Common Drug Review
Clinical Review Report

April 2017

Drug	Reslizumab (Cinqair)
Indication	Cinqair (reslizumab) is indicated as an add-on maintenance treatment of adult patients with severe eosinophilic asthma who: are inadequately controlled with medium-to-high-dose inhaled corticosteroids and an additional asthma controller(s) (e.g., LABA); and have a blood eosinophil count of ≥ 400 cells/µL at initiation of the treatment.
Reimbursement request	As per indication
Dosage form(s)	10 mg/mL vial, concentrate for solution for intravenous infusion
NOC Date	July 20, 2016
Manufacturer	Teva Canada Innovation

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in allergy and clinical immunology who provided input on the conduct of the review and the interpretation of findings.

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ABBREVIATIONS

ACQ-7	Asthma Control Questionnaire 7
AQLQ	Asthma Quality of Life Questionnaire
ASUI	Asthma Symptoms Utility Index
CDR	CADTH Common Drug Review
CI	confidence interval
CPK	creatine phosphokinase
CrI	credible interval
FAS	full analysis set
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in one second
GINA	Global Initiative for Asthma
ICS	inhaled corticosteroid
IgE	immunoglobulin E
IgG	immunoglobulin G
ITT	intention-to-treat population
IV	intravenous
LABA	long-acting beta-agonist
MCID	minimal clinically important difference
MD	mean difference
MPPI	minimal patient-perceivable improvement
NMA	network meta-analysis
OCS	oral corticosteroid
PEF	peak expiratory flow
RCT	randomized controlled trial
RR	relative risk
SABA	short-acting beta-agonist
SD	standard deviation

EXECUTIVE SUMMARY

Introduction

Asthma is a common chronic respiratory disorder characterized by reversible airway obstruction, pulmonary inflammation, airway hyper-responsiveness, and airway remodelling.[1,2] Patients with asthma typically present with paroxysmal or persistent symptoms of wheezing, dyspnea, chest tightness, sputum production, and coughing that are associated with airflow limitation and airway hyper-responsiveness to endogenous and exogenous stimuli (e.g., exercise; viral respiratory infections; or exposure to certain allergens, irritants, or gases).[2] Severe eosinophilic asthma is an asthma phenotype characterized by the presence of eosinophils in the airways and sputum, despite compliance with conventional asthma therapy.[3] Severe asthma can have a profound effect on patients' day-to-day lives, such as limiting physical activity, reducing performance at work or school, restricting social interactions, and leading to stigma. It may also necessitate frequent physician and emergency room visits.

Reslizumab is a humanized immunoglobulin G (IgG)4 kappa monoclonal antibody that binds to human interleukin-5, thereby reducing the production and survival of eosinophils. Reslizumab was approved by Health Canada as add-on maintenance treatment for adult patients with severe eosinophilic asthma who are inadequately controlled with medium- to high-dose inhaled corticosteroids (ICSs) and an additional asthma controller(s) (e.g., long-acting beta-agonist [LABA]) and who have a blood eosinophil count of ≥ 400 cells/µL at initiation of the treatment. The recommended dose is 3 mg/kg administered by intravenous (IV) infusion every four weeks.[4]

Indication under review
Add-on maintenance treatment of adult patients with severe eosinophilic asthma who are inadequately controlled with medium-to-high-dose ICS and an additional asthma controller(s) (e.g., LABA) and who have a blood eosinophil count of ≥ 400 cells/µL at initiation of the treatment.
Reimbursement criteria requested by sponsor
As per indication

The objective of this report was to perform a systematic review of the beneficial and harmful effects of reslizumab for the treatment of severe eosinophilic asthma in adults whose symptoms are inadequately controlled with medium- to high-dose ICS and an additional asthma controller(s) and who have a blood eosinophil count of ≥ 400 cells/µL.

Results and Interpretation

Included Studies

A total of four double-blind randomized controlled trials (RCTs) met the inclusion criteria: two identical 52-week pivotal trials (Studies 3082 and 3083), and two supporting 16-week trials (Studies 3081 and 3084). All trials compared reslizumab 3 mg/kg IV every four weeks with placebo. Study 3081 also included a reslizumab 0.3 mg/kg group, which was not summarized in this report. All trials enrolled patients with inadequately controlled asthma despite therapy with medium to high doses of ICS with or without other controller medication(s), which they maintained during the double-blind treatment period. Three of the trials enrolled patients with elevated blood eosinophil levels (≥ 400 cells/µL).

The objective of the pivotal trials was to assess the efficacy of reslizumab on the frequency of asthma exacerbations over a one-year treatment period. In total, 489 and 464 patients with inadequately controlled asthma and elevated eosinophil levels were randomized in Studies 3082 and 3083, respectively. The objective of Study 3081 was to assess the efficacy of reslizumab versus placebo in terms of changes in forced expiratory volume in one second (FEV_1) among patients with inadequately controlled asthma and elevated eosinophil levels (N = 315). Study 3084 tested the change in FEV_1 relative to baseline eosinophil levels in patients with inadequately controlled asthma (reslizumab N = 398; placebo N = 98).

The patients enrolled had a mean age ranging from 43.0 to 47.5 years across the treatment groups. The majority of patients were female (55% to 66%), white (65% to 85%), and had asthma on average for 18 to 26 years. In the pivotal trials, patients had had an average of 1.9 to 2.1 asthma exacerbations in the previous year (range [redacted]) whereas, in the supporting trials, 54% to 57% of patients in Study 3081, and 38% to 42% of patients in Study 3084 had had an exacerbation in the past year.

The evidence is limited by the lack of head-to-head clinical trials, and of studies examining safety and efficacy beyond one year of treatment.

Efficacy

In the 52-week pivotal trials, the patients who receive reslizumab were less likely to report a clinically important asthma exacerbation (requiring treatment with systemic corticosteroids for three days or more, hospitalization, or an emergency department or physician's visit for treatment) than those who received placebo (Study 3082: 38% versus 54%, Study 3083: 25% versus 45%) (Table 1). The differences between treatments in the frequency of adjudicated exacerbation events were statistically significant and clinically important, according to the clinical expert consulted for this review, with an adjusted rate ratio of 0.50 (95% confidence interval [CI] 0.37 to 0.67) in Study 3082, and 0.41 (95% CI, 0.28 to 0.59) in Study 3083, for reslizumab versus placebo. Similar rate ratios were observed for the reduction in exacerbations requiring systemic corticosteroids, or requiring oral corticosteroids; however, these outcomes were outside the statistical hierarchy. Reslizumab statistically significantly delayed the first asthma exacerbation, compared with placebo, with adjusted hazard ratios of 0.58 (95% CI, 0.44 to 0.75; Study 3082) and 0.49 (95% CI, 0.35 to 0.67; Study 3083).

In contrast to these findings, the clinical importance was unclear for the differences observed in quality of life, asthma symptoms, and pulmonary function in the pivotal trials. Although statistical significance was achieved, the between-group differences in the change from baseline to week 16 in the Asthma Quality of Life Questionnaire (AQLQ), Asthma Control Questionnaire 7 (ACQ-7), Asthma Symptoms Utility Index (ASUI), and FEV_1 did not exceed minimal clinically important differences (Table 1). Modest between-treatment differences in the change from baseline in FEV_1 were reported in the supporting trials (adjusted mean difference [redacted]) and in the pivotal trials (adjusted mean difference 0.07 to 0.10 L) at 16 weeks for reslizumab versus placebo. In the pivotal trials, no statistically significant difference was found between groups on the use of short-acting beta-agonists (SABAs), and the change from baseline in blood eosinophil levels was not statistically significant as a result of failure of a prior outcome in the statistical hierarchy.

No head-to-head trials comparing reslizumab with other drugs for severe eosinophilic or allergic asthma were identified. The manufacturer provided an indirect treatment comparison examining the efficacy and safety of reslizumab, mepolizumab, and omalizumab in patients with moderate to severe

inadequately controlled asthma. The network meta-analysis pooled data from 25 open-label and double-blind RCTs, and found no statistically significant differences between treatments in asthma symptoms, quality of life, pulmonary function, or the frequency of asthma exacerbations. The network meta-analysis had a number of sources of heterogeneity, including differences in asthma severity and type (eosinophilic or allergic asthma), different definitions of asthma exacerbations, and follow-up time for the included studies. Four of the omalizumab RCTs were open label, which could bias the reporting of subjective outcomes and adverse events.

Harms

The majority of patients reported one or more adverse events during the trials (52-week pivotal trials: 76% to 87%; 16 week trials: 55% to 74%, across the treatment groups) (Table 2). Asthma, nasopharyngitis, upper respiratory tract infections, and headache were the most commonly reported adverse events. Asthma was reported more frequently in the placebo (19% to 52%) than in the reslizumab groups (13% to 40%) in all studies.

In the 52-week pivotal trials, serious adverse events were reported more frequently in the placebo groups (10% to 14%) than in the reslizumab groups (8% to 10%). In the 16-week supporting trials, 1% to 4% of placebo patients and 4% of reslizumab patients reported a serious adverse event. The frequency of withdrawals due to adverse events ranged from 2% to 7% in reslizumab groups and from 3% to 12% in the placebo groups. No safety signals beyond what was observed in the double-blind trials were identified in the open-label extension study (Study 3085).

In total, five patients, all of whom were randomized to reslizumab, reported an anaphylactic reaction. Three of these reactions occurred during or shortly after a reslizumab dose, and these patients were withdrawn from reslizumab treatment.

Conclusions

Add-on therapy with reslizumab was associated with statistically and clinically important reductions in the frequency of asthma exacerbations over one year, compared with placebo, in patients with eosinophilic asthma that was uncontrolled by medium- to high-dose ICS and, for most patients, another controller medication. Treatment with reslizumab, however, did not demonstrate clinically important differences versus placebo in asthma-related symptoms, quality of life, or pulmonary function (as measured by the ACQ-7, ASUI, AQLQ, and FEV_1). No between-treatment differences were observed in the use of rescue SABAs in the two pivotal double-blind RCTs.

Serious anaphylactic adverse events were reported among patients exposed to reslizumab. Considering that RCTs are not designed to identify rare or infrequent adverse events, and that reslizumab is part of a new class of drugs with a unique mechanism of action, additional data are required to determine the long-term safety of reslizumab.

No direct evidence is available comparing reslizumab with other drugs for eosinophilic or allergic asthma. Indirect evidence suggests that there are no substantial differences between reslizumab and mepolizumab 100 mg in terms of efficacy. No conclusions can be drawn concerning the relative efficacy of reslizumab versus omalizumab because the indirect treatment comparison was not limited to the "overlap population" — those patients with allergic asthma and elevated eosinophil levels, who would be suitable patients for treatment with either drug. The efficacy and safety of reslizumab beyond one year of treatment is unknown.

TABLE 1: SUMMARY OF EFFICACY RESULTS

Outcome / Treatment Group	N	Patients With ≥ 1 Events, N (%)	Adjusted Exacerbation Rate (95% CI)[a]		Adjusted Rate Ratio (95% CI), *P* Value
ASTHMA EXACERBATIONS[B]					
Study 3082					
Placebo	244	132 (54)	1.8 (1.4 to 2.4)		0.50 (0.37 to 0.67) *P* < 0.0001
Reslizumab	245	92 (38)	0.9 (0.7 to 1.2)		
Study 3083					
Placebo	232	105 (45)	2.1 (1.3 to 3.4)		0.41 (0.28 to 0.59) *P* < 0.0001
Reslizumab	232	59 (25)	0.9 (0.5 to 1.3)		
Outcomes / Study / Treatment Group	**N**	**Baseline Mean (SD)**	**N**	**LS Mean Change From Baseline to Week 16 (SE)**	**Adjusted Mean Difference Versus Placebo (95% CI), *P* Value**
AQLQ Score					
STUDY 3082					
Placebo	242	4.16 (1.09)	229	0.70 ([redacted])	0.24 (0.05 to 0.43) *P* = 0.014
Reslizumab	243	4.30 (1.12)	228	0.93 ([redacted])	
STUDY 3083					
Placebo	231	4.22 (1.08)	216	0.78 ([redacted])	0.21 (0.03 to 0.39) *P* = 0.026
Reslizumab	229	4.35 (1.02)	213	0.99 ([redacted])	
ACQ-7 Score					
STUDY 3082					
Placebo	244	2.76 (0.88)	241	–0.68 ([redacted])	–0.27 (–0.40 to –0.13) *P* = 0.0001
Reslizumab	245	2.66 (0.85)	242	–0.94 ([redacted])	
STUDY 3083					
Placebo	232	2.61 (0.79)	228	–0.66 ([redacted])	–0.20 (–0.33 to –0.07) *P* = 0.003
Reslizumab	232	2.57 (0.89)	230	–0.86 ([redacted])	
FEV_1 (L)					
STUDY 3082					
Placebo	244	1.93 (0.79)	228	0.14 ([redacted])	0.07 (0.001 to 0.14) *P* = 0.048
Reslizumab	245	1.89 (0.73)	232	0.21 ([redacted])	
STUDY 3083					
Placebo	232	2.00 (0.67)	214	0.12 ([redacted])	0.10 (0.02 to 0.18) *P* = 0.011
Reslizumab	232	2.13 (0.78)	214	0.22 ([redacted])	
STUDY 3081					
Placebo	105	2.22 ([redacted])	84	0.14 (0.06)	0.17 (0.04 to 0.29) *P* = 0.012
Reslizumab	103	2.17 ([redacted])	91	0.30 (0.06)	
STUDY 3084					
OVERALL POPULATION					
Placebo	97	2.17 ([redacted])	83	0.19 ([redacted])	0.07 (–0.03 to 0.17) *P* = 0.17[c]
Reslizumab	394	2.10 ([redacted])	344	0.26 ([redacted])	
SUBGROUP – EOSINOPHIL COUNT ≥ 0.4×10^9/L					
Placebo	19	2.15 ([redacted])	13	0.002 ([redacted])	0.13 (0.008 to 0.53) *P* = 0.04[c]
Reslizumab	77	2.22 ([redacted])	69	0.27 ([redacted])	

ACQ-7 = Asthma Control Questionnaire 7; AQLQ = Asthma Quality of Life Questionnaire; CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; LS = least squares; SD = standard deviation; SE = standard error.

[a] Events per person per year.

[b] Adjudicated exacerbations from the first dose of study drug to 2 weeks after the end of the treatment (52 weeks) or the early withdrawal visit.

[c] Exploratory outcome; outside the statistical hierarchy.

Source: Clinical Study Report.[5-8]

TABLE 2: SUMMARY OF HARMS

Adverse Event, n (%)	Study 3082 52 Weeks		Study 3083 52 Weeks		Study 3081 16 Weeks		Study 3084 16 Weeks	
	Placebo N = 243	**Reslizumab N = 245**	**Placebo N = 232**	**Reslizumab N = 232**	**Placebo N = 105**	**Reslizumab N = 103**	**Placebo N = 97**	**Reslizumab N = 395**
Adverse events	206 (85)	197 (80)	201 (87)	177 (76)	66 (63)	61 (59)	72 (74)	218 (55)
SAEs	34 (14)	24 (10)	23 (10)	18 (8)	1 (1)	4 (4)	4 (4)	16 (4)
Anaphylactic reactions	0	0	0	2 (0.9)	0	0	0	2 (0.5)
WDAEs	8 (3)	4 (2)	9 (4)	8 (3)	10 (10)	6 (6)	12 (12)	29 (7)

SAE = serious adverse event; WDAE = withdrawal due to adverse events.
Source: Clinical Study Report.[5-8]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Asthma is a common chronic respiratory disorder characterized by reversible airway obstruction, pulmonary inflammation, airway hyper-responsiveness, and airway remodelling.[1,2] Patients with asthma typically present with paroxysmal or persistent symptoms of wheezing, dyspnea, chest tightness, sputum production, and coughing that are associated with airflow limitation and airway hyper-responsiveness to endogenous and exogenous stimuli (e.g., exercise; viral respiratory infections; or exposure to certain allergens, irritants, or gases).[2] Although asthma can be diagnosed at any age, it often starts in childhood. In 2015, Statistics Canada estimated that 2.4 million Canadians aged 12 and older had a diagnosis of asthma,[9] representing 12% of all Canadian children and 8% of all Canadian adults.[9]

Asthma has a range of heterogeneous phenotypes; symptoms may differ by presentation, etiology, and pathophysiology. Severe eosinophilic asthma is an asthma phenotype characterized by the presence of eosinophils in the airways and sputum, despite compliance with conventional asthma therapy.[3] Eosinophils are mediators of the allergic inflammatory response and contribute to airway hyper-responsiveness and remodelling.[3,10] Tissue eosinophilia is present in 40% to 60% of patients with asthma, and conventional therapies with inhaled corticosteroids (ICSs) typically reduce total airway eosinophils in these patients.[3] However, 5% to 10% of all asthma patients (50% of patients with severe asthma) continue to experience exacerbations and symptoms, with persistent airway eosinophils, despite high-dose ICSs.[3]

1.2 Standards of Therapy

Given the heterogeneous phenotypes of asthma, treatment is individualized to each patient's unique circumstances and customized as necessary. The primary goals for asthma management include long-term maintenance of asthma control[2] with the least amount of medication and minimization of adverse events.[11] Asthma control, according to the Canadian Thoracic Society guidelines, is based on several characteristics, including:

- frequency of daytime and nighttime symptoms
- frequency of exacerbations
- frequency of absences from work or school due to asthma
- ability to complete normal physical activity
- need for a fast-acting beta-agonist
- forced expiratory volume in one second (FEV_1) or peak expiratory flow (PEF)
- diurnal variation in PEF
- eosinophil levels in sputum.[2]

Asthma control may prevent or minimize the risks of short- and long-term complications, further morbidity, and death.[2] It has been reported that much of asthma-related morbidity is associated with poor management as a result of under-use of or poor adherence to maintenance therapy.[12]

According to the guidelines published by the Canadian Thoracic Society, a stepwise approach to pharmacological therapy is recommended to achieve and maintain asthma control.[2] This involves escalating pharmacological treatment, as necessary, to gain control (i.e., step-up) and then reducing treatment (i.e., step-down) to the minimum required with respect to dose and number of medications for maintenance.[2] Current Canadian and international guidelines recommend that treatment for

patients with asthma in all age groups be initiated with low-dose ICSs.[2,13] If control is not gained or maintained, second-line agents may be added, such as a long-acting beta-agonist (LABA) or leukotriene receptor antagonist, or the ICS dose can be titrated upward.[2] For individuals whose asthma remains uncontrolled on ICS + LABA, further increases in ICS dose or the addition of leukotriene receptor antagonists are recommended. For a specific subset of patients with uncontrolled asthma on high-dose ICS who exhibit a positive skin test or in vitro reactivity to a perennial aeroallergen, omalizumab, an anti-immunoglobulin E (IgE) antibody, may be an option (Table 3). In 2015 mepolizumab was approved as add-on therapy for adults with severe, uncontrolled eosinophilic asthma (Table 3).

