3 months (SD = 2.21 months) in the placebo and mepolizumab treatment groups, respectively. A total of 134 patients continued in the follow-up after week 52;, the overall mean duration of time in the follow-up period was 5.40 months (SD = 0.55 months). The mean duration of time spent in the no-treatment follow-up period was similar between placebo and mepolizumab groups at 5.42 months (SD = 0.45 months) and 5.37 months (SD = 0.63 months), respectively.

### *Treatment Adherence*

A total of 160 patients (80%) in the placebo group and 180 patients (87%) in the mepolizumab group received all 13 treatment administrations. The mean number of treatments administered between the groups was similar (placebo: 12.0 [SD = 2.53]; mepolizumab: 12.2 [SD = 2.4]). The median number of treatments administered was 13 in both groups.

### *Prior Medications*

The medications used before beginning treatment with the investigational product are summarized in Table 13.

Overall, 98% of patients were receiving medications before the start of the study treatment. The most common medications were in the Anatomical Therapeutic Chemical classes of "respiratory system" (98%) and "dermatological" (88%). Across those classes, the proportion of patients receiving medications was similar between treatment groups.

Sixty-one patients (15%) and 6 patients (1%) were documented using LTRA or allergen immunotherapy, respectively. Leukotriene receptor antagonists were initiated before the first dose of the investigational product in 17% and 12% of patients in the placebo and mepolizumab groups, respectively. Allergen immunotherapy was initiated before the first dose of the investigational product in 2% and 0.97% of patients in the placebo and mepolizumab groups, respectively.

## Table 13: Medications Started Prior to Treatment — ITT Population

| | SYNAPSE | |
|---|---|---|
| ATC class of medication | Placebo (n = 201) | Mepolizumab (n = 206) |
| **Any medication,[a] n (%)** | **195 (97)** | **204 (99)** |
| Respiratory system | 194 (97) | 204 (99) |
| Mometasone furoate | 116 (58) | 116 (56) |
| Salbutamol | 56 (28) | 54 (26) |
| Fluticasone propionate + salmeterol xinafoate | 43 (21) | 37 (18) |
| Budesonide + formoterol fumarate | 33 (16) | 28 (14) |
| Budesonide | 26 (13) | 32 (16) |
| Dermatological | 175 (87) | 184 (89) |
| Mometasone furoate | 116 (58) | 116 (56) |
| Budesonide | 26 (13) | 32 (16) |
| Alimentary tract and metabolism | 77 (38) | 74 (36) |
| Budesonide | 26 (13) | 32 (16) |
| Cardiovascular system | 73 (36) | 72 (35) |
| Nervous system | 61 (30) | 47 (23) |
| Paracetamol | 20 (10) | 16 (8) |
| Systemic hormonal preparations, excluding sex hormones and insulins | 54 (27) | 53 (26) |
| Budesonide | 26 (13) | 32 (16) |
| Sensory organs | 32 (16) | 32 (16) |
| Genitourinary system and sex hormones | 26 (13) | 26 (13) |
| Blood and blood-forming organs | 26 (13) | 17 (8) |
| Musculoskeletal system | 23 (11) | 20 (10) |
| Various | 12 (6) | 11 (5) |
| Anti-infectives for systemic use | 8 (4) | 7 (3) |

| ATC class of medication | SYNAPSE | |
|---|---|---|
| | Placebo (n = 201) | Mepolizumab (n = 206) |
| Antineoplastic and immunomodulating agents | 4 (2) | 7 (3) |
| **Medications of interest, n (%)** | | |
| LTRA | 36 (17) | 25 (12) |
| Montelukast | 19 (9) | 11 (5) |
| Montelukast sodium | 17 (8) | 14 (7) |
| Allergen immunotherapy | 4 (2) | 2 (0.97) |
| Pollen and plant extract | 3 (1) | 0 |
| House dust and mite | 1 (0.50) | 0 |
| Not otherwise specified | 0 | 2 (0.97) |

ATC = Anatomical Therapeutic Chemical; ITT = intention to treat; LTRA = leukotriene receptor antagonist.

Note: Includes medications started before the first dose of investigational product. A medication may be included in more than 1 ATC category and appear more than once.

[a]Medication is reported in individual ATC class if used by more than 10% in either the placebo or mepolizumab group.

Source: SYNAPSE Clinical Study Report.[8]

*Concomitant Medications*

Concomitant medications started during the treatment period are summarized in Table 14.

Overall, 87% of patients in the placebo group and 82% of patients in the mepolizumab group started medication during the treatment period. The 2 most common concomitant medications started during the treatment period related to the respiratory system (placebo: 66%; mepolizumab: 56%) and alimentary tract and metabolism (placebo: 56%; mepolizumab: 52%).

A greater proportion of patients in the placebo group than in the mepolizumab group started systemic corticosteroid for any reason during the treatment period (46% compared with 34%).

Six patients were on LTRA treatment during the study period. Leukotriene receptor antagonist was initiated in 4 patients (2%) in the placebo group and 2 patients (1%) in the mepolizumab group. While concomitant use of allergen immunotherapies was permitted in the SYNAPSE trial, their use could not be initiated, or their dosing regimen changed, between screening and the end of the study period. Thus, no patients were started on allergen immunotherapy during the study period.

Concomitant treatment with rescue or reliever inhaler with short-acting beta2-agonist during the study treatment period was documented in 20 patients, with a greater proportion of patients in the placebo group reporting its use (placebo: 9%; mepolizumab: 1%).

## Table 14: Concomitant Medications Started During the Treatment Period — ITT Population

| ATC class of medication | SYNAPSE | |
|---|---|---|
| | Placebo (n = 201) | Mepolizumab (n = 206) |
| **Any medication,[a] n (%)** | **174 (87)** | **168 (82)** |
| Respiratory system | 133 (66) | 116 (56) |
| Prednisolone | 32 (16) | 31 (15) |
| Ibuprofen | 27 (13) | 21 (10) |
| Alimentary tract and metabolism | 113 (56) | 107 (52) |
| Prednisone | 34 (17) | 30 (15) |
| Prednisolone | 32 (16) | 31 (15) |
| Sensory organs | 111 (55) | 96 (47) |
| Prednisolone | 32 (16) | 31 (15) |
| Methylprednisolone | 21 (10) | 6 (3) |
| Anti-infectives for systemic use | 103 (51) | 89 (43) |
| Amoxicillin + clavulanic acid | 24 (12) | 17 (8) |
| Nervous system | 102 (51) | 89 (43) |
| Paracetamol | 52 (26) | 45 (22) |
| Ibuprofen | 27 (13) | 21 (10) |
| Dermatological | 98 (49) | 75 (36) |
| Prednisolone | 32 (16) | 31 (15) |
| Methylprednisolone | 21 (10) | 6 (3) |
| Systemic hormonal preparations, excluding sex hormones and insulin | 96 (48) | 74 (36) |
| Prednisone | 34 (17) | 30 (15) |
| Prednisolone | 32 (16) | 31 (15) |
| Methylprednisolone | 21 (10) | 6 (3) |
| Cardiovascular system | 87 (43) | 77 (37) |
| Prednisolone | 32 (16) | 31 (15) |
| Ibuprofen | 27 (13) | 21 (10) |
| Musculoskeletal system | 62 (31) | 53 (26) |
| Ibuprofen | 27 (13) | 21 (10) |
| Genitourinary system and sex hormones | 47 (23) | 39 (19) |
| Ibuprofen | 27 (13) | 21 (10) |
| Blood and blood-forming organs | 34 (17) | 32 (16) |
| Various | 37 (18) | 20 (10) |
| Antineoplastic and immunomodulating agents | 2 (0.99) | 6 (3) |

| ATC class of medication | SYNAPSE | |
|---|---|---|
| | Placebo (n = 201) | Mepolizumab (n = 206) |
| Antiparasitic products, insecticides, and repellents | 2 (0.99) | 0 |
| **Systemic corticosteroids**[a] | | |
| Any systemic corticosteroids | 92 (46) | 70 (34) |
| Prednisone | 34 (17) | 30 (15) |
| Prednisolone | 32 (16) | 31 (15) |
| Methylprednisolone | 21 (10) | 6 (3) |
| **Medications of interest** | | |
| LTRA | 4 (2) | 2 (1) |
| Montelukast | 1 (0.50) | 1 (0.50) |
| Montelukast sodium | 3 (1) | 1 (0.50) |
| **Rescue or reliever inhaler** | | |
| Short-acting beta2-agonist inhaler | 18 (9) | 2 (1) |
| Salbutamol | 10 (5) | 1 (0.50) |
| Salbutamol sulphate | 2 (0.99) | 1 (0.50) |
| Ipratropium bromide + salbutamol sulphate | 3 (1) | 0 (0) |
| Ipratropium bromide + salbutamol | 1 (0.50) | 0 (0) |
| Terbutaline sulphate | 2 (0.99) | 0 (0) |

ATC = Anatomical Therapeutic Chemical; ITT = intention to treat; LTRA = leukotriene receptor antagonist.

Note: Includes medications started between first and last dose plus 28 days (inclusive) of investigational product. A medication may be included in more than 1 ATC category and appear more than once.

[a]Medications are reported in individual ATC class if used by more than 10% in either the placebo or mepolizumab group.

Source: SYNAPSE Clinical Study Report.[8]

## Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported below. Refer to Appendix 3 for detailed data on exploratory symptom end points.

### *Severity of Nasal Polyps*

The co-primary end point of total endoscopic nasal polyp score is summarized in Table 15.

At the end of the 52-week treatment period, the mean change in total endoscopic nasal polyp score from baseline was −0.1 (SD = 1.46) and −0.9 (SD = 1.90) in the placebo and mepolizumab groups, respectively. The median change from baseline in the placebo and mepolizumab groups was 0 (IQR, −1.0 to 1.0) and −1.0 (IQR, −2.0 to 0.0), respectively. The adjusted median difference in change from baseline to week 52 was statistically significant in favour of mepolizumab compared to placebo (−0.73; 95% CI, −1.11 to −0.34; P < 0.001).

## Table 15: Total Endoscopic Nasal Polyp Score — ITT Population

| Total endoscopic nasal polyp score | SYNAPSE | |
|---|---|---|
| | Placebo (n = 201) | Mepolizumab (n = 206) |
| **Baseline score** | | |
| Mean (SD) | 5.6 (1.41) | 5.4 (1.17) |
| Median | 6.0 | 5.0 |
| **End of treatment period at week 52** | | |
| **Week 52 score** | | |
| Mean (SD) | 5.4 (1.85) | 4.5 (1.85) |
| Median | 6.0 | 5.0 |
| **Improvement from baseline, n (%)** | | |
| ≥ 5-point improvement | 2 (1) | 6 (3) |
| 4-point improvement | 5 (2) | 16 (8) |
| 3-point improvement | 11 (5) | 23 (11) |
| 2-point improvement | 8 (4) | 29 (14) |
| 1-point improvement | 31 (15) | 30 (15) |
| No change | 83 (41) | 57 (28) |
| Worsening | 61 (30) | 45 (22) |
| **Change from baseline** | | |
| Mean (SD) change | −0.1 (1.46) | −0.9 (1.90) |
| Median change from baseline | 0 | −1.0 |
| IQR | −1.0 to 1.0 | −2.0 to 0.0 |
| **Analysis of change from baseline** | | |
| Adjusted treatment difference in medians (95% CI)[a] | | −0.73 (−1.11 to −0.34) |
| P value[b] | | < 0.001 |

CI = confidence interval; IQR = interquartile range; ITT = intention to treat; SD = standard deviation.

Note: Patients with nasal surgery or sinuplasty who withdrew from study before visit were assigned their worst observed score before nasal surgery or sinuplasty. Patients with no nasal surgery or sinuplasty who withdrew from study before visit were assigned their worst observed score before study withdrawal. Patients with missing visit data were assigned their worst observed score before the missing visit.

[a]Quantile regression with covariates of treatment group, geographic region, baseline score, and log(e) baseline blood eosinophil count.

[b]Based on Wilcoxon rank sum test.

Source: SYNAPSE Clinical Study Report.[8]

### Responder Analysis

Response to treatment according to the total endoscopic nasal polyp score is summarized in Table 16. Response to treatment was defined as a patient who had an improvement (decrease) of 1.0 point or more from baseline in the absence of surgery or sinuplasty.

Twenty-eight percent and 50% of patients in the placebo and mepolizumab groups demonstrated a 1-point or greater improvement in their total endoscopic nasal polyp score

at the end of the 52-week treatment period. The odds ratio of being a responder in the mepolizumab group compared to in the placebo group was 2.74 (95% CI, 1.80 to 4.18).

### Subgroup Analysis

Results of the subgroup analyses in patients with or without concurrent asthma and in patients with or without prior surgery for nasal polyps in terms of change from baseline in total endoscopic nasal polyp score at week 52 are summarized in Table 17. No formal hypothesis testing was done; therefore, whether the effect of mepolizumab differs between these subgroups is unknown.

## Table 16: Response to Treatment Based on Total Endoscopic Nasal Polyp Score at Week 52 — ITT Population

| Response status | SYNAPSE | |
|---|---|---|
| | Placebo (n = 201) | Mepolizumab (n = 206) |
| Responders,[a] n (%) | 57 (28) | 104 (50) |
| Nonresponders, n (%) | 144 (72) | 102 (50) |
| No change or worsening | 77 (38) | 62 (30) |
| **Analysis of group difference**[b] | | |
| Odds ratio (95% CI) to placebo | — | 2.74 (1.80 to 4.18) |
| P value | — | < 0.001 |

CI = confidence interval; ITT = intention to treat.

Note: Patients with nasal surgery or sinuplasty who withdrew from study before visit were assigned their worst observed score before nasal surgery or sinuplasty. Patients with no nasal surgery or sinuplasty who withdrew from study before visit were assigned their worst observed score before study withdrawal. Patients with missing visit data were assigned their worst observed score before the missing visit.

[a]Defined as a patient with a 1-point or greater improvement from baseline in endoscopic nasal polyp score and the absence of surgery or sinuplasty before that visit.

[b]Analysis performed using a logistic regression model with covariates of treatment group, geographic region, baseline score, and log(e) baseline blood eosinophil count.

Source: SYNAPSE Clinical Study Report.[8]

## Table 17: Subgroup Analysis of Change From Baseline in Total Endoscopic Nasal Polyp Score at Week 52 — ITT Population

| Total endoscopic nasal polyp score | SYNAPSE | |
|---|---|---|
| | Placebo (n = 201) | Mepolizumab (n = 206) |
| **Asthma** | | |
| **Concurrent asthma** | | |
| n | 149 | 140 |
| Responders,[a] n (%) | 44 (30) | 74 (53) |
| Median change from baseline[b] | 0.0 | −1.0 |
| Difference in medians (95% CI) | — | −1.0 (−1.40 to −0.60) |
| **No concurrent asthma** | | |
| n | 52 | 66 |
| Responders,[a] n (%) | 13 (25) | 30 (45) |

| Total endoscopic nasal polyp score | SYNAPSE | |
|---|---|---|
| | Placebo (n = 201) | Mepolizumab (n = 206) |
| Median change from baseline[b] | 0.0 | 0.0 |
| Difference in medians (95% CI) | — | −0.42 (−0.98 to 0.13) |
| **Previous surgeries** | | |
| **1 previous surgery** | | |
| n | 81 | 108 |
| Responders,[a] n (%) | 29 (36) | 60 (56) |
| Median change from baseline[b] | 0.0 | −1.0 |
| Difference in medians (95% CI) | — | −1.0 (−1.51 to −0.49) |
| **2 previous surgeries** | | |
| n | 47 | 47 |
| Responders,[a] n (%) | 15 (32) | 19 (40) |
| Median change from baseline[b] | 0.0 | 0.0 |
| Difference in medians (95% CI) | — | 0.0 (−0.80 to −0.80) |
| **> 2 previous surgeries** | | |
| n | 73 | 51 |
| Responders,[a] n (%) | 13 (18) | 25 (49) |
| Median change from baseline[b] | 0.0 | 0.0 |
| Difference in medians (95% CI) | — | −0.20 (−0.86 to 0.46) |

CI = confidence interval; ITT = intention to treat.

Note: Patients with nasal surgery or sinuplasty who withdrew from study before visit were assigned their worst observed score before nasal surgery or sinuplasty. Patients with no nasal surgery or sinuplasty who withdrew from study before visit were assigned their worst observed score before study withdrawal. Patients with missing visit data were assigned their worst observed score before the missing visit.

[a]Defined as a patient with a 1-point or greater improvement from baseline and the absence of surgery or sinuplasty before that visit.

[b]Quantile regression with covariates of treatment group, region (except in the analysis by region), baseline score, and log(e) baseline blood eosinophil count (except in the analysis by baseline blood eosinophil count).

Source: SYNAPSE Clinical Study Report.[8]

### No-Treatment Follow-Up Period

At the end of the no-treatment follow-up period at week 76, the median and mean change from baseline in the total endoscopic nasal polyp score for patients in the placebo group were 0.0 (IQR, −1.0 to 1.0) and −0.1 (SD = 1.59), respectively. For patients in the mepolizumab group, the median and mean change from baseline were −1.0 (IQR, −2.0 to 0.0) and −1.2 (SD = 1.80), respectively.

### *Nasal Obstruction*

The co-primary end point of nasal obstruction VAS score is summarized in Table 18.

In the 4-week period from week 49 to week 52, the mean change in nasal obstruction VAS score from baseline was −2.45 (SD = 3.15) and −4.24 (SD = 3.42) in the placebo and mepolizumab groups, respectively. The median change from baseline in the placebo and mepolizumab groups was −0.82 (IQR, −4.84 to 0.0) and −4.41 (IQR, −7.27 to −0.36),

respectively. The adjusted median difference in change from baseline to week 52 was statistically significant in favour of mepolizumab compared to placebo (−3.14; 95% CI, −4.09 to −2.18; P < 0.001).

Twenty-three percent and 44% of patients in the placebo and mepolizumab groups, respectively, demonstrated a greater than 5-point improvement in their nasal obstruction VAS score.

## Table 18: Nasal Obstruction VAS Score — ITT Population

| | SYNAPSE | |
|---|---|---|
| Nasal obstruction VAS score | Placebo (n = 201) | Mepolizumab (n = 206) |
| **Baseline** | | |
| Mean (SD) | 9.02 (0.83) | 8.92 (0.83) |
| Median | 9.14 | 9.01 |
| **End of treatment period at week 52** | | |
| **Weeks 49 to 52** | | |
| Mean (SD) | 6.57 (3.26) | 4.68 (3.49) |
| Median | 8.00 | 4.31 |
| **Change from baseline** | | |
| Mean (SD) | −2.45 (3.15) | −4.24 (3.42) |
| Median | −0.82 | −4.41 |
| IQR | −4.84 to 0.0 | −7.27 to −0.36 |
| **Analysis of change from baseline** | | |
| Adjusted treatment difference in medians (95% CI)[a] | — | −3.14 (−4.09 to −2.18) |
| P value[b] | — | < 0.001 |

CI = confidence interval; IQR = interquartile range; ITT = intention to treat; SD = standard deviation; VAS = visual analogue scale.

Note: Patients with nasal surgery or sinuplasty who withdrew from study before visit were assigned their worst observed score before nasal surgery or sinuplasty. Patients with no nasal surgery or sinuplasty who withdrew from study before visit were assigned their worst observed score before study withdrawal. Patients with missing visit data were assigned their worst observed score before the missing visit.

[a]Quantile regression with covariates of treatment group, geographic region, baseline score, and log(e) baseline blood eosinophil count.

[b]Based on Wilcoxon rank sum test.

Source: SYNAPSE Clinical Study Report.[8]

### Subgroup Analysis

Subgroup analyses in patients with or without asthma and with or without previous surgery were carried out on the median difference in change from baseline in nasal obstruction VAS score at week 49 to week 52; this is summarized in Table 19. No formal hypothesis testing was conducted; therefore, whether the effect of mepolizumab differs between these subgroups is unknown.

## Table 19: Subgroup Analysis of Change From Baseline Nasal Obstruction VAS Score at Weeks 49 to 52 — ITT Population

| Nasal obstruction VAS score | SYNAPSE | |
|---|---|---|
| | Placebo (n = 201) | Mepolizumab (n = 206) |
| **Asthma** | | |
| **Concurrent asthma** | | |
| n | 149 | 140 |
| Median change from baseline[a] | −0.75 | −4.27 |
| Difference in medians (95% CI) | — | −2.88 (−3.97 to −1.79) |
| **No concurrent asthma** | | |
| n | 52 | 66 |
| Median change from baseline[a] | −1.40 | −4.69 |
| Difference in medians (95% CI) | — | −3.12 (−5.23 to −1.02) |
| **Previous surgeries** | | |
| **1 previous surgery** | | |
| n | 81 | 108 |
| Median change from baseline[a] | −2.15 | −4.74 |
| Difference in medians (95% CI) | — | −2.46 (−3.94 to −0.97) |
| **2 previous surgeries** | | |
| n | 47 | 47 |
| Median change from baseline[a] | −0.75 | −4.31 |
| Difference in medians (95% CI) | — | −0.77 (−3.27 to 1.72) |
| **> 2 previous surgeries** | | |
| n | 73 | 51 |
| Median change from baseline[a] | −0.22 | −3.49 |
| Difference in medians (95% CI) | — | −3.50 (−4.90 to −2.10) |

CI = confidence interval; ITT = intention to treat; VAS = visual analogue scale.

[a]Quantile regression with covariates of treatment group, region (except in the analysis by region), baseline score, and log(e) baseline blood eosinophil count (except in the analysis by baseline blood eosinophil count).

Source: SYNAPSE Clinical Study Report.[8]

### No-Treatment Follow-Up Period

At the end of the no-treatment follow-up period, at weeks 73 to 76, the median change from baseline in the nasal obstruction VAS score for patients in the mepolizumab group was −3.89 (IQR, −6.76 to −0.72). For patients in the placebo group, the median change from baseline was −0.80 (IQR, −5.25 to 0.00).

*Symptoms*

Nasal Symptom Composite VAS Score

The secondary end point of nasal symptom composite VAS score is summarized in Table 20.

In the 4-week period from week 49 to week 52, the mean change in nasal symptom composite VAS score from baseline was −2.19 (SD = 2.82) and −3.81 (SD = 3.19) in the placebo and mepolizumab groups, respectively. The median change from baseline in the placebo and mepolizumab groups was −0.89 (IQR, −4.06 to 0.0) and −3.96 (IQR, −6.68 to −0.32), respectively. The adjusted median difference in change from baseline to week 52 was statistically significant in favour of mepolizumab compared to placebo (−2.68; 95% CI, −3.44 to −1.91; P = 0.020).

Twenty percent and 37% of patients in the placebo and mepolizumab groups, respectively, demonstrated a greater than 5-point improvement in their nasal symptom composite VAS score.

## Table 20: Nasal Symptoms Composite VAS Score, Weeks 49 to 52 — ITT Population

| | SYNAPSE | |
|---|---|---|
| Nasal symptom composite VAS score[a] | Placebo (n = 201) | Mepolizumab (n = 206) |
| **Baseline** | | |
| Mean (SD) | 9.02 (0.83) | 8.96 (0.80) |
| Median | 9.18 | 9.11 |
| **Weeks 49 to 52** | | |
| Mean (SD) | 6.82 (2.89) | 5.15 (3.22) |
| Median | 7.75 | 4.88 |
| **Change from baseline** | | |
| Mean (SD) | −2.19 (2.82) | −3.81 (3.19) |
| Median | −0.89 | −3.96 |
| IQR | −4.06 to 0.0 | −6.68 to −0.32 |
| **Analysis of change from baseline** | | |
| Adjusted treatment difference in medians (95% CI)[b] | — | −2.68 (−3.44 to −1.91) |
| Unadjusted P value[c] | — | < 0.001 |
| Multiplicity-adjusted P value[c,d] | — | 0.020 |

CI = confidence interval; IQR = interquartile range; ITT = intention to treat; SD = standard deviation; VAS = visual analogue scale.

Note: Patients with nasal surgery or sinuplasty who withdrew from study before visit were assigned their worst observed score before nasal surgery or sinuplasty. Patients with no nasal surgery or sinuplasty who withdrew from study before visit were assigned their worst observed score before study withdrawal. Patients with missing visit data were assigned their worst observed score before the missing visit.

[a]Nasal symptom composite VAS score is composed of the individual VAS scores of nasal obstruction, nasal discharge, mucus in the throat, and loss of smell.

[b]Quantile regression with covariates of treatment group, geographic region, baseline score, and log(e) baseline blood eosinophil count.

[c]Based on Wilcoxon rank sum test.

[d]Multiplicity controlled through testing end points following a predefined hierarchy.

Source: SYNAPSE Clinical Study Report.[8]

### Nasal Symptom and Facial Pain Composite VAS Score

The other end point of nasal symptom and facial pain composite VAS score is summarized in Table 21.

In the 4-week period from week 49 to week 52, the mean change in nasal symptom and facial pain composite VAS score from baseline was −2.24 (SD = 2.88) and −3.80 (SD = 3.18) in the placebo and mepolizumab groups, respectively. The median change from baseline in the placebo and mepolizumab groups was −0.99 (IQR, −4.29 to 0.0) and −3.88 (IQR, −6.45 to −0.25), respectively. The adjusted median difference in change from baseline to week 52 favoured the mepolizumab group compared to the placebo group (−2.50; 95% CI, −3.33 to −1.67).

Twenty-one percent and 38% of patients in the placebo and mepolizumab groups, respectively, demonstrated a greater than 5-point improvement in their nasal symptom and facial pain composite VAS score.

## Table 21: Nasal Symptom and Facial Pain Composite VAS Score, Weeks 49 to 52 — ITT Population

| Nasal symptom and facial pain composite VAS score[a] | SYNAPSE | |
|---|---|---|
| | Placebo (n = 201) | Mepolizumab (n = 206) |
| **Baseline** | | |
| Mean (SD) | 8.77 (1.08) | 8.72 (1.00) |
| Median | 8.99 | 8.87 |
| **Weeks 49 to 52** | | |
| Mean (SD) | 6.53 (2.92) | 4.92 (3.23) |
| Median | 7.34 | 4.52 |
| **Change from baseline** | | |
| Mean (SD) | −2.24 (2.88) | −3.80 (3.18) |
| Median | −0.99 | −3.88 |
| IQR | −4.29 to 0.0 | −6.45 to −0.25 |
| **Analysis of change from baseline** | | |
| Adjusted treatment difference in medians (95% CI)[b] | — | −2.50 (−3.33 to −1.67) |
| Unadjusted P value[c] | — | < 0.001 |

CI = confidence interval; IQR = interquartile range; ITT = intention to treat; SD = standard deviation; VAS = visual analogue scale.

Note: Patients with nasal surgery or sinuplasty who withdrew from study before visit were assigned their worst observed score before nasal surgery or sinuplasty. Patients with no nasal surgery/sinuplasty who withdrew from study before visit were assigned their worst observed score before study withdrawal. Patients with missing visit data were assigned their worst observed score before the missing visit.

[a]Nasal symptom and facial pain composite VAS score is composed of the individual VAS scores of nasal obstruction, nasal discharge, mucus in the throat, loss of smell, and facial pain.

[b]Quantile regression with covariates of treatment group, geographic region, baseline score, and log(e) baseline blood eosinophil count.

[c]Based on Wilcoxon rank sum test.

Source: SYNAPSE Clinical Study Report.[8]

### Loss of Smell

The secondary end point of loss of smell VAS score is summarized in Table 22.

In the 4-week period from week 49 to week 52, the mean change in loss of smell VAS score from baseline was −1.38 (SD = 2.65) and −2.83 (SD = 3.61) in the placebo and mepolizumab groups, respectively. The median change from baseline in the placebo and mepolizumab groups was 0 (IQR, −1.28 to 0.0) and −0.53 (IQR, −5.60 to 0.0), respectively. The adjusted median difference in change from baseline to week 52 was statistically significant in favour of mepolizumab compared to placebo (−0.37; 95% CI, −0.65 to −0.08; P = 0.020).

Thirteen percent and 30% of patients in the placebo and mepolizumab groups, respectively, demonstrated a 5-point or greater improvement in their loss of smell VAS score.

### No-Treatment Follow-Up Period

At the end of the no-treatment follow-up period, at week 76, the median change from baseline in the loss of smell VAS score was 0.0 (IQR, −3.56 to 0.0) for patients in the placebo group and −1.22 (IQR, −5.89 to 0.0) for patients in the mepolizumab group.

## Table 22: Loss of Smell VAS Score, Weeks 49 to 52 — ITT Population

| | SYNAPSE | |
|---|---|---|
| Loss of Smell VAS Score | Placebo (n = 201) | Mepolizumab (n = 206) |
| **Baseline** | | |
| Mean (SD) | 9.68 (0.60) | 9.63 (0.83) |
| Median | 9.97 | 9.97 |
| **End of study treatment at week 52** | | |
| **Weeks 49 to 52** | | |
| Mean (SD) | 8.30 (2.82) | 6.80 (3.69) |
| Median | 9.93 | 8.93 |
| **Change from baseline** | | |
| Mean (SD) | −1.38 (2.65) | −2.83 (3.61) |
| Median | 0.0 | −0.53 |
| IQR | −1.28 to 0.0 | −5.60 to 0.0 |
| **Analysis of change from baseline** | | |
| Adjusted treatment difference in medians (95% CI)[a] | — | −0.37 (−0.65 to −0.08) |
| Multiplicity-adjusted P value[b,c] | — | 0.020 |

CI = confidence interval; IQR = interquartile range; ITT = intention to treat; SD = standard deviation; VAS = visual analogue scale.

Note: Patients with nasal surgery or sinuplasty who withdrew from study before visit were assigned their worst observed score before nasal surgery or sinuplasty. Patients with no nasal surgery or sinuplasty who withdrew from study before visit were assigned their worst observed score before study withdrawal. Patients with missing visit data were assigned their worst observed score before the missing visit.

[a]Quantile regression with covariates of treatment group, geographic region, baseline score, and log(e) baseline blood eosinophil count.

[b]Based on Wilcoxon rank sum test.

[c]Multiplicity controlled through testing end points following a predefined hierarchy.

Source: SYNAPSE Clinical Study Report.[8]

*Nasal Congestion*

The exploratory outcome of nasal congestion as assessed by PnIF is presented in Table 23.

At week 52, the mean change from baseline in PnIF was greater in the mepolizumab group than in the placebo group (32.5 [SD = 57.98] and 11.2 [SD = 65.78], respectively). Similarly, the median change from baseline to week 52 in PnIF was greater in the mepolizumab group than in the placebo group (30.0 [IQR, 0.0 to 60.0] and 0.0 [IQR, −20.0 to 50.0], respectively).

## Table 23: Peak Nasal Inspiratory Flow at Week 52 — ITT Population

| Peak nasal inspiratory flow | SYNAPSE | |
|---|---|---|
| | Placebo (n = 201) | Mepolizumab (n = 206) |
| **Baseline** | | |
| Mean (SD) | 101.6 (69.97) | 101.5 (58.41) |
| Median | 90.0 | 92.5 |
| **Week 52** | | |
| Mean (SD) | 112.8 (78.09) | 134.0 (70.81) |
| Median | 100.0 | 130.0 |
| **Change from baseline**[a] | | |
| Mean (SD) | 11.2 (65.78) | 32.5 (57.98) |
| Median | 0.0 | 30.0 |
| IQR | −20.0 to 50.0 | 0.0 to 60.0 |

IQR = interquartile range; ITT = intention to treat; SD = standard deviation.

Note: Patients with nasal surgery or sinuplasty who withdrew from study before visit were assigned their worst observed score before nasal surgery or sinuplasty. Patients with no nasal surgery or sinuplasty who withdrew from study before visit were assigned their worst observed score before study withdrawal. Patients with missing visit data were assigned their worst observed score before the missing visit.

[a]Method used to calculate the mean and median change from baseline to week 52 as well as the difference in change from baseline between placebo and mepolizumab groups was not available in the Clinical Study Report of SYNAPSE.

Source: SYNAPSE Clinical Study Report.[8]

*Health-Related Quality of Life*

Sino-Nasal Outcome Test 22The secondary end point of SNOT-22 is summarized in Table 24 and Figure 4.

At the end of the 52-week treatment period, the mean change in total SNOT-22 score from baseline was −15.7 (SD = 23.93) and −29.4 (SD = 24.67) in the placebo and mepolizumab groups, respectively. The median change from baseline in the placebo and mepolizumab groups was −14.0 (IQR, −31.0 to 0.0) and −30.0 (IQR, −46.0 to −4.0), respectively. The adjusted median difference in change from baseline to week 52 was statistically significant in favour of mepolizumab compared to placebo (−16.49; 95% CI, −23.57 to −9.42; P = 0.003).

## Table 24: SNOT-22 Total Score at Week 52 — ITT Population

| SNOT-22 total score | SYNAPSE | |
|---|---|---|
| | Placebo (n = 201) | Mepolizumab (n = 206) |
| **Baseline** | | |
| n | 198 | 205 |
| Mean (SD) | 64.4 (19.04) | 63.7 (17.64) |
| Median | 64.0 | 64.0 |
| **End of study period at week 52** | | |
| **Week 52** | | |
| n | 201 | 206 |
| Mean (SD) | 48.7 (26.69) | 34.1 (24.89) |
| Median | 50.0 | 29.0 |
| **Change from baseline** | | |
| n | 198 | 205 |
| Mean (SD) | −15.7 (23.93) | −29.4 (24.67) |
| Median | −14.0 | −30.0 |
| IQR | −31.0 to 0.0 | −46.0 to −4.0 |
| **Analysis of change from baseline** | | |
| Adjusted treatment difference in medians (95% CI)[a] | — | −16.49 (−23.57 to −9.42) |
| Multiplicity-adjusted P value[b,c] | — | 0.003 |

CI = confidence interval; IQR = interquartile range; ITT = intention to treat; SD = standard deviation; SNOT-22 = Sino-Nasal Outcome Test 22.

Note: Patients with nasal surgery or sinuplasty who withdrew from study before visit were assigned their worst observed score before nasal surgery or sinuplasty. Patients with no nasal surgery or sinuplasty who withdrew from study before visit were assigned their worst observed score before study withdrawal. Patients with missing visit data were assigned their worst observed score before the missing visit.

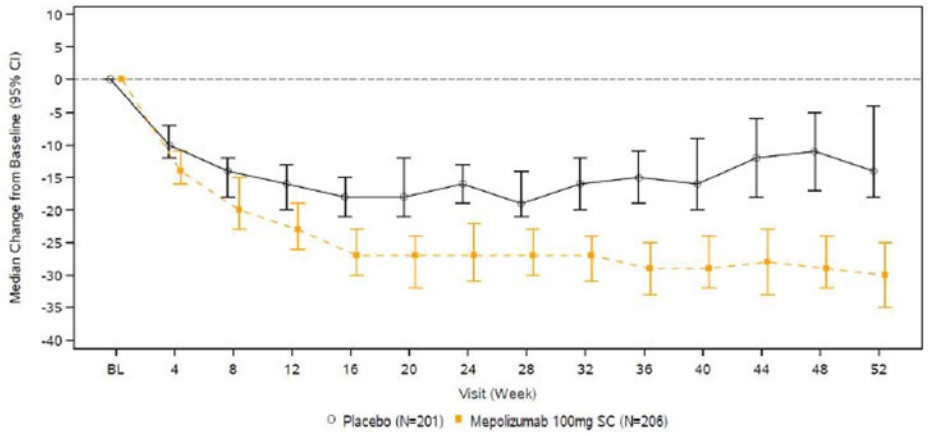
[a]Quantile regression with covariates of treatment group, geographic region, baseline score, and log(e) baseline blood eosinophil count.

[b]Based on Wilcoxon rank sum test.

[c]Multiplicity controlled through testing end points following a predefined hierarchy.

Source: SYNAPSE Clinical Study Report.[8]

## Figure 4: Median Change From SNOT-22 Total Score by Visit — ITT Population




CI = confidence interval; ITT = intention to treat; SC = subcutaneous; SNOT-22 = Sino-Nasal Outcome Test 22.
Source: SYNAPSE Clinical Study Report.[8]

### Responder Analysis

Response to treatment as measured by the SNOT-22 total score was defined as improvement (decrease) of 8.9 points or more from baseline at a given point of time, and is summarized in Table 25.

Fifty-four percent and 73% of patients in the placebo and mepolizumab groups, respectively, demonstrated an 8.9-point or greater improvement in their total SNOT-22 score at the end of the 52-week treatment period. The odds ratio of being a responder in the mepolizumab group compared to in the placebo group was 2.44 (95% CI, 1.60 to 3.73).

## Table 25: Response to Treatment Based on SNOT-22 at Week 52 — ITT Population

| | SYNAPSE | |
|---|---|---|
| SNOT-22 score | Placebo (n = 201) | Mepolizumab (n = 206) |
| n | 198 | 205 |
| Responders,[a] n (%) | 106 (54) | 150 (73) |
| Nonresponders, n (%) | 92 (46) | 55 (27) |
| ≥ 1-point to < 8.9-point improvement | 13 (7) | 8 (4) |
| No change or worsening | 15 (8) | 9 (4) |
| **Analysis of group difference**[b] | | |
| Odds ratio (95% CI) to placebo | — | 2.44 (1.60 to 3.73) |
| P value | — | < 0.001 |

CI = confidence interval; ITT = intention to treat; SNOT-22 = Sino-Nasal Outcome Test 22.
[a]Defined as a patient with an 8.9-point or greater improvement (decrease) from baseline at a given time point and the absence of surgery or sinuplasty before that visit.
[b]Analysis performed using a logistic regression model with covariates of treatment group, geographic region, baseline score, and log(e) baseline blood eosinophil count.
Source: SYNAPSE Clinical Study Report.[8]

### No-Treatment Follow-Up Period

At the end of the no-treatment follow-up period at week 76, the median and mean change from baseline in the SNOT-22 total score for patients in the placebo group were −10.0 (IQR, −32.0 to 0.0) and −16.7 (SD = 25.80), respectively. For patients in the mepolizumab group, the median and mean change from baseline were −26.5 (IQR, −46.0 to 11.5) and −28.5 (SD = 26.76), respectively.

### Short Form (36) Health Survey

The exploratory end point of SF-36 is summarized in Table 26.

At the end of the 52-week treatment period, the median change from baseline for the PCS and MCS was 0.0 (IQR, −1.75 to 4.61) and 0.0 (IQR, −3.75 to 5.76), respectively, for the placebo group. For the mepolizumab group, the median change from baseline for the PCS and MCS was 6.75 (IQR, 0.0 to 12.59) and 1.20 (IQR, −2.60 to 10.08), respectively.

## Table 26: Short Form (36) Health Survey at Week 52 — ITT Population

| Short Form (36) Health Survey | SYNAPSE | |
|---|---|---|
| | Placebo (n = 201) | Mepolizumab (n = 206) |
| **Physical component summary** | | |
| **Baseline** | | |
| n | 198 | 205 |
| Mean (SD) | 44.78 (7.82) | 43.76 (8.05) |
| Median | 45.39 | 44.83 |
| **Week 52** | | |
| n | 200 | 206 |
| Mean (SD) | 46.7 (8.11) | 50.79 (7.55) |
| Median | 47.18 | 51.98 |
| **Change from baseline**[a] | | |
| n | 198 | 205 |
| Mean (SD) | 1.89 (7.65) | 6.99 (8.35) |
| Median | 0.0 | 6.75 |
| IQR | −1.75 to 4.61 | 0.0 to 12.59 |
| **Mental component summary** | | |
| **Baseline** | | |
| n | 198 | 205 |
| Mean (SD) | 45.49 (10.83) | 44.65 (10.65) |
| Median | 47.27 | 45.38 |
| **Week 52** | | |
| n | 200 | 206 |

| Short Form (36) Health Survey | SYNAPSE | |
|---|---|---|
| | Placebo (n = 201) | Mepolizumab (n = 206) |
| Mean (SD) | 46.58 (11.54) | 48.71 (10.69) |
| Median | 49.65 | 51.03 |
| **Change from baseline[a]** | | |
| n | 198 | 205 |
| Mean (SD) | 1.04 (10.23) | 4.0 (10.45) |
| Median | 0.0 | 1.20 |
| IQR | −3.75 to 5.76 | −2.60 to 10.08 |

IQR = interquartile range; ITT = intention to treat; SD = standard deviation.

Note: Lower scores indicate worse quality of life.

[a]Differences in change from baseline to week 52 in the Short Form (36) Health Survey between placebo and mepolizumab groups were not available in the Clinical Study Report of SYNAPSE.

Source: SYNAPSE Clinical Study Report.[8]

*Systemic Steroid Use for Nasal Polyps*

The secondary end point of systemic steroid use for nasal polyps is presented in Table 27.

Over the 52-week treatment period, 37% and 25% of patients in the placebo and mepolizumab groups, respectively, required at least 1 course of systemic steroid treatment for nasal polyps.

The probability of systemic steroid use for nasal polyps was lower in the mepolizumab group than in the placebo group throughout the 52-week treatment period (Figure 5). By week 52, the probability of requiring an initial course of systemic steroids for nasal polyps was 37.5% (95% CI, 31.1% to 44.6%) in the placebo group and 25.4% (95% CI, 20.0% to 32.1%) in the mepolizumab group.

## Table 27: Systemic Steroid Use for Nasal Polyps up to Week 52 — ITT Population

| Systemic steroid use | SYNAPSE | |
|---|---|---|
| | Placebo (n = 201) | Mepolizumab (n = 206) |
| **At end of the study treatment, week 52** | | |
| Patients with at least 1 course, n (%) | 74 (37.5) | 52 (25.4) |
| **Number of courses, n (%)** | | |
| Number of total courses | 201 | 206 |
| 0 | 127 (63) | 154 (75) |
| 1 | 43 (21) | 32 (16) |
| 2 | 18 (9) | 17 (8) |
| 3 | 9 (4) | 0 |
| 4 | 3 (1) | 0 |
| 5 | 0 | 2 |
| 6 | 1 | 1 |

| Systemic steroid use | SYNAPSE | |
|---|---|---|
| | Placebo (n = 201) | Mepolizumab (n = 206) |
| **Analysis of group difference** | | |
| Odds ratio to placebo (95% CI)[a] | — | 0.58 (0.36 to 0.92) |
| Multiplicity-adjusted P value[a,b] | — | 0.02 |

CI = confidence interval; ITT = intention to treat.

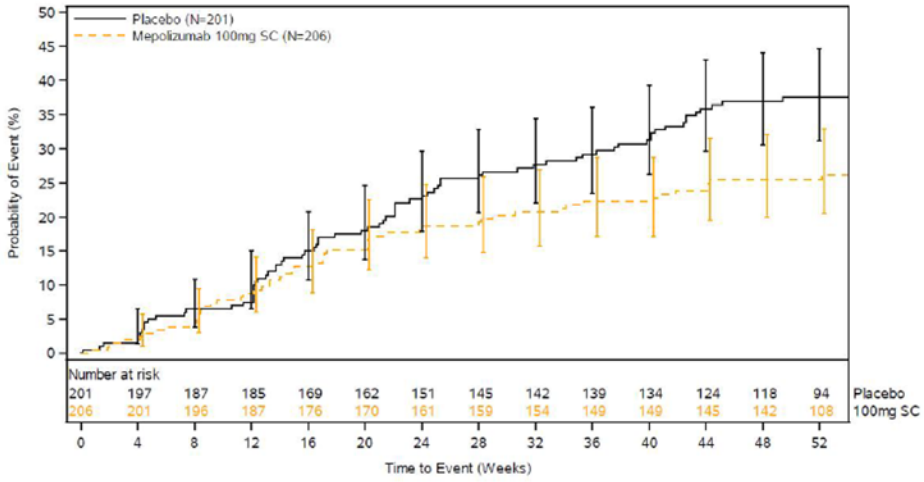
Note: Difference in the number of patients requiring systemic steroids for nasal polyps up to week 52 between placebo and mepolizumab groups was not available in the Clinical Study Report of SYNAPSE.

[a]Analysis using logistic regression model with covariates of treatment group, geographic region, number of oral corticosteroid courses for nasal polyps in last 12 months (0, 1, > 1 as ordinal), baseline total endoscopic score (centrally read), baseline nasal obstruction visual analogue scale score, and log(e) baseline blood eosinophil count.

[b]Multiplicity controlled through testing end points following a predefined hierarchy.

Source: SYNAPSE Clinical Study Report.[8]

## Figure 5: Kaplan-Meier Time to First Course of Systemic Steroids for Nasal Polyps — ITT Population




ITT = intention to treat; SC = subcutaneous.

Source: SYNAPSE Clinical Study Report.[8]

### No-Treatment Follow-Up Period

At the end of the no-treatment follow-up period, at week 76, at least 1 course of systemic steroids for nasal polyps was required by 51% and 32% of patients in the placebo and mepolizumab groups, respectively.

#### *Nasal Inflammation*

Nasal inflammation was not assessed in the SYNAPSE trial.

#### *Nasal Polyp Surgery*

The key secondary end point of time to first nasal polyp surgery is summarized in Table 28.

By week 52, 23% and 9% of patients in the placebo and mepolizumab groups, respectively, had overgone nasal surgery.

The estimated risk of having surgery before week 52 was 23.6% (95% CI, 18.3% to 30.0%) in the placebo group and 9.2% (95% CI, 5.9% to 14.2%) in the mepolizumab group.

The probability of undergoing nasal surgery at any time before week 52 was statistically significantly lower in the mepolizumab group than in the placebo group (hazard ratio = 0.43; 95% CI, 0.25 to 0.76; P = 0.003).

No-Treatment Follow-Up Period

Sixty-five patients in the placebo group and 69 patients in the mepolizumab group entered the no-treatment follow-up period. By week 76, 31% and 9% of patients in the placebo and mepolizumab groups, respectively, had undergone nasal polyp surgery. The probability of nasal surgery was 30.8% (95% CI, 21.1% to 43.6%) in the placebo group and 8.7% (95% CI, 4.0% to 18.4%) in the mepolizumab group.

The probably of having nasal surgery before week 24 was 9.1% (95% CI, 5.8% to 14.0%) in the placebo group and 4.0% (95 CI, 2.0% to 7.8%) in the mepolizumab group.