1.3 Drug

Reslizumab is a humanized immunoglobulin G (IgG)4 kappa monoclonal antibody that binds to human interleukin-5, thereby reducing the production and survival of eosinophils; however, the precise mechanism of action in asthma has not been established.[4] Reslizumab was approved by Health Canada as add-on maintenance treatment for adult patients who have severe eosinophilic asthma and who are inadequately controlled with medium- to high-dose ICS and an additional asthma controller(s) (e.g., LABA) and who have a blood eosinophil count of ≥ 400 cells/µL at initiation of the treatment. The recommended dose is 3 mg/kg administered by intravenous (IV) infusion every four weeks.

Indication under review
Add-on maintenance treatment of adult patients with severe eosinophilic asthma who are inadequately controlled with medium-to-high-dose ICS and an additional asthma controller(s) (e.g., LABA) and have a blood eosinophil count of ≥ 400 cells/µL at initiation of the treatment.
Reimbursement criteria requested by sponsor
As per indication

TABLE 3: KEY CHARACTERISTICS OF RESLIZUMAB, MEPOLIZUMAB, AND OMALIZUMAB

	Reslizumab	Mepolizumab	Omalizumab
Mechanism of Action	Anti-IL-5 antibody	Anti-IL-5 antibody	Anti-IgE antibody
Indication[a]	Add-on maintenance treatment of adult patients with severe eosinophilic asthma who are inadequately controlled with medium- to high-dose ICS and an additional asthma controller(s) (e.g., LABA) and have a blood eosinophil count of ≥ 400 cells/µL at initiation of treatment	Add-on maintenance treatment of adult patients (≥ 18 years) with severe eosinophilic asthma (≥ 150 cells/µL at treatment initiation or ≥ 300 cells/µL in past 12 months) whose symptoms are inadequately controlled with high-dose ICS and an additional asthma controller(s)	Treatment of adults and adolescents (≥ 12 years) with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled on ICSs
Route of Administration	IV infusion	SC	SC

	Reslizumab	Mepolizumab	Omalizumab
Recommended Dosage	3 mg/kg every 4 weeks	100 mg every 4 weeks	150 to 375 mg every 2 or 4 weeks depending on body weight and serum IgE level
Serious Side Effects / Safety Issues	Anaphylaxis, injection-site reactions, infection	Injection-site reactions, infection, systemic allergic reaction	Anaphylaxis, injection-site reactions, infection

ICS = inhaled corticosteroid; IgE = immunoglobulin E; IL-5 = interleukin-5; IV = intravenous; LABA = long-acting beta-agonist; SC = subcutaneous.
[a] Health Canada indication.
Source: Product monographs.[4,14,15]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of reslizumab 10 mg/mL IV solution for the treatment of severe eosinophilic asthma in adults whose symptoms are inadequately controlled with medium- to high-dose ICS and an additional asthma controller(s) and have a blood eosinophil count of ≥ 400 cells/µL.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase III studies were selected for inclusion based on the selection criteria presented in Table 4.

TABLE 4: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adults (≥ 18 years) with severe eosinophilic asthma whose symptoms are inadequately controlled with medium- to high-dose ICS and an additional asthma controller(s) and have a blood eosinophil count of ≥ 400 cells/µL Subgroups of interest: • baseline asthma-control medication • baseline peripheral eosinophil count • baseline IgE levels • previous use of omalizumab or mepolizumab
Intervention	Reslizumab 3 mg/kg IV every four weeks as add-on therapy to a medium- to high-dose ICS and an additional asthma controller(s)
Comparators	ICS in combination with: • LABA • LTRA • LABA + LAMA • LABA + LTRA • omalizumab • mepolizumab • chronic oral corticosteroids Rescue medication (e.g., SABA, SAMA) may be used for acute exacerbations.
Outcomes	**Key efficacy outcomes:** Acute asthma exacerbations[a] Hospitalizations, emergency department visits, or physician visits due to asthma Exacerbation[a] Use of oral corticosteroids[a] Quality of life[a] Days of missed school or work[a] **Other efficacy outcomes:** Change in pulmonary function (e.g., PEF, FEV_1) Symptom reduction (e.g., ACQ-7)[a] Change in number of asthma-symptom–free days/nights[a] Frequency of nocturnal awakenings[a] Reduction of use of ICSs Reduction of use of rescue medication Blood or sputum eosinophil levels Mortality

	Harms outcomes: AEs, SAEs, WDAEs Notable harms/harms of special interest: opportunistic infection, injection-site reactions, malignancies, myopathy, anaphylaxis, hypersensitivity
Study Design	Published and unpublished phase III RCTs

ACQ-7 = Asthma Control Questionnaire 7; AE = adverse event; ICS = inhaled corticosteroid; IgE = immunoglobulin E; LABA = long-acting beta-agonist; LAMA = long-acting muscarinic antagonist; LTRA = leukotriene receptor antagonist; PEF = peak expiratory flow; RCT = randomized controlled trial; SABA = short-acting beta-agonist; SAE = serious adverse event; SAMA = short-acting muscarinic antagonist; WDAE = withdrawal due to adverse events.
[a] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

The literature search was performed by an information specialist using a peer-reviewed search strategy. Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were reslizumab AND Cinqair. No methodological filters were applied to limit retrieval. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on January 18, 2017. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters):

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

Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR 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 one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented Table 5; excluded studies (with reasons) are presented in 0.

3. RESULTS

3.1 Findings From the Literature

A total of four studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized Table 5: Details of Included Studies and described in Section 3.2. A list of excluded studies is presented in APPENDIX 3.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

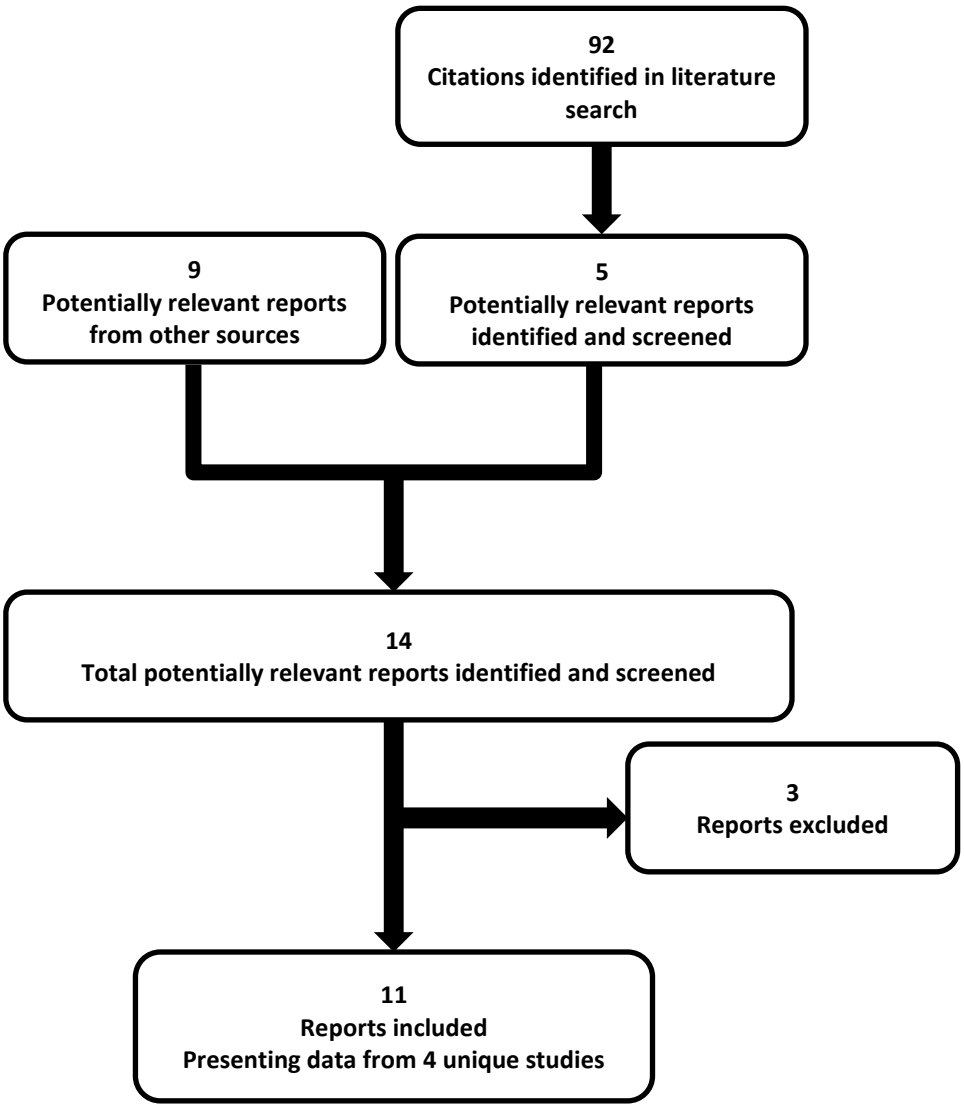


TABLE 5: DETAILS OF INCLUDED STUDIES

		Study 3082	Study 3083	Study 3081	Study 3084
DESIGNS & POPULATIONS	**Study Design**	DB RCT	DB RCT	DB RCT	DB RCT
	Locations	Asia, North America, South America, Europe, South Africa (3082), Australia and New Zealand (3082)		Europe, North America, South America, Israel	US
	Randomized (N)	489	464	315	492
	Inclusion Criteria	• Aged 12 to 75 years with inadequately controlled asthma (ACQ-7 score ≥ 1.5) • Receiving at least a medium dose of ICS (fluticasone propionate ≥ 440 mcg per day or equivalent) ± another controller (including oral corticosteroids up to 10 mg prednisone or equivalent daily) at stable doses for prior 30 days • Eosinophil count of ≥ 400 cells/µL during screening period • At least one asthma exacerbation that required systemic corticosteroids (for ≥ 3 days) in the past 12 months • Airway reversibility of 12% or more with SABA		• Aged 12 to 75 years with inadequately controlled asthma (ACQ-7 score ≥ 1.5) • Receiving at least a medium dose of ICS (fluticasone propionate ≥ 440 mcg per day or equivalent) ± another controller (excluding oral corticosteroids) at stable doses for prior 30 days • Eosinophil count of ≥ 400 cells/µL during screening period • Airway reversibility (≥ 12% with SABA)	• Aged 18 to 65 years with inadequately controlled asthma (ACQ-7 score ≥ 1.5) • Receiving at least a medium dose of ICS (fluticasone propionate ≥ 440 mcg per day or equivalent) ± another controller (excluding oral corticosteroids) • Airway reversibility (12% with SABA)
	Exclusion Criteria	• Asthma exacerbation during the screening period or 4 weeks before screening • Hypereosinophilic syndrome • Other lung disease (e.g., COPD, pulmonary fibrosis, lung cancer) • Current smoker (within 6 months) • Use of systemic immunosuppressive, immunomodulating, or other biologic agent within 6 months • Prior use of reslizumab, mepolizumab, or benralizumab • Inadequately controlled aggravating		• Currently using or had used systemic corticosteroids in the last 30 days • Hypereosinophilic syndrome • Other lung disease (e.g., COPD, pulmonary fibrosis, lung cancer) • Current smoker (within 6 months) • Use of systemic immunosuppressive, immunomodulating, or other biologic agent within 6 months • Prior use of reslizumab, mepolizumab, or benralizumab • Inadequately controlled aggravating	• Currently using or had used systemic corticosteroids in the last 30 days • Hypereosinophilic syndrome • Other lung disease (e.g., COPD, pulmonary fibrosis, lung cancer) • Current smoker (within 6 months)

		Study 3082	Study 3083	Study 3081	Study 3084
		condition (e.g., rhinitis, GERD, uncontrolled diabetes) • Immunodeficiency • Active or recent infection		condition (e.g., rhinitis, GERD, uncontrolled diabetes) • Immunodeficiency • Current infection	• Use of systemic immunosuppressive, immunomodulating, or other biologic agent within 6 months • Prior use of reslizumab, mepolizumab, or benralizumab • Inadequately controlled aggravating condition (e.g., rhinitis, GERD, uncontrolled diabetes) • Immunodeficiency • Current infection
DRUGS	**Intervention**	Reslizumab 3 mg/kg every 4 weeks IV (13 doses)		Reslizumab 3 mg/kg every 4 weeks IV (4 doses) Reslizumab 0.3 mg/kg every 4 weeks IV	Reslizumab 3 mg/kg every 4 weeks IV (4 doses)
	Comparator(s)	Placebo every 4 weeks IV		Placebo every 4 weeks IV	Placebo every 4 weeks IV
DURATION	**Phase**	III		III	III
	Screening	2 to 4 weeks		2 to 4 weeks	3 weeks
	Double-blind	52 weeks		16 weeks	16 weeks
	Follow-up	90 days		90 days	12 weeks
OUTCOMES	**Primary End Point**	Asthma exacerbation frequency		Change from baseline in FEV_1	Change from baseline in FEV_1 relative to baseline eosinophil levels
	Other End Points	Change from baseline in: • FEV_1 • AQLQ • ACQ-7 • ASUI • SABA use • blood eosinophils		Change from baseline in: • ACQ-7 • AQLQ • ASUI • rescue SABA use • blood eosinophils	Change from baseline in: • FEV_1 • ACQ-7 • rescue SABA use • blood eosinophils

		Study 3082	Study 3083	Study 3081	Study 3084
		Time to first clinical asthma exacerbation Harms		Harms	Harms
NOTES	**Publications**	Castro et al. 2015[16,17]		Bjermer et al. 2016[18]	Corren et al. 2016[19]

ACQ-7 = Asthma Control Questionnaire 7; AQLQ = Asthma Quality of Life Questionnaire; ASUI = Asthma Symptoms Utility Index; COPD = chronic obstructive pulmonary disease; DB = double-blind; FEV_1 = forced expiratory volume in 1 second; GERD = gastroesophageal reflux disease; ICS = inhaled corticosteroid; IV = intravenous; RCT = randomized controlled trial; SABA = short-acting beta-agonist.
Note: Four additional reports were included (FDA reports,[20,21] CADTH Common Drug Review submission,[22] Health Canada reports[23]).
Source: Clinical Study Report.[5-8]

3.2 Included Studies

3.2.1 Description of Studies

A total of four double-blind randomized controlled trials (RCTs) met the inclusion criteria: two identical pivotal trials (Studies 3082 and 3083) and two supporting trials (Studies 3081 and 3084) (Table 5).

The objective of the pivotal trials was to assess the efficacy of reslizumab versus placebo on the frequency of asthma exacerbations over a 12-month treatment period, in patients with inadequately controlled asthma and elevated eosinophil levels. Patients were randomized to reslizumab (3 mg/kg IV every four weeks) or placebo using interactive response technology and computerized central randomization, stratified by regular maintenance oral corticosteroid use (yes/no) and region (US or non-US). In total, 489 and 464 patients were randomized in Studies 3082 and 3083, respectively.

The objective of the supporting trials was to assess the efficacy of reslizumab versus placebo in terms of changes in FEV_1 (Study 3081) or change in FEV_1 relative to baseline eosinophil levels (Study 3084) over 16 weeks. In Study 3081, patients with inadequately controlled asthma and elevated eosinophil levels (N = 315) were randomized 1:1:1 to reslizumab (3 mg/kg IV every four weeks), reslizumab (0.3 mg/kg IV) or placebo (stratified by occurrence of asthma exacerbation in previous year [yes/no] and age group [12 to 17, or ≥ 18 years]). Randomization was performed separately at each site, using interactive response technology. In Study 3084, patients with inadequately controlled asthma (N = 492) were randomized 4:1 to reslizumab (3 mg/kg IV every four weeks) or placebo via interactive response technology. Randomization was stratified by the occurrence of asthma exacerbation in previous year (yes/no).

Patients in Studies 3081, 3082, and 3083 had the option to enter the open-label extension study (Study 3085) at the end of the double-blind trials. Those who did not enter the extension study were followed for 90 days after the end of treatment.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

The inclusion criteria for the four trials were similar and included patients with inadequately controlled asthma receiving at least medium-dose ICS (≥ 440 mcg/day of fluticasone or equivalent) with or without another controller medication (Table 5). The pivotal trials (Studies 3082 and 3083) enrolled patients who had had at least one asthma exacerbation in the past year, and three of the trials (Studies 3082, 3083, and 3081) also required that patients have a blood eosinophil count ≥ 400 cells/µL during the screening period.

All of the trials excluded patients with other lung diseases, current or recent smokers (within last six months), immunodeficiency, or recent infection.

b) Baseline Characteristics

The patients enrolled were predominantly adults (95% to 100%) with mean age in each treatment group ranging from 43.0 to 47.5 years (Table 6). The majority of patients were female (55% to 66%) and white (65% to 85%), and had had asthma on average for 18 to 26 years. In the pivotal trials, patients had had an average of 1.9 to 2.1 asthma exacerbations in the previous year (range [redacted]) whereas, in the supporting trials, 54% to 57% of patients in Study 3081, and 38% to 42% of patients in Study 3084 had had an exacerbation in the past year. The mean blood eosinophil counts were similar in Studies 3082, 3083, and 3081 (range 0.59 to 0.70 × 10^9 cells/L), and were lower in Study 3084 (0.28 × 10^9

cells/L). The total daily dose of ICS was also lower in Study 3084 (range 616 mcg to 628 mcg) than in the other three trials (757 mcg to 856 mcg).

Ongoing use of ICS was a requirement in all trials, with [redacted] of patients using an inhaler containing ICS alone, or combined with a LABA ([redacted] Overall, [redacted] of patients in Study 3082 and [redacted] of patients in Study 3083 were receiving an ICS with a LABA, with similar proportions between treatment groups. The percentage of patients using an ICS with a LABA was [redacted] in Study 3081 and [redacted] for Study 3084, in the placebo and reslizumab groups, respectively.

The patient characteristics were generally balanced between groups within Studies 3083, 3081, and 3084. However, in Study 3082, there were some imbalances, with a number of patients misclassified with regard to their use of oral corticosteroids, which was a stratification variable in the interactive response system. As a result of these errors, there were more patients in the reslizumab group who used oral corticosteroids at baseline ([redacted]) than in the placebo group ([redacted]). Misclassification of oral corticosteroid use also occurred in Study 3083, but the difference between groups was less apparent (placebo [redacted]; reslizumab [redacted]).

Misclassification of patients' exacerbations history (a stratification factor at randomization) also occurred in Studies 3081 and 3084, although a limited number of patients were misclassified ([redacted], and the numbers were balanced between groups.

TABLE 6: SUMMARY OF BASELINE CHARACTERISTICS

Characteristic	Study 3082		Study 3083		Study 3081		Study 3084	
	Placebo N = 244	Reslizumab N = 245	Placebo N = 232	Reslizumab N = 232	Placebo N = 105	Reslizumab N = 106	Placebo N = 98	Reslizumab N = 398
Age, years, mean (SD)	46.7 ( )	46.6 ( )	47.5 ( )	46.4 ( )	44.2 ( )	43.0 ( )	45.1 ( )	44.9 ( )
Adults (≥ 18 years), n (%)					100 (95)	101 (95)		
Female, n (%)	161 (66)	142 (58)	150 (65)	144 (62)	62 (59)	62 (58)	54 (55)	261 (66)
Caucasian, n (%)	182 (75)	173 (71)	169 (73)	168 (72)	85 (81)	90 (85)	73 (74)	260 (65)
Patients with asthma exacerbation in past year, n (%)	244 (100)	245 (100)	232 (100)	231 (> 99)	57 (54)[a]	60 (57)[a]	37 (38)[b]	166 (42)[b]
Asthma exacerbations in past year, mean (SD), [median, range]	2.1 (2.3)	1.9 (1.6)	2.0 (1.8)	1.9 (1.6)	NR	NR	NR	NR
FEV_1, L, mean (SD)	1.93 (0.79)	1.89 (0.73)	2.00 (0.67)	2.13 (0.78)	2.22 ( )	2.19 ( )	2.18 ( )	2.10 ( )
% predicted FEV_1, mean (SD)	65 (20)	64 (19)	68 (19)	70 (21)	71 (20)	70 (18)	67 (16)	67 (16)
Airway reversibility, %, mean (SD)	26 (18)	26 (15)	29 (24)	28 (16)	25 ( )	26 ( )	24 ( )	26 ( )
Patient-reported use of SABA in past 3 days, n (%)	188 (77)	170 (69)	181 (78)	182 (78)				
Blood eosinophil count (10^9/L), mean (SD)[c]	0.62 (0.59)	0.70 (0.77)	0.69 (0.68)	0.61 (0.41)	0.60 ( )	0.59 ( )	0.28 ( )	0.28 ( )
ACQ-7 score, mean (SD)	2.8 (0.9)	2.7 (0.9)	2.6 (0.8)	2.6 (0.9)	2.5 ( )	2.6 ( )	2.6 ( )	2.6 ( )
Time since asthma diagnosis, years, mean (SD)	18.8 (14.2)	19.7 (15.2)	18.7 (13.3)	18.2 (14.4)	20.7 ( )	20.4 ( )	25.8 ( )	26.2 ( )
History of nasal polyps, n (%)								
History of allergic rhinitis								
Oral corticosteroid use at baseline, n (%)					--[f]	--[f]	--[f]	--[f]
Total daily dose ICS at baseline, mcg, mean (SD)	848 (442)	824 (380)	757 (274)	856 (588)	757 (371)	814 (453)		
Medications for obstructive airway disease used in past 4 weeks, n (%)								
SABA								

Characteristic	Study 3082		Study 3083		Study 3081		Study 3084	
	Placebo N = 244	Reslizumab N = 245	Placebo N = 232	Reslizumab N = 232	Placebo N = 105	Reslizumab N = 106	Placebo N = 98	Reslizumab N = 398
ICS + LABA	[redacted]							
ICS								
Systemic corticosteroids								
Leukotriene inhibitors								
LABA								
Omalizumab								

ACQ-7 = Asthma Control Questionnaire 7; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; LABA = long-acting beta-agonist; NR = not reported; SABA = short-acting beta-agonist; SD = standard deviation.

[a] In Study 3081, 5 patients were misclassified at randomization as having an asthma exacerbation in the previous year, and 6 patients were misclassified as not having an exacerbation.

[b] In Study 3084, 5 patients were misclassified at randomization as having an asthma exacerbation within the last 12 months, and 8 patients were misclassified as not having an asthma exacerbation.

[c] Patients were required to have at least 1 eosinophil count ≥ 400 cells/L during the screening period, which may or may not have occurred at the baseline assessment.

[d] Data summarized in Table 7 are based on information from electronic case report forms. The use of oral corticosteroids was a stratification variable at randomization, based on data inputted into the interactive response technology. In all, 6.6% of placebo patients and 11.4% of reslizumab patients were misclassified in the interactive response technology.[20]

[e] Data summarized in Table 7 are based on information from electronic case report forms. The use of oral corticosteroids was a stratification variable at randomization, based on data inputted into the interactive response technology. In all, 6.5% of placebo patients and 4.7% of reslizumab patients were misclassified in the interactive response technology.[20]

[f] Current use of systemic corticosteroids was an exclusion criterion.

Source: Clinical Study Report,[5-8] FDA Statistical Review.[21]

3.2.3 Interventions

In all four trials, patients were randomized to placebo or reslizumab 3 mg/kg IV infusion every four weeks. Study 3081 also included a third treatment group of reslizumab 0.3 mg/kg every four weeks. This group will not be discussed in this report, as the dosage is not consistent with the Health Canada–approved dose.[4]

Patients in the pivotal trials (Studies 3082 and 3083) were treated with 13 doses (52 weeks) and those in the supporting trials (Studies 3081 and 3084) received four doses (16 weeks) of study drug.

In order to maintain blinding, patients in the placebo group received a specific volume of placebo, which varied according to the patient's weight. Patients and investigators were blinded to eosinophil counts as well as pharmacokinetic and anti-drug antibodies assay results during the study period.

In all trials, patients maintained their background asthma therapies at the same dose during the trials. The enrolment criteria specified that patients had to be treated with ICS (daily dose ≥ 440 mcg of fluticasone or equivalent), but could also be receiving other controller therapy. In Studies 3082 and 3083, patients using oral corticosteroids (up to 10 mg of prednisone daily, or equivalent) were enrolled, provided the dose of steroids was stable for 30 days before screening and was continued during the trial. Patients using systemic corticosteroids at screening were excluded from Studies 3081 and 3084. In Study 3084, any patients who had an asthma event that required systemic corticosteroids were withdrawn from the trial.

In all trials, patients were prohibited from using interleukin-5 monoclonal antibodies (reslizumab, mepolizumab, or benralizumab) at any time; omalizumab or any other biologic therapies, immunosuppressive or immunomodulatory agents, and anti–tumour necrosis factor monoclonal antibodies within six months before screening; and live attenuated vaccines within 12 weeks of enrolment.

Key concomitant medications that patients received during the double-blind studies are summarized in Table 7. In Studies 3082, 3083, and 3084, more patients in the placebo group than in the reslizumab group received systemic corticosteroids and systemic antibacterials (Table 7). The use of systemic antihistamines was higher in the placebo group than in the reslizumab group in all trials.

TABLE 7: SUMMARY OF COMMON CONCOMITANT MEDICATIONS BY THERAPEUTIC CLASS

Medication	Study 3082		Study 3083		Study 3081		Study 3084	
	Placebo N = 243	Reslizumab N = 245	Placebo N = 232	Reslizumab N = 232	Placebo N = 105	Reslizumab N = 103	Placebo N = 97	Reslizumab N = 395
Drugs for obstructive airway diseases	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Systemic corticosteroids	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Systemic antibacterials	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nasal preparation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Systemic antihistamines	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Clinical Study Report.[5-8]

3.2.4 Outcomes

In the pivotal trials (Studies 3082 and 3083), the primary outcome was the frequency of asthma exacerbations over the 52-week study period. Exacerbations were defined as either:

- use of systemic corticosteroids or an increase in the use of ICS treatment for three days or more (dose had to increase two-fold for those already on corticosteroids), or
- asthma-related emergency treatment, including at least one unscheduled visit to the physician's office for nebulizer treatment or other urgent treatment, visit to the emergency room for asthma-related treatment, or asthma-related hospitalization.

In addition, the patient had to show one other measurement indicating worsening signs or symptoms of asthma:

- decrease in $FEV_1 \geq 20\%$ from baseline
- decrease in PEF ≥ 30% from baseline on two consecutive days, or
- worsening of symptoms or other clinical signs, per physician evaluation.

All reported asthma exacerbation events were adjudicated by a blinded adjudication committee. All asthma exacerbations were considered part of the same event if:

- they occurred within seven days of an increase in baseline corticosteroid dose, or the completion of a course of systemic corticosteroids
- they involved an unscheduled visit to an emergency department, urgent care facility, or physician's office for treatment within the same seven-day period
- they involved hospital admission for asthma (≥ 24 hours) within the same seven-day period.

Patients who experienced an exacerbation could continue in the study after receiving medical therapy.

In the pivotal trials, secondary outcomes included FEV_1, Asthma Control Questionnaire 7 (ACQ-7), Asthma Quality of Life Questionnaire (AQLQ), time to first asthma exacerbation, Asthma Symptom Utility Index (ASUI), SABA use, and blood eosinophil levels. Exploratory responder analyses were conducted for the proportion of patients who achieved a change ≥ 0.5 points, the minimal clinically important difference (MCID) for the ACQ and AQLQ.

In Study 3081, the primary outcome was the change from baseline in FEV_1 over 16 weeks, and, in Study 3084, the primary outcome was the change from baseline in FEV_1 to week 16, relative to baseline eosinophil levels (i.e., testing whether the interaction between the treatment effect and eosinophil count was significant). These supporting trials also analyzed other pulmonary-function measures, asthma symptoms, SABA use, and eosinophil levels as secondary or exploratory outcomes; however, this report focused on the FEV_1 results.

In all trials, patients were assessed every four weeks for efficacy and safety outcomes, except for quality of life (AQLQ), which was measured at baseline and weeks 16, 32, and 52 in the pivotal trials. In all studies, SABAs were withheld for six hours, and LABAs for 12 hours, before spirometry. Use of SABAs was based on patients' recall of the number of puffs of SABAs used in the three days before each study visit.

FEV_1 is the maximal volume of air after a full inspiration that can be forcibly exhaled in one second and is measured electronically by spirometry. Although it is widely used in clinical trials to evaluate the effectiveness of asthma treatments, there is little literature on the MCID for FEV_1-based measures. Historically, an MCID of 100 mL has been proposed, although little evidence exists to support this value. One study estimated a 230 mL (range 170 mL to 280 mL) change in FEV_1 to be the minimal patient-perceivable improvement (0: Validity of Outcomes).[24]

ACQ-7 is a patient-reported instrument that measures the adequacy of asthma treatment; it consists of seven items, including five items on symptoms (nighttime awakenings, symptom severity upon awakening, activity limitation due to asthma, shortness of breath due to asthma, and wheezing), one item on rescue bronchodilator use, and one item on FEV_1, in terms of percentage of predicted normal. Questions are scored on a seven-point scale, which ranges from 0 (indicating good control) to 6 (poor control). The overall score is the mean of all seven questions, with higher scores indicating poorer control. Patients recall their relevant experiences during the previous seven days. An MCID of 0.5 points has been reported in the literature.[25]

AQLQ is a 32-question quality-of-life instrument that includes four domains (symptoms, activity limitation, emotional function, and environmental stimuli). Patients respond using a seven-point scale from 7 (no impairment) to 1 (severe impairment), based on their recall of their experience over the previous two weeks. For five of the activity questions, patients identify which activities are most limited by their asthma, and these activities were scored throughout Studies 3082 and 3083.[6,7] An MCID of 0.5 points has been reported in the literature.[26-28]

ASUI is a patient-reported 11-item instrument designed to assess the frequency and severity of asthma symptoms (wheeze, shortness of breath, cough, and awakening at night) and side effects of asthma treatment, weighted by patient preferences. It is scored from 0 to 1, with lower scores indicating worse asthma symptoms. An MCID of 0.09 points has been reported in the literature.[29]

In the reslizumab trials, an adverse event was defined as any untoward medical occurrence that developed or worsened in severity during the trial, including any events that occurred after the patient signed informed consent, whether or not they were considered related to the study drug. A serious adverse event was any event that resulted in death, was life-threatening, required hospitalization or prolongation of hospitalization, caused persistent or significant disability or incapacity, was a congenital

anomaly, or was an important medical event that jeopardized the patient and required medical attention.

3.2.5 Statistical Analysis

In Studies 3082 and 3083, the primary outcome was the frequency of asthma exacerbations, which was tested using a negative binomial regression model including treatment arm and stratification variables (US versus other region, oral corticosteroid use) and using the logarithm of follow-up time, excluding summed duration of exacerbations, as the offset. Sensitivity analyses were conducted using an offset that did not exclude the follow-up time during an exacerbation, and that used a multiple imputation procedure for missing data. Rate ratios and 95% confidence intervals (CIs) were estimated using a negative binomial model, and the likelihood based chi-square test (two-sided, 0.05 significance level) was used to test for between-group differences. The analysis included all events between the first dose of study drug and two weeks after the end of the treatment period (week 52 or early withdrawal visit), and all exacerbation events were adjudicated by a blinded committee. Exploratory secondary analyses were conducted of the frequency of exacerbations that required oral or systemic corticosteroids, or emergency department visits or hospitalizations, but these were outside the statistical testing hierarchy.

A hierarchical multiple-testing procedure was used to test the primary outcome (exacerbation frequency) and then secondary outcomes in the following order:

- change from baseline in FEV_1 to week 16 and overall change over first 16 weeks
- change from baseline AQLQ to week 16
- change from baseline ACQ-7 over first 16 weeks
- time to first clinical asthma exacerbation
- change from baseline ASUI over first 16 weeks
- change from baseline SABA use (puffs per day) over first 16 weeks
- change from baseline blood eosinophil count over 16 and 52 weeks.