## Table 28: Time to First Nasal Polyp Surgery up to Week 52 — ITT Population

| Time to first nasal polyp surgery | SYNAPSE | |
|---|---|---|
| | Placebo (n = 201) | Mepolizumab (n = 206) |
| **Time to first surgery by week 52** | | |
| Patients with at least 1 surgery, n (%) | 46 (23) | 18 (9) |
| Probability of surgery (95% CI)[a] | 23.6 (18.3 to 30.3) | 9.2 (5.9 to 14.2) |
| **Analysis of group difference** | | |
| Hazard ratio (95% CI)[b] | — | 0.43 (0.25 to 0.76) |
| Multiplicity-adjusted P value[b,c] | — | 0.003 |

CI = confidence interval; ITT = intention to treat.

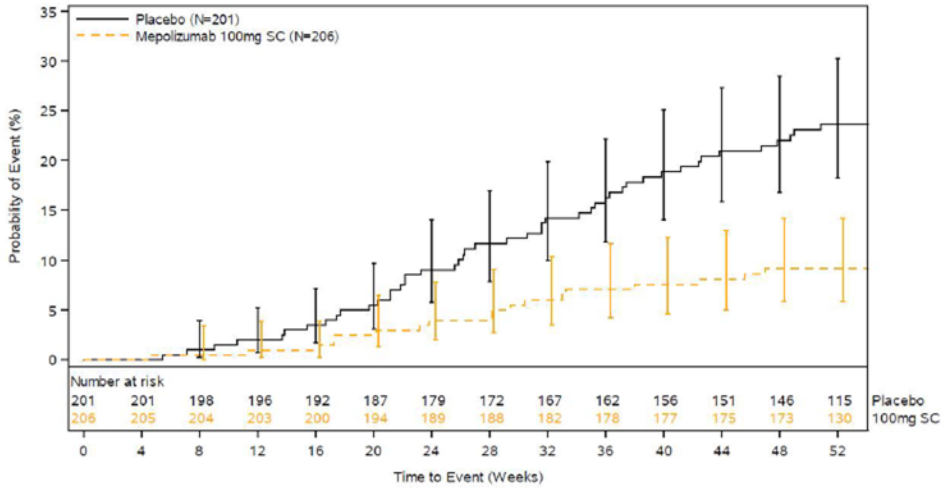
[a]Kaplan-Meier estimate.

[b]Estimated from a Cox proportional hazard model with covariates of treatment group, geographic region, baseline total endoscopic score (centrally read), baseline nasal obstruction VAS score, log(e) baseline blood eosinophil count, and number of previous surgeries (1, 2, > 2 as ordinal).

[c]Multiplicity controlled through testing end points following a predefined hierarchy.

Source: SYNAPSE Clinical Study Report.[8]

## Figure 6: Kaplan-Meier Time to First Nasal Surgery up to Week 52 — ITT Population




ITT = intention to treat; SC = subcutaneous.
Source: SYNAPSE Clinical Study Report.[8]

### *Work Productivity*

At week 52, improvements were observed across all WPAI-GH domains, except work time missed due to health (Table 29). At week 52, impairment while working due to health was reported by 22.9% and 18.5% of patients in the placebo group and mepolizumab group, respectively. Overall work impairment due to health was reported by 27.0% and 20.6% of patients in the placebo and mepolizumab groups, respectively. Activity impairment due to health was reported by 27.1% and 19.2% of patients in the placebo and mepolizumab groups, respectively. Finally, 6.4% and 4.3% of patients reported work time missed due to health in the placebo and mepolizumab groups, respectively.

## Harms

Only those harms identified in the review protocol are reported below. Refer to Table 30 for detailed harms data.

### *Adverse Events*

At least 1 AE was reported by 84% and 82% of patients in the placebo and mepolizumab groups, respectively. The 3 most common AEs reported were nasopharyngitis (placebo: 23%; mepolizumab: 25%), headache (placebo: 22%; mepolizumab: 18%), and sinusitis (placebo: 11%; mepolizumab: 5%). The following AEs were reported in less than 10% but greater than 5% of patients in either treatment group: epistaxis, asthma, nasal polyps, back pain, upper respiratory tract infection, acute sinusitis, cough, bronchitis, oropharyngeal pain, otitis media, and arthralgia.

### *Serious AEs*

Serious AEs were reported in 7% and 6% of patients in the placebo and mepolizumab groups, respectively. No single serious AE was reported in more than 1% of patients in either treatment group.

## Table 29: WPAI-GH Questionnaire — ITT Population

| WPAI-GH | SYNAPSE | |
|---|---|---|
| | Placebo (n = 201) | Mepolizumab (n = 206) |
| **Work time missed due to health** | | |
| **Day 1** | | |
| n | 151 | 153 |
| Mean, % of patients (SD) | 5.0 (12.88) | 4.9 (12.91) |
| Median, % of patients | 0 | 0 |
| **Week 52** | | |
| n | 115 | 130 |
| Mean, % of patients (SD) | 6.4 (17.59) | 4.3 (12.63) |
| Median, % of patients | 0 | 0 |
| **Impairment while working due to health** | | |
| **Day 1** | | |
| n | 148 | 151 |
| Mean, % of patients (SD) | 50.1 (30.77) | 48.1 (28.95) |
| Median, % of patients | 55.0 | 50.0 |
| **Week 52** | | |
| N | 113 | 128 |
| Mean, % of patients (SD) | 22.9 (25.45) | 18.5 (23.71) |
| Median, % of patients | 10.0 | 10.0 |
| **Overall work impairment due to health** | | |
| **Day 1** | | |
| n | 151 | 153 |
| Mean, % of patients (SD) | 50.8 (31.82) | 49.5 (29.76) |
| Median, % of patients | 57.1 | 50.0 |
| **Week 52** | | |
| n | 115 | 130 |
| Mean, % of patients (SD) | 27.0 (28.69) | 20.6 (26.4) |
| Median, % of patients | 20.0 | 10.0 |
| **Activity impairment due to health** | | |
| **Day 1** | | |
| n | 198 | 204 |
| Mean, % of patients (SD) | 53.2 (29.07) | 53.4 (27.99) |
| Median, % of patients | 60.0 | 60.0 |

| WPAI-GH | SYNAPSE | |
|---|---|---|
| | Placebo (n = 201) | Mepolizumab (n = 206) |
| **Week 52** | | |
| n | 176 | 185 |
| Mean, % of patients (SD) | 27.1 (28.14) | 19.2 (24.09) |
| Median, % of patients | 20.0 | 10.0 |

ITT = intention to treat; SD = standard deviation; WPAI-GH = Work Productivity and Activity Impairment — General Health.

Note: Change from baseline to week 52 and difference in change from baseline to week 52 in the WPAI-GH questionnaire were not available in the Clinical Study Report of SYNAPSE.

Source: SYNAPSE Clinical Study Report.[8]

### *Withdrawals due to AEs*

Two percent of patients in each group discontinued treatment due to any AE. The AEs contributing to withdrawal from treatment were not specified.

### *Mortality*

Death occurred in 1 patient in the placebo group. The 1 death was related to a fatal myocardial infarction during the follow-up period after week 52.

### *Notable Harms*

Potential opportunistic infections were reported by 3.48% and 1.46% of patients in the placebo and mepolizumab groups, respectively. Opportunistic infections reported by patients in the placebo group included herpes zoster, oral herpes, candida infection, and oropharyngeal candidiasis. In the mepolizumab group, herpes zoster, oral herpes, and candida infections were reported. Serious infections were reported by 2% and 0.49% of patients in the placebo and mepolizumab groups, respectively. Serious infections reported included acute sinusitis, cellulitis, and influenza in the placebo group and pneumonia in the mepolizumab group.

Local injection site reactions were reported by 1.0% patients in the placebo group and 2.43% of patients in the mepolizumab group. Systemic site reactions were reported in 0.50% and 0.97% of patients in the placebo and mepolizumab groups, respectively. There were no events meeting the criteria for an anaphylaxis event.

In the placebo group 0%, 1.0%, and 0.50% of patients reported, respectively, serious cardiac disorders; serious cardiac, vascular, and thromboembolic events; and serious ischemic events. In the mepolizumab group, serious cardiac disorders; serious cardiac, vascular, and thromboembolic events; and serious ischemic events were reported by 1 patient each.

## Critical Appraisal

### *Internal Validity*

The SYNAPSE trial employed appropriate methods for blinding, treatment allocation, and randomization. Baseline demographic and disease characteristics were generally balanced between the treatment groups, except that a greater proportion of patients in the placebo group than in the mepolizumab group had had 2 or more previous surgeries (60% versus 48%). Even though all the study patients had undergone at least 1 surgery, a higher proportion of patients with repeated surgery would have indicated that patients in the placebo group had more likely had recurrent disease than patients in the mepolizumab group in the past

## Table 30: Summary of Harms — Safety Population

| Harms | SYNAPSE | |
|---|---|---|
| | Placebo (n = 201) | Mepolizumab (n = 206) |
| **Patients with ≥ 1 AE** | | |
| n (%) | 168 (84) | 169 (82) |
| Most common events,[a] n (%) | | |
| Nasopharyngitis | 46 (23) | 52 (25) |
| Headache | 44 (22) | 37 (18) |
| Sinusitis | 22 (11) | 10 (5) |
| Epistaxis | 18 (9) | 17 (8) |
| Asthma | 18 (9) | 4 (2) |
| Nasal polyps | 16 (8) | 8 (4) |
| Back pain | 14 (7) | 15 (7) |
| Upper respiratory tract infection | 14 (7) | 12 (6) |
| Acute sinusitis | 13 (6) | 13 (6) |
| Cough | 13 (6) | 7 (3) |
| Bronchitis | 13 (6) | 10 (5) |
| Oropharyngeal pain | 10 (5) | 16 (8) |
| Otitis media | 10 (5) | 5 (2) |
| Arthralgia | 5 (2) | 13 (6) |
| **Patients with ≥ 1 SAE[b]** | | |
| n (%) | 14 (7) | 12 (6) |
| **Patients who stopped treatment due to AEs** | | |
| n (%) | 4 (2) | 4 (2) |
| **Deaths** | | |
| n (%) | 1 (0.50) | 0 |
| Fatal myocardial infarction during the follow-up period after week 52 | 1 (0.50) | 0 |
| **Notable harms** | | |
| Events, n (%) | | |
| Systemic site reactions | 1 (0.50) | 2 (0.97) |
| Local injection site reactions | 2 (1.0) | 5 (2.43) |
| Serious infections | 4 (2) | 1 (0.49) |
| Potential opportunistic infections | 7 (3.48) | 3 (1.46) |
| Serious cardiac disorders | 0 (0) | 1 (0.49) |

| Harms | SYNAPSE | |
|---|---|---|
| | Placebo (n = 201) | Mepolizumab (n = 206) |
| Serious CVT events | 2 (1.0) | 1 (0.49) |
| Serious ischemic events | 1 (0.50) | 1 (0.49) |

AE = adverse event; CVT = cardiac, vascular, and thromboembolic; SAE = serious adverse event.

[a]Frequency of 5% or greater in either treatment group.

[b]There were no reported SAEs > 1% in either the placebo or mepolizumab group.

Source: SYNAPSE Clinical Study Report.[8]

10 years. While it is unclear whether the need for more surgery was a function of disease severity or disease duration, it is a potential marker of treatment resistance. Further, more patients had asthma at baseline in the placebo group than in the mepolizumab group (74% versus 68%). Also, a greater proportion of patients in the placebo group than in the mepolizumab group initiated therapy with LTRA before treatment with the study drug (17% versus 12%); a potential confounding effect of LTRA therefore cannot be ruled out. However, more patients in the mepolizumab group than in the placebo group experienced at least 1 asthma exacerbation in the 12 months before screening (26% versus 15%) and at least 1 asthma exacerbation requiring systemic corticosteroids but not requiring hospitalization or emergency room visit in the 12 months before screening (20% versus 12%). Overall, these baseline imbalances may have had an impact on the assessment of differences in treatment effects between groups, yet the magnitude and direction of the bias remain uncertain.

Other between-group imbalances — namely, greater use of concomitant medications and greater protocol deviations in the placebo group, as well as inclusion of patients who demonstrated improvement in nasal polyp scores between screening and randomization — may have influenced the treatment effect. During the treatment period, a greater proportion of patients in the placebo group than in the mepolizumab group initiated concomitant treatment with any systemic corticosteroid (46% versus 34%). Likewise, a greater proportion of patients in the placebo group than in the mepolizumab group, albeit a low percentage overall, made use of a rescue short-acting beta2-agonist inhaler (9% versus 1%). According to the clinical expert consulted by CADTH for this review, the use of systemic corticosteroids for any reason or the use of rescue corticosteroid (but not short-acting beta2-agonist) medication for asthma may improve nasal polyp symptoms, thereby potentially introducing bias against mepolizumab into the results. While the impact of these additional interventions could not be assessed due to the small percentage of patients requiring their use during the study period, it is possible that the placebo group benefited from the additional therapies. A greater proportion of patients in the placebo group than in the mepolizumab group discontinued treatment I (17% versus 11%), and a substantial proportion of patients were documented with an incomplete (42% versus 31%) or missing (6% versus 4%) end point assessment. I majority of missed or incomplete assessments were due to missing clinical chemistry, hematology, and/or urinalysis due to spoiled samples; however, missed visits or phone calls related to patient diary, HRQoL, and work productivity occurred in 10% and 5% of patients in the placebo and mepolizumab groups, respectively. To mitigate discontinuation and missed assessments, patients were assigned their worst observed score before withdrawal or missed assessment. However, the high percentage of major protocol violations (65% in the placebo group versus 55% in the mepolizumab group) may have compromised the quality of the data from this trial, thereby having an impact on the assessment of efficacy outcomes.

The primary efficacy outcomes were obtained with instruments that have been similarly used in other CRSwNP trials, and the process used to carry out the outcome measures was well described and assessed in a blinded fashion. The selected outcomes conformed with the FDA's industry guidance for CRSwNP trials.[43] There appears to be low risk of bias due to the selection of the reported results, and the results presented followed a prespecified analysis plan.

SNOT-22, SF-36, and WPAI-GH were used to assess HRQoL, and symptom VAS scores were used to assess efficacy. The reliability and validity of these outcome measures, with the exception of SNOT-22, in the setting of CRSwNP were seldom studied or not studied. Recall bias would be highly likely across clinical or non-clinical settings, especially for self-administrated tools; the recall period of SNOT-22 was up to 2 weeks. The quality of the trial data on subjective efficacy outcomes is a significant concern, particularly in the large amount of missing or incomplete assessments (48% versus 35% for the placebo and mepolizumab groups, respectively). Overall, these limitations cast uncertainty on the true effect of mepolizumab as an add-on maintenance therapy in patients with CRSwNP on symptoms, quality of life, and work productivity.

While the SYNAPSE trial included a 6-month no-treatment follow-up period, only the first 200 patients were eligible to be included in that trial period. As the follow-up period was not designed for hypothesis testing, the follow-up period was not taken into consideration in the sample size determination. As a result, the long-term durability of the treatment effect associated with mepolizumab could not be adequately assessed. This raises the question of how much of the maintained treatment effect observed during the follow-up period in the mepolizumab group was due to mepolizumab versus standard of care with INCS, given that full onset of action of intranasal steroids may be delayed for some patients.[9] Indeed, during the no-treatment follow-up period, the placebo group maintained some of the treatment effect experienced in the trial. However, the treatment effect observed for the mepolizumab group at the end of the treatment period (weeks 49 to 52) slowly declined to the end of the no-treatment follow-up period (weeks 73 to 76). As noted by the clinical expert consulted by CADTH for this review, adherence to persistent daily INCS may have led to the placebo group maintaining the modest improvement experienced during the treatment period. Consequently, uncertainty exists in how much of the treatment effect observed in the mepolizumab group was due to the efficacy of mepolizumab versus the effectiveness of MF therapy, although both groups were on INCS therapy.

Regarding the statistical analysis, the study was powered to assess the co-primary outcomes (i.e., change from baseline in total endoscopic nasal polyp score and change from baseline in mean nasal obstruction VAS score) and the key secondary outcome (i.e., time to first nasal surgery). All analyses were performed using the ITT method, ensuring that the prognostic balance created from randomization was maintained. Patients who stopped or deviated from the interventions were properly accounted for in the ITT approach. Secondary efficacy end points were addressed using the multiplicity hierarchical testing procedure, which controlled for type I error. Missing data or symptom assessments that occurred after surgery were addressed using nonresponder imputation. While the nonresponder imputation approach may be considered appropriate as patients are assigned the worst-case scenario, it may cause biased estimation in some cases. Sensitivity analyses were conducted using tipping point analysis and were per-protocol treated to confirm study results. The results were found to be consistent with the ITT results.

The study had prespecified the analysis of all continuous outcomes with the median instead of the mean. When the distribution of the data is extremely skewed, the median is the preferred alternative. Otherwise, the mean is the most appropriate option in estimating the central tendency of measures when the normal distribution is approximate, especially when all potential outliers are identified and excluded. When the normality assumption is nearly satisfied, a calculation of the mean and an estimation of the difference in the mean change from baseline to the end of the study would ideally represent the average treatment effect of the study drug, which would render the study results more interpretable than if the median were used; this would also be applicable to the difference in treatment effect between treatment arms.

Several subgroup analyses were performed to examine the consistency of the treatment effect observed for the co-primary and key secondary efficacy end points. However, the interpretation of the effect of mepolizumab between the subgroups is unknown because no formal hypothesis testing was conducted.

### *External Validity*

Table 31 summarizes the generalizability of the evidence.

The demographic characteristics of the study population were considered by the clinical expert consulted by CADTH to be generally reflective of the relevant population with CRSwNP in Canada. There are a few notable details of the SYNAPSE trial that may, however, impact generalizability to the Canadian setting.

#### Enriched Patient Population

Overall, the study population represented patients who were more likely to adhere to the long-term use of the study drug. The 4-week run-in period further excluded patients who met the study eligibility criteria (severe CRSwNP with at least 1 surgery for recurrent nasal polyps and refractory to standard of care) but who were intolerant or poorly adherent to the study drug or procedures (21% did not meet the continuation criteria). An enrichment design tends to overestimate the treatment effectiveness in the clinical practice setting.

#### Prior Treatment With INCS

The SYNAPSE trial required patients to have had treatment with INCS for at least 8 weeks in the period before screening. Treatment with INCS is first-line treatment for CRSwNP in the Canadian setting. According to the clinical expert, the 8-week treatment period with INCS pre-screening employed in the SYNAPSE trial was an ideal choice since full relief from intranasal steroids may not be seen for at least 6 weeks with daily use. However, the clinical expert added that ideally patients should be on daily INCS for at least 3 months to determine their full effect.

#### Concurrent Asthma

Seventy-one percent of the study population were documented as having concurrent asthma. According to the clinical expert, a high proportion of patients with CRSwNP in clinical practice have concurrent asthma.

#### Standard of Care (Co-Interventions)

Mepolizumab was employed as an add-on therapy to standard of care in the SYNAPSE trial. Standard of care in the SYNAPSE trial was MF nasal spray. As noted by the clinical expert, use of MF nasal spray is reflective of standard of care in the Canadian practice setting. The

clinical expert added that ideally patients should be on daily intranasal steroids for at least 3 months to determine their full effect. Additional interventions allowed in the SYNAPSE trial included saline nasal douching and/or an occasional short course of high-dose OCS and/or antibiotics when required. As with MF nasal spray, these additional interventions are consistent with standard of care in the Canadian practice setting.

### Assessing Treatment Response

Endoscopic nasal polyp score and nasal obstruction VAS score were the defined co-primary end points in the SYNAPSE trial. In the clinical practice setting, the applicability of the nasal obstruction VAS symptom score and the endoscopic nasal polyp score to determine the course of treatment is limited. The clinical expert noted that SNOT-22 and change in polyp size are usually used to determine response to treatment. In practice, SNOT-22 is used by ear, nose, and throat specialists as 1 means of deciding whether to proceed with surgery. The European Position Paper on Rhinosinusitis and Nasal Polyps has identified a cut-off SNOT-22 score of greater than 40 as being indicative of severe CRSwNP.[10] A score of greater than 30 was identified by Gallo et al. (2020) as predictive of the greatest likelihood of improvement from surgery, although the likelihood of meeting the MID was less likely in patients with a lower score.[44] The clinical expert added that if reduction in nasal polyp size or obstruction is not accompanied by improved symptoms, patients are unlikely to continue with treatment. As noted by the Canadian Rhinology Working Group, response to biologics in the treatment of CRSwNP should be based on both subjective and objective improvement.[45] Improvement should be noted in some or all of a patient's major symptoms and in their endoscopy or CT scan.

Likewise, the PnIF was used in the SYNAPSE trial to objectively assess nasal congestion, yet it is not routinely used in clinical practice. The clinical expert noted that PnIF is an ideal outcome measure to objectively assess improvement since it is affected by both polyp size and nasal mucosa inflammation. However, the cost associated with its use has precluded it from routine use.

### Setting

The SYNAPSE trial included 8 Canadian sites consisting of 34 patients; patients living in Canada accounted for 8.2% of the study population. The randomization schedule employed in the trial was stratified by country regions, taking into account standard of care and regulatory considerations. However, Canada was included in the Rest of World region, along with Argentina, Australia, Russia, and the Republic of Korea. It was unclear why Canada was not grouped with the US as part of North America, given the protocol's stated intent of allocating countries into regions in part based on medical standard of care. This point was also recognized by Health Canada.[27] In follow-up, Health Canada requested additional analysis grouping Canada with North America, which the sponsor provided. The additional analysis demonstrated that the results were consistent with the primary analyses.[27] Overall, the clinical expert consulted by CADTH felt that the trial results were generalizable to the Canadian practice setting.

## Table 31: Assessment of Generalizability of Evidence for Mepolizumab

| Domain | Factor | Evidence | CADTH's assessment of generalizability |
|---|---|---|---|
| **Population** | Enriched patient population | Almost a quarter of patients who entered the screening period were | Study population represented a patient population who complied well with the |

| Domain | Factor | Evidence | CADTH's assessment of generalizability |
|---|---|---|---|
| | | excluded from randomization because they did not meet the continuation criteria. | study criteria and met the criteria for good treatment compliance. |
| | Prior treatment with INCS | In the period before screening, patients needed to have had treatment with INCS for at least 8 weeks. | I clinical expert remarked that the 8-week pre-screening treatment period with INCS was an ideal choice since full relief from INCS may not be seen for at least 6 weeks with daily use. |
| | Concurrent asthma | 71% of the study population had concurrent asthma. | According to the clinical expert, this is representative of the CRSwNP population. |
| **Co-intervention** | Requirement of daily MF nasal spray | At the start of the run-in period and throughout the study, patients were placed on MF at the maximum prescribed dose (if not already) or according to the local label, if available, or in line with local standard of care. | Use of MF nasal spray as standard of care is routine in the Canadian practice setting. The clinical expert recommended that study patients should have been on daily MF treatment for 3 months before starting the trial. |
| | Additional interventions | If required, saline nasal douching and/or an occasional short course of high-dose OCS and/or antibiotics were permitted during the study period. | The additional interventions permitted as standard of care in the SYNAPSE trial are consistent with standard of care in the Canadian practice setting. |
| **Treatment response** | Endoscopic nasal polyp score | Endoscopic nasal polyp score and nasal obstruction VAS score were the defined co-primary end points in the SYNAPSE trial. | According to the clinical expert, SNOT-22 is usually used to determine response to treatment in clinical practice. If reduction in nasal polyp size or obstruction is not accompanied by improved symptoms, then patients are unlikely to continue with treatment. |
| | Nasal obstruction VAS score | | |
| | PnIF | Used in the clinical trial to assess nasal congestion. | PnIF is an objective measure to assess improvement in nasal congestion as it considers polyp size and mucosa. However, it is not routinely used in clinical practice due to cost. |
| **Setting** | Multinational, multicentre study | Trial included 8 Canadian sites consisting of 34 patients. Patients living in Canada accounted for 8.2% of the study population. | The clinical expert felt that the trial results were generalizable to the Canadian setting. |

CRSwNP = chronic rhinosinusitis with nasal polyps; INCS = intranasal corticosteroids; MF = mometasone furoate; PnIF = peak nasal inspiratory flow; SNOT-22 = Sino-Nasal Outcome Test 22; VAS = visual analogue scale.

## Indirect Evidence

A focused literature search for indirect treatment comparisons dealing with CRSwNP was run in MEDLINE All (1946–) via Ovid and Embase (1974–) via Ovid on June 6, 2022. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. No indirect treatment comparisons were included in the sponsor's submission to CADTH or identified in the literature search.

### Other Relevant Evidence

No long-term extension studies or other relevant studies were included in the sponsor's submission to CADTH or identified in the literature search.

## Discussion

### Summary of Available Evidence

The current CADTH systemic review included 1 phase III, multicentre, randomized, double-blind, placebo-controlled, parallel group trial: the SYNAPSE trial (N = 414). The SYNAPSE trial evaluated the clinical efficacy and safety of 100 mg/mL mepolizumab as an add-on maintenance treatment in adults with recurrent CRSwNP not adequately controlled on optimized medical treatment and who had had at least 1 prior nasal polyp surgery in the past 10 years. The SYNAPSE study comprised a 4-week run-in period followed by a 52-week treatment period in which patients were randomized to receive either mepolizumab 100 mg/mL or matching placebo delivered by subcutaneous injection using a prefilled safety syringe. I first 200 patients randomized into the study entered a 6-month no-treatment follow-up period following their week 52 visit to assess maintenance of response. All patients remained on standard of care treatment with daily MF nasal spray throughout the study. If required, saline nasal douching and/or an occasional short course of high-dose OCS and/or antibiotics were permitted. The co-primary efficacy end points were change from baseline in endoscopic nasal polyp score at week 52 and change from baseline in nasal obstruction VAS score during the 4 weeks before week 52. The key secondary end point was time to first actual surgery for nasal polyps by week 52. Other secondary end points of interest to this review included change from baseline in overall VAS symptom score, change from baseline in SNOT-22 score, the proportion of participants requiring systemic steroids for nasal polyps, change from baseline in composite VAS symptom score (combining VAS scores for nasal obstruction, nasal discharge, mucus in the throat, and loss of smell), and change from baseline in loss of smell VAS score.

The 414 patients were randomized to receive either mepolizumab or matching placebo, 207 in each group. The study population aligned with the Health Canada indication and with the sponsor's reimbursement request and proposed reimbursement criteria. .

The SYNAPSE trial was limited by between-group imbalances at baseline: more patients in the placebo group were on LTRA at baseline and more patients in the placebo group had had more than 1 prior nasal polyp surgery. Furthermore, more patients in the placebo group made use of concomitant medications, and the group experienced greater protocol deviations. Finally, questions remain about how much of the treatment effect observed during the study period in the mepolizumab group was due to mepolizumab versus standard of care with MF nasal spray. Despite these limitations, the study results were found to be generalizable to the clinical setting. A small percentage of patients who experienced improvement in nasal polyp score between screening and baseline were included in the study despite having a nasal polyp score of less than 5 at baseline. The inclusion of patients with a nasal polyp score of less than 5 was also noted by Health Canada, and clarification was requested.[27] In clarification, the sponsor noted that the small number of patients who demonstrated an improvement between screening and baseline were still included in the study because all patients met all the randomization criteria, so despite improvement in nasal polyp score, the patients still

presented with severe disease, and because the inclusion of these patents did not change the median score for either treatment group, which was the basis of the analysis plan to use medians with a non-parametric Wilcoxon rank test.

No indirect treatment comparisons or other evidence were included in the sponsor's submission to CADTH or identified in the literature search.

## Interpretation of Results

### Efficacy

In the SYNAPSE trial, treatment with mepolizumab resulted in a statistically significant improvement compared to placebo in nasal obstruction as measured by the VAS and in endoscopic nasal polyp score. Treatment with mepolizumab also resulted in a statistically significant improvement compared to placebo in time to first nasal polyp surgery, change from baseline in SNOT-22 total score, composite VAS symptom score, individual VAS symptom score for loss of smell, and difference in the proportion of patients requiring systemic steroids for nasal polyps. Patients treated with mepolizumab reported less health-related impairment in work and activity.

The magnitude of change from baseline between groups in total endoscopic nasal polyp score was relatively modest. According to the clinical expert consulted by CADTH, patients with CRSwNP are treatment resistant. The implication of type 2 inflammation, presence of comorbid asthma and/or nonsteroidal anti-inflammatory drug-exacerbated respiratory disease, high corticosteroid use, and/or sino-nasal surgical history that often accompany CRSwNP represent a difficult-to-treat population under existing treatment regimens.[14] For these reasons, the clinical expert stated that even small improvements to total endoscopic nasal polyp scores are considered clinically relevant. Indeed, the MID associated with a clinically meaningful change is an improvement of at least 1 point.[31] In the SYNAPSE trial, half of all patients in the mepolizumab group met the criteria for a clinically meaningful improvement in their total endoscopic nasal polyp score at the end of the treatment period. According to the clinical expert, the response to treatment as defined by the total endoscopic nasal polyp score would be considered acceptable in the clinical setting.

However, the clinical expert consulted by CADTH added that uptake of treatment should not be based on reduction in nasal polyp size alone. Endoscopic improvement must be also accompanied by improvement in CRSwNP symptoms. This sentiment was also expressed by the Canadian Rhinology Working Group.[45] In the SYNAPSE trial, significant improvement was observed in the co-primary end point of nasal obstruction VAS score and the secondary end points of overall VAS symptom score, composite VAS symptom score, and individual VAS symptom score for loss of smell. The magnitude of the treatment effect for nasal obstruction VAS score and composite VAS symptom score was modest yet acceptable according to the clinical expert. For loss of smell, however, the magnitude of the treatment effect was considered small. According to the clinical expert, it is difficult to regain smell once lost. While the VAS for total sino-nasal symptom severity is used to assess disease severity and monitor the course of the disease, and can be used for treatment decisions and to determine disease burden in the clinical setting,[46] there is no established MID on which to base response to treatment. According to the clinical expert, a change in the score between 20% and 50% of the baseline VAS score is considered acceptable in clinical practice. In the SYNAPSE trial, the change in mean score from baseline across the VAS end points fell within this range.

In the SYNAPSE trial, time to first nasal surgery was designated as the key secondary end point. The clinical expert consulted by CADTH gave surgery for nasal polyps a lower ranking of importance among CRSwNP outcomes since it is difficult to standardize across patients and surgeons. However, in the SYNAPSE trial, where all patients had had previous surgery and a quarter were felt to require surgery by the end of the treatment period, one could make the argument that it could have been ranked higher. Despite the clinical expert ranking of the end point, a reduced need for surgery was deemed to be important from the input received from the patient groups. In the SYNAPSE trial, the probability of undergoing nasal surgery at any time before the end of the study period was significantly lower in the mepolizumab group than in the placebo group. Moreover, the longer the duration of treatment, the greater the treatment effect on the probability of requiring surgery for nasal polyps. However, the durability of the treatment effect could not be assessed due to the short duration of, and the low number of patients entering, the follow-up period.

As noted by the clinical expert, SNOT-22 is used in clinical practice to determine response to treatment. In the SYNAPSE trial, the magnitude of change from baseline was both significant and clinically meaningful. In fact, almost three-quarters of the patients in the mepolizumab group were considered responders, exceeding the MID established for SNOT-22. Just over half the patients in the placebo group were also considered responders. Moreover, change from baseline in the placebo group exceeded the established MID for SNOT-22.[37] In fact, the treatment response in the placebo group was observed across multiple end points. In seeking clarification from the clinical expert about why the placebo group would exhibit such an improvement in SNOT-22 score, the expert noted that standard of care treatment with MF nasal spray is an effective treatment. Indeed, a 2016 systematic review demonstrated MF nasal spray to be an effective treatment of inflammatory diseases of the nose and paranasal sinuses while improving quality of life and other symptoms.[47] Due to the effectiveness of MF nasal spray, the clinical expert would have preferred the study protocol to require patients to be on daily MF treatment for 3 months before starting the trial. The clinical expert noted that the improvement observed in both the mepolizumab and placebo groups may not have been driven by improvement in nasal polyps alone. According to the clinical expert, the benefits derived from daily MF treatment may be reflecting improvement in sinusitis, nasal turbinate edema, and secretion, leading to symptomatic and objective improvement despite polyps being resistant to steroids. Consequently, this observation introduces uncertainty about how much of the treatment effect observed in the mepolizumab group was due to the efficacy of mepolizumab versus the effectiveness of MF therapy, although both groups were taking INCS. Further, recall bias could occur depending on the setting in which surveys were administered (i.e., clinical versus non-clinical), especially for self-administrated tools; the recall period for SNOT-22 was up to 2 weeks. Finally, the quality of the trial data on subjective efficacy outcomes is a concern due to missing or incomplete assessments related to patient diary, HRQoL, and work productivity (10% versus 5% for placebo versus mepolizumab).

The clinical expert explained that in clinical practice, response to treatment is primarily based on the severity of nasal congestion. The clinical expert noted that PnIF, a measure of nasal congestion, is an ideal outcome measure to assess objective improvement since it is affected by both polyp size and nasal mucosa inflammation. In the SYNAPSE trial, the mepolizumab group demonstrated an improvement in nasal congestion in excess of the MID for the PnIF. However, no analysis of treatment difference was conducted between the groups. Moreover, PnIF was absent from the statistical testing hierarchy. As a result, conclusions cannot be made about the efficacy of mepolizumab to improve nasal congestion. This represents a

missed opportunity to demonstrate an objective treatment effect on an outcome that is considered important in the clinical setting.

Patient group input indicated a desire for decreased reliance on OCS and other steroids. Although a significantly lower proportion of patients in the mepolizumab group required at least 1 course of systemic steroids for nasal polyps than in the placebo group during the SYNAPSE trial, the overall proportion of patients requiring systemic steroids was low. According to the clinical expert, the low proportion of patients in the placebo group requiring systemic steroids may be a function of persistent use of the MF nasal steroids (standard of care). As discussed above, it is uncertain how much of the treatment effect observed in the mepolizumab group was due to the efficacy of mepolizumab versus the effectiveness of MF therapy.

The absence of any long-term extension studies hinders any conclusions about the durability of treatment with mepolizumab on CRSwNP efficacy end points.

### Harms

Mepolizumab appeared to be well tolerated, with no concerning safety signals identified. The overall safety profile of mepolizumab in SYNAPSE appeared consistent with its established safety profile as add-on maintenance therapy across other indications.[45]

The product monograph for mepolizumab documents the following common side effects of mepolizumab: headache, injection site reactions (pain, redness, swelling, itching, or a burning feeling at the injection site), back pain, and tiredness (fatigue). Mouth or throat pain and joint pain have also been reported with CRSwNP. The product monograph also contains warmings for serious side effects, including allergic (hypersensitivity) reactions such as anaphylaxis and herpes zoster infections that can cause shingles.

### Other Considerations

The sponsor included in its submission application suggested reimbursement criteria related to the initiation, administration, and renewal of mepolizumab. The suggested reimbursement criteria and evidence of support for those criteria are detailed in Table 32.

The SYNAPSE trial and input from the clinical expert supports the use of mepolizumab in adult patients with a documented diagnosis of severe and recurrent CRSwNP inadequately controlled by INCS. However, how severity of nasal polyps and response to treatment were defined in the SYNAPSE trial differed from the definition used in clinical practice as noted by the clinical expert. In addition, the clinical expert suggested that the duration of time patients are on INCS before initiating treatment with mepolizumab should be longer than what was required by the SYNAPSE trial.

## Table 32: Sponsor-Suggested Reimbursement Criteria and Evidence of Support

| Sponsor-suggested reimbursement criteria | Evidence of support |
|---|---|
| **Initiation criteria** | |
| Add-on to standard of care for adult patients (aged 18 years or older) with severe nasal polyps inadequately controlled by INCS alone, defined as: | The patient population in the SYNAPSE trial were adult patients 18 years or older with recurrent CRSwNP. Patients had a history of at least 1 prior surgery for nasal polyps in the past 10 years, had recurrent nasal polyps despite treatment with current standard of care, and were in current need of nasal |

| Sponsor-suggested reimbursement criteria | Evidence of support |
|---|---|
| | polyp surgery.<br>Severity of CRSwNP in the SYNAPSE trial was defined via an obstruction VAS symptom score of > 5, severity consistent with the need for surgery as described by an overall VAS symptom score > 7, and an endoscopic bilateral nasal polyp score ≥ 5. |
| Documented diagnosis of CRSwNP through either CT or endoscopy; and | In the SYNAPSE trial, nasal polyps were diagnosed by endoscopy or historical CT scan. |
| Symptoms persisting for at least 8 to 12 weeks despite treatment with INCS | In the SYNAPSE trial, patients were required to have had 8 weeks of treatment with INCS before screening. In addition, patients were required to have shown CRS symptoms for at least 12 weeks. The clinical expert stressed that, ideally, patients should have been on daily MF therapy for at least 3 months before study entry due to MF therapy's effectiveness in relieving CRSwNP symptoms. |
| **Administration criteria** | |
| Patients must be managed by a physician experienced in the treatment of CRSwNP (allergist, ENT, respirologist) | In the clinical practice setting, endoscopy is performed by ENTs or allergists who are trained to perform nasal endoscopy. As such, the clinical expert suggested that patients should be managed by either ENTs or allergists. |
| Prior to initiating mepolizumab, a baseline assessment of patient-reported symptoms and/or quality of life (i.e., SNOT-22 or VAS) is taken | According to the clinical expert, VAS scores are not routinely used in clinical practice. Assessment of patient-reported symptoms and/or quality of life are generally done using SNOT-22, as described by the clinical expert. |
| **Renewal criteria** | |
| Clinical response should be assessed after 1 year | According to the clinical expert, initial response to therapy should be assessed after 8 to 12 months, since a period of 6 months of persistent treatment is required to reach a steady state. |
| Improvement in patient-reported symptoms from baseline assessment (i.e., SNOT-22, VAS) in the first year of treatment, or maintenance of improvement in subsequent years of treatment | According to the clinical expert, response to treatment is based on the severity of nasal congestion. As described, SNOT-22, rather than VAS scales, is generally used in clinical practice to assess response to treatment. |

CRS = chronic rhinosinusitis; CRSwNP = chronic rhinosinusitis with nasal polyps; ENT = ear, nose, and throat specialist; INCS = intranasal corticosteroids; MF = mometasone furoate; SNOT-22 = Sino-Nasal Outcome Test 22; VAS = visual analogue scale.

## Conclusions

Based on the SYNAPSE trial, mepolizumab as an add-on maintenance therapy in combination with standard of care was efficacious in achieving endoscopic improvement and relief of nasal obstruction as measured by the VAS in patients with severe recurrent CRSwNP inadequately controlled by inhaled nasal corticosteroids alone. Moreover, mepolizumab was found to be efficacious in prolonging time to nasal surgery, reducing the need for systemic corticosteroids for nasal polyps, and improving CRSwNP symptoms. However, the magnitude of the treatment effect was modest. Based on the response observed in the placebo group and on input from the clinical expert consulted by CADTH, the extent to which these improvements were due to treatment with mepolizumab remains uncertain. Mepolizumab appeared to be well tolerated. However, due to lack of head-to-head trials or availability of indirect treatment comparisons, it remains unknown how mepolizumab compares to other

similar maintenance therapy for severe recurrent CRSwNP in efficacy and safety. Despite these limitations, mepolizumab fills an unmet need for more treatment options for patients with severe CRSwNP inadequately controlled with standard of care.

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# Appendix 1: Literature Search Strategy

Note that this appendix has not been copy-edited.

## Clinical Literature Search

### Overview

**Interface:** Ovid

**Databases:**

- MEDLINE All (1946 to present)
- Embase (1974 to present)

Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

**Date of search:** June 6, 2022

**Alerts:** Biweekly search updates until project completion

**Search filters applied:** No filters were applied to limit retrieval by study type.

**Limits:**

- Conference abstracts: excluded

## Table 33: Syntax Guide

| Syntax | Description |
|---|---|
| / | At the end of a phrase, searches the phrase as a subject heading |
| MeSH | Medical Subject Heading |
| .fs | Floating subheading |
| exp | Explode a subject heading |
| * | Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings |
| # | Truncation symbol for one character |
| ? | Truncation symbol for one or no characters only |
| adj# | Requires terms to be adjacent to each other within # number of words (in any order) |
| .ti | Title |
| .ot | Original title |
| .ab | Abstract |
| .hw | Heading word; usually includes subject headings and controlled vocabulary |
| .kf | Keyword heading word |
| .dq | Candidate term word (Embase) |

| Syntax | Description |
|---|---|
| **.pt** | Publication type |
| **.mp** | Mapped term |
| **.rn** | Registry number |
| **.nm** | Name of substance word (MEDLINE) |
| **.yr** | Publication year |
| **.jw** | Journal title word (MEDLINE) |
| **.jx** | Journal title word (Embase) |
| **freq = #** | Requires terms to occur # number of times in the specified fields |
| **medall** | Ovid database code: MEDLINE All, 1946 to present, updated daily |
| **oemezd** | Ovid database code; Embase, 1974 to present, updated daily |
| **cctr** | Ovid database code; Cochrane Central Register of Controlled Trials |

## Multi-Database Strategy

1. (Nucala* or mepolizumab* or bosatria* or SB240563 or SB 240563).ti,ab,kf,rn,nm,ot,hw.
2. 90Z2UF0E52.rn,nm.
3. or/1-2
4. exp Sinusitis/ or exp rhinitis/
5. (rhino sinusitis or rhinosinusitis).ti,ab,kf.
6. (inflamm* adj5 sinus*).ti,ab,kf.
7. or/4-6
8. exp chronic disease/
9. exp Recurrence/
10. (chronic or persis* or recur* or flareup* or flare up*).ti,ab,kf.
11. or/8-10
12. CRSsNP*.ti,ab,kf.
13. ((sinusitis or rhinitis or rhinosinusitis) adj3 (chronic or persis* or recur*)).ti,ab,kf.
14. Nasal Polyps/
15. ((nose or nasal or rhino* or rhinitis or sinus* or sinonasal) adj3 (papilloma* or polyp*)).ti,ab,kf.
16. (rhinopolyp* or CRSwNP*).ti,ab,kf.
17. or/12-16
18. and/7,11
19. or/17-18
20. and/3,19
21. 20 use medall

22. *Mepolizumab/
23. (Nucala* or mepolizumab* or bosatria* or SB240563 or SB 240563).ti,ab,kf,dq.
24. or/22-23
25. exp sinusitis/ or Chronic rhinitis/ or rhinitis/
26. (rhino sinusitis or rhinosinusitis).ti,ab,kf,dq.
27. (inflamm* adj5 sinus*).ti,ab,kf,dq.
28. or/25-27
29. exp chronic disease/
30. exp Recurrent disease/
31. (chronic or persis* or recur* or flareup* or flare up*).ti,ab,kf,dq.
32. or/29-31
33. CRSsNP*.ti,ab,kf,dq.
34. ((sinusitis or rhinitis or rhinosinusitis) adj3 (chronic or persis* or recur*)).ti,ab,kf,dq.
35. Nose Polyp/ or chronic rhinosinusitis/ or chronic rhinitis/ or chronic sinusitis/
36. ((nose or nasal or rhino* or rhinitis or sinus* or sinonasal) adj3 (papilloma* or polyp*)).ti,ab,kf,dq.
37. (rhinopolyp* or CRSwNP*).ti,ab,kf,dq.
38. or/33-37
39. and/28,32
40. or/38-39
41. and/24,40
42. 41 use oemezd
43. (conference abstract or conference review).pt.
44. 42 not 43
45. or/21,44
46. remove duplicates from 45

## Clinical Trials Registries

*ClinicalTrials.gov*

Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials.

[Search – mepolizumab, Nucala]

*WHO ICTRP*

International Clinical Trials Registry Platform, produced by WHO. Targeted search used to capture registered clinical trials.

[Search terms – mepolizumab, Nucala, rhinosinusitis]

*Health Canada's Clinical Trials Database*

Produced by Health Canada. Targeted search used to capture registered clinical trials.

[Search terms – mepolizumab, Nucala]

*EU Clinical Trials Register*

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms – mepolizumab, Nucala, rhinosinusitis]

## Grey Literature

**Search dates**: May 27, 2022, to June 3, 2022

**Keywords**: mepolizumab, Nucala, rhinosinusitis

**Limits**: None

**Updated**: Search updated before the completion of stakeholder feedback period

Relevant websites from the following sections of the CADTH grey literature checklist Grey Matters: A Practical Tool for Searching Health-Related Grey Literature were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trials Registries
- Databases (free)
- Internet Search

# Appendix 2: Excluded Studies

Note that this appendix has not been copy-edited.

## Table 34: Excluded Studies

| Reference | Reason for Exclusion |
|---|---|
| Han et al. 2021[30] | Duplicate study |
| Bachert et al. 2022[48] | Duplicate study |
| Mullol et al. 2022[49] | No added information |
| Hopkins et al. 2021[50] | Study design |
| Lee et al. 2021[51] | No added information |
| Tabberer et al. 2021[52] | No added information |
| Hopkins et al. 2020[53] | No added information |

# Appendix 3: Detailed Outcome Data

Note that this appendix has not been copy-edited.

## Overall Symptoms

The secondary end point of overall VAS score is summarized in Table 35.

In the 4-week period from week 49 to week 52, at the end of the 52-week treatment period, the mean (SD) change in overall VAS score from baseline was −2.45 (3.08) and −4.27 (3.43) in the placebo and mepolizumab groups, respectively. The median change from baseline in the placebo and mepolizumab group was −0.90 (IQR, −4.76 to 0.00) and −4.48 (IQR, −7.04 to −0.40), respectively. The adjusted median difference in change from baseline to week 52 was statistically significant in favour of mepolizumab compared to placebo (−3.18; 95% CI, −4.10 to −2.26; P = 0.003).

Of note, 22% and 47% of patients in the placebo and mepolizumab group demonstrated ≥ 5-point improvement in their overall VAS score, respectively.