Statistical testing was interpreted inferentially if the previous outcome in the hierarchy was significant ($P < 0.05$). Week 16 was the pre-specified time point for analysis of secondary change from baseline outcomes for which type I error was controlled. There was no control of type I error for other outcomes or time points. Subgroup analyses were conducted for patients with percentage of predicted $FEV_1 < 85\%$ at baseline. This subgroup was outside the statistical testing hierarchy, and no testing was conducted for the subgroup with percentage of predicted $FEV_1 \geq 85\%$.

Pulmonary function, eosinophil counts, SABA use, and ACQ, AQLQ, and ASUI scores were analyzed using a mixed-effect model of repeated measures with treatment, visit, treatment–visit interaction, and stratification variables as fixed effects, patient as random effect, and the baseline value as a covariate. Sex and height were included in models that analyzed lung-function outcomes. Time to asthma exacerbation was analyzed using Kaplan–Meier methods, distribution differences compared by log-rank test were adjusted for stratification factors, and the hazard ratio and 95% CI were estimated using a stratified Cox proportional hazard model.

Other exploratory outcomes included a responder analysis for the ACQ and AQLQ. A stratified Cochran–Mantel–Haenszel test was used to analyze the proportion of patients with at least a 0.5-point reduction in ACQ-7, and those with at least a 0.5-point increase in AQLQ score from baseline. Those with missing data were classified as non-responders.[20]

With 480 patients enrolled in Study 3082 and 460 patients in Study 3083, the pivotal trials had 90% power to detect a 33% reduction in exacerbation frequency with reslizumab versus placebo (two-sided, 0.05 significance level), assuming 1.2 or more events for the mean annual exacerbation rate in the placebo group, 5% or 9% dropout rate, and 10% false-positive rate for the blood eosinophil test at enrolment. The mean annual event rate was extrapolated from mepolizumab studies and other published event rate data in patients with severe asthma. Study 3082 was originally powered for change in FEV_1 as a co-primary outcome, but this outcome was changed to a secondary outcome in a protocol change.

A number of protocol changes were made over the course of the pivotal trials. Key changes are summarized in Table 8. Of note, the definition of exacerbation was finalized after all patients had been enrolled in the pivotal trials.

TABLE 8: KEY PROTOCOL CHANGES IN THE PIVOTAL TRIALS

Date	N enrolled		Description
	Study 3082	Study 3083	
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Source: Clinical Study Report.[6,7]

In Study 3081, the primary outcome was the change from baseline in FEV_1 over 16 weeks, which was analyzed using a mixed-effects model for repeated measures (MMRM) with treatment, visit, treatment–visit interaction, sex, and stratification variables as fixed effects, patient as random effect, and height and baseline FEV_1 value as covariates. The treatment effect for each dose versus placebo was tested sequentially (3 mg/kg, then 0.3 mg/kg) using a two-sided test (0.05 significance level). If the 3 mg/kg dose was not significant, the 0.3 mg dose comparison was not interpreted inferentially. There was no imputation for missing data in the primary analyses; however, sensitivity analyses were run using a multiple imputation method for missing data.

Study 3081, with 100 patients per group, was estimated to have 90% power to detect a difference between reslizumab and placebo using a two-sided test at the 0.05 significance level, based on a

predicted effect size of 0.47 with each reslizumab dose. The predicted effect size was based on a phase II reslizumab trial that showed a change from baseline in FEV_1 of 204 mL (standard deviation [SD] 334 mL) compared with placebo.

The primary outcome of Study 3084 was the change from baseline in FEV_1 to week 16, relative to baseline eosinophil levels. It was analyzed using a linear regression model that included treatment, blood eosinophil count at baseline, and the interaction between eosinophil levels and treatment. The interaction was tested at a 0.10 significance level in the full analysis set (FAS) population. Treatment differences and 95% CI levels were estimated for the following baseline eosinophil counts: 0.4×10^9/L, 0.3×10^9/L, 0.2×10^9/L, and 0.1×10^9/L. Descriptive statistics were provided for change from baseline in FEV_1 to week 16 for subgroups according to baseline eosinophil levels (e.g., $\geq 0.4 \times 10^9$/L and $< 0.4 \times 10^9$/L). The key secondary outcomes were the change from baseline in FEV_1 and change from baseline in ACQ score, to week 16. A sequential testing procedure was performed for the primary and key secondary outcomes.

Study 3084 was powered to test the hypothesis that reslizumab treatment improves FEV_1 more in patients with high blood eosinophil levels at baseline than in those with low eosinophil levels. With 400 reslizumab patients and 100 placebo patients, the study had 90% power to detect a regression slope beta coefficient ≥ 0.195, assuming that the SD for eosinophil levels is ≥ 0.25 and the SD for random error is ≤ 0.30 using a 0.05 two-sided significance level.

a) Analysis Populations

In the pivotal trials, efficacy outcomes were evaluated based on the intention-to-treat population (ITT), which included all randomized patients. Sensitivity analyses were conducted using the FAS, which included all randomized patients who received at least one dose of study medication. If the patient used specific confounding medications within the previous seven days of that study visit, then data from pulmonary function, SABA use, and ACQ, AQLQ, and ASUI assessments were excluded from the FAS. Confounding medications included the addition of a LABA, a long-acting muscarinic antagonist or an oral or systemic corticosteroid, if not taken at baseline, or an increase in dose of these medications for patients who received these treatments at baseline.

In Studies 3081 and 3084, efficacy analyses were based on the FAS population and excluded visit outcome data if the patients received a confounding medication in the prior seven days (addition of a LABA, a long-acting muscarinic antagonist, or an oral or systemic corticosteroid, if not taken at baseline).

In the four trials, safety was evaluated for all patients who received at least one dose of study medication.

3.3 Patient Disposition

Of the 4,491 patients screened for enrolment, 31% to 57% met the inclusion criteria and were randomized in one of the four trials (Table 9). Failure to meet the inclusion criteria was the most common reason for exclusion in all of the studies.

Across the four trials, a total of 1,764 patients were randomized, with 98 to 244 patients assigned to a placebo group, and 106 to 398 patients assigned to a reslizumab 3 mg/kg group. In the 52-week pivotal trials, 12% and 14% of placebo patients, and 11% and 13% of reslizumab patients withdrew from the studies. Withdrawal of consent was the most common reason reported (5% to 6%). Withdrawal rates

were higher in the 16-week supporting trials, with 19% of placebo and 17% of reslizumab patients withdrawing from Study 3081 and Study 3084. In Study 3084, two study sites were terminated due to procedural violations, and all patients' data were excluded from the analysis (N = 15).

TABLE 9: PATIENT DISPOSITION

	Study 3082		Study 3083		Study 3081		Study 3084	
	Placebo	**Reslizumab**	**Placebo**	**Reslizumab**	**Placebo**	**Reslizumab**	**Placebo**	**Reslizumab**
Screened, N	1,486		1,111		1,025		869	
Randomized, N (%)	489 (33)[a]		464 (42)[b]		315 (31)[c,d]		496 (57)[e]	
	244	245	232	232	105	106	98	398
Did not receive treatment, n (%)	1	0	0	0	0	3	1	3
Withdrew from study, n (%)	29 (12)	27 (11)	33 (14)	30 (13)	20 (19)	18 (17)	19 (19)	68 (17)
Adverse event	8 (3)	4 (2)	9 (4)	8 (3)	9 (9)	7 (7)	11 (11)	32 (8)
Lack of efficacy	0	0	4 (2)	2 (1)	2 (2)	1 (1)	0	1 (< 1)
Consent withdrawn	14 (6)	11 (5)	15 (6)	11 (5)	2 (2)	4 (4)	4 (4)	18 (5)
Protocol violation	2 (1)	3 (1)	1 (< 1)	2 (1)	4 (4)	2 (2)	2 (2)	3 (< 1)
Lost to follow-up	3 (1)	2 (1)	1 (< 1)	1 (< 1)	2 (2)	1 (1)	2 (2)	9 (2)
Non-compliance	0	2 (1)	2 (1)	3 (1)	0	0	0	0
Other	2 (1)	5 (2)	1 (< 1)	3 (1)	1 (1)	3 (3)	0	5 (1)
ITT, N (%)	244 (100)	245 (100)	232 (100)	232 (100)	–	–	–	–
FAS, N (%)	243 (> 99)	245 (100)	232 (100)	232 (100)	105 (100)	103 (97)	97 (99)	395 (> 99)
Safety, N (%)	243 (> 99)	245 (100)	232 (100)	232 (100)	105 (100)	103 (97)	97 (99)	395 (> 99)

FAS = full analysis set; ITT = intention-to-treat.

[a] Reason for screening failure: inclusion criteria not met (n = 888), exclusion criteria (n = 12), consent withdrawn (n = 23), adverse event (n = 17), lost to follow-up (n = 7), other (n = 50).

[b] Reason for screening failure: inclusion criteria not met (n = 584), exclusion criteria (n = 8), consent withdrawn (n = 25), adverse event (n = 3), lost to follow-up (n = 4), other (n = 23)

[c] Reason for screening failure: inclusion criteria not met (n = 626), exclusion criteria (n = 18), consent withdrawn (n = 22), adverse event (n = 9), lost to follow-up (n = 7), other (n = 28).

[d] The trial included a third treatment arm for reslizumab 0.3 mg/kg (N = 104).

[e] Reason for screening failure: inclusion criteria not met (n = 267), exclusion criteria (n = 42), consent withdrawn (n = 20), adverse event (n = 6), lost to follow-up (n = 7), other (n = 16). Two study sites were terminated as a result of protocol violations, and all 15 patients enrolled from these sites were excluded from all analyses. These 15 patients (placebo: n = 4, reslizumab: n = 11) were not included in the total number of patients randomized.

Source: Clinical Study Report.[5-8]

3.4 Exposure to Study Treatments

The median treatment exposure was one year for all treatment groups in Studies 3082 and 3083, with 78% and 83% of patients, respectively, completing 13 or more infusions of study drug (Table 10). In the supporting trials, the median treatment exposure was 113 days for all treatment groups, although numerically fewer placebo patients (80%) in Study 3081 completed all four infusions than in the reslizumab group (88%).

TABLE 10: SUMMARY OF DRUG EXPOSURE

	Study 3082		Study 3083		Study 3081		Study 3084	
	Placebo N = 243	Reslizumab N = 245	Placebo N = 232	Reslizumab N = 232	Placebo N = 105	Reslizumab N = 103	Placebo N = 97	Reslizumab N = 395
Duration of exposure, days, median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 4 complete infusions,[a] n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 13 complete infusions,[a] n (%)	[redacted]	[redacted]	[redacted]	[redacted]	–	–	–	–

[a] Complete infusion defined as having received at least 75% of the planned dose.
Source: Clinical Study Report.[5-8]

3.5 Critical Appraisal

3.5.1 Internal Validity

In all four RCTs, patients were randomized using an interactive response system with adequate allocation concealment. A placebo injection (with the volume adjusted according to patient weight) was used to maintain blinding. In addition, patients and investigators were blinded to blood eosinophil levels during the trial. There were no obvious differences in the occurrence of adverse events that would lead to substantial unblinding. Across treatment groups, 11% to 14% of patients withdrew from the pivotal trials, and 17% to 19% of patients withdrew from the supporting trials. The proportions were similar between treatment groups. In the pivotal trials, [redacted] of patients completed all 13 study drug infusions.

In general, the baseline patient characteristics were well balanced between groups. In the pivotal trials, there was a misclassification of patients' oral corticosteroid use at randomization (a stratification variable). This led to an imbalance between groups, with more severe asthma patients in the placebo group in Study 3082 (16% versus 10% using oral corticosteroids), which potentially biased results in favour of reslizumab. However, an FDA analysis showed that this imbalance did not appear to affect results.[20] In the supporting studies, there was a misclassification of patients' recent exacerbation history, but the number of patients was low ([redacted], and the misclassification was well balanced between groups. In general, reporting of prior and concurrent medications to treat asthma lacked clarity and

made it difficult to identify the proportion of patients whose characteristics were consistent with the Health Canada–approved indication.

The primary outcome of the pivotal trials — exacerbation frequency — is an important outcome to patients. Of note, the definition of exacerbations changed over the course of the trial, and an adjudication committee was added partway through the trials. The final exacerbation definition was approved (based on FDA input) once all patients were enrolled. Changing the primary outcome definition after patients had been enrolled is less than ideal, but because all events were adjudicated by a blinded independent committee according to set criteria, this should mitigate any potential bias in favour of one study treatment. The FDA stated that the timing and nature of these key protocol amendments did not a priori discredit the data, and the final definition of exacerbations and the plan for independent adjudication of these events were consistent with regulatory and expert guidance.[20,21] The final exacerbation definition was also accepted Health Canada.[23]

The pivotal trials also examined asthma symptoms and quality of life using accepted instruments (ACQ-7 and AQLQ). SABA use was based on patient recall of the number of puffs used over past three days and may have been subject to recall bias. There was no mention of patient diary to record number of puffs used, which could have improved the accuracy of the data.

The analysis in the pivotal trials was based on the ITT population; however, the supporting trials were based on a modified ITT population (FAS). There was no imputation for missing data for the primary outcome analyses in any of the trials. Sensitivity analyses using multiple imputation methods generally showed results similar to those from the primary analysis in Studies 3082 and 3083; however, in Study 3084 the sensitivity analysis results were more favourable to reslizumab. The clinical importance of these differences is unclear.

The pivotal trials used a statistical testing hierarchy to control type I error. The results of the blood eosinophil analysis should not be interpreted inferentially, as a prior outcome failed in the hierarchy. Some important exacerbation outcomes (i.e., those requiring hospitalization or systemic steroids) were outside the statistical hierarchy and thus are considered exploratory. Except for the subpopulations of patients with percentage of predicted $FEV_1 < 85\%$, no subgroup analyses were planned. Several post hoc subgroup analyses were conducted using pooled data from the two pivotal trials, with no control of multiplicity. Caution is warranted when interpreting these findings.

Three of the trials enrolled patients with an elevated eosinophil count, which was consistent with the population meeting the Health Canada–approved indication. In Study 3084, relatively few patients with eosinophil levels ≥ 400 cells/µL were enrolled (20%), and the study was not designed to test this group; thus, the subgroup data should be interpreted with caution. Study 3084 tested multiple thresholds for eosinophil levels; thus, there is an increased risk of type I error. Furthermore, the interaction term *P* values were not reported for the subgroup analyses.

The FDA raised concerns with regard to the collection of safety data, which may have limited the analysis of key safety signals.[20] Data on anaphylaxis events were not prospectively collected using the criteria of the National Institute of Allergy and Infectious Disease/ Food Allergy and Anaphylaxis Network, and there was no collection of post-infusion vital signs, which may detect changes in blood pressure as well as in heart and respiratory rate associated with anaphylaxis. With few details on adverse events available, it was not possible to generate narratives retrospectively for events such as

anaphylaxis.[20] Post-infusion safety-data collection was less rigorous than in previous reslizumab trials for eosinophilic esophagitis.[20] The FDA noted that creatine phosphokinase (CPK) levels were collected before each infusion (trough level), and not after an infusion, when levels would be elevated if elevation were related to drug exposure. Patients in the reslizumab group reported more musculoskeletal adverse events in the first 24 hours following an infusion, and more patients in this group had elevated CPK levels, compared with placebo.[20] No CPK levels were collected in the extension Study 3085.[20] Due to the infrequent measurement of CPK levels, reslizumab-related muscle injury may be under-reported. The FDA also noted that the imbalance in baseline oral corticosteroid use in Study 3082 could obscure safety signals, such as infection and myopathy, that may be associated with systemic corticosteroids and reslizumab.[20]

3.5.2 External Validity

According to the clinical expert consulted for this review, the populations enrolled in the trials were representative of Canadians with moderate to severe asthma. Three of the four RCTs enrolled patients with uncontrolled asthma and elevated eosinophil levels (≥ 400 cells/µL per the Canadian product monograph). Although the inclusion criteria required patients to be treated with only medium doses of ICS, the mean daily doses ranged from 757 mcg to 856 mcg, and 82% to 86% of patients in the pivotal trials were receiving an ICS with a LABA. Thus, most patients enrolled in the pivotal trials would be consistent with the population meeting the Health Canada–approved indication. Of note, 43% to 69% of patients failed screening, and few Canadians were enrolled (N = 17), although in total 220 patients (17%) in Studies 3082, 3083, and 3081 were from the US. Although the pivotal trials included patients younger than 18 years, few adolescents were enrolled (3%, N = 25), and inclusion of these patients is unlikely to affect the generalizability of the results.

Exacerbations are an important outcome to patients, and the one-year treatment period was likely sufficient to see difference between groups; however, longer-term safety and efficacy data are needed. No data were reported on other outcomes considered important according to patient groups, such as missed school or work days and steroid-sparing effects. No direct evidence comparing reslizumab with omalizumab or mepolizumab were available.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol (Section 2.2, Table 4) are reported in this section. See APPENDIX 4 for detailed efficacy data.

Not all efficacy outcomes identified in the protocol or by patient groups were reported in the included studies. No data were available on the number of days of missed school or work, or symptom-free days, and no trial was designed to assess steroid-sparing effects of reslizumab. The frequency of nocturnal awakenings was not reported directly, but was part of asthma-symptom questionnaires used in the pivotal trials. Mortality was reported as an adverse event.

3.6.1 Asthma Exacerbations

The proportion of patients with an adjudicated asthma exacerbation was 54% versus 38%, and 45% versus 25%, for the placebo versus reslizumab groups in Studies 3082 and 3083, respectively (Table 11). The asthma exacerbation rate was statistically significantly lower for reslizumab versus placebo in Studies 3082 (adjusted rate ratio 0.50; 95% CI, 0.37 to 0.67, $P < 0.0001$), and 3083 (adjusted rate ratio 0.41; 95% CI, 0.28 to 0.59, $P < 0.0001$).

Sensitivity analyses, in which the offset did not exclude follow-up time when patients were experiencing an exacerbation, and using a multiple imputation method for missing data, showed results similar to those of the primary analysis of asthma exacerbations. Post hoc analyses examining the impact of misclassification of patients' prior oral corticosteroid use showed findings similar to those of the primary results.[20,23]

When specific subtypes of exacerbations were examined, exacerbations requiring systemic or oral corticosteroids showed results similar to those of the analysis of all exacerbations (adjusted rate ratio range 0.39 to 0.45), although these analyses were outside the statistical hierarchy (Table 11). Exacerbations requiring hospitalization or an emergency department visit were reported less frequently (4% to 9% of patients), and exploratory analyses showed an adjusted rate ratio of 0.66 and 0.69 for Studies 3082 and 3083, respectively, with CIs that included the null value (Table 11).

TABLE 11: ASTHMA EXACERBATIONS OVER 52 WEEKS

Outcome / Study / Treatment Group	N	Patients With ≥ 1 Events, n (%)	Events per Person, Mean (SD)	Adjusted Exacerbation Rate (95% CI)[a]	Adjusted Rate Ratio (95% CI)[a]	*P* Value
Asthma Exacerbations[b]						
Study 3082						
Placebo	244	132 (54)	1.3 ([redacted])	1.8 ([redacted])	0.50 (0.37 to 0.67)	< 0.0001
Reslizumab	245	92 (38)	0.7 ([redacted])	0.9 ([redacted])		
Study 3083						
Placebo	232	105 (45)	1.0 ([redacted])	2.1 ([redacted])	0.41 (0.28 to 0.59)	< 0.0001
Reslizumab	232	59 (25)	0.5 ([redacted])	0.9 ([redacted])		
Exacerbations Requiring Systemic Corticosteroids for ≥ 3 Days[b]						
Study 3082						
Placebo	244	[redacted]	1.1 ([redacted])	1.6 ([redacted])	0.45 (0.33 to 0.62)	< 0.0001[c]
Reslizumab	245	[redacted]	0.6 ([redacted])	0.7 ([redacted])		
Study 3083						
Placebo	232	[redacted]	0.8 ([redacted])	1.7 ([redacted])	0.39 (0.26 to 0.58)	< 0.0001[c]
Reslizumab	232	[redacted]	0.4 ([redacted])	0.6 ([redacted])		
Exacerbations Requiring Oral Corticosteroids for ≥ 3 Days[b]						
Study 3082						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reslizumab	[redacted]	[redacted]	[redacted]	[redacted]		
Study 3083						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reslizumab	[redacted]	[redacted]	[redacted]	[redacted]		
Exacerbations Requiring Hospitalization or ER Visit[b]						
Study 3082						

Outcome / Study / Treatment Group	N	Patients With ≥ 1 Events, n (%)	Events per Person, Mean (SD)	Adjusted Exacerbation Rate (95% CI)[a]	Adjusted Rate Ratio (95% CI)[a]	*P* Value
Placebo	244	[redacted]	0.17 ([redacted])	0.2 ([redacted])	0.66 (0.32 to 1.36)	0.26[c]
Reslizumab	245	[redacted]	0.10 ([redacted])	0.1 ([redacted])		
Study 3083						
Placebo	232	[redacted]	0.06 ([redacted])	0.05 ([redacted])	0.69 (0.29 to 1.65)	0.40[c]
Reslizumab	232	[redacted]	0.04 ([redacted])	0.03 ([redacted])		
Exacerbations Requiring Hospitalization[b]						
Study 3082						
Placebo	[redacted]	[redacted]	[redacted]	NR	NR	NR
Reslizumab	[redacted]	[redacted]	[redacted]	NR		
Study 3083						
Placebo	[redacted]	[redacted]	[redacted]	NR	NR	NR
Reslizumab	[redacted]	[redacted]	[redacted]	NR		
Exacerbations Requiring ER Visit[b]						
Study 3082						
Placebo	[redacted]	[redacted]	[redacted]	NR	NR	NR
Reslizumab	[redacted]	[redacted]	[redacted]	NR		
Study 3083						
Placebo	[redacted]	[redacted]	[redacted]	NR	NR	NR
Reslizumab	[redacted]	[redacted]	[redacted]	NR		

CI = confidence interval; ER = emergency room; NR = not reported; SD = standard deviation.
[a] Events per person per year, estimated using a negative binomial regression model adjusted for baseline oral corticosteroid use and region, and with the logarithm of follow-up time excluding summed duration of exacerbation events as the offset.
[b] Adjudicated exacerbations from the first dose of study drug to 2 weeks after the end of the treatment (52 weeks) or the early withdrawal visit.
[c] Outside the statistical hierarchy.
Source: Clinical Study Report.[6,7]

Post hoc subgroup analyses were conducted for asthma exacerbations using pooled data from Studies 3082 and 3083 (Appendix 5, Table 20). The exacerbation rate ratios were generally similar for subgroups that did and did not use oral corticosteroids (0.32 and 0.50), LABAs (0.45 and 0.51), or leukotriene receptor antagonists (0.31 and 0.58) at baseline. In these subgroups, the rate of exacerbations was lower in the reslizumab group than in the placebo group, and the 95% CIs did not include the null value. *P* values for interaction terms were not reported.

The analysis of time to first asthma exacerbation was statistically significant, favouring reslizumab versus placebo, in both pivotal trials (Table 12). Kaplan–Meier graphs for the time to first exacerbation event are presented in APPENDIX 4, Figure 2 and Figure 3. In Study 3082, the median time to first exacerbation was not estimable for the reslizumab group and was 34.9 weeks (95% CI, 23.3 weeks to not estimable) for placebo. The median time to first exacerbation could not be estimated for either group in Study 3083.

TABLE 12: TIME TO FIRST ASTHMA EXACERBATION

Time to First Exacerbation[a]	Adjusted Hazard Ratio (95% CI) Reslizumab Versus Placebo[b]	*P* Value[c]
Study 3082	0.58 (0.44 to 0.75)	< 0.0001
Study 3083	0.49 (0.35 to 0.67)	< 0.0001

CI = confidence interval.
[a] Adjudicated exacerbations from the first dose of study drug to 2 weeks after the end of the treatment (52 weeks) or the early withdrawal visit.
[b] Adjusted for baseline use of oral corticosteroids (yes/no) and region (US or other).
[c] *P* value based on Cox proportional hazard model; log-rank test *P* value not reported.
Source: Clinical Study Report.[6,7]

3.6.2 Quality of Life

Baseline AQLQ scores were 4.2 in the placebo groups and 4.3 to 4.4 in the reslizumab groups of Studies 3082 and 3083 (Table 13). The mean scores increased by 0.7 to 1.0 points by 16 weeks, suggesting improvement in all treatment groups. The differences between reslizumab and placebo were statistically significant; however, the adjusted mean difference (MD) of 0.2 points, observed in both pivotal trials, did not exceed the MCID of 0.5 points. Exploratory analyses of AQLQ scores over 52 weeks showed an adjusted MD of 0.2 to 0.3 points for reslizumab versus placebo.

Exploratory responder analyses were conducted, comparing the proportion of patients with a change in AQLQ scores that exceeded the MCID (Table 14). Numerically more patients in the reslizumab groups (66% to 75%) reported a 0.5-point increase in AQLQ score at 16 weeks and 52 weeks, compared with patients in the placebo groups (55% to 65%).

3.6.3 Asthma Symptoms

In Studies 3082 and 3083, the mean baseline ACQ-7 scores ranged from 2.6 to 2.8 across treatment groups (Table 13). At week 16, the mean scores had decreased by 0.7 points in the placebo groups and 0.9 points in the reslizumab groups. For both pivotal trials, the differences between treatments were statistically significant (adjusted MD 0.3 and 0.2), but did not exceed the MCID of 0.5 points. Similar treatment effects were reported over 52 weeks (adjusted MD 0.3 and 0.2), which was an exploratory analysis. Numerically more patients in the reslizumab groups reported a 0.5-point increase in ACQ-7 scores at 16 weeks (69% to 70%) and 52 weeks (77% to 81%), compared with those in the placebo groups (58% to 65%) (Table 14).

At baseline in Studies 3082 and 3083, the mean ASUI scores ranged from 0.61 to 0.66, and had increased by 0.08 to 0.17 points at week 16 (Table 13). At week 16, the differences between groups were statistically significant favouring reslizumab (adjusted MD 0.06 and 0.04); however, in neither trial did the differences exceed the MCID of 0.09. At 52 weeks, the same treatment effects were reported; however, these analyses were outside the statistical hierarchy.

TABLE 13: ASTHMA SYMPTOMS AND QUALITY OF LIFE OUTCOMES

Time Point	Baseline		Week 16			Week 52		
Outcomes / Study / Treatment Group	**N**	**Baseline Mean (SD)**	**N**	**LS Mean Change From Baseline (SE)[a]**	**Adjusted Mean Difference Versus Placebo (95% CI), *P* Value [A]**	**N**	**LS Mean Change From Baseline (SE)[a]**	**Adjusted Mean Difference Versus Placebo (95% CI), *P* Value [A]**
AQLQ Score[b]								
Study 3082								
Placebo	242	4.16 (1.09)	229	0.70 ( )	0.24 (0.05 to 0.43)	231	0.79 ( )	0.30 (0.14 to 0.47)
Reslizumab	243	4.30 (1.12)	228	0.93 ( )	*P* = 0.014	233	1.09 ( )	*P* = 0.0004[c]
Study 3083								
Placebo	231	4.22 (1.08)	216	0.78 ( )	0.21 (0.03 to 0.39)	221	0.89 ( )	0.23 (0.07 to 0.40)
Reslizumab	229	4.35 (1.02)	213	0.99 ( )	*P* = 0.026	216	1.12 ( )	*P* = 0.005[c]
ACQ-7 Score[d]								
Study 3082								
Placebo	244	2.76 (0.88)	241	–0.68 ( )	–0.27 (–0.40 to	241	–0.76 ( )	–0.26 (–0.39 to –0.12)
Reslizumab	245	2.66 (0.85)	242	–0.94 ( )	−0.13) *P* = 0.0001	242	–1.02 ( )	*P* = 0.0002[c]
Study 3083								
Placebo	232	2.61 (0.79)	228	–0.66 ( )	–0.20 (–0.33 to –	228	–0.80 ( )	–0.24 (–0.37 to –0.11)
Reslizumab	232	2.57 (0.89)	230	–0.86 ( )	0.07) *P* = 0.003	230	–1.04 ( )	*P* = 0.0003[c]
ASUI Score[d]								
Study 3082								
Placebo	241	0.61 (0.20)	238	0.11 ( )	0.06 (0.03 to 0.08)	238	0.13 ( )	0.06 (0.04 to 0.08)
Reslizumab	241	0.63 (0.19)	238	0.17 ( )	*P* < 0.0001	238	0.19 ( )	*P* < 0.0001[c]
Study 3083								
Placebo	229	0.65 (0.19)	224	0.08 ( )	0.04 (0.01 to 0.06)	224	0.11 ( )	0.04 (0.01 to 0.06)
Reslizumab	228	0.66 (0.20)	227	0.11 ( )	*P* = 0.004	227	0.15 ( )	*P* = 0.001[c]

ACQ-7 = Asthma Control Questionnaire 7; AQLQ = Asthma Quality of Life Questionnaire; ASUI = Asthma Symptom Utility Index; CI = confidence interval; LS = least squares; SD = standard deviation; SE = standard error.

[a] Mixed-effects model for repeated measures (MMRM) including treatment, visit, treatment by visit interaction, region, oral corticosteroid use at baseline, and baseline value.

[b] Analyzed as change from baseline to week 16, and change from baseline over 52 weeks.

[c] Exploratory outcome; outside the statistical testing hierarchy.

[d] Analyzed as change from baseline over 16 weeks, and over 52 weeks.

Source: Clinical Study Report.[6,7]

TABLE 14: RESPONDER ANALYSES

Outcome/ Study / Treatment Group	N	Week 16		Week 52	
		n/N (%)	*P* Value	n/N (%)	*P* Value
Patients with 0.5-point increase in AQLQ score[a]					
Study 3082					
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reslizumab	[redacted]	[redacted]		[redacted]	
Study 3083					
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reslizumab	[redacted]	[redacted]		[redacted]	
Patients with 0.5-point reduction in ACQ-7 score[a]					
Study 3082					
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reslizumab	[redacted]	[redacted]		[redacted]	
Study 3083					
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reslizumab	[redacted]	[redacted]		[redacted]	

ACQ-7 = Asthma Control Questionnaire 7; AQLQ = Asthma Quality of Life Questionnaire.
[a] Change from baseline to week 16 or to week 52.
[b] Exploratory outcome; outside the statistical hierarchy.
Source: Clinical Study Report.[6,7]

3.6.4 Pulmonary Function

Studies 3082 and 3083 analyzed FEV_1 as the change from baseline to week 16 (Table 15), as well as the change from baseline over 16 weeks (Table 16). These analyses were part of the statistical testing hierarchy. The change from baseline in FEV_1 over 52 weeks was also reported as an exploratory outcome (Table 16). At baseline, the mean FEV_1 was 1.93 L to 2.00 L in the placebo groups and 1.89 L to 2.13 L in the reslizumab groups. At 16 weeks, FEV_1 increased 0.12 L to 0.14 L in the placebo groups, and 0.21 L to 0.22 L in the reslizumab groups (Table 15). The differences between reslizumab and placebo were statistically significant (adjusted MD 0.07 to 0.10); however, the differences were below the minimal patient-perceivable improvement values reported in the literature (0.23 L). Similar treatment effects were reported for the change from baseline in FEV_1 over 16 weeks (adjusted MD 0.09 to 0.14 L), or over 52 weeks (adjusted MD 0.09 to 0.13) (Table 16).

The change from baseline to week 16 in FEV_1 was the primary outcome in Study 3081. FEV_1 values increased 0.14 L from a baseline of 2.22 L in the placebo group and 0.30 L from a baseline of 2.17 L in the reslizumab 3 mg/kg group, for an adjusted MD of 0.17 L; 95% CI, 0.04 to 0.29, $P = 0.012$ (Table 15). Similar results were reported for the analysis of change from baseline over 16 weeks (Table 16).

In Study 3084, the primary efficacy outcome failed to show a statistically significant interaction between the baseline eosinophil count and the change from baseline in FEV_1 at week 16 (slope difference 0.30 standard error 0.26, $P = 0.24$). Sensitivity analyses that did not exclude any data from patients with confounding medications in past seven days showed similar results to the primary analysis (FAS population). However, sensitivity analyses that used multiple imputation methods for missing data showed different results (slope difference 0.75, standard error 0.28, $P = 0.0086$), which suggests an association between baseline eosinophils and reslizumab treatment effect.

In Study 3084, the change from baseline in FEV_1 to week 16 cannot be interpreted inferentially because of the failure of the primary outcome. In the overall population, no clinically important differences were reported for reslizumab versus placebo (adjusted MD 0.07 L; 95% CI, –0.03 to 0.17). In the subgroup of patients with a baseline eosinophil level ≥ 400 cells/µL (N = 96) an adjusted MD of 0.13 L was observed, compared with an adjusted MD of 0.03 L for the subgroup with eosinophil counts < 400 cells/µL (N = 392, *P* value for interaction term was not reported) (Table 15).