### Table 35: Overall VAS Symptom Score, Weeks 49 to 52 (ITT Population)

| Outcome | SYNAPSE | |
|---|---|---|
| | Placebo (n = 201) | Mepolizumab (n = 206) |
| **Baseline** | | |
| Mean (SD) | 9.10 (0.72) | 9.04 (0.77) |
| Median | 9.20 | 9.12 |
| **End of study treatment at week 52** | | |
| **Weeks 49 to 52** | | |
| Mean (SD) | 6.65 (3.23) | 4.76 (3.46) |
| Median | 7.96 | 4.18 |
| **Change from baseline** | | |
| Mean (SD) | −2.45 (3.08) | −4.27 (3.43) |
| Median change from baseline | −0.90 | −4.48 |
| IQR | −4.76 to 0.00 | −7.04 to −0.40 |
| **Analysis of change from baseline** | | |
| Adjusted treatment difference in medians (95% CI)[a] | — | −3.18 (−4.10 to −2.26) |
| Unadjusted P value[b,c] | — | < 0.001 |
| Multiplicity-adjusted P value[b,c] | — | 0.003 |

CI = confidence interval; IQR = interquartile range; SD = standard deviation; VAS = visual analogue scale.

[a]Quantile regression with covariates of treatment group, geographic region, baseline score, and log(e) baseline blood eosinophil count.

[b]Based on Wilcoxon rank sum test.

[c]Multiplicity controlled through testing end points following a predefined hierarchy.

Note: Patients with nasal surgery or sinuplasty who withdrew from study before visit were assigned their worst observed score before nasal surgery or sinuplasty. Patients with no nasal surgery or sinuplasty who withdrew from study before visit were assigned their worst observed score before study withdrawal. Patients with missing visit data were assigned their worst observed score before the missing visit.

Source: SYNAPSE Clinical Study Report.[8]

## Nasal Discharge

The other end point of nasal discharge VAS symptom scores is summarized in Table 36.

In the 4-week period from week 49 to week 52, at the end of the 52-week treatment period, the mean (SD) change in nasal discharge VAS score from baseline was −2.45 (3.23) and −4.23 (3.46) in the placebo and mepolizumab groups, respectively. The median change from baseline in the placebo and mepolizumab group was −0.85 (IQR, −4.80 to 0.0) and −4.51 (IQR, −7.19 to −0.27), respectively. The adjusted median difference in change from baseline to week 52 favoured the mepolizumab group compared to the placebo group (−3.26; 95% CI, −4.29 to −2.23).

Of note, 23% and 47% of patients in the placebo and mepolizumab group demonstrated a > 5-point improvement in their nasal discharge VAS score, respectively.

### Table 36: Nasal Discharge VAS Symptom Scores, Weeks 49 to 52 (ITT Population)

| | SYNAPSE | |
|---|---|---|
| Outcome | Placebo (n = 201) | Mepolizumab (n = 206) |
| **Baseline** | | |
| Mean (SD) | 8.78 (1.25) | 8.78 (1.07) |
| Median | 9.04 | 8.93 |
| **End of study treatment at week 52** | | |
| **Weeks 49 to 52** | | |
| Mean (SD) | 6.33 (3.31) | 4.55 (3.47) |
| Median | 7.48 | 4.13 |
| **Change from baseline** | | |
| Mean (SD) | −2.45 (3.23) | −4.23 (3.46) |
| Median | −0.85 | −4.51 |
| IQR | −4.80 to 0.0 | −7.19 to −0.27 |
| **Analysis of change from baseline** | | |
| Adjusted treatment difference in medians (95% CI)[a] | — | −3.26 (−4.29 to −2.23) |
| Unadjusted P value[b] | — | < 0.001 |

CI = confidence interval; IQR = interquartile range; SD = standard deviation; VAS = visual analogue scale.

[a]Quantile regression with covariates of treatment group, geographic region, baseline score, and log(e) baseline blood eosinophil count.

[b]Based on Wilcoxon rank sum test.

Note: Patients with nasal surgery or sinuplasty who withdrew from study before visit were assigned their worst observed score before nasal surgery or sinuplasty. Patients with no nasal surgery or sinuplasty who withdrew from study before visit were assigned their worst observed score before study withdrawal. Patients with missing visit data were assigned their worst observed score before the missing visit.

Source: SYNAPSE Clinical Study Report.[8]

## Mucus in Throat

The other end point of mucus in throat VAS symptom scores is summarized in Table 37.

In the 4-week period from week 49 to week 52, at the end of the 52-week treatment period, the mean (SD) change in mucus in throat VAS score from baseline was −2.24 (3.27) and −3.93 (3.50) in the placebo and mepolizumab groups, respectively. The median change

from baseline in the placebo and mepolizumab group was −0.97 (IQR, −4.83 to 0.0) and −4.21 (IQR, −6.80 to −0.06), respectively. The adjusted median difference in change from baseline to week 52 favoured the mepolizumab group compared to the placebo group (−3.12; 95% CI, −4.23 to −2.02).

Of note, 24% and 43% of patients in the placebo and mepolizumab group demonstrated a > 5-point improvement in their mucus in throat VAS score, respectively.

### Table 37: Mucus in Throat VAS Symptom Score, Weeks 49 and 52 (ITT Population)

| Outcome | SYNAPSE | |
|---|---|---|
| | Placebo (n = 201) | Mepolizumab (n = 206) |
| **Baseline** | | |
| Mean (SD) | 8.58 (1.63) | 8.51 (1.61) |
| Median | 9.07 | 8.88 |
| **End of study treatment at week 52** | | |
| **Weeks 49 and 52** | | |
| Mean (SD) | 6.15 (3.40) | 4.59 (3.51) |
| Median | 7.22 | 4.16 |
| **Change from baseline** | | |
| Mean (SD) | −2.43 (3.27) | −3.93 (3.50) |
| Median | −0.97 | −4.21 |
| IQR | −4.83 to 0.0 | −6.80 to −0.06 |
| **Analysis of change from baseline** | | |
| Adjusted treatment difference in medians (95% CI)[a] | — | −3.12 (−4.23 to −2.02) |
| Unadjusted P value[b] | — | < 0.001 |

CI = confidence interval; IQR = interquartile range; SD = standard deviation; VAS = visual analogue scale.

[a]Quantile regression with covariates of treatment group, geographic region, baseline score, and log(e) baseline blood eosinophil count.

[b]Based on Wilcoxon rank sum test.

Note: Patients with nasal surgery or sinuplasty who withdrew from study before visit were assigned their worst observed score before nasal surgery or sinuplasty. Patients with no nasal surgery or sinuplasty who withdrew from study before visit were assigned their worst observed score before study withdrawal. Patients with missing visit data were assigned their worst observed score before the missing visit.

Source: SYNAPSE Clinical Study Report.[8]

## Facial Pain

The other end point of facial pain VAS symptom scores is summarized in Table 38.

In the 4-week period from week 49 to week 52, at the end of the 52-week treatment period, the mean (SD) change in facial pain VAS score from baseline was −2.38 (3.35) and −3.71 (3.61) in the placebo and mepolizumab groups, respectively. The median change from baseline in the placebo and mepolizumab group was −0.68 (IQR, −5.02 to 0.0) and −3.63 (IQR, −6.90 to 0.0), respectively. The adjusted median difference in change from baseline to week 52 favoured the mepolizumab group compared to the placebo group (−2.17; 95% CI, −3.27 to −1.06).

Of note, 25% and 42% of patients in the placebo and mepolizumab group demonstrated a > 5-point improvement in their facial pain VAS score, respectively.

## Table 38: Facial Pain VAS Symptom Score, Weeks 49 to 52 (ITT Population)

| Outcome | SYNAPSE | |
|---|---|---|
| | Placebo (n = 201) | Mepolizumab (n = 206) |
| **Baseline** | | |
| Mean (SD) | 7.77 (2.72) | 7.76 (2.51) |
| Median | 8.87 | 8.52 |
| **End of study treatment at week 52** | | |
| **Weeks 49 and 52** | | |
| Mean (SD) | 5.39 (3.62) | 4.05 (3.64) |
| Median | 5.77 | 3.17 |
| **Change from baseline** | | |
| Mean (SD) | −2.38 (3.35) | −3.71 (3.61) |
| Median | −0.68 | −3.63 |
| IQR | −5.02 to 0.0 | −6.90 to 0.0 |
| **Analysis of change from baseline** | | |
| Adjusted treatment difference in medians (95% CI)[a] | — | −2.17 (−3.27 to −1.06) |
| Unadjusted P value[b] | — | < 0.001 |

CI = confidence interval; IQR = interquartile range; SD = standard deviation; VAS = visual analogue scale.

[a]Quantile regression with covariates of treatment group, geographic region, baseline score, and log(e) baseline blood eosinophil count.

[b]Based on Wilcoxon rank sum test.

Note: Patients with nasal surgery or sinuplasty who withdrew from study before visit were assigned their worst observed score before nasal surgery or sinuplasty. Patients with no nasal surgery or sinuplasty who withdrew from study before visit were assigned their worst observed score before study withdrawal. Patients with missing visit data were assigned their worst observed score before the missing visit.

Source: SYNAPSE Clinical Study Report.[8]

# Appendix 4: Description and Appraisal of Outcome Measures

Note that this appendix has not been copy-edited.

## Aim

To describe the following outcome measures and review their measurement properties (validity, reliability, responsiveness to change, and MID):

- Endoscopic Nasal Polyps Score
- Symptoms Visual Analogue Scale
- SNOT-22
- Short Form-36 Health Survey version 2
- Work Productivity and Activity Impairment Index – General Health

## Findings

### Table 39: Summary of Outcome Measures and Their Measurement Properties in the SYNAPSE Trial

| Outcome measure | Description and type of scale | Conclusions about measurement properties | MID |
|---|---|---|---|
| Endoscopic Nasal Polyps Score | Endoscopic Nasal Polyps Score was determined by a health care staff using image recordings of nasal endoscopies.[8]<br>The score was determined by the polyp size (0 = no polyps; 4 = large polyps causing almost complete congestion/ obstruction of the inferior meatus).<br>The total score was the sum of the right and left nostril scores; scores can range from 0 to 8 with higher scores indicating worse status. | Studies determining the psychometric properties of the endoscopic nasal polyps score were not identified in the literature in the setting of CRSwNP. | Using anchor-based methods,[a] Han et al.[31] estimated the MCID in the nasal polyps score to be 1 point in adult patients with CRSwNP who were medically managed. |
| Symptoms VAS | Symptoms VAS was used to assess patient-perceived symptoms. Patients indicated on a VAS the severity of each nasal polyposis symptoms (nasal obstruction; nasal discharge; feeling of mucus in the throat; loss of smell; facial pain; and nasal polyps symptoms) at its worst over the previous 24 hours.[8]<br>Nasal symptoms and facial pain composite score was the sum of nasal obstruction, nasal discharge, mucus in throat, loss of smell, and facial pain scores.<br>VAS was a measurement scale | Studies determining the psychometric properties of the nasal polyposis symptoms VAS were not identified in the literature in the setting of CRSwNP. | A MID in the nasal polyposis symptoms VAS was not identified in the literature in the setting of CRSwNP. |

| Outcome measure | Description and type of scale | Conclusions about measurement properties | MID |
|---|---|---|---|
| | from 0 to 100; patients selected a point on the line that represented their current state, between the left- (0 = none) and right-hand side of the scale (100 = as bad as you can imagine). Values for the VAS were divided by 10 and reported to one decimal place (0 = none; 10 = as bad as you can imagine). | | |
| SNOT-22 Questionnaire | SNOT-22 is a 22-item self-reported questionnaire used to assess symptoms and impacts related to CRS. The recall period was over the past 2 weeks. Response to each question ranged from 0 (no problem) to 5 (the problem is as bad as it can be). The final score was the sum of the individual scores for each question and ranged from 0 to 110, with higher scores indicating a greater impact of CRS on HRQoL.[8]<br><br>The 22 items of SNOT-22 were categorized into domains based on a separate psychometric analysis of data from mepolizumab phase II study in CRSwNP: nasal, non-nasal, ear/facial, sleep, fatigue, and emotional consequences. | Hopkins et al.[37] reported the psychometric properties of SNOT-22 in adult patients with CRS and/or nasal polyposis who received surgical intervention:<br><br>**Validity**: SNOT-22 was able to discriminate between patients with CRS and healthy controls ($P < 0.0001$). SNOT-22 was also able to discriminate between patients with CRS in and out of subgroups, including revision surgery, less than 1 year of symptoms, asthma, Aspirin sensitivity ($P < 0.0001$ for each subgroup), and who smoke tobacco ($P < 0.005$).<br><br>**Reliability**: Acceptable internal consistency was demonstrated by a Cronbach alpha of 0.91. Acceptable test-retest reliability was demonstrated by the coefficient of 0.93 at 10 to 14 days from baseline in a separate cohort of patients waitlisted for surgical intervention for nasal polyps or rhinosinusitis.<br><br>**Responsiveness**: SNOT-22 scores decreased at 3 months post-surgery ($P < 0.0001$); effect size in all patients, patients with CRS with polyps, and without polyps was 0.81, 0.90, and 0.63, respectively. Further, Lidder et al.[54] demonstrated responsiveness of the SNOT-22 total score in adult patients with CRS who received medical intervention (Cohen d effect size = −0.70) and surgical intervention (Cohen d effect size = −1.56). | Using anchor-based methods,[b] Hopkins et al.[37] estimated the MID to be 8.9 points in the SNOT-22 score in patients with CRS and/or nasal polyposis who had received surgical intervention.<br><br>Using distribution-based methods, Chowdhury et al.[55] estimated the mean MCID to be 9.0 points in the SNOT-22[c] total score in adult patients with CRS who elected endoscopic sinus surgery.<br><br>Using anchor-based methods[d] and distribution-based methods, Phillips et al. (2018)[56] and Phillips et al. (2021)[57] suggested the MCID to be 12 points on the SNOT-22[e] in medically managed adult patients with CRS but noted it was specific but not sensitive for identifying patients with CRS experiencing improvement in symptoms or general health.<br><br>Using distribution-based methods, Chowdhury et al.[58] estimated the mean MCID to be 8.0 points in the SNOT-22[c] total score in adult patients with CRS who elected continued medical therapy. |

| Outcome measure | Description and type of scale | Conclusions about measurement properties | MID |
|---|---|---|---|
| SF-36 Health Survey version 2 | SF-36 version 2 was a 36-item short-form survey used to assess general HRQoL in a variety of clinical contexts.[8]<br>The survey assessed 8 health domains: (1) limitations in physical activities because of health problems; (2) limitations in social activities because of physical or emotional problems; (3) limitations in usual role activities because of physical health problems; (4) bodily pain; (5) general mental health (psychological distress and well-being); (6) limitations in usual role activities because of emotional problems; (7) vitality (energy and fatigue); and (8) general health perceptions.<br>There were 2 component summary scores: mental and physical. Health concepts were scored on a scale of 0 to 100, with higher scores indicating a more favourable health state. | Studies determining the psychometric properties of the SF-36 version 2 were not identified in the literature in the setting of CRSwNP. | A MID in the SF-36 version 2 was not identified in the literature in the setting of CRSwNP. |
| WPAI-GH | WPAI-GH is a self- or interviewer-administered questionnaire consisting of 6 questions used to assess impairments in paid and unpaid work based on absenteeism, presenteeism (reduced effectiveness while working), overall work productivity loss (absenteeism plus presenteeism), and activity impairment in the past 7 days.[8]<br>WPAI-GH outcomes are scored as impairment percentages (0% to 100%), with higher percentages indicating greater impairment to work productivity and daily activity. | Studies determining the psychometric properties of the WPAI-GH were not identified in the literature in the setting of CRSwNP. | A MID in the WPAI-GH was not identified in the literature in the setting of CRSwNP. |

CRS = chronic rhinosinusitis; CRSwNP = chronic rhinosinusitis with nasal polyps; HRQoL = health-related quality of life; MCID = minimal clinically important difference; MID = minimal important difference; SF-36 = Short Form-36; SNOT-22 = Sino-Nasal Outcome Test 22; VAS = visual analogue scale; WPAI-GH = Work Productivity and Activity Impairment Index – General Health.

[a]Anchor measures were 3.8- and 8.9-point improvement in the SNOT-22 rhinologic symptoms domain and total scores, respectively, and 1-category of improvement in the rhinosinusitis visual analogue scale score.

[b]Patient-reported transition rating scale was used to assess pre- and post-operative health and HRQoL on a 5-point scale (1 = much better; 5 = much worse). The MID was based on the difference between the mean change in SNOT-22 score for patients who reported their symptoms as "about the same" and "a little better" on the patient-reported transition rating scale.

[c]The 22 items of the SNOT-22 used in this study were categorized into 5 symptom domain scores: rhinologic, extranasal rhinologic, ear/facial, psychological dysfunction, and sleep dysfunction.

[d]Anchor questions were (1) patients were asked to compare their sinus symptoms at the follow-up visit relative to date of enrolment, and (2) compare their general health at the follow-up visit relative to date of enrolment, rated on a 5-item scale ranging from much worse to much better. The minimal clinically important difference was based on the difference between the mean change in SNOT-22 score for patients who responded to the anchor questions with "about the same" and "a little better."

[e]The 22 items of the SNOT-22 used in these studies were categorized into 4 symptom domain scores: nasal, sleep, ear/facial discomfort, and emotional.

CADTH

# Pharmacoeconomic Review

## List of Tables



## List of Figures

## Abbreviations

| | |
|---|---|
| **AE** | adverse event |
| **BIA** | budget impact analysis |
| **CRS** | chronic rhinosinusitis |
| **CRSwNP** | chronic rhinosinusitis with nasal polyps |
| **ICER** | incremental cost-effectiveness ratio |
| **INCS** | intranasal corticosteroids |
| **LY** | life-year |
| **NCS** | nasal congestion score |
| **NIHB** | non-insured health benefits |
| **NPS** | nasal polyp score |
| **OCS** | oral corticosteroids |
| **QALY** | quality-adjusted life-year |
| **SC** | subcutaneous |
| **SEA** | severe eosinophilic asthma |
| **SF-6D** | Short Form 6 Dimensions |
| **SNOT-22** | Sino-Nasal Outcome Test 22 |
| **SoC** | standard of care |
| **WTP** | willingness to pay |

# Executive Summary

The executive summary comprises 2 tables (Table 1 and Table 2) and a conclusion.

## Table 1: Submitted for Review

| Item | Description |
|---|---|
| **Drug product** | Mepolizumab (Nucala), 100 mg/mL for subcutaneous injection |
| **Submitted price** | Mepolizumab, 100 mg/mL, lyophilized powder or solution in prefilled autoinjector or solution in safety syringe: $2,100.61 |
| **Indication** | As add-on maintenance treatment with INCS in adult patients with severe CRSwNP inadequately controlled by INCS alone |
| **Health Canada approval status** | NOC |
| **Health Canada review pathway** | Standard |
| **NOC date** | November 5, 2021 |
| **Reimbursement request** | As per indication |
| **Sponsor** | GlaxoSmithKline Inc. |
| **Submission history** | Previously reviewed: Yes<br>Indication: Severe eosinophilic asthma<br>Recommendation date: June 16, 2016<br>Recommendation: Reimburse with clinical criteria and/or conditions |

CRSwNP = chronic rhinosinusitis with nasal polyps; INCS = intranasal corticosteroids; NOC = Notice of Compliance.

## Table 2: Summary of Economic Evaluation

| Component | Description |
|---|---|
| **Type of economic evaluation** | Cost–utility analysis<br>Markov model |
| **Target population** | As add-on maintenance treatment with INCS in adult patients with severe CRSwNP inadequately controlled by INCS alone |
| **Treatment** | Mepolizumab plus standard of care (INCS and nasal saline irrigation with intermittent OCS for severe symptoms) |
| **Comparator** | Standard of care alone |
| **Perspective** | Canadian publicly funded health care payer |
| **Outcomes** | QALYs, LYs |
| **Time horizon** | 10 years |
| **Key data source** | SYNAPSE pivotal trial informed relevant efficacy and safety parameters |
| **Submitted results** | ICER = $324,344 per QALY (incremental costs = $176,515; incremental QALYs = 0.57) |

| Component | Description |
|---|---|
| **Key limitations** | There is uncertainty in the magnitude of treatment effect with mepolizumab with respect to endoscopic improvement and relief of nasal obstruction and limited evidence on the duration of this treatment effect based on the available trial data.<br><br>Assessment of response at 24 weeks as assumed in the sponsor's base case may not align with the expected management of CRSwNP in clinical practice and is not aligned with the sponsor's proposed reimbursement criteria (1 year). The time point at which response is assessed affects the magnitude of benefit and the incremental costs associated with mepolizumab.<br><br>The sponsor's submission incorporated treatment-specific utility values. This approach likely double counts treatment benefits with mepolizumab and is counter to best practice guidance, which recommends the use of health state–specific utilities, with differences in QALYs driven by treatment efficacy.<br><br>Assessment of response according to a quality-of-life scale (SNOT-22) was used in the sponsor's base case, as opposed to response according to the nasal polyp or congestion score, which were the primary end points in the SYNAPSE trial. The nasal polyp score and nasal congestion score are considered more objective measures of response, and some differences in response were observed based on the measure used, which affects the estimated cost-effectiveness of mepolizumab.<br><br>A lifetime time horizon, rather than the 10-year time horizon used by the sponsor, is more appropriate for a decision problem involving a population of patients with CRSwNP because of the chronic nature of the disease. While this had minimal impact in the sponsor's base case, this limitation is of greater concern when the treatment effect of mepolizumab is expected to wane. |
| **CADTH reanalysis results** | The CADTH reanalysis removed treatment-specific utilities and applied health state–specific utilities. CADTH was unable to address the limitations concerning the lack of long-term clinical efficacy data.<br><br>The CADTH reanalysis found that mepolizumab is associated with an ICER of $380,251 per QALY gained (incremental costs: $176,515; incremental QALYs: 0.46) and that the probability of cost-effectiveness at a WTP threshold of $50,000 per QALY is 0%.<br><br>A price reduction of approximately 86% is required to achieve cost-effectiveness at this threshold. Scenarios exploring the uncertainty surrounding the duration of treatment effect, measurement of response, and time point at which response is assessed led to substantial changes in the results and suggest that even greater price reductions with mepolizumab may be required. |

CRSwNP = chronic rhinosinusitis with nasal polyps; ICER = incremental cost-effectiveness ratio; INCS = intranasal corticosteroids; LY = life-year; OCS = oral corticosteroids; QALY = quality-adjusted life-year; SNOT-22 = Sino-Nasal Outcome Test 22; WTP = willingness to pay.

## Conclusions

The CADTH clinical review found that mepolizumab as an add-on maintenance therapy in combination with standard of care (SoC) was efficacious in achieving endoscopic improvement and relief of nasal obstruction symptoms in patients with severe chronic rhinosinusitis with nasal polyps (CRSwNP) inadequately controlled by intranasal corticosteroids (INCS) alone. Mepolizumab was also found to be efficacious in prolonging time to nasal surgery. However, the magnitude of the treatment effect was modest. Furthermore, it is uncertain how much of the treatment effect observed in those receiving mepolizumab was due to the efficacy of mepolizumab versus the effectiveness of SoC, based on the response observed in the placebo group and clinical expert input. The durability of the treatment effect of mepolizumab could also not be adequately assessed.

CADTH undertook reanalyses by removing treatment-specific utilities to address 1 of the limitations in the sponsor's submission. In the CADTH base case, mepolizumab plus SoC was more effective and more costly than SoC alone (incremental costs = $176,515; incremental quality-adjusted life-years [QALYs] = 0.46), resulting in an incremental cost-effectiveness

ratio (ICER) of $380,251 per QALY gained. Using the CADTH base case, a price reduction of approximately 86% is necessary to achieve cost-effectiveness at a willingness-to-pay (WTP) threshold of $50,000 per QALY. These results were aligned with the findings from the sponsor's base case, with mepolizumab unlikely to be a cost-effective treatment option without a substantial reduction in price.