TABLE 15: FEV_1 — CHANGE FROM BASELINE TO WEEK 16

Time Point	Baseline		Week 16		
Outcomes / Study / Treatment Group	**N**	**Baseline Mean (SD)**	**N**	**LS Mean Change From Baseline (SE)**	**Adjusted Mean Difference Versus Placebo (95% CI), *P* Value**
FEV_1 (L) Change to Week 16					
Study 3082 [a]					
Placebo	244	1.93 (0.79)	228	0.14 (0.03)	0.07 (0.001 to 0.14)
Reslizumab	245	1.89 (0.73)	232	0.21 (0.03)	*P* = 0.048
Study 3083 [a]					
Placebo	232	2.00 (0.67)	214	0.12 (0.04)	0.10 (0.02 to 0.18)
Reslizumab	232	2.13 (0.78)	214	0.22 (0.04)	*P* = 0.011
Study 3081 [a]					
Placebo	105	2.22 (0.81)	84	0.14 (0.06)	0.17 (0.04 to 0.29)
Reslizumab	103	2.17 (0.78)	91	0.30 (0.06)	*P* = 0.012
Study 3084 [b]					
Overall population					
Placebo	97	2.17 (0.63)	83	0.19 (0.04)	0.07 (–0.03 to 0.17)
Reslizumab	394	2.10 (0.69)	344	0.26 (0.02)	*P* = 0.17[c]
Subgroup – Eosinophil Count ≥ 0.4 × 10^9/L					
Placebo	19	2.15 (0.61)	13	0.002 (0.12)	0.13 (0.008 to 0.53)
Reslizumab	77	2.22 (0.81)	69	0.27 (0.06)	*P* = 0.04[c]
Subgroup – Eosinophil Count < 0.4 × 10^9/L					
Placebo	76	2.18 ([redacted])	68	0.22 ([redacted])	0.03 (–0.07 to 0.14)
Reslizumab	316	2.07 ([redacted])	275	0.25 ([redacted])	*P* = 0.54[c]

CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; LS = least squares; SD = standard deviation; SE = standard error.

[a] Mixed-effects model for repeated measures (MMRM) including treatment, visit, treatment by visit interaction, stratification variables, height, sex, baseline FEV_1, and patient (random effect) in the ITT population (Study 3082, 3083) or FAS population (3081).

[b] Inferential statistics derived from a linear regression model with treatment, blood eosinophil count at baseline, and interaction of treatment and eosinophil count as fixed effects for the FAS population.

[c] Exploratory outcome; outside the statistical testing hierarchy.

Source: Clinical Study Report.[5-8]

TABLE 16: FEV_1 — CHANGE FROM BASELINE OVER 16 OR 52 WEEKS

Time Point	Baseline		Week 16			Week 52		
Outcomes / Study / Treatment Group	**N**	**Baseline Mean (SD)**	**N**	**LS Mean Change From Baseline (SE)**	**Adjusted Mean Difference Versus Placebo (95% CI), *P* Value**	**N**	**LS Mean Change From Baseline (SE)**	**Adjusted Mean Difference Versus Placebo (95% CI), *P* Value**
FEV_1 (L) Change Over Time								
Study 3082[a]								
Placebo	244	1.93 (0.79)	241	0.11 ( )	0.14 (0.08 to 0.20)	241	0.11 ( )	0.13 (0.06 to 0.19)
Reslizumab	245	1.89 (0.73)	243	0.25 ( )	*P* < 0.001	243	0.24 ( )	*P* < 0.0001[b]
Study 3083[a]								
Placebo	232	2.00 (0.67)	227	0.09 ( )	0.09 (0.03 to 0.16)	227	0.11 ( )	0.09 (0.03 to 0.15)
Reslizumab	232	2.13 (0.78)	230	0.19 ( )	*P* = 0.004	230	0.20 ( )	*P* = 0.006[b]
Study 3081[a]								
Placebo	105	2.22 ( )	103	0.13 (0.05)	0.16 (0.06 to 0.26)		NA	NA
Reslizumab	103	2.17 ( )	102	0.29 (0.05)	*P* = 0.0018[b]			
Study 3084[c]								
Placebo	97	2.17 ( )	96	0.18 (0.04)	0.08 (–0.006 to 0.16)		NA	NA
Reslizumab	394	2.10 ( )	390	0.25 (0.02)	*P* = 0.070[b]			

CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; LS = least squares; NA = not available; SD = standard deviation; SE = standard error.

[a] Analyzed using mixed-effects model for repeated measures (MMRM) including treatment, visit, treatment by visit interaction, stratification variables, height, sex, baseline FEV_1 and patient (random variable), in the ITT population (Study 3082, 3083) or FAS population (Study 3081).

[b] Exploratory outcome; outside the statistical testing hierarchy.

[c] Inferential statistics derived from a linear regression model with treatment, blood eosinophil count at baseline, and interaction of treatment and eosinophil count, FAS population.

Source: Clinical Study Report.[5-8]

3.6.5 Short-Acting Beta-Agonist Use

In the pivotal trials, the mean baseline SABA dose was 2.7 puffs/day in the placebo groups, and 2.4 to 2.9 puffs/day in the reslizumab groups (Table 17). At week 16, usage had declined on average by 0.4 to 0.6 puffs/day, with no statistically significant differences between groups (adjusted MD –0.06 to –0.28 puffs/day). Similar results were reported for the change from baseline in SABA use over 52 weeks.

3.6.6 Blood Eosinophil Count

In Studies 3082 and 3083, the change from baseline in blood eosinophil counts could not be interpreted inferentially because of the failure of a prior outcome (SABA use) in the statistical hierarchy. The mean baseline eosinophil counts ranged from 0.62×10^9 cells/L to 0.69×10^9 cells/L in the placebo groups, and from 0.61×10^9 cells/L to 0.70×10^9 cells/L in the reslizumab groups (Table 17). At week 16, the mean eosinophil counts decreased 0.08×10^9 cells/L to 0.12×10^9 cells/L, and 0.56×10^9 cells/L to 0.58×10^9 cells/L in the placebo and reslizumab groups respectively, for an adjusted MD of 0.47×10^9 cells/L to 0.48×10^9 cells/L favouring reslizumab. Similar results were reported for the change from baseline over 52 weeks.

3.7 Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). See 0 for detailed harms data.

3.7.1 Adverse Events

The majority of patients reported one or more adverse events during the trials (52-week trials: 76% to 87%; 16-week trials: 55% to 74%) (Table 18). Asthma, nasopharyngitis, upper respiratory tract infections, and headache were the most commonly reported adverse events. Asthma was reported more frequently in the placebo (19% to 52%) than the reslizumab groups (13% to 40%) in all studies.

3.7.2 Serious Adverse Events

In the pivotal trials, serious adverse events were reported more frequently in the placebo group (10% to 14%) than the reslizumab group (8% to 10%). In the supporting trials, 1% to 4% of placebo patients and 4% of reslizumab patients reported a serious adverse event (Table 18).

3.7.3 Withdrawals Due to Adverse Events

Numerically more patients in the placebo groups (3% to 12%) stopped treatment because of adverse events than in the reslizumab groups (2% to 7%) (Table 18). Of note, any patients in Study 3084 who had an asthma event that required systemic corticosteroids were withdrawn from the trial.

3.7.4 Mortality

One patient died of a drug overdose in the placebo group of Study 3082. No other deaths were reported in the four RCTs.

3.7.5 Notable Harms

In total, five reslizumab patients experienced an anaphylactic reaction, four of which were considered serious adverse events (Table 18, Table 19). Details regarding these events are summarized in APPENDIX 4, Table 21. Three of the events occurred during or shortly after a dose of reslizumab, and resolved without sequelae with standard treatments. Two of the events were attributed to exposure to other allergens (walnuts, allergy immunotherapy injection). No patients in a placebo group reported anaphylaxis. The frequency of other potential hypersensitivity events, such as immune system disorders

or skin and subcutaneous tissue disorders, was similar between groups (Table 19). Infusion-related adverse events were reported in [redacted] of placebo and [redacted] of reslizumab patients.

Infection or infestations were reported by [redacted] of patients in the placebo groups and [redacted] of patients in the reslizumab groups. In [redacted] of patients per treatment group, the infection was a serious adverse event (Table 19).

Neoplasms were infrequent and occurred in 0% to 2% of patients per treatment group (Table 19). The frequency of musculoskeletal adverse events ranged from 4% to 18% of patients, and elevated CPK levels, from 0% to 4%. An FDA review of the maximum CPK level per patient (placebo N = 730, reslizumab N = 1,131) reported that more patients in the reslizumab group had moderate, severe, or life-threatening increases in CPK (13%, 4%, and 0.8%, respectively), compared with those in the placebo group (10%, 3%, and 0.4%, respectively).[20] The FDA reported that none of these events progressed to rhabdomyolysis with acute renal failure; however, given the timing of the CPK testing (i.e., before study drug dose), the prevalence of CPK elevations observed in the RCTs is likely an underestimate.[20]

Asthma exacerbations, reported as an adverse event, occurred more frequently among patients who received placebo (20% to 55%) than among those who received reslizumab (13% to 41%) (Table 19).

TABLE 17: OTHER OUTCOMES

Time Point	Baseline		Week 16			Week 52		
Outcomes / Study / Treatment Group	**N**	**Baseline Mean (SD)**	**N**	**LS Mean Change From Baseline (SE)[a]**	**Adjusted Mean Difference Versus Placebo (95% CI), *P* Value[a]**	**N**	**LS Mean Change From Baseline (SE)[a]**	**Adjusted Mean Difference Versus Placebo (95% CI), *P* Value[a]**
SABA Use (Puffs per Day)[b,c]								
Study 3082								
Placebo	241	2.7 (3.2)	238	–0.4 ([redacted])	–0.28 (–0.60 to 0.05) *P* = 0.092	238	–0.4 ([redacted])	–0.15 (–0.47 to 0.16) *P* = 0.34[d]
Reslizumab	242	2.4 (2.8)	240	–0.6 ([redacted])		238	–0.6 ([redacted])	
Study 3083								
Placebo	201	2.7 (2.4)	188	–0.4 ([redacted])	–0.06 (–0.41 to 0.29) *P* = 0.73	194	–0.6 ([redacted])	–0.18 (–0.50 to 0.14) *P* = 0.27[d]
Reslizumab	204	2.9 (2.8)	180	–0.5 ([redacted])		192	–0.7 ([redacted])	
Blood Eosinophil Count (Cells × 10^9/L)[c]								
Study 3082								
Placebo	244	0.62 (0.59)	241	–0.12 ([redacted])	–0.47 (–0.51 to –0.42) NS[e]	241	–0.13 ([redacted])	–0.46 (–0.49 to –0.42) *P* = < 0.0001[d]
Reslizumab	245	0.70 (0.77)	243	–0.58 ([redacted])		243	–0.58 ([redacted])	
Study 3083								
Placebo	232	0.69 (0.68)	226	–0.08 ([redacted])	–0.48 (–0.52 to –0.44) NS[e]	226	–0.08 ([redacted])	–0.49 (–0.53 to –0.45) *P* < 0.0001[d]
Reslizumab	232	0.61 (0.41)	230	–0.56 ([redacted])		230	–0.57 ([redacted])	

CI = confidence interval; LS = least squares; NS = not statistically significant; SABA = short-acting beta-agonist; SD = standard deviation; SE = standard error.

[a] Mixed-effects model for repeated measures (MMRM) including treatment, visit, treatment by visit interaction, region, oral corticosteroid use at baseline, and baseline value.

[b] Based on patient-reported number of puffs of SABA used in the 3 days before each study visit.

[c] Analyzed as change from baseline over 16 weeks, and over 52 weeks.

[d] Exploratory outcome; outside the statistical testing hierarchy.

[e] Not statistically significant because of failure to achieve significance in a prior outcome in the statistical hierarchy.

Source: Clinical Study Report;.[6,7]

TABLE 18: HARMS

	Study 3082 52 Weeks		Study 3083 52 Weeks		Study 3081 16 Weeks		Study 3084 16 Weeks	
Adverse Events	**Placebo N = 243**	**Reslizumab N = 245**	**Placebo N = 232**	**Reslizumab N = 232**	**Placebo N = 105**	**Reslizumab N = 103**	**Placebo N = 97**	**Reslizumab N = 395**
Subjects with ≥ 1 adverse events, n (%)	206 (85)	197 (80)	201 (87)	177 (76)	66 (63)	61 (59)	72 (74)	218 (55)
Most common adverse events[a]								
Asthma	127 (52)	97 (40)	118 (51)	67 (29)	20 (19)	16 (16)	19 (20)	50 (13)
Nasopharyngitis	33 (14)	28 (11)	56 (24)	45 (19)	4 (4)	6 (6)	5 (5)	13 (3)
Upper respiratory tract infection	32 (13)	39 (16)	16 (7)	8 (3)	3 (3)	5 (5)	11 (11)	42 (11)
Headache	30 (12)	19 (8)	17 (7)	33 (14)	6 (6)	11 (11)	4 (4)	13 (3)
Sinusitis	29 (12)	21 (9)	10 (4)	9 (4)	3 (3)	4 (4)	7 (7)	22 (6)
Influenza	23 (9)	18 (7)	7 (3)	6 (3)	2 (2)	1 (1)	3 (3)	8 (2)
Bronchitis	24 (10)	13 (5)	14 (6)	2 (< 1)	5 (5)	2 (2)	6 (6)	14 (4)
Urinary tract infection	11 (5)	13 (5)	10 (4)	7 (3)	3 (3)	4 (4)	0	10 (3)
Back pain	13 (5)	13 (5)	8 (3)	12 (5)	1 (1)	0	3 (3)	6 (2)
SAEs								
Patients with ≥ 1 SAE, n (%)	34 (14)	24 (10)	23 (10)	18 (8)	1 (1)	4 (4)	4 (4)	16 (4)
Anaphylactic reaction	0	0	0	2 (0.9)	0	0	0	2 (0.5)
WDAEs								
WDAEs, n (%)	8 (3)	4 (2)	9 (4)	8 (3)	10 (10)	6 (6)	12 (12)	29 (7)
Asthma	1 (0.4)	0	3 (1)	2 (1)	9 (9)	4 (4)	8 (8)	21 (5)
Anaphylaxis	0	0	0	2 (1)	0	0	0	1 (0.2)
Deaths								
Number of deaths, n (%)	1 (0.4)	0	0	0	0	0	0	0
Cause of death	Drug overdose							

SAE = serious adverse event; WDAE = withdrawal due to adverse events.
[a] Frequency ≥ 5% in a pivotal trial.
Source: Clinical Study Report.[5-8]

TABLE 19: NOTABLE HARMS

	Study 3082 52 Weeks		Study 3083 52 Weeks		Study 3081 16 Weeks		Study 3084 16 Weeks	
Notable harms	**Placebo N = 243**	**Reslizumab N = 245**	**Placebo N = 232**	**Reslizumab N = 232**	**Placebo N = 105**	**Reslizumab N = 103**	**Placebo N = 97**	**Reslizumab N = 395**
Potential hypersensitivity adverse events								
Immune system disorders (SOC)								
Anaphylaxis								
Drug hypersensitivity								
Other hypersensitivity events								
Skin and subcutaneous tissue disorders (SOC)								
Infusion-related adverse event								
General disorders and administration site conditions (SOC)								
Infection and infestation (SOC)								
SAE								
Neoplasms (SOC)								
SAE								
Myopathy								
Musculoskeletal and connective tissue disorders (SOC)								
Elevated CPK levels								
Myalgia								
Asthma exacerbation								

CPK = creatine phosphokinase; SAE = serious adverse event; SOC = system organ class.
Source: Clinical Study Report.[5-8]

4. DISCUSSION

4.1 Summary of Available Evidence

A total of four double-blind RCTs met the inclusion criteria: two identical pivotal trials (Studies 3082 and 3083) and two supporting trials (Studies 3081 and 3084). All trials enrolled patients with inadequately controlled asthma despite therapy with ICS, with or without another controller medication. Three of the trials enrolled patients with elevated eosinophil levels. The pivotal trials assessed the efficacy of reslizumab versus placebo on the frequency of asthma exacerbations over a 12-month treatment period. The supporting trials evaluated the efficacy of reslizumab versus placebo in terms of changes in FEV_1 (Study 3081) or change in FEV_1 relative to baseline eosinophil levels (Study 3084) over 16 weeks.

For reslizumab, evidence of safety and efficacy beyond one year is unknown, as is the impact of treatment on outcomes that patients report as important; namely, missed school or work days, or corticosteroid-sparing effects. No direct evidence is available comparing the efficacy and safety of reslizumab to those of other drugs for eosinophilic or allergic asthma.

4.2 Interpretation of Results

4.2.1 Efficacy

In the 52-week pivotal trials, the patients who received reslizumab were less likely to report a clinically important asthma exacerbation (requiring treatment with systemic corticosteroids for three or more days, hospitalization, or emergency department or physician's visit for treatment) than those who received placebo (Study 3082: 38% versus 54%; Study 3083: 25% versus 45%). The differences between treatments in the frequency of adjudicated exacerbation events were statistically significant, with an adjusted rate ratio of 0.50 (95% CI, 0.37 to 0.67) in Study 3082, and 0.41 (95% CI, 0.28 to 0.59) in Study 3083, for reslizumab versus placebo. According to the clinical expert consulted for this review, these differences were clinically relevant. Similar rate ratios were observed for the reduction in exacerbations requiring systemic corticosteroids or oral corticosteroids. These outcomes, however, were outside the statistical hierarchy, and the studies were not designed to test for treatment effects on asthma exacerbations of differing severity. Reslizumab statistically significantly delayed the first asthma exacerbation, compared with placebo, with adjusted hazard ratios of 0.58 (Study 3082) and 0.49 (Study 3083).