Given the lack of clinical data informing the long-term clinical efficacy of mepolizumab, the cost-effectiveness of mepolizumab compared to SoC is associated with uncertainty. A scenario analysis exploring the impact of waning the treatment effect led to a significant reduction in the benefit (i.e., QALY gains) associated with mepolizumab, increasing the ICER to $677,900 per QALY. Further, the results are driven by the time point at which response is assessed and the measure used to determine response. Should response be assessed at 52 weeks, rather than the 24 weeks assumed in the base case, or based on objective measures such as the nasal polyp score (NPS) or the nasal congestion score (NCS), or if the treatment effect is expected to wane, the result would likely be that a greater price reduction would be required.

## Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups, clinician groups, and drug plans that participated in the CADTH review process.

Patient input was provided by 2 groups: Asthma Canada and the Patient Lung Groups of the British Columbia Lung Association. Survey respondents indicated that CRSwNP symptoms negatively impact daily life by decreasing quality of life, causing sleep disturbances, impacting ability to attend work or school, and requiring hospital visits. Patients reported using nasal sprays to manage CRSwNP, undergoing surgery, using corticosteroids, or using a biologic (e.g., dupilumab or omalizumab) to treat nasal polyps. Side effects most commonly associated with treatments included altered sense of smell, allergic reactions, sinus infection, and headaches. Both patient groups expressed concern about short- and long-term side effects associated with oral corticosteroids (OCS) in patients who have not experienced adequate control of their CRSwNP with previous lines of therapy. Patients and caregivers indicated that the most important outcomes for new treatment options include easier management of symptoms; decreased anxiety about nasal polyps; decreased reliance on OCS; reduced need for surgery; and improved treatment administration methods. Patients indicated that potential side effects of mepolizumab would be tolerable in exchange for improved CRSwNP management.

No clinician group input was received for this review.

Drug plan input expressed concerns surrounding the lack of active comparator in the SYNAPSE trial and issues with certain INCS (mometasone and budesonide) not being reimbursed in certain provinces. Drug plans also noted potential concerns with eligibility for patients without prior nasal polyp surgery as well as accessibility issues regarding CT imaging or nasal endoscopy for diagnosis. Drug plans also expressed uncertainty surrounding evaluation of treatment response across the various scales used in the trial (visual analogue scale, NPS, and Sino-Nasal Outcome Test 22 [SNOT-22]), as well as the definitions of loss of response and disease progression. Dose escalation beyond 100 mg was also unclear, as was

whether treatment would continue for the duration of the patient's lifetime. Lastly, drug plans expressed concern surrounding the potential budget impact of reimbursing mepolizumab given the large incremental costs across the first 3 years of listing.

One of these concerns was addressed in the sponsor's model:

- Clinical effectiveness was based on treatment response, with the inclusion of surgical outcomes as well as asthma exacerbations, OCS use, and antibiotics use.

In addition, CADTH addressed another of these concerns, as follows:

- CADTH considered the impact of a treatment waning effect on results; however, a strict definition of loss of response or disease progression was not determined or considered.

CADTH was unable to address the following concerns raised from stakeholder input:

- Lack of long-term clinical efficacy data for mepolizumab versus SoC for the treatment of CRSwNP beyond the trial follow-up period.
- The impact of dose escalation beyond 100 mg with mepolizumab.

# Economic Review

The current review is for mepolizumab (Nucala) as add-on maintenance treatment with INCS in adult patients with severe CRSwNP inadequately controlled by INCS alone.

## Economic Evaluation

### Summary of Sponsor's Economic Evaluation

*Overview*

The sponsor submitted a cost–utility analysis of mepolizumab plus SoC compared with SoC alone. The model population comprised adult patients with recurrent, refractory, severe CRSwNP inadequately controlled by INCS alone. The target population was aligned with the Health Canada–indicated population and reimbursement request. SoC comprised INCS and nasal saline irrigation with intermittent courses of OCS when short-term relief of severe symptoms is required.

Mepolizumab is available in 100 mg (100 mg/mL) prefilled autoinjector or safety syringes for self-administered subcutaneous injection and as lyophilized powder for reconstitution and administration. The recommended dosage is 100 mg every 4 weeks, and the annual cost of treatment is $27,308 based on a unit cost of $2,100.61 per dose. The weighted annual cost of SoC per patient was assumed by the sponsor to be zero due to corticosteroids being "relatively inexpensive" and included in both the mepolizumab and SoC alone arms with equal usage.[1]

The outcomes modelled included QALYs and life-years over a time horizon of 10 years and a cycle length of 4 weeks. The base-case analysis was conducted from the Canadian public health care system perspective, with costs and outcomes discounted at 1.5%.

*Model Structure*

The sponsor submitted a Markov model with health states based on treatment response ("response" and "no response" health states) assessed at 24 weeks and 52 weeks. The model also included health states based on outcomes of posttreatment nasal surgery ("post-surgery — response," "post-surgery — no response," and "post-surgery — recurrence" health states). Response to initial treatment was defined based on achievement of an 8.9-point or greater improvement in SNOT-22 score. Alternate response assessment criteria were implemented as a scenario analysis and used the definition of an NPS of at least 1 or an NCS of at least3. Nonresponders were defined patients whose response did not meet the defined response criteria or as patients who had surgery, regardless of whether the criteria were achieved. The submitted model also included a "death" state based on general population mortality as well as a risk of surgery-related mortality.

All patients with CRSwNP enter the model either on treatment with mepolizumab plus SoC or with SoC alone. Following response assessment at 24 weeks, patients classified as nonresponders were assumed to discontinue treatment with mepolizumab and switch to SoC alone. Patients defined as responders at week 24 could either continue treatment or discontinue mepolizumab and enter the "no response" health state at a secondary assessment time point at week 52. All patients during each model cycle were at risk of experiencing asthma exacerbations and CRSwNP flares. Responders were assumed to not be at risk of requiring surgery, whereas nonresponders experienced a per-cycle probability of subsequent surgery. Upon posttreatment nasal surgery, patients experienced a probability of postsurgical disease recurrence for which they could then receive subsequent surgeries. A figure of the submitted model is available in Appendix 3.

*Model Inputs*

The baseline patient characteristics in the sponsor's model were aligned with the SYNAPSE trial (mean age 48.8 years; 64.9% male).[2]

Clinical efficacy (i.e., treatment response) was based on the 52-week SYNAPSE trial. The pivotal trial compared mepolizumab to placebo in patients with severe CRSwNP, with the primary end point being NPS or NCS response definition. However, the definition of response in the model was based on the secondary outcome of achievement of an 8.9-point or greater gain in SNOT-22 score at 24 weeks. Response assessment using the primary end point (NPS or NCS response definition) was available for a scenario analysis. Response was assessed again at 52 weeks, with probabilities of response conditional on achieving a prior response at 24 weeks, as defined by the SNOT-22 criteria. Responders at week 52 were assumed to remain responders for the duration of the model time horizon of 10 years. Post-trial annual loss of effect and post-trial annual treatment discontinuation rates were assumed to be 0; clinical effectiveness after week 52 was assumed to remain constant for the duration of the model time horizon.

The proportion of patients requiring surgery was directly derived from the SYNAPSE trial, which differed by treatment arm up to week 24. For weeks 24 to 52, the probability of surgery differed by previous 24-week response status (based on SNOT-22 response definition) and by treatment received. After the trial period of 52 weeks, nonresponders were assumed to require surgery at a constant annual rate of 11.4%.[3] Post-surgery responders were assumed to lose response to surgery at a rate of 38.4% per year, after which they were eligible to receive another surgery. All patients were assumed to initially respond to surgery in the sponsor's base case. Asthma exacerbation rates were derived from the SYNAPSE trial as

well, which differed by treatment arm up to week 24. Between 24 weeks and 52 weeks, the rate of asthma exacerbations differed depending on response status (based on the SNOT-22 response definition) and treatment received, similarly to the probability of requiring surgery. Asthma exacerbation resource utilization was assumed to be the same for both treatment arms and included OCS use, emergency department visit, or hospitalization, with the distribution of asthma exacerbations requiring each based on the SYNAPSE trial.[2] CRSwNP flares were characterized by OCS use and/or antibiotics, based on data from the SYNAPSE trial. The mean number of OCS and antibiotic courses was taken from the pivotal trial and differed based on response status (SNOT-22 response definition) and treatment arm, similar to surgery and asthma exacerbations. No treatment-related adverse events (AEs) were included in the base-case analysis, although the probability of surgical complications was included.[4] Risk of all-cause mortality was incorporated based on Canadian life tables and applied equally to all patients and health states.[5] Patients who underwent nasal polyp surgery experienced an increased risk of death of 0.01% associated with surgery, estimated from Scangas et al. (2021).[6]

Treatment-specific utility values were derived by mapping SNOT-22 scores from the SYNAPSE trial to the EQ-5D using a published mapping algorithm that was developed using data collected from patients with chronic rhinosinusitis (CRS) in Canada.[7] All patients entered the model with a baseline utility based on the pooled SYNAPSE trial population, with utilities between week 0 and week 24 based on treatment arm using an analysis of the least squares mean change from baseline at each assessment time point (i.e., 4-week cycles) and a mixed-model repeated measures analysis with various covariates (treatment group, geographic region, baseline blood eosinophil count, visits, and so forth). After week 24, treatment-specific utility values were based on having achieved the SNOT-22 response definition using the same change from baseline methodology and remained constant after week 52. A utility gain related to surgery was derived from the SYNAPSE study by calculating the difference in utility scores pre- and post-surgery in the SoC arm. Disutilities related to surgery[8] and asthma exacerbation requiring OCS, emergency department visit, or hospitalization were incorporated in the sponsor's model.[9]

Costs considered in the model included drug acquisition costs for mepolizumab, health care resource utilization costs, administration costs, and AE costs. Relevant costs were inflated to 2022 Canadian dollars. Drug acquisition costs for mepolizumab were sourced from the sponsor.[1] SoC costs were deemed relatively inexpensive and excluded from the analysis as they were assumed to be the same (i.e., zero) regardless of treatment received. No administration costs were assumed to be associated with mepolizumab given it can be self-administered. Direct medical costs of nasal polyp surgery were obtained from a Canadian modelling study based on a weighted cost of endoscopic polypectomy in a clinic versus the costs of endoscopic sinus surgery ($3,865.52).[10] Surgical complications were estimated at $260.29 and generally attributed to epistaxis.[10] Costs of asthma exacerbation were based on severity and stratified based on OCS use, emergency department visit, and hospitalization. These costs included costs related to a telephone call, home day visit, home night visit, practice visit, outpatient attendance, and prednisone course dose.[11-14] The OCS cost for CRSwNP flares was based on ear, nose, and throat specialist visits and a course of prednisone;[11,15] antibiotic costs for CRSwNP flares were based on a 10-day course of doxycycline 100 mg twice daily.[15] No health state costs were considered.

## Summary of Sponsor's Economic Evaluation Results

All analyses were run probabilistically (500 iterations for the base-case and scenario analyses). The deterministic and probabilistic results were similar. The probabilistic findings are presented in the sections that follow.

### *Base-Case Results*

Mepolizumab was associated with incremental costs of $176,515 and 0.57 incremental QALYs in comparison to SoC alone, resulting in an ICER of $311,763 per QALY gained (Table 3).

Additional results from the sponsor's submitted economic evaluation base case are presented in Appendix 3.

### *Sensitivity and Scenario Analysis Results*

The sponsor conducted several scenario analyses including an alternate measure of response using NPS or NCS response criteria from the SYNAPSE trial, Short Form 6 Dimensions (SF-6D) utility values, a 53-week surgery wait time, an 85% surgical success rate, and a 3-dose mepolizumab administration training cost. The ICER was most sensitive to SF-6D utility values, resulting in an increased ICER of $453,923 per QALY. The ICER was robust to changes in all other scenario analyses conducted.

## CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications for the economic analysis:

- **Uncertainty regarding the magnitude and durability of treatment effect with mepolizumab:** The sponsor incorporated treatment response in the model based on the proportion of patients in the trial who achieved an 8.9-point or greater increase in SNOT-22 score and assumed that the treatment benefit observed at 52 weeks in the trial with mepolizumab would be sustained over the model time horizon of 10 years. The CADTH clinical review concluded that mepolizumab was efficacious based on the results of the SYNAPSE trial; however, uncertainty remains in the effect of mepolizumab given the modest magnitude of treatment effect observed and the difficulty discerning how much of the benefit is attributable to the effectiveness of concomitant SoC. Furthermore, the durability of treatment effect beyond the SYNAPSE trial is highly uncertain. The sponsor did not include potential waning of treatment effect in its base-case analysis, although a post-trial annual loss of effect was provided as an option in the model. The

## Table 3: Summary of the Sponsor's Economic Evaluation Results

| Drug | Total costs, $ | Incremental costs, $ | Total QALYs | Incremental QALYs | ICER vs. SoC, $/QALY |
|---|---|---|---|---|---|
| SoC | 3,087 | Reference | 5.80 | Reference | Reference |
| Mepolizumab | 179,601 | 176,515 | 6.37 | 0.57 | 311,763 |

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SoC = standard of care.

Note: The submitted analysis is based on the publicly available prices of the comparator treatments. The sponsor-submitted ICER has been corrected from the sponsor's submitted pharmacoeconomic report to reflect the ICER based on the average total costs and QALYs as opposed to the average ICER over 500 simulations as presented by the sponsor.

Source: Sponsor's pharmacoeconomic submission.[1]

limitations with the available clinical evidence introduce uncertainty into the sponsor's cost-effectiveness estimates.

  - CADTH assessed the impact of including a post-trial annual loss of effect of 4.3% as a scenario analysis, such that the treatment benefit observed with mepolizumab reached approximately similar response rates observed with SoC after 10 years.

- **Uncertainty surrounding assessment of response:** The sponsor's model included an initial assessment of response occurring at 24 weeks, followed by conditional assessment of response at 52 weeks based on previously being a responder. The sponsor selected an initial response assessment at 24 weeks based on clinical expert opinion on best practice. However, the estimated response rates do not align with the assessment of overall response at 52 weeks observed in the trial, regardless of prior response status. The response rates estimated by the sponsor and used in the model were [redacted] and [redacted] for patients receiving mepolizumab or SoC alone, respectively; however, overall response rates from the SYNAPSE trial at 52 weeks were 73.2% and 53.5% for the mepolizumab and SoC alone arms, respectively. The sponsor's approach predicts a greater difference in the proportion of patients achieving a response than if it had used the 52-week data. The absolute difference in response when using the conditional response rates was [redacted], whereas the difference when using the overall response rates from the trial was 19.7%.

  Furthermore, the sponsor's submission included suggested reimbursement criteria, which included assessment of clinical response after 1 year of treatment. However, the sponsor's base case does not align with this. The overall 52-week response data are most relevant to such a scenario, and patients would remain on treatment with mepolizumab until 52 weeks unless they received surgical treatment. The reimbursement criteria are counter to the rationale provided by the sponsor to justify the use of the 24-week and subsequent conditional 52-week assessment data.

  Overall, there is uncertainty in the appropriate response assessment time point. CADTH notes that if a 1-year time point is used, the sponsor's base case underestimates the incremental costs associated with mepolizumab and overestimates the incremental QALYs. Consequently, the cost-effectiveness of mepolizumab is likely overestimated in comparison with SoC.

  - CADTH assessed the impact of treatment assessment occurring at 52 weeks in a scenario analysis.

- **Inappropriate use of treatment-specific utilities and uncertainty in derivation of utilities:** In the sponsor's model, treatment-specific utilities were applied using least squares mean change from baseline at each 4-week time point from baseline to 24 weeks before assessment of treatment response and differed by responder status following week 24. Additional disutilities were included based on the occurrence of events. Treatment-specific utilities are generally considered to be inappropriate, and health state and event–specific utilities are preferred, as per CADTH Guidelines for the Economic Evaluation of Health Technologies.[16] The sponsor's assumption that treatment itself is associated with a utility benefit does not meet face validity; utilities should be health state and event driven and associated with response, as opposed to treatment specific. The inclusion of disutilities based on the occurrence of events in addition to using treatment-specific utilities results in the double-counting of the impacts of treatment on clinical events, overestimating the benefit associated with mepolizumab.

  The sponsor also mapped SNOT-22 scores from the SYNAPSE trial to obtain EQ-5D estimates using an algorithm based on data collected from patients with CRS in Canada.[7] However, mapping is not recommended for the derivation of utilities as per CADTH

Guidelines for the Economic Evaluation of Health Technologies in Canada.[16] Mapping is unlikely to successfully capture the utility relationship between 2 measures due to high variability in predictive value depending on the instruments being mapped, the algorithm used, and the severity of the health states included. This approach introduces uncertainty into the derivation of the utility values informing the sponsor's model.

  - CADTH removed treatment-specific utilities such that utilities were health state and event specific in the reanalysis. CADTH could not address limitations regarding the derivation of utilities via mapping.

- **Relevance of SNOT-22 versus NPS or NCS to determine treatment response:** The sponsor used response according to SNOT-22 (an 8.9-point or greater improvement leading to the patient being defined as a responder) to determine treatment response in the submitted model. CADTH notes that the SYNAPSE trial had NPS or NCS (NPS improvement > 1 or NCS improvement > 3) as the primary end point, whereas response by SNOT-22 score was an exploratory end point. While CADTH acknowledges that SNOT-22 is used in Canadian clinical practice to make treatment decisions, the use of objective scoring measures such as response according to NPS or NCS is preferred and is better aligned with the pivotal trial, as indicated by the clinical expert feedback obtained by CADTH.

  Notably, the sponsor used NPS or NCS response criteria in a scenario analysis, demonstrating that the ICER increased when using the NPS or NCS response criteria in comparison with the sponsor's base case, which used SNOT-22 response criteria. In addition to being misaligned with the primary outcome from the SYNAPSE trial, the use of SNOT-22 scores to capture response may overestimate the cost-effectiveness of mepolizumab.

  - CADTH assessed the impact of using NPS or NCS response criteria in a scenario analysis.

- **Time horizon may not be appropriate for decision problem:** The sponsor's time horizon in the submitted model is 10 years. However, treatment with mepolizumab for CRSwNP is expected to be chronic, with patients expected to be treated well beyond 10 years. As a result, the time horizon should be over the patient's lifetime to ensure all costs and benefits of treatment are captured. CADTH notes that the lifetime time horizon was not expected to impact the ICER due to the sponsor's assumption of sustained treatment benefit and the accrual of costs at a similar rate over time. However, potential treatment waning is a relevant concern given the uncertainty surrounding long-term clinical effectiveness of mepolizumab, as described above. Therefore, the length of the model time horizon in the context of potential treatment waning is likely to influence estimates of the cost-effectiveness of mepolizumab, which is important given the uncertainty surrounding long-term clinical effectiveness, as highlighted in the CADTH appraisal of the sponsor's economic evaluation.

  - CADTH tested the impact of implementing a lifetime time horizon to reflect clinical practice and expected use of mepolizumab.

Additionally, the following key assumptions were made by the sponsor and have been appraised by CADTH (refer to Table 4).

## CADTH Reanalyses of the Economic Evaluation

### *Base-Case Results*

The CADTH base case was derived by making changes in model parameter values and assumptions, in consultation with clinical experts. CADTH undertook a stepped reanalysis that applied health state–specific utility values. Details of the change to derive the CADTH

reanalysis are presented in Table 5. The summary of the CADTH reanalysis is presented in Table 6 (disaggregated results presented in Appendix 4).

In the CADTH base case, mepolizumab was associated with a total cost of $179,601 and 6.35 QALYs compared to $3,087 and 5.89 QALYs for patients receiving SoC alone. The ICER for mepolizumab compared to SoC was $380,251 per QALY gained, with a probability of being cost-effective of 0%, at a WTP threshold of $50,000 per QALY. Detailed information and disaggregated results are presented in Table 11 in Appendix 4.

*Scenario Analysis Results*

CADTH performed price reduction analyses based on the sponsor base case and CADTH base-case reanalysis. Based on the CADTH base case, a price reduction of approximately 86% would be required to achieve cost-effectiveness at a WTP threshold of $50,000 per QALY (Table 7).

CADTH performed additional scenario analyses to determine the impact of alternative assumptions on the cost-effectiveness of mepolizumab. CADTH assessed the impact of including the following: a treatment waning effect with mepolizumab (4.3% reduction per year); response assessment occurring at 52 weeks and using the efficacy inputs based on

## Table 4: Key Assumptions of the Submitted Economic Evaluation — Not Noted as Limitations to the Submission

| Sponsor's key assumption | CADTH comment |
|---|---|
| Treatment administration would not result in additional costs | Reasonable. Mepolizumab can be self-administered, and the impact of a 3-dose administration training cost was assessed and deemed to be minimally impactful to the ICER. |
| Costs of SoC were assumed to be $0 | Reasonable. Patients in both treatment arms will receive SoC, and usage is not expected to differ across arms. Therefore, incremental costs are likely unaffected. |
| AEs were excluded | Reasonable. Frequency of severe AEs was not expected to differ across treatment arms. |

AE = adverse event; ICER = incremental cost-effectiveness ratio; SoC = standard of care.

## Table 5: CADTH Revisions to the Submitted Economic Evaluation

| Stepped analysis | Sponsor's value or assumption | CADTH value or assumption |
|---|---|---|
| **Corrections to sponsor's base case** | | |
| None | — | — |
| **Changes to derive the CADTH base case** | | |
| 1. Utility values | Treatment-specific utility values for within trial period and health states | Health state–specific utility values applied. Set difference between mepolizumab utilities and SoC utilities to 0 during week 0 to week 20 and applied the mepolizumab utilities to SoC in weeks 24 and beyond for all health states. |
| CADTH base case | — | Reanalysis 1 |

SoC = standard of care.

the 52-week data from the SYNAPSE trial (73.2% for mepolizumab; 53.5% for SoC); response assessment using NPS or NCS; and a lifetime time horizon.

Inclusion of a treatment waning effect for mepolizumab resulted in an increase in the ICER to $677,900 per QALY. This demonstrates that an assumption of sustained treatment benefit is a major driver of estimates of cost-effectiveness, although the long-term clinical efficacy of mepolizumab is uncertain. An alternate response assessment occurring at 52 weeks instead of 24 weeks resulted in an ICER of $499,664 per QALY, due in part to less benefit and greater drug acquisition costs derived with mepolizumab in comparison with the CADTH base case. Implementing NPS or NCS response criteria resulted in an increase in the ICER to $509,684 per QALY. Lastly, incorporating a lifetime time horizon of 51 years resulted in a slightly decreased ICER of $368,609. CADTH notes that the lifetime time horizon resulted in a slight decrease in the ICER estimate due to the sustained treatment benefit and continued

## Table 6: Summary of the Stepped Analysis of the CADTH Reanalysis Results

| Stepped analysis | Drug | Total costs, $ | Total QALYs | ICER, $/QALY |
|---|---|---|---|---|
| Sponsor's base case<br>*Deterministic* | SoC | 3,024 | 5.80 | Ref. |
| | Mepolizumab | 179,604 | 6.37 | 312,545 |
| CADTH reanalysis 1 (substitution with health state utilities) | SoC | 3,024 | 5.89 | Reference |
| | Mepolizumab | 179,604 | 6.35 | 381,398 |
| CADTH base case (reanalysis 1)<br>*Probabilistic* | SoC | 3,087 | 5.89 | Reference |
| | Mepolizumab | 179,601 | 6.35 | 380,251[a] |

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SoC = standard of care.