In contrast to these findings, the clinical importance was unclear for the differences observed in quality of life, asthma symptoms, and pulmonary function; although the analyses of change from baseline to or over 16 weeks, all achieved statistical significance. The between-group differences in AQLQ, ACQ-7, ASUI, and FEV_1 did not exceed the MCIDs reported in the literature. Of note, the response rate for changes in quality of life and symptom scores in the placebo groups was relatively high, with 55% to 65% of placebo patients reporting a 16-week change in the AQLQ or ACQ-7 score that was greater than the MCID. Patient adherence to background therapies may be better in a clinical trial setting than in the real world, which may explain, in part, the high placebo response observed.

Modest between-treatment differences in the change from baseline in FEV_1 were reported in the supporting trials (adjusted MD [redacted]) and in the pivotal trials (adjusted MD 0.07 L to 0.10 L) at 16 weeks for reslizumab versus placebo. The magnitude of the differences in FEV_1 may not be unexpected, given the patient population enrolled. The clinical expert consulted for this review stated that it may be difficult to achieve substantial changes in FEV_1 with add-on therapy in patients with

protracted, uncontrolled asthma, who have significant airway remodelling and may thus now have irreversible changes in their lung function.

In the pivotal trials, no statistically significant difference was found between groups in the use of SABAs, and the change from baseline in blood eosinophil levels was not statistically significant as a result of failure of a prior outcome in the statistical hierarchy.

The four studies were run concurrently, so the results of the dose-finding trial (Study 3081) and the trial evaluating treatment response by eosinophil counts (Study 3084) could not be used to inform the design of the pivotal trials. Study 3084 failed to detect a statistically significant interaction between the change in FEV_1 and baseline blood eosinophil levels, which was the primary outcome. Although exploratory subgroup analyses showed a statistically significant treatment effect favouring reslizumab in patients with blood eosinophil levels ≥ 400 cells/µL, and no significant difference between groups in the subgroup with eosinophil levels < 400 cells/µL, the interaction *P* values were not reported.

None of the included studies collected data on the number of school or work days missed or evaluated corticosteroid-sparing effects, which are outcomes that were reported as important to patients.

There was no direct evidence comparing reslizumab with other drugs for severe eosinophilic or allergic asthma. However, a head-to-head trial may not have been feasible, considering the availability of key comparators (i.e., mepolizumab or omalizumab) at the time the reslizumab trials were initiated. While placebo-controlled trials may be required for regulatory approval, these studies have limitations for health technology assessment. The manufacturer provided an indirect treatment comparison in the form of a network meta-analysis (NMA) examining the efficacy and safety of reslizumab, mepolizumab, and omalizumab in patients with moderate to severe inadequately controlled asthma (APPENDIX 7). This NMA pooled data from 25 open-label and double-blind RCTs, and found no statistically significant differences between treatments on the frequency of asthma exacerbations, asthma symptoms, quality of life, or pulmonary function. The NMA had a number of sources of heterogeneity and other limitations that could affect the validity of the results. One limitation was the different enrolment criteria for the RCTs, which varied in terms of severity of asthma. In addition, not all patients with allergic asthma enrolled in omalizumab trials would meet the blood eosinophil thresholds to qualify for treatment with anti-interleukin-5 drugs. The trials used different definitions of asthma exacerbations, and follow-up time varied. Four of the omalizumab RCTs were open label, which could bias the reporting of subjective outcomes and adverse events. These limitations should be considered when interpreting the results of the NMA.

4.2.2 Harms

In general, the frequency of most adverse events was similar in the reslizumab and placebo groups in the four RCTs. In the 52-week pivotal trials, serious adverse events were reported more frequently in the placebo group (10% to 14%) than the reslizumab group (8% to 10%), and in the 16-week supporting trials, 1% to 4% of placebo patients and 4% of reslizumab patients reported a serious adverse event. Numerically more patients in the placebo groups (3% to 12%) stopped treatment because of adverse events than in the reslizumab groups (2% to 7%). Asthma, asthma exacerbations, and infections were reported more frequently among patients who received placebo than reslizumab.

Anaphylaxis was more common in patients treated with reslizumab (5 events) than in those receiving placebo (0 events). Three of the five events occurred during or shortly after a dose of reslizumab and

were deemed related to the treatment. No anaphylaxis events related to reslizumab were reported in the open-label extension study (APPENDIX 6). The frequency of other hypersensitivity events and infusion-related adverse events was generally similar between reslizumab and placebo. Although the pivotal trials showed no clear increased risk of musculoskeletal adverse events, the FDA noted that severe elevations of CPK levels were reported more frequently among those receiving reslizumab.[20] The clinical implications of these findings is unclear, as no cases progressed to rhabdomyolysis with acute renal failure.[20] The FDA noted that, given the timing of the CPK testing (i.e., before study drug dose), the prevalence of CPK elevations observed in the RCTs is likely an underestimate.[20]

No new safety signals were identified in the extension study (Study 3085), which included 1,052 patients from Studies 3081, 3082, and 3083. Study 3085 was stopped early after patients had been treated, on average, for one year (APPENDIX 6). Although the reasons for discontinuation were not clearly stated, the manufacturer reports that the trial objectives were sufficiently met and the decision to terminate did not result from new safety concerns.[30]

The available safety data are limited by the number of patients exposed and the relatively short duration of treatment (up to one year in controlled trials). Furthermore, the FDA identified limitations regarding the collection of safety data, which could affect the assessment of anaphylactic events and possible muscle-related toxicity.[20] Although the NMA supplied by the manufacturer suggested some differences among reslizumab, omalizumab, or mepolizumab in the frequency of adverse events, due to limitations of the RCTs, no conclusions can be drawn concerning the comparative safety of these treatments (APPENDIX 7).

4.3 Potential Place in Therapy

This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

The clinical expert consulted by CDR noted that, among those patients with moderate to severe eosinophilic asthma who remain symptomatic despite adherence to first- and second-line therapies, treatment options are limited. Therefore, there is an unmet need in this population.

ICSs suppress inflammation generally; long-acting bronchodilators and anti-muscarinic drugs are helpful to open airways; and leukotriene receptor antagonists are helpful in a minority of patients who are responders to the drug.[2,31] Despite these available treatments, there remains a small subset of patients with asthma, predominantly an eosinophilic inflammatory phenotype, who remain symptomatic, with exacerbations, hospitalizations, emergency department visits, and need for oral corticosteroids (either frequently for exacerbations, or chronically for long-term control), despite adhering to standards of care. In these patients who remain symptomatic despite moderate to high doses of combination ICS/LABA inhalers, with or without other add-on therapies such as tiotropium bromide or montelukast, the availability of new biologic therapies (that target the immune mediators of the disease) could be important.

Reslizumab has been shown (in the appropriately selected population) to reduce exacerbations by approximately 50%. It has also been shown to reduce exposure to oral corticosteroids (by reducing exacerbations that required systemic corticosteroids), which is a drug fraught with adverse effects and long-term health consequences when used frequently.

Reslizumab should not be considered a first-line therapy for allergic/eosinophilic asthma. Rather, it should be reserved for those with moderate to severe persistent asthma and a peripheral eosinophil count > 400 /µL who remain symptomatic despite ICS/LABA (or who are intolerant to the adverse effects of ICS/LABA) and have not responded to other add-on options such as montelukast or tiotropium bromide. However, given that montelukast has limited and typically restricted reimbursement and that tiotropium bromide is not listed on drug plan formularies for this indication, this may be an impractical additional consideration for patient selection. The clinical expert does not foresee barriers to identifying suitable patients, as access to a complete blood count with differential blood count is not an ultra-specialized test restricted to tertiary or quaternary care centres. The main limitation of reslizumab is that it requires IV administration and, given the potential risk of anaphylaxis as observed in clinical trials, should be restricted to use by practitioners and centres with expertise in the treatment of these types of adverse reactions.

5. CONCLUSIONS

Add-on therapy with reslizumab was associated with statistically and clinically important reductions in the frequency of asthma exacerbations over one year, compared with placebo, in patients with eosinophilic asthma that was uncontrolled by medium- to high-dose ICS and, for most patients, another controller medication. Treatment with reslizumab, however, did not demonstrate clinically important differences versus placebo in asthma-related symptoms, quality of life, or pulmonary function (as measured by the ACQ-7, ASUI, AQLQ, and FEV_1). No between-treatment differences were observed in the use of rescue SABA drugs in the two pivotal double-blind RCTs.

Serious anaphylactic adverse events were reported among patients exposed to reslizumab. Considering that RCTs are not designed to identify rare or infrequent adverse events, and that reslizumab is part of a new class of drugs with a unique mechanism of action, additional data are required to determine the long-term safety of reslizumab.

No direct evidence is available comparing reslizumab with other drugs for eosinophilic or allergic asthma. Indirect evidence suggests no substantial differences between reslizumab and mepolizumab 100 mg in terms of efficacy. No conclusions can be drawn concerning the relative efficacy of reslizumab versus omalizumab because the indirect treatment comparison was not limited to the "overlap population" — those patients with allergic asthma and elevated eosinophil levels who would be suitable for treatment with either drug. The efficacy and safety of reslizumab beyond one year of treatment is unknown.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input
Two patient groups submitted input: the Asthma Society of Canada (ASC)/National Asthma Patient Alliance (NAPA) and the British Columbia Lung Groups.

The ASC/NAPA is a national, charitable volunteer-supported organization whose aim is to enhance the quality of life and health of people living with asthma and associated allergies. The ASC provides health-education services and advocates on behalf of Canadians with asthma through its grassroots patient group (NAPA), and engages in research to improve asthma-prevention and -management strategies. The patient research that forms a significant part of this submission was supported by educational grants from Novartis Pharmaceuticals Canada Inc., Roche Canada, and Boston Scientific Ltd. Additional funding for the ASC was received from seven other pharmaceutical companies, including Teva. ASC has declared no conflicts of interest with regard to corporate members and joint working arrangements. Information from a medical briefing from Teva Canada was used to help prepare its submission.

The British Columbia Lung Groups/British Columbia Lung Association (BCLG) is a charitable organization. The BCLG's role is to improve respiratory health and overall quality of life through programs, education, research, training, treatment, advocacy, and prevention of lung disease, including asthma. The BCLG works together with the Canadian Lung Association and other partners to help the one in five Canadians who have breathing problems. From time to time, BCLG has received unrestricted educational grants from five pharmaceutical companies. BCLG has declared no conflict of interest in the preparation of its submission.

2. Condition-Related Information
Information provided by the ASC was based on a mixed-methods study involving 24 patient interviews and an online quantitative survey of 200 individuals with severe asthma conducted by ASC in 2014 (Severe Asthma: The Canadian Patient Journey). Additional details of disease definitions and treatment options have been drawn from online material published on the ASC's website, US prescribing information for reslizumab, guidelines, and review articles. The BCLG did not specify how patient input was gathered for this submission, but stated that the BCLG is involved in asthma research and has staff who consult with patients and caregivers who are dealing with asthma.

Eosinophilic asthma is a subtype of asthma characterized by the presence of eosinophils in the inflamed tissues; the eosinophils can be detected through examination of the sputum. The disease often presents in adulthood, in patients with few or no allergies.

While members of both patient groups identified a number of common symptoms and challenges experienced by persons living with asthma, including wheezing, shortness of breath, coughing, tightness in the chest, and fatigue, the ASC emphasized the impact of severe asthma on patients' daily lives. Severe asthma affected patients' day-to-day lives in the following aspects: 70% of survey respondents reported decreased physical activity, > 50% reported reduced performance at work or school, two-thirds experienced restricted social interactions and felt stigmatized, and nearly half of respondents reported increased emergency room visits in the 12 months preceding this study, with one in five individuals

requiring hospitalization. Activity restriction as a result of uncontrolled asthma symptoms was of particular concern, with ASC study participants stating:

"I'm just so tired that I can't do anything anymore. Severe asthma has changed everything."
"I can't even take my son hiking because of my health. My limitations affect other people and it makes me angry that I can't do the things other can and that I used to be able to do."

Both patient groups indicated that the burden of asthma may extend to caregivers. Caregivers may experience an emotional burden (e.g., stress, anxiety) and/or financial impact (e.g., time off work) as a result of having to care for a person with severe asthma. Sleep may be interrupted and other aspects of a caregiver's daily life may also be adversely affected.

3. Current Therapy-Related Information
Current treatment options for the management of asthma symptoms include a combination of long-term controller medications (e.g., long-acting bronchodilators, leukotriene receptor antagonists, inhaled corticosteroids, and oral corticosteroids) and/or fast-acting reliever medications for acute symptoms (e.g., short-acting bronchodilators). Newer treatment options include omalizumab for allergic asthma, and mepolizumab or reslizumab for eosinophilic asthma. Patients with severe eosinophilic asthma may require long-term oral corticosteroids to help control inflammation if other treatment options are inadequate.

The ASC noted that many patients with severe asthma did not appear to use their medications as directed and were not always well prepared to manage their symptoms. Cited barriers to optimal asthma control included a lack of efficacy, unpleasant adverse effects, patients' misperception that their asthma was well controlled, as well as financial constraints affecting access to medication. The ASC expressed particular concern regarding the use of oral corticosteroids in patients who do not achieve adequate asthma control with an inhaled corticosteroid drug. They report that systemic corticosteroids are associated with short-term and long-term adverse effects, both in terms of physical changes and patients' psychological and emotional well-being. BCLG also pointed out that current medications work for some patients, but not all. Both ASC and BCLG stated that there are unmet treatment needs for patients with severe asthma who are unable to adequately control their symptoms and exacerbations with currently available therapies. Additional therapies are needed that go beyond symptomatic relief and will improve overall lung function. Patients require new treatment options such as reslizumab, a medication for severe eosinophilic asthma, as the disease progresses.

4. Expectations About the Drug Being Reviewed
ASC collected information on reslizumab through a PubMed search of the published literature, the US prescribing information, and interviews with clinical trial participants. BCLG's information was based on the organization's participation in asthma research and provision of patient services and programs, as well as on several support group meetings for patients with asthma in British Columbia.

Two patients reported a positive experience with reslizumab as part of a clinical trial. Patients who had used reslizumab said,
"From experience, I expect, except for one day out of each month, that I will forget I have asthma."
"Asthma does take its toll, and it is more than just a physical burden to carry… I expect that burden to be lifted forever with [this treatment]."

While participants indicated some concern at having to have the medication administered by infusion at the doctor's office, there was a positive response to needing to receive only one dose monthly.

Patients with no experience with reslizumab treatment expected that using the drug would improve their asthma control, allowing them to function normally while completing household activities, walking, and enjoying life; to avoid visits to the emergency department or admission to hospital; to sleep without nighttime symptoms; to exercise without asthma symptoms; and to return to work. Reslizumab will provide another treatment option for those with severe eosinophilic asthma who have an inadequate response to current therapies.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	September 01, 2016
Alerts:	Weekly search updates until January 18, 2017
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical 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
adj	Requires words are adjacent to each other (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

Multi-database Strategy
(DCP 835 or DCP835 or sch 55700 or sch55700 or cinquil* or cinqaero* or cinqair* or reslizumab* or 35A26E427H).ti,ab,ot,rn,hw,nm,kf.
241473-69-8.rn,nm.
1 or 2
3 use pmez
*reslizumab/
(DCP 835 or DCP835 or sch 55700 or sch55700 or cinquil* or cinqaero* or cinqair* or reslizumab* or 35A26E427H).ti,ab,kw.
5 or 6
7 use oemezd
4 or 8

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	August 2016
Keywords:	Reslizumab (Cinqair), asthma
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters), were searched:

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

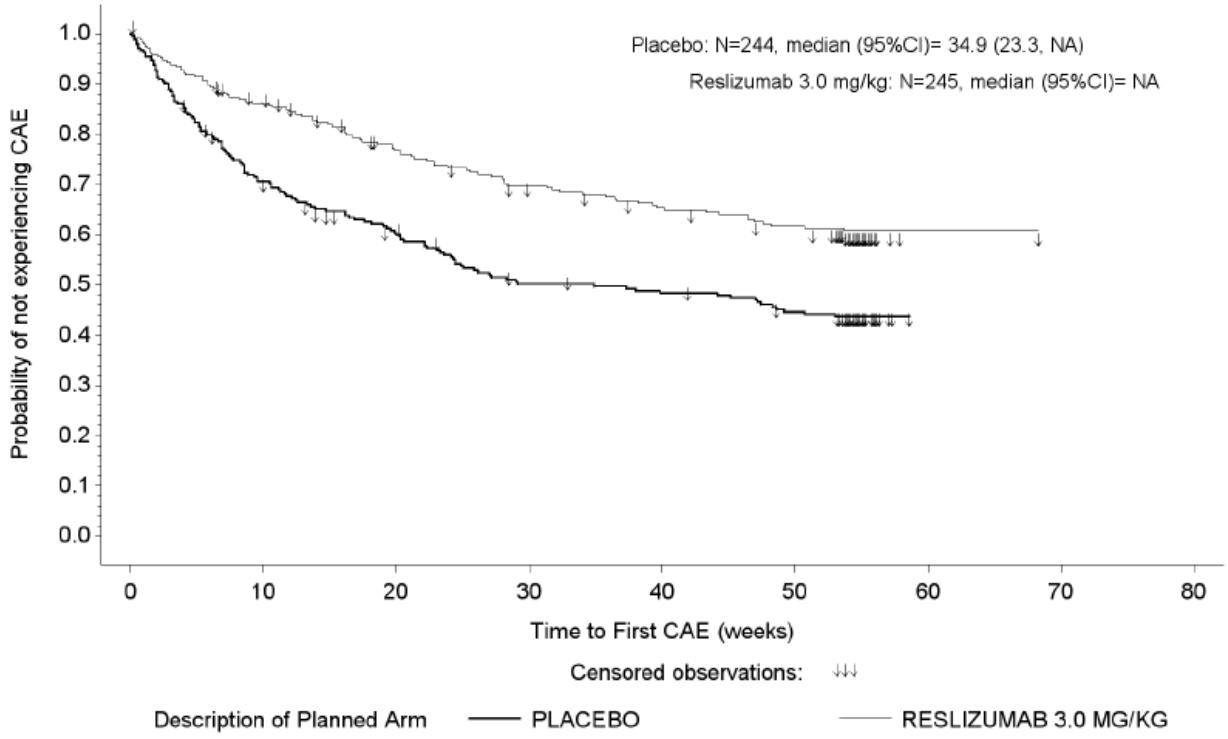
APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Murphy K, Jacobs J, Bjermer L, Shalit Y, Garin M. Long-term safety and efficacy of reslizumab in patients with inadequately controlled, moderate-to-severe asthma and elevated blood eosinophil counts: An open-label extension study [abstract]. Am J Respir Crit Care Med. 2015;191. (Presented at 20150515;-20150520. Conference Publication: (var.pagings). 191 (no pagination), 2015. Date of Publication: 2015.).	Not an RCT
Clinical Study Report: 3085. An open-label extension study to evaluate the long-term safety and efficacy of reslizumab (3.0 mg/kg) as treatment for patients with eosinophilic asthma who completed a prior Teva-sponsored study in eosinophilic asthma [CONFIDENTIAL internal manufacturer's report]. Frazer (PA): Teva Global Branded Pharmaceutical Products R&D, Inc.; 2016 Jun 4.	Not an RCT
Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, Young J, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. Am J Respir Crit Care Med. 2011 Nov 15;184(10):1125-32.	Phase II trial

RCT = randomized controlled trial.

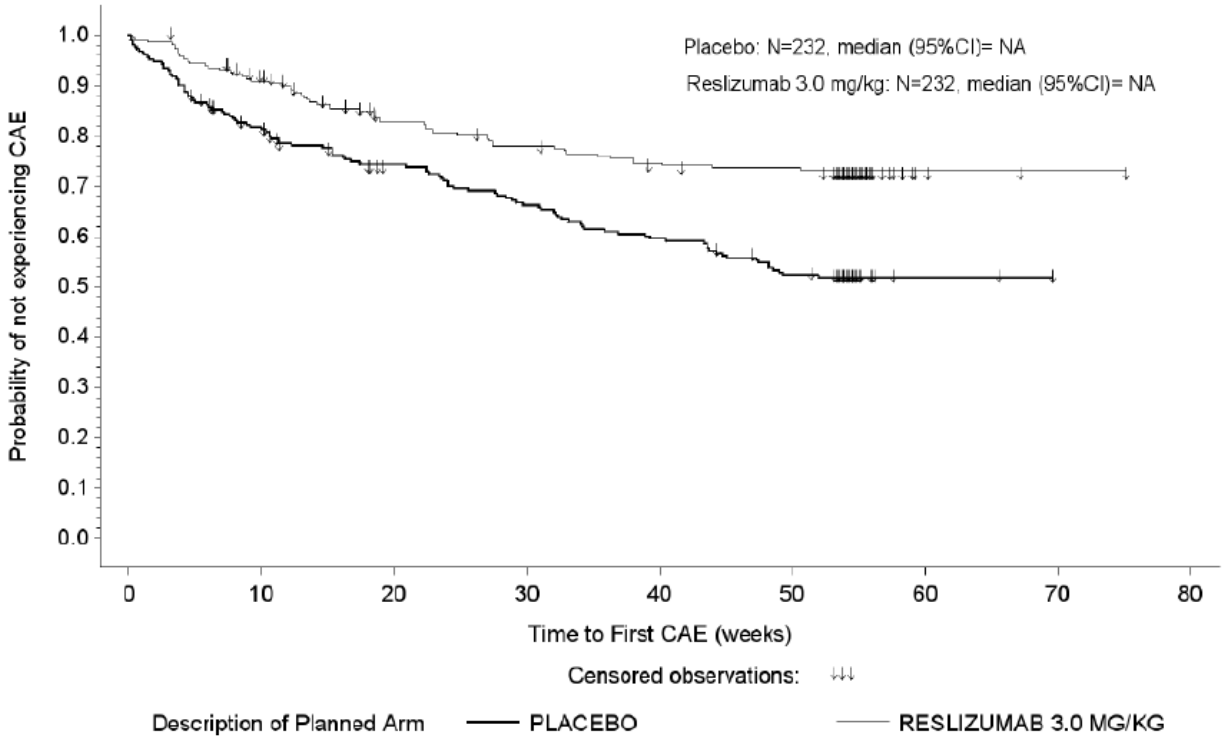
APPENDIX 4: DETAILED OUTCOME DATA

FIGURE 2: TIME TO FIRST EXACERBATION — STUDY 3082



CAE = clinical asthma exacerbation; CI = confidence interval; NA = not applicable.
Source: Clinical Study Report.[6]

FIGURE 3: TIME TO FIRST EXACERBATION — STUDY 3083



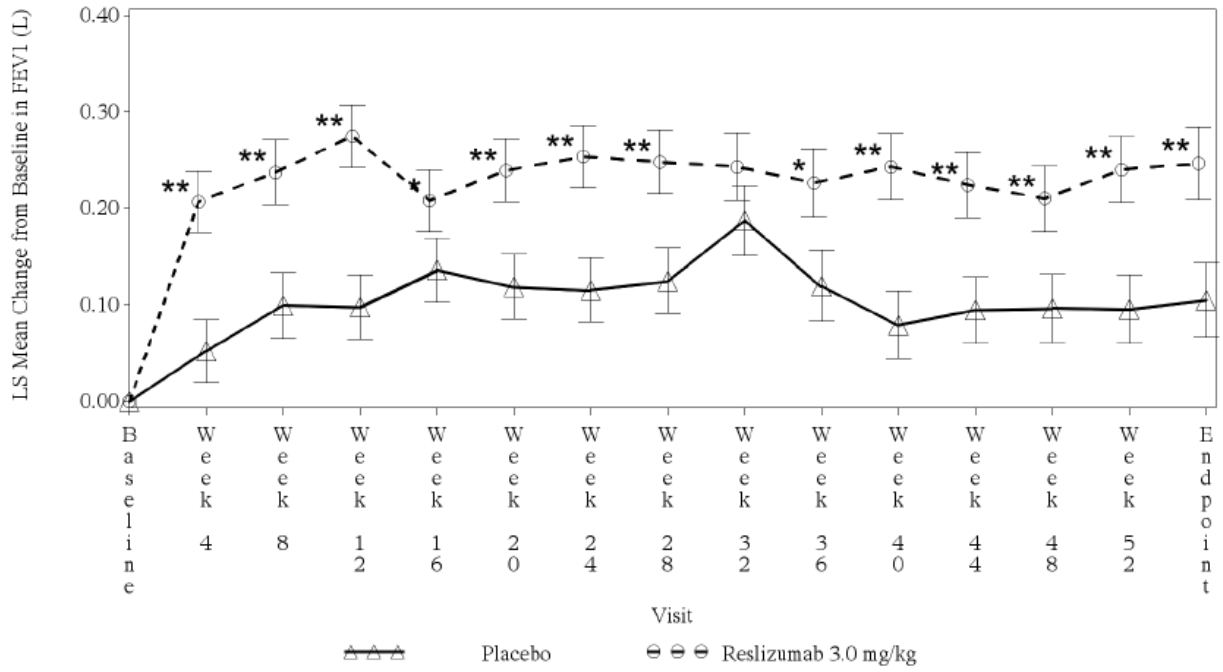
CAE = clinical asthma exacerbation; CI = confidence interval; NA = not applicable.
Source: Clinical Study Report.[7]

TABLE 20: POST HOC POOLED SUBGROUP DATA FROM STUDY 3082 AND 3083

Subgroup	Placebo N = 476		Reslizumab N = 477		Reslizumab Versus Placebo
	Number of Patients With ≥ 1 Exacerbation n/N (%)	Adjusted Exacerbation Event Rate (95% CI)[a]	Number of Patients With ≥ 1 Exacerbation, n/N (%)	Adjudicated Exacerbation Event Rate (95% CI)[a]	Exacerbation Rate Ratio (95% CI)
OCS use at baseline					
Yes	[redacted]	2.04 ([redacted])	[redacted]	0.65 ([redacted])	0.32 (0.18 to 0.55)
No	[redacted]	1.40 ([redacted])	[redacted]	0.69 ([redacted])	0.50 (0.39 to 0.64)
LABA use at baseline					
Yes	[redacted]	184 ([redacted])	[redacted]	0.83 ([redacted])	0.45 (0.35 to 0.58)
No	[redacted]	1.63 ([redacted])	[redacted]	0.84 ([redacted])	0.51 (0.29 to 0.89)
LTRA use at baseline					
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

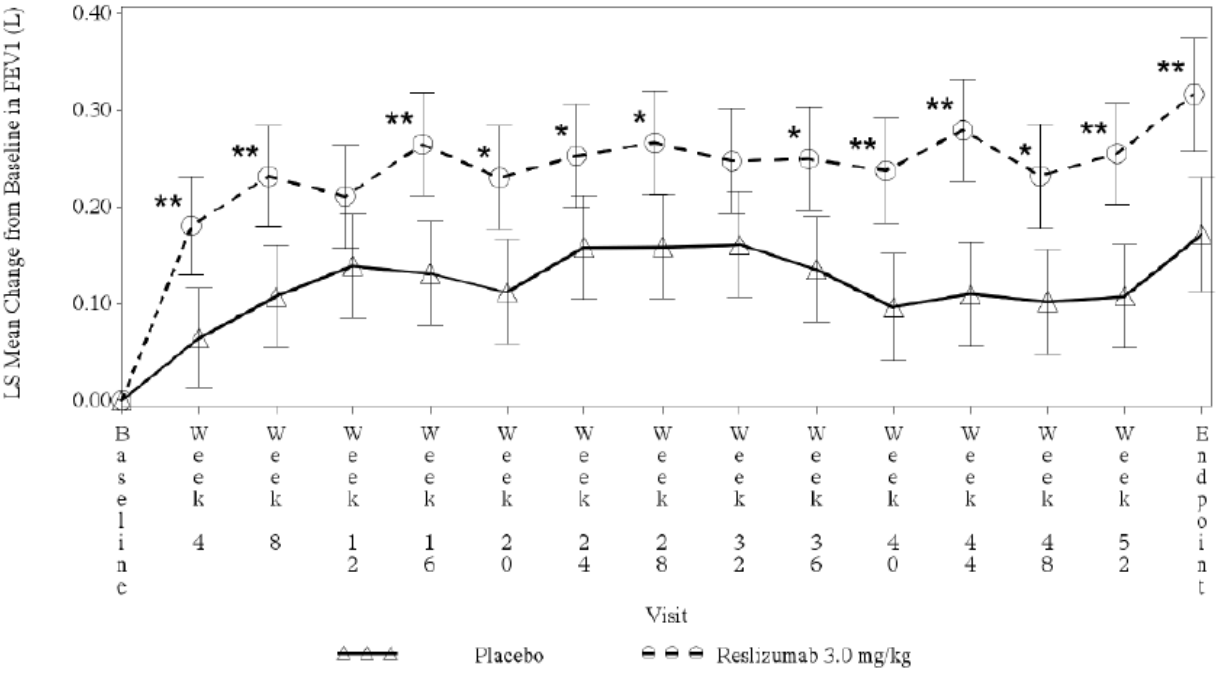
CI = confidence interval; LABA = long-acting beta-agonist; LTRA = leukotriene receptor antagonist; OCS = oral corticosteroid.
[a] Events per person per year.
Source: Health Canada's Reviewer's Report.[23]

FIGURE 4: CHANGE FROM BASELINE IN FEV_1 (L) — STUDY 3082



FEV_1 = forced expiratory volume in 1 second; LS = least squares.
Source: Clinical Study Report.[6]

FIGURE 5: CHANGE FROM BASELINE IN FEV_1 (L) — STUDY 3083



FEV_1 = forced expiratory volume in 1 second; LS = least squares.
Source: Clinical Study Report.[7]

TABLE 21: DESCRIPTION OF ANAPHYLACTIC ADVERSE EVENTS IN RESLIZUMAB-TREATED PATIENTS

Study	Timing	Description	Treatment and Outcome
3082	[redacted]	[redacted]	[redacted]
3083	[redacted]	[redacted]	[redacted]
3083	[redacted]	[redacted]	[redacted]
3084	[redacted]	[redacted]	[redacted]
3084	[redacted]	[redacted]	[redacted]

Source: Clinical Study Report,[6-8] FDA Medical Review.[20]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the validity and minimal clinically important difference (MCID) of the following outcome measures:

- Asthma Quality of Life Questionnaire (AQLQ)
- Forced expiratory volume in one second (FEV_1)
- Asthma Control Questionnaire 7 (ACQ-7)
- Asthma Symptom Utility Index (ASUI)

Findings

These outcome measures are briefly summarized in Table 22.

TABLE 22: VALIDITY AND MINIMAL CLINICALLY IMPORTANT DIFFERENCE OF OUTCOME MEASURES

Instrument	Type	Evidence of Validity	MCID (MID or Similar Parameter)	References
AQLQ	AQLQ is a patient-reported assessment of functional impairments experienced by patients with asthma. It includes 32 questions grouped into 4 domains: (1) symptoms, (2) activity limitations, (3) emotional function, and (4) environmental stimuli. Each question is scored on a 7-point Likert scale, which ranges from 7 (no impairment) to 1 (severe impairment). The overall score is calculated as the mean of all questions, and the 4 domain scores are the means of the scores for the questions in the respective domains.	Yes	0.5[a]	Juniper et al.[26] Wyrwich et al.[27] Wyrwich et al.[28]
FEV_1	FEV_1 is the volume of air that can be forcibly expired in 1 second after a full inspiration.	Yes	MPPI: 10.4% change from baseline, or 230 mL (range 170 mL to 280 mL)	Santanello et al.[24]
ACQ	ACQ is a patient-reported tool to assess asthma control in patients ≥ 6 years of age. It comprises the following 7 questions, of which the mean of the results is the overall score ranging from 0 for well-controlled asthma to 6 for extremely poorly controlled asthma: • Daytime symptoms • Nighttime awakening/symptoms • Activity limitation • Rescue treatment requirements (use of SABA)	Yes	0.5	Barnes et al. [32] Juniper et al. [33] Jia et al. [34] Juniper et al. [35]

Instrument	Type	Evidence of Validity	MCID (MID or Similar Parameter)	References
	• Lung function (FEV_1) • Shortness of breath • Wheezing			
ASUI	The ASUI is an 11-item instrument designed to assess the frequency and severity of asthma symptoms and side effects weighted by patient preferences. The summary ASUI score is on a continuous scale from 0 to 1, with lower scores indicating worse asthma symptoms. ASUI appears to provide validated outcomes for use in clinical trials of therapies for patients with asthma. The suggested MID for ASUI is 0.09.	Yes	0.09	Revicki et al.[36] Bime et al.[29]

ACQ-7 = Asthma Control Questionnaire 7; AQLQ = Asthma Quality of Life Questionnaire; ASUI = Asthma Symptoms Utility Index; FEV_1 = forced expiratory volume in 1 second; MCID = minimal clinically important difference; MID = minimal important difference; MPPI = minimal patient-perceivable improvement.

Asthma Quality of Life Questionnaire

AQLQ is a patient-reported, disease-specific, health-related quality-of-life measure that was developed to evaluate asthma in the clinical trial setting.[37] There are two versions of AQLQ, the original AQLQ and the standardized AQLQ (AQLQs). In the AQLQs, the five patient-specific activities in the original AQLQ were replaced by five generic activities.[38] The AQLQ includes 32 questions grouped into four domains: (1) symptoms, (2) activity limitations, (3) emotional function, and (4) environmental stimuli