Note: The CADTH reanalysis is based on publicly available prices of the comparator treatments. All presented analyses are deterministic, with the exception of the CADTH base case, which is presented probabilistically.

[a]The ICER has been corrected to reflect average total costs and average total QALYs as opposed to the average ICER over 500 simulations as presented by the sponsor.

## Table 7: CADTH Price Reduction Analyses

| Analysis | ICERs for mepolizumab vs. SoC ($/QALY) | |
|---|---|---|
| **Price reduction, %** | **Sponsor base case** | **CADTH reanalysis** |
| No price reduction | 311,763 | 380,251 |
| 10 | 280,339 | 341,924 |
| 20 | 248,915 | 303,597 |
| 30 | 217,492 | 265,270 |
| 40 | 186,068 | 226,943 |
| 50 | 154,644 | 188,616 |
| 60 | 123,221 | 150,290 |
| 70 | 91,797 | 111,963 |
| 80 | 60,373 | 73,636 |
| 90 | 28,949 | 35,309 |

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SoC = standard of care.

accrual of costs, which did not largely impact the ratio of cost-effectiveness as captured by the ICER. Across the scenario analyses conducted by CADTH, the price reductions required to achieve cost-effectiveness at a WTP threshold of $50,000 per QALY ranged from approximately 86% to 97%.

## Issues for Consideration

CADTH notes that dupilumab and omalizumab are indicated by Health Canada for the treatment of CRSwNP.[17,18] However, the cost-effectiveness of mepolizumab relative to dupilumab and omalizumab was not assessed, as neither was deemed to be a relevant comparator based on the CADTH submission requirements. The comparative clinical efficacy of mepolizumab versus other biologic treatments, and therefore the cost-effectiveness of mepolizumab in this context, is presently unknown.

## Overall Conclusions

The CADTH clinical review found that mepolizumab as an add-on maintenance therapy in combination with SoC was efficacious in achieving endoscopic improvement and relief of nasal obstruction symptoms in patients with severe CRSwNP inadequately controlled by INCS alone. Mepolizumab was also found to be efficacious in prolonging time to nasal surgery. However, the magnitude of the treatment effect was modest. Furthermore, it is uncertain how much of the treatment effect observed in those receiving mepolizumab was due to the efficacy of mepolizumab versus the effectiveness of SoC based on the response observed in the placebo group and clinical expert input. The durability of the treatment effect of mepolizumab could also not be adequately assessed.

CADTH undertook reanalyses by removing treatment-specific utilities to address 1 of the limitations in the sponsor's submission. In the CADTH base case, mepolizumab plus SoC was more effective and more costly than SoC alone (incremental costs = $176,515; incremental QALYs = 0.46), resulting in an ICER of $380,251 per QALY gained. Using the CADTH base case, a price reduction of approximately 86% is necessary to achieve cost-effectiveness at a WTP threshold of $50,000 per QALY. These results were aligned with the findings from the sponsor's base case, with mepolizumab unlikely to be a cost-effective treatment option without a substantial reduction in price.

Given the lack of clinical data informing the long-term clinical efficacy of mepolizumab, the cost-effectiveness of mepolizumab compared to SoC is associated with uncertainty. A scenario analysis exploring the impact of waning treatment effect led to a significant reduction in the benefit (i.e., QALY gains) associated with mepolizumab, increasing the ICER to $677,900 per QALY. Further, the results are driven by the time point at which response is assessed and the measure used to determine response. Should response be assessed at 52 weeks, rather than the 24 weeks assumed in the base case, or be based on objective measures such as the NPS or NCS, or if the treatment effect is expected to wane, a greater price reduction is likely to be required.

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# Appendix 1: Cost Comparison Table

Note that this appendix has not been copy-edited.

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical experts. Comparators may be recommended (appropriate) practice or actual practice. Existing Product Listing Agreements are not reflected in the table and as such, the table may not represent the actual costs to public drug plans.

## Table 8: CADTH Cost Comparison Table for Severe CRSwNP

| Treatment | Strength | Form | Price ($) | Recommended dosage | Daily cost ($) | Annual cost ($) |
|---|---|---|---|---|---|---|
| Mepolizumab (Nucala) | 100 mg/mL | Vial of powder for SC injection | 2,100.6100 | 100 mg every 4 weeks | 74.82 | 27,308 |
| | | Prefilled syringe for SC injection | | | | |
| | | Prefilled autoinjector for SC injection | | | | |

CRSwNP = chronic rhinosinusitis with nasal polyps; mg = milligram; mL = millilitre; SC = subcutaneous.

Note: Sponsor-submitted price.[19]

# Appendix 2: Submission Quality

Note that this appendix has not been copy-edited.

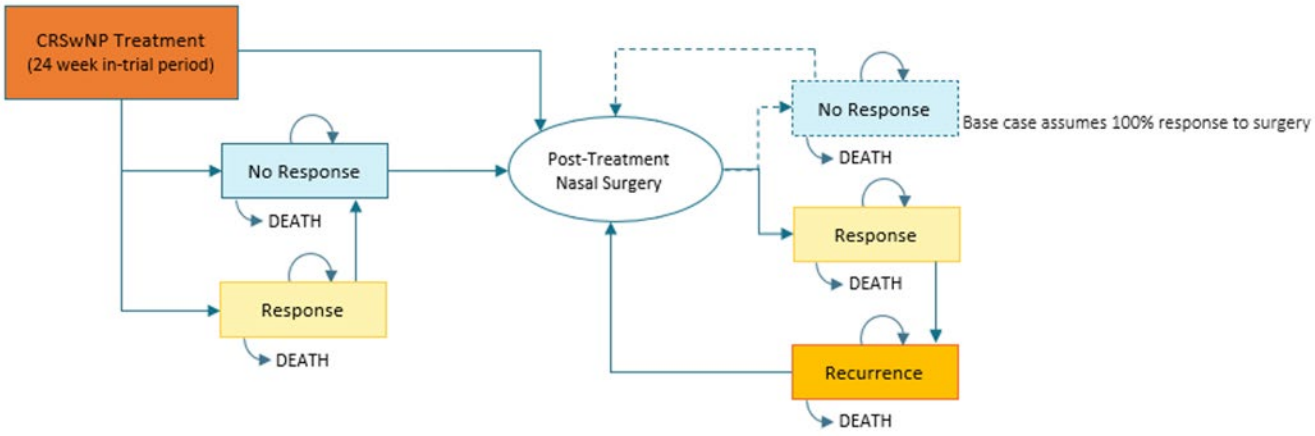
## Table 9: Submission Quality

| Description | Yes/No | Comments |
|---|---|---|
| Population is relevant, with no critical intervention missing, and no relevant outcome missing | Yes | No comment. |
| Model has been adequately programmed and has sufficient face validity | Yes | No comment. |
| Model structure is adequate for decision problem | Yes | No comment |
| Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis) | Yes | No comment. |
| Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem | Yes | No comment. |
| The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough details) | No | The model's flexibility to account for an alternate assessment period was placed in hidden cells by the sponsor. Technical documentation regarding the derivation of clinical inputs (i.e., 52-week responders based on previous responders at 24-week response assessment) was not available in the sponsor's submitted report. |

# Appendix 3: Additional Information on the Submitted Economic Evaluation

Note that this appendix has not been copy-edited.

## Figure 1: Model Structure




Source: Sponsor's pharmacoeconomic submission.[1]

## Detailed Results of the Sponsor's Base Case

## Table 10: Disaggregated Summary of the Sponsor's Economic Evaluation Results

| Parameter | Mepolizumab | SoC | Incremental |
|---|---|---|---|
| **Discounted LYs** | | | |
| Total | 9.13 | 9.13 | 0 |
| **Discounted QALYs** | | | |
| Total | 6.37 | 5.80 | 0.57 |
| In Trial | 0.28 | 0.26 | 0.02 |
| Responder | 4.67 | 3.01 | 1.66 |
| Nonresponder | 0.49 | 0.84 | −0.36 |
| Effective Surgery | 0.39 | 0.71 | −0.32 |
| Recurrence or Failed | 0.53 | 0.98 | −0.44 |
| **Discounted costs ($)** | | | |
| Total | 179,601 | 3,087 | 176,515 |
| Acquisition | 177,876 | 0 | 177,876 |
| Administration | 0 | 0 | 0 |
| Surgery | 1,381 | 2,491 | −1,110 |
| Asthma Exacerbations | 176 | 328 | −152 |

| Parameter | Mepolizumab | SoC | Incremental |
|---|---|---|---|
| Other | 168 | 268 | −100 |
| ICER ($/QALY) | 311,763 | | |

ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year; SoC = standard of care.

# Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation Detailed Results of CADTH Base Case

Note that this appendix has not been copy-edited.

## Table 11: Disaggregated Summary of CADTH's Economic Evaluation Results

| Parameter | Mepolizumab | SoC | Incremental |
|---|---|---|---|
| **Discounted LYs** | | | |
| Total | 9.13 | 9.13 | 0 |
| **Discounted QALYs** | | | |
| Total | 6.35 | 5.89 | 0.46 |
| In Trial | 0.27 | 0.26 | 0.01 |
| Responder | 4.67 | 3.10 | 1.57 |
| Nonresponder | 0.49 | 0.84 | −0.36 |
| Effective Surgery | 0.39 | 0.71 | −0.32 |
| Recurrence or Failed | 0.53 | 0.98 | −0.44 |
| **Discounted costs ($)** | | | |
| Total | 179,601 | 3,087 | 176,515 |
| Acquisition | 177,876 | 0 | 177,876 |
| Administration | 0 | 0 | 0 |
| Surgery | 1,381 | 2,491 | −1,110 |
| Asthma Exacerbations | 176 | 328 | −152 |
| Other | 168 | 268 | −100 |
| ICER ($/QALY) | 380,251 | | |

ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year; SoC = standard of care.

## Scenario Analyses

## Table 12: Summary of CADTH's Scenario Analyses Results

| Scenario | Scenario Analysis | Total Costs ($) | Total QALYs | ICER ($/QALY)[a] |
|---|---|---|---|---|
| CADTH Base Case | SoC | 3,087 | 5.89 | Reference |
| | Mepolizumab | 179,601 | 6.35 | 380,251 |
| Scenario 1: Treatment Waning Effect | SoC | 3,087 | 5.89 | Reference |
| | Mepolizumab | 154,419 | 6.11 | 677,900 |

| Scenario | Scenario Analysis | Total Costs ($) | Total QALYs | ICER ($/QALY)[a] |
|---|---|---|---|---|
| Scenario 2: Response Assessment at 52 Weeks | SoC | 2,329 | 5.68 | Reference |
| | Mepolizumab | 190,200 | 6.06 | 499,664 |
| Scenario 3: NPS/NCS Response Criteria | SoC | 3,473 | 5.80 | Reference |
| | Mepolizumab | 158,769 | 6.10 | 509,684 |
| Scenario 4: Lifetime Time Horizon | SoC | 7,695 | 17.04 | Reference |
| | Mepolizumab | 506,757 | 18.39 | 368,609 |

ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year; SoC = standard of care.

[a]The ICER has been corrected to reflect average total costs and average total QALYs as opposed to the average ICER over 500 simulations as presented by the sponsor.

Note: Reanalyses are based on publicly available prices of the comparator treatments.

# Appendix 5: Submitted Budget Impact Analysis and CADTH Appraisal

Note that this appendix has not been copy-edited.

## Table 13: Summary of Key Take-Aways

| Key Take-Aways of the BIA |
|---|
| • **CADTH identified the following key limitations with the sponsor's analysis:**<br>◦ The target population size is associated with uncertainty. The inputs used to derive the target population, while deemed plausible, may have limited generalizability to the Canadian context, and the availability of mepolizumab may increase the anticipated diagnosis rate of CRSwNP, increasing the eligible population size.<br>◦ The market uptake of mepolizumab is uncertain and based on internal sponsor forecasting which could not be validated by CADTH.<br>◦ Uncertainty surrounding treatment eligibility was raised by the drug plans, particularly regarding the requirement of prior nasal polyp surgery, bilateral nasal polyps, or prior treatment with INCS for 8 weeks before initiation with mepolizumab. This issue could not be addressed by CADTH.<br>• CADTH did not undertake a reanalysis of the sponsor's BIA due to key limitations being primarily focused on uncertainty in parameters used to derive the target population and market shares. CADTH accepted the sponsor's base case, which estimated the budget impact of mepolizumab to be $30,401,285 in year 1, $34,843,638 in year 2, and $38,893,040 in year 3, for a 3-year total of $104,137,963. When these parameters were tested in scenario analyses, the results were significantly affected by an increase in the number of patients diagnosed with CRSwNP, as well as the anticipated uptake of mepolizumab. |

BIA = budget impact analysis; CRSwNP = chronic rhinosinusitis with nasal polyps; INCS = intranasal corticosteroids.

## Summary of Sponsor's Budget Impact Analysis

The submitted budget impact analysis (BIA) assessed the introduction of mepolizumab as an add-on maintenance treatment in adult patients with severe CRSwNP inadequately controlled by INCS alone.[20] The analysis took the perspective of CADTH-participating Canadian public drug plans using a top-down epidemiological approach and incorporated drug acquisition costs. A time horizon of 3 years was taken. The target population size was estimated using prevalence of patients with CRS, followed by further specification of patients with CRSwNP, those receiving INCS, proportion of patients with persistent symptoms (at least 8 to 12 weeks) and without severe eosinophilic asthma, and lastly by determining the proportion of patients enrolled in public drug plans. The sponsor assumed that patients requiring additional treatment with surgery would represent patients with CRSwNP with persistent symptoms for at least 8 to 12 weeks. The base-case analysis considers SoC alone (INCS) in the reference scenario and the new drug scenario considered the reimbursement of mepolizumab in addition to add-on therapy to INCS. Key inputs to the BIA are documented in Table 15.

## Table 14: Summary of Key Model Parameters

| Parameter | Sponsor's estimate (reported as year 1 / year 2 / year 3, if appropriate) |
|---|---|
| **Target population** | |
| Population aged 18 years or older | 25,340,577 |
| Prevalence of CRS[21] | 5% |
| Proportion of patients diagnosed with CRSwNP[22] | 6.1% |
| Proportion of patients receiving INCS[23] | 90.4% |
| Proportion of patients with persistent symptoms (8 to 12 weeks minimum)[23] | 45.9% |

| Parameter | Sponsor's estimate (reported as year 1 / year 2 / year 3, if appropriate) |
|---|---|
| Proportion of patients without severe eosinophilic asthma (SEA)[24] | 87.6% |
| Proportion of patients eligible for public reimbursement | Jurisdiction-specific[a] |
| Number of patients eligible for drug under review | 17,395 / 17,599 / 17,803 |
| **Market uptake (3 years)** | |
| Uptake (reference scenario)<br>Mepolizumab plus SoC<br>SoC | <br>0% / 0% / 0%<br>100% / 100% / 100% |
| Uptake (new drug scenario)<br>Mepolizumab plus SoC<br>SoC | <br>[redacted]% / [redacted]% / [redacted]%<br>[redacted]% / [redacted]% / [redacted]% |
| **Cost of treatment (per patient)** | |
| Cost of treatment over 1 year<br>Mepolizumab plus SoC[b]<br>SoC[b] | <br>$27,308<br>$0 |

CRS = chronic rhinosinusitis; CRSwNP = chronic rhinosinusitis with nasal polyps; SoC = standard of care.

[a]Projected proportion of patients eligible for public reimbursement was based on jurisdiction-specific sponsor research.

[b]INCS costs were assumed to be zero by the sponsor since they were not expected to differ based on treatment with mepolizumab.

## Summary of the Sponsor's BIA Results

The sponsor's estimated budget impact of funding mepolizumab as an add-on maintenance treatment in adult patients with severe CRSwNP inadequately controlled by INCS alone was $30,401,285 in year 1, $34,843,638 in year 2, and $38,893,040 in year 3, for a 3-year total of $104,137,963.

In the sponsor's scenario analyses, tripling the proportion of patients diagnosed with CRSwNP resulted in increased costs to the drug plans over 3 years by 195%. Increasing the proportion of those with persistent symptoms from 45.9% to 50.5% resulted in increased costs to the drug plans over 3 years by 10%. Increasing the proportion of those without concurrent SEA from 87.6% to 96.4% also resulted in increased costs to the drug plans over 3 years by 10%.

## CADTH Appraisal of the Sponsor's BIA

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the results of the BIA:

- **Uncertainty regarding the estimated size of the target population:** Although most inputs were deemed to be plausible based on clinical expert feedback obtained by CADTH, it was noted that uncertainty remains in the sponsor's estimates, such as the proportion of CRS patients with nasal polyps, proportion of CRSwNP patients receiving INCS, proportion of CRSwNP patients with persistent symptoms, and proportion of those with concurrent SEA. It is uncertain whether these estimates sourced from literature are representative of the population in Canada, as they were sourced from countries in the EU or UK. Notably, the diagnosis rate of CRSwNP in the new drug scenario could likely rise given the availability of mepolizumab in the context of no other biologic treatments for this condition being covered by public drug plans. However, CADTH acknowledges that the sponsor tested alternate values for these inputs, with their individual impact on the budget impact described in the summary of results section above. The estimated target population remains a major driver of budget impact estimates, and the underestimation of any input parameters would likely lead to an underestimated budget impact.

- CADTH could not address this limitation in reanalysis and notes that the sponsor tested alternate parameters to derive target population in scenario analyses.

- **Uncertainty regarding market shares of mepolizumab:** The market uptake of mepolizumab was assumed to be [redacted]% in year 1, [redacted]% in year 2, and [redacted]% in year 3 based on the sponsor's internal forecasting. The accuracy of the sponsor's internal market shares could not be validated by CADTH, although the estimates were deemed to be plausible based on clinical expert feedback obtained by CADTH. Uncertainty remains in these estimates and increases in the projected market shares would likely lead to sizable increases in the anticipated budget impact of reimbursing mepolizumab.
  - CADTH doubled the anticipated market shares of mepolizumab in a scenario analysis.
- **Target population is potentially underestimated by excluding those not covered by drug plans:** The sponsor assumed that 60% of patients would be eligible for public coverage by drug plans in all jurisdictions excluding non-insured health benefits (NIHB), where 100% of patients were assumed to be eligible. Given that the sponsor's assumption was based on internal sponsor estimates and could not be validated, CADTH explored the impact of increasing public drug coverage in a scenario analysis.
  - In a scenario analysis, CADTH increased public coverage to 80% for jurisdictions where coverage was assumed to be 60%.
- **Uncertainty regarding eligibility for mepolizumab:** Drug plans highlighted uncertainty regarding prior therapy or patient characteristics required for eligibility. Specifically, patients in the pivotal trial were noted to have received at least 1 prior nasal polyp surgery in the past 10 years and had bilateral nasal polyps. It was uncertain whether patient eligibility for public coverage would be restricted by prior nasal polyp surgery or having bilateral nasal polyps. Furthermore, all patients in the trial were treated with INCS for at least 8 weeks before initiating mepolizumab. Drug plans found it was uncertain whether implementation advice would specify use of INCS at the Health Canada–approved dose for nasal polyps for at least 8 weeks before initiation of mepolizumab as well. Patient eligibility for mepolizumab based on prior therapy or patient characteristics remains unclear and may have notable impacts on the budget impact analysis.
  - CADTH could not address this limitation.

## CADTH Reanalyses of the BIA

CADTH did not conduct a base case reanalysis, Scenario analysis were conducted to assess the impact of changing key parameters within the sponsor BIA as outlined in Table 15. The results of the CADTH scenario analyses are presented in Table 16. CADTH accepted the sponsor's base case but conducted several scenario analyses.

## Table 15: CADTH Revisions to the Submitted Budget Impact Analysis

| Stepped analysis | Sponsor's value or assumption | CADTH value or assumption |
|---|---|---|
| **Changes to derive the CADTH scenario analyses** | | |
| Scenario analysis 1: Doubled market shares of mepolizumab | SoC: [redacted]% / [redacted]% / [redacted]%<br>Mepolizumab: [redacted]% / [redacted]% / [redacted]% | SoC: [redacted]% / [redacted]% / [redacted]%<br>Mepolizumab: [redacted]% / [redacted]% / [redacted]% |
| Scenario analysis 2: Increased public coverage to 80% | Non-NIHB jurisdictions: 60%<br>NIHB: 100% | Non-NIHB jurisdictions: 80%<br>NIHB: 100% |

NIHB; non-insured health benefits; SoC = standard of care.

The scenario analysis assessing doubled market shares of mepolizumab led to a 3-year budget impact of $208,275,926. An additional scenario analysis assessing the impact of increasing public drug coverage from 60% to 80% resulted in a 3-year budget impact of $137,155,345. The anticipated 3-year budget impact was estimated to be $14,579,315 if the price of mepolizumab was reduced by 86% to reach the price at which the ICER would be below a $50,000 per QALY threshold according to price reduction analyses conducted on the CADTH base case.

## Table 16: Detailed Breakdown of the CADTH Reanalyses of the BIA

| Stepped analysis | Scenario | Year 0 (current situation) | Year 1 | Year 2 | Year 3 | Three-year total |
|---|---|---|---|---|---|---|
| Submitted base case | Reference | $0 | $0 | $0 | $0 | $0 |
| | New drug | $0 | $30,401,285 | $34,843,638 | $38,893,040 | $104,137,963 |
| | Budget impact | $0 | $30,401,285 | $34,843,638 | $38,893,040 | $104,137,963 |
| CADTH scenario analysis 1: Doubled market shares | Reference | $0 | $0 | $0 | $0 | $0 |
| | New drug | $0 | $60,802,570 | $69,687,276 | $77,786,080 | $208,275,926 |
| | Budget impact | $0 | $60,802,570 | $69,687,276 | $77,786,080 | $208,275,926 |
| CADTH scenario analysis 2: public coverage 80% | Reference | $0 | $0 | $0 | $0 | $0 |
| | New drug | $0 | $40,041,455 | $45,891,101 | $51,222,789 | $137,155,345 |
| | Budget impact | $0 | $40,041,455 | $45,891,101 | $51,222,789 | $137,155,345 |
| CADTH scenario analysis 3: 86% price reduction | Reference | $0 | $0 | $0 | $0 | $0 |
| | New drug | $0 | $4,256,180 | $4,878,109 | $5,445,026 | $14,579,315 |
| | Budget impact | $0 | $4,256,180 | $4,878,109 | $5,445,026 | $14,579,315 |

BIA = budget impact analysis.

CADTH

# Stakeholder Input

# List of Tables

# Patient Input

## Asthma Canada

### About Asthma Canada

Asthma Canada is the only national health charity solely dedicated to providing evidence-based, education, management tools and support programs for Canadians living with asthma and other related respiratory conditions. We advocate to improve the quality of life for people living with asthma and invest and support strategic research to ultimately find a cure. For nearly 50 years, Asthma Canada has proudly served as the national voice for Canadians living with asthma. We empower patients with evidence-based information, education programs and support asthma research in Canada. Asthma Canada is a registered charitable organization (BIN 89853-7048-RR0001). Our vision is a world without asthma, and our mission is to help Canadians with asthma lead healthy lives through education, advocacy and research. Based in Toronto, Ontario, we operate under the direction of a volunteer Board of Directors and provide programs and services to people living with asthma and their caregivers through our website, e-newsletters, social media channels, and the Asthma & Allergy HelpLine. Asthma Canada provides our services freely for all Canadians - coast to coast, via phone, email, social media, print resources and online. In addition, the Asthma Canada Member Alliance (ACMA) is the community arm and voice of Asthma Canada made up of people living with asthma, parents/caregivers, healthcare professionals, and anyone who has been affected by asthma. ACMA has more than 8,000 people living with asthma and allergies and other comorbidities, caregivers, healthcare providers, and other interested participants from all regions of Canada.

### Information Gathering

The patient perspective in this submission was pulled from an online survey, independently developed and launched in 2022 to seek the perspectives of people living with severe chronic rhinosinusitis with nasal polyps (CRSwNP) as well as caregivers. The survey was open from April 27th and closed on May 24th, 2022. We received 17 responses with participants from British Columbia (3), Alberta (1 Saskatchewan (1), Manitoba (1), Ontario (8), Quebec (1) and Nova Scotia (1).

### Disease Experience

Nasal polyps are soft, painless, non-cancerous growths on the lining of nasal passages or sinuses. They hang down like teardrops or grapes in nasal passages. They may make you feel like you have a cold. If the polyps are small, you may not have many symptoms. But larger growths or groups of nasal polyps can block nasal passages, causing you to lose your sense of smell or have trouble breathing or frequent infections. The blocked nasal passages and sinuses can also worsen asthma symptoms.

While overall prevalence of nasal polyps is low (about 4% of the population), it is more common in people with asthma. For example, one study found that 16.5% of people with asthma over 40 years of age have nasal polyps.

Nasal polyps are a subgroup of chronic rhinosinusitis. But not all people with this condition will develop nasal polyps. Chronic rhinosinusitis is defined as having two or more symptoms that persist for more than 12 weeks, including facial pain/pressure, nasal discharge with pus, nasal obstruction and decreased sense of smell during chronic inflammation and nasal

polyps. While about 7% of people with asthma have chronic rhinosinusitis with nasal polyps (CRSwNP), 20-60% of people with CRSwNP have asthma.

Studies have shown that patients with nasal polyps and asthma have more severe asthma than those who don't have polyps. For example, one study found that people with asthma and nasal polyps have increased airway obstruction, more inflammatory cells and reduced asthma control compared to those without nasal polyps.

Patients with asthma and CRSwNP report it affects their quality of life, including physical functioning, body pain and vitality. If polyps are not removed, they can lead to worsening asthma symptoms if you already have asthma.

> I had an extremely difficult time living with nasal polyps. I had endoscopic sinus surgery in 2009 and revisional surgery in 2014. Since December 2015, I have been on a biologic medication, which has helped my sinusitis, allergies and asthma. I still have nasal polyps, but they aren't affecting my breathing at this time. I am forever thankful and grateful that I was able to get funding for the biologic medication and that it has helped my respiratory health and well-being.

Some of the symptoms of nasal polyps include:

- a stuffy or blocked nose and feeling congested
- trouble breathing with your nose (because the polyps block your airflow and do not allow mucus from your nose to drain)
- frequent sneezing
- postnasal drip
- a runny nose
- trouble with your sense of smell – it may be decreased or absent
- loss of sense of taste

Our survey found that the most difficult side effects of current nasal polyp treatment are: changes to sense of smell (63%), allergic reactions (36%), mental/mood changes (27%), increased risk of sinus infection (27%), headaches/dizziness (18%), and ineffectiveness (18%).

**What is the most frustrating/difficult thing about living with nasal polyps (CRSwNP)?**

> Not being able to smell properly and nasal spray really doesn't help.
>
> Constant nasal drip.
>
> Sense of smell and taste impacted.
>
> The fact that they hurt me.
>
> Severe inflammation and sneezing esp at night.

CRSwNP symptoms impact both the patient and family's quality of life. Challenges faced by patients and families include: 90% impacted quality of life, 30% missed work or school days, 20% experienced financial difficulties, and 20% had hospital visits. For caregivers particularly: 66% experienced an impact on sleep, 44% managed frequent doctor's appointments and 33% had to manage multiple medications and doses.

Patients may experience fatigue and have less energy to work and exercise. Making and keeping friends and colleagues can be made more difficult due to the symptoms of the disease or activity limitations. School and work are important parts of everyone's lives however patients may not be able to attend and concentrate due to disease symptoms, fatigue, and exacerbations. Sleep can be disturbed and patients and caregivers are often called on to deal with symptoms in the night (66% of survey participants noted sleep as a concern).

> I was frequently very worried about her [daughter] quality of life which meant I would avoid travel, massage her for hours when she had trouble sleeping or was in pain. Because we could afford it, I was very indulgent in not having her use up her depleted energy by cleaning up her messes in kitchen - or anywhere else, let her go to countless musicals in NYC or Chicago on weekends, just to give her a lift. So much of my life was focussed on alleviating some of the awful symptoms.

### Experiences With Currently Available Treatments

In current Canadian practice, the cornerstones of CRSwNP management are:

- Nasal spray. One of the most common ways to treat nasal polyps is with nasal corticosteroid spray, which helps shrink polyps and reduce irritation.
- Oral medication. Oral corticosteroids can also reduce the size of polyps, but if taken for a long period, they can cause adverse effects, including cataracts, osteoporosis, increased risk of infection and elevated blood sugar, which can lead to diabetes.
- Surgery. If using a nasal spray or oral steroids does not help, endoscopic surgery can remove the polyps and fix the sinuses to help prevent more polyps.

A newer way to shrink or reduce polyps is to use biologic therapies, which are also used to treat moderate to severe asthma. For nasal polyps, biologics may be used when the usual medications or surgery have not been successful. While oral corticosteroids affect the whole body (which is why they can cause widespread side effects), biologics are more precise, targeting specific cytokines that circulate in your body and drive inflammation and the development of polyps.

**How effective do you find your current treatment is in controlling the common aspects of nasal polyps (CRSwNP)?**

> Not very effective, but it is better then nothing

> It does help but it doesn't take them away. If I miss one dose I can't smell for days.

> Life changing!!! The polyps have completely disappeared. Sure hope this lasts as we had almost 6 years of awful symptoms and very aggressive polyps.

Our survey found that 39% use nasal sprays, 17% use oral corticosteroids, 28% have had surgery, and 17% are currently using an available biologic (i.e. dupilumab, omalizumab). 1 of 4 of respondents felt that their current treatment wasn't working or was ineffective and another 18% felt that they continued to have poor symptom control even with currently available treatments.

**Do you have any concerns about the side effects of these treatments? Which side effects are most bothersome and why?**

> I realize I don't really understand the status of my nasal polyps. They were removed but I understand they do grow back. I take itraconazole to fight fungal infection prescribed by my sinus doc. This drug is harmful to my liver.

> Yes, I am concerned about side effects. Right now I am okay with the medications that I am taking for my respiratory health, including nasal polyps. On the other hand thanks to the biologic medication, my respiratory issues have been stable. Also, sinus surgery is a temporary solution to a permanent problem. Surgery usually lasts about five years. My last surgery was eight years ago, which is due to the excellence of my surgeon as well as being on a biologic.

> Nose bleeds are a great concern to me. I have them weekly, if not daily from my nasal steroids.

> We are concerned about the potential for unknown long-term use of the biologic will have on our 24 year old daughter. She's been on the drug for 10 months so far.

> Loss of sense of smell...ongoing for over 5 years.

Managing day-to-day symptoms was the most important aspect to control (36%) for nasal polyps; followed by taking medication correctly and amount of medication needed (18% respectively), with cost of medication at 9%.

> When treatment wasn't working and my daughter had no sense of smell or able to breathe through her nose, it was awful: interrupted sleep, no pleasure in food, bloated face from steroids, chronic sinus pain.

Financial considerations are another critical barrier to optimal medication use. While this online survey found that most respondents were not experiencing financial difficulties as a result of CRSwNP, this was mostly because they had pre-existing coverage via insurance. Many people with CRSwNP also have comorbidities in asthma and allergies, resulting in numerous prescriptions required.

**Do you experience financial difficulties as a result of nasal polyps (CRSwNP)?**

> Fortunately, the medication is covered on my medical plan.

> I have individual insurance, whereby I pay a monthly fee. I then pay 20% for my prescriptions. That is really helpful because inhalers for my asthma are expensive. My insurance does not cover biologics. Once again, I am thankful and grateful that I was able to get funding for a medication that has been working well for me.

> I can't imagine how people manage without financial resources.

The use of oral corticosteroids in patients who fail to achieve adequate control using nasal sprays deserves special mention due to the short- and long-term side effects of the systemic use of oral corticosteroids. This issue is of particular concern to the population of patients with CRSwNP and Severe Asthma, where many patients depend on long-term oral corticosteroids to provide some degree of inflammation control after other options prove to be inadequate. Although potentially helpful in the short-term, these medications have a long list of side effects if taken for longer periods of time and at higher doses. Side effects include weight gain, acne, excess facial hair, mood swings, high blood pressure, hyperactivity, high

blood sugar, increased infection. In the long term, oral corticosteroids can cause osteopenia, osteoporosis, glaucoma, cataracts, and heart disease. (See: Appropriate Use of Oral Corticosteroids in Asthma).

**Do you have concerns about adverse effects from the use of oral corticosteroids (i.e. Prednisone)?**

> Don't take it anymore but am concerned by short term emotional effects and long-term effects such as osteoporosis.
>
> I have many serious concerns about the use of Prednisone. Prednisone is a great drug, but also a very dangerous drug, regarding side effects.
>
> She was on Prednisone at least 5 times from the age of 19 to 23. Very concerning if that will affect her later. Also, she has hyper-mobile joints and is prone to injury as she is quite physically active.

## Improved Outcomes

Survey participants indicated their expectations for a new medication and ranked these expectations in the following order:

1. Easier Management of Symptoms (63%)
2. Less Anxiety About my Nasal Polyps (45%)
3. Reduce reliance on OCS/steroids (36%)
4. Reduce need for surgery (36%)
5. Improved Process for Taking Medication (27%)

> It is hard to go places when your nose won't stop bleeding.
>
> It is really hard not being able to smell. It affects your life everyday all day.

63% of survey participants indicated that the benefits of the new treatment would be worth tolerating potential side effects to improve management of CRSwNP.

**How would these possible benefits improve your life?**

> You have made me think I need to see my sinus doc as I am always phlegmy and maybe I need a clean out and tune up.
>
> Improve family life and physical health.
>
> Allow more active life.
>
> Regain sense of smell...eliminate polyps.

## Experience With Drug Under Review

Our survey showed two respondents experience with the drug under review at this time. In addition, 63% of respondents in our survey said they'd tolerate the potential side effects of mepolizumab treatment to see an improvement in the management of their CRSwNP. Most patients will have tried and used many other treatments before using mepolizumab. The

addition of a new biologic for CRSwNP provides more options so they can tailor treatments to their needs. Patients and caregivers value a reduction in other medications, such as oral corticosteroids and less medication side effects.

**Have you used mepolizumab as part of a clinical trial or through any other means? Can you please detail more about your experience?**

> At this time, I am not experiencing any side effects. The medication has truly improved my quality of life. I can breathe...
>
> My polyps is generally improved - I have not had an exacerbation since I started about a year ago.

## Companion Diagnostic Test

Asthma Canada is not aware of any current companion diagnostic test for the drug under review beyond standard CRSwNP diagnostics.

## Anything Else?

The ability for those living with CRSwNP to access and afford new and innovative drugs in Canada is essential to our community's wellbeing. It can be the difference between living an active, productive life and not being able to function or breathe. The addition of a new biologic for CRSwNP provides another treatment option so they can tailor treatments to their needs. Patients and caregivers value a reduction in other medications, such as oral corticosteroids and inhalers and less medication side effects.

> I wish others could understand how difficult it is to live with nasal polyps and the treatment options. I hope I never go back to the days when I was mouth breathing due to the overgrowth of the nasal polyps. Mouth breathing affected my quality of life, such as sleeping, exercising and socializing.

## Patient Group Conflict of Interest Declaration – Asthma Canada

**Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.**

No.

**Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.**

No.

**List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.**

## Table 1: Financial Disclosures for Asthma Canada

| Company | $0 to 5,000 | $5,001 to 10,000 | $10,001 to 50,000 | In Excess of $50,000 |
|---|---|---|---|---|
| AstraZeneca | – | – | – | X |
| Sanofi Genzyme | – | – | – | X |
| GSK | – | – | – | X |
| Novartis | – | – | X | – |
| Sanofi Pasteur | – | – | X | – |
| Pfizer | – | – | X | – |

## British Columbia Lung Association and Lung Groups

### About British Columbia Lung Association and Lung Groups

The Mission of the British Columbia Lung Association (BCLA) is to improve lung health and to lead lung health initiatives. Our vision is healthy lungs for everyone. Our role is to improve respiratory health and overall quality of life through programs, education, research, training, treatment, advocacy and prevention of lung disease.

The BCLA is a major Canadian charitable organization with more than a century of experience and leadership in lung disease prevention, treatment and management. Today our areas of interest and expertise include the entire scope of respiratory diseases including Asthma, Severe Rhinosinusitis with Nasal Polyps, Occupational Asthma, Idiopathic Pulmonary Fibrosis, ILD Interstitial Lung Disease, COPD (chronic bronchitis and emphysema), Lung Cancer, Sleep Apnea, Influenza, Pneumonia, and Tuberculosis. We work together with other Canadian Associations and other partners to help the one in five Canadian who have breathing problems.

Our staff and volunteers include health professionals and interested individuals and patients with a broad range of training and experience in lung disease and lung health that enables our organization to develop and lead programs of education and health promotion at the highest standard. The British Columbia Lung Association provides approximately $1.2 million each year to internationally recognized physicians and scientist doing research in BC on lung diseases. All funding proposals go through rigorous national peer review system so that the most promising research can be explored. This world class research is discovering the causes of lung disease, finding new treatments, and giving hope for a future free of lung disease.

www.bc.lung.ca

### Conflict of Interest Declaration – British Columbia Lung Association and Lung Groups

The British Columbia Lung Association has several sources of funding for programs and operations and is supported by individual and corporate donations, and through service contracts with government organizations. Funding sources include direct mail campaigns such as the Christmas Seals campaign, memorial giving, bequests, Special events such as Climb the Wall: Stair Climb for the fight against lung disease!, Bicycle Trek for life and breath now virtual because of COVID-19. The Lung Association, does, from time to time receive program grants from health industry/pharmaceutical companies. Our relations and

interactions with pharmaceutical companies remain transparent and positions of the Lung Association are developed without industry influence.

The BCLA has received health educator's & patient program grants from the following pharmaceutical companies: GlaxoSmithKline, $50,000(2020), Astra Zeneca, $10,00(2019), professional education, Boehringer Ingelheim, $20,000(2019) patient education program, Sanofi, $8,000(2019), Influenza Awareness, Novartis $15,000(2019) Asthma patient education

a) We have the following declaration(s) of conflict of interest in respect of corporate members and joint working, sponsorship, or funding arrangements:
b) We have the following declaration(s) of conflict of interest in respect of those playing a significant role in compiling this submission:

Neither the principal author, nor the BCLA, has conflicts to declare in respect to the compiling of this submission

## Information Gathering

The BCLA is significantly invested and involved in Asthma and other respiratory disease research and provision of patient services and programs. We have Certified Respiratory Educators on staff providing expert educational consultations to respiratory patients, their family members and caregivers dealing with Asthma and other lung diseases. The vast knowledge and experience garnered through research, best practice guidelines and direct involvement with patients is the basis of the information provided.

## Impact of Condition on Patients

Severe Asthma, with chronic rhinosinusitis and Nasal Polyps constitutes illness that is a large proportion of all patients with asthma but it is a major public health problem with considerable effect on morbidity, mortality, as well as a high burden on health care resources. Regardless of effective treatments being widely available and the existence of treatment guidelines, a large population of severe asthma with rhinosinusitis with Nasal Polyps cases remain uncontrolled. Achieving and maintaining rhinosinusitis & nasal polyps control in this group of patients is, therefore, of utmost importance.

Asthma is a complex heterogeneous disease, with different pathogenic mechanisms, clinical presentations, and responses to treatments, usually characterized by chronic airway inflammation. Wheeze, shortness of breath, chest tightness and cough that vary over time and intensity, together with variable expiratory airflow limitation. Asthma affects an estimated 241 million children and adults in the world. Approximately 5-10 percent of the asthmatic population is affected with severe asthma, rhinosinusitis and nasal polyps requiring high-dose inhaled & oral corticosteroids (ICS & OCS) in addition to a second controller (and/or systemic corticosteroids) to prevent it from the disease becoming uncontrolled or for asthma that remains uncontrolled despite combination therapy. There are 3.8 million patients with asthma in Canada and in BC we have 323,500 prevalent cases (2012/2013). That amounts to 16,000 new cases in BC. The prevalence of asthma with rhinosinusitis & nasal polyps in BC has steadily increased since 2000/01. There are 5% of the asthma population in BC who are diagnosed with severe asthma. And many more with rhinosinusitis & Nasal Polyps.

Breathlessness & shortness of breath are some of the key symptom and complaints of patients with asthma & nasal polyps with rapid decline in lung function intolerance. Breathlessness can affect day-to day activities such as showering, climbing stairs, getting dressed and eating. As inflammation in the lungs gets worse, breathlessness may prevent

all activities. The physical deterioration of the individual with severe asthma complicated with rhinosinusitis & nasal polyps profound and commonly emotionally demanding. The goal of therapy is to relieve symptoms, prolong life, reduce disability and stabilize lung function and slow disease progression to allow physical and social functioning to the highest - level possible. Medication side - effects are particularly common & problematic with OCS (oral corticosteroid) which in the past were a mainstay of treatment for severe asthma. With rhinosinusitis & nasal polyps Adverse effects of long-term OCS include obesity, diabetes, osteoporosis, cataracts, hypertension and adrenal suppression, psychological side-effects such as depression and anxiety are particularly concerning for patients. Even short-term use of OCS is associated with sleep disturbance, and increased risk of infection and thromboembolism. Strategies to minimize need of OCS are therefore a high priority.

Severe asthma with rhinosinusitis & nasal polyps sufferers will often require assistance and become increasingly dependent on others to the most basic human task of daily living activities. Depression and feelings of hopelessness are common among patients with severe asthma especially with difficulty breathing.

Lung attacks or flare-ups drive disease progression. As the disease progresses frequency of flare-ups increase, overall lung function and lung health typically decline and risk of hospital admission increases as well as rate of mortality.

### Patients' Experiences With Current Therapy

The therapies used for severe asthma with nasal polyps & rhinosinusitis are recommended and written in the guidelines by the Canadian Thoracic Society.

In two BC Severe Asthma Clinic both Respirologist have a lot of patients with severe asthma with rhinosinusitis & nasal Polyps who have participated in the Clinical Trials of (Nucala Mepolizumab) I have spoken to some patients (9 patients in total) who are members of our BC Lung Support Group that are taking (Nucala Mepolizumab) they are very happy & excited about the maintained effects of the new biologic medication as an add on maintenance therapy. Today with most patients with rhinosinusitis with nasal polyps remains out of reach for many patients especially seniors who no longer have private coverage and rely strictly on government funding for access. Nucala SC statistically and clinically relevant benefits, reducing severe attacks improving lung function & sustaining control. Mepolizumab Nucala was very well tolerated.

Unmet Needs: Of critical importance to the treatment of patients with rhinosinusitis & nasal polyps are medicines that will help reduce or stop the progression of the disease and subsequent hospitalizations. Additional therapies are needed that go beyond symptomatic relief. New treatments are urgently needed that will work to improve overall lung function. New treatment options are required as the disease progresses.

The BCLA believes that access to medications such as ( Mepolizumab Nucala) as an add-on maintenance treatment for moderate to severe rhinosinusitis with nasal polyps characterized by type 2 inflammation and as a maintenance therapy for oral-corticosteroid-dependent rhinosinusitis with nasal polyps to improve lung function will serve to reduce cost on admissions to hospital and improve the overall lung health of patients with the disease. The BCLA support the quick access to evidenced- based respiratory medications such as that for rhinosinusitis with nasal polyps patients and recommended by the Canadian Thoracic Society

We recognize that not all patients or individuals respond the same to various types of formulations of medications and BCLA support having access to the medications to which a particular patient responds better. The new medication is given subcutaneously.

**Unmet Needs**: Medications are of critical importance in the treatment and management of Severe rhinosinusitis with nasal polyps. It improves lung function and breathing, reduce lung attacks and prevent patients with repeat admission to hospital there by improving the lives of patients

### Impact on Caregivers

Our health care system places a lot of demands on both the patient and caregivers. Caregivers are often the spouse, the children and other relations. Financial challenges are the obvious ones, depending on the level of reimbursement for medicine.

Another major impact identified by patients and care givers is physical activity. The impact is most noticeable on patients' progressive inability to perform daily tasks as they begin to notice that they had previously taken for granted (e.g. negotiating a staircase that they climb every day because of breathlessness)

As the patient's condition deteriorates, they tend to stay at home more which means that their fitness levels further deteriorate and their body's ability to use oxygen efficiently is further compromised. As the condition progresses, further compromises are made in patient's independence with huge implications for caregivers. Patients with Severe rhinosinusitis with nasal polyps and their caregivers experience anxiety and depression. This disease has a progressive debilitating course and sadly it increases mortality.

Caring for someone with this condition as well as someone with rhinosinusitis, & nasal polyps can be both physically and emotionally demanding. Caregivers may experience a great deal of stress and anxiety, resulting from their loved one's deterioration. Frequently these feelings have a negative impact on the caregiver's health and well- being. Frequent visits to medical professionals, increasing medical needs, restrictions in activities leading to the caregiver taking a larger role may impact the caregiver significantly. The BCLA sponsor and help a number of support groups in BC called "Better Breather's Group" they are for individuals with Lung Conditions and their caregivers and help the caregiver cope more effectively.

### Information Gathering

The BCLA is significantly invested and involved in severe asthma, rhinosinusitis with nasal polyps and other respiratory research and provision of patient's services and programs. On staff we have Canadian Certified Respiratory Educator's that provide educational expert consultations to respiratory patients with these conditions, their family members and caregivers. The vast knowledge and experience garnered through research, best practice guidelines and direct involvement with patients is the basis of the information.

### What Are the Expectations for the New Drug or What Experiences Have Patients Had With the New Drug?

Nucala is an add-on maintenance treatment of chronic rhinosinusitis with nasal polyps for patients who have an insufficient response to nasal corticosteroids.

Many patients with rhinosinusitis with nasal polyps have suboptimal control despite available therapies

Some side effects: reactions at injection site are common but minor, Blood eosinophilia occurs in some patients.

### Additional Information

On behalf of our adult patients with severe rhinosinusitis with nasal polyps patients, please make easy access of Nucala Mepolizumab as an add-on maintenance treatment with intranasal corticosteroids

Many …many …thanks

## Clinician Input

No submissions were received from clinician groups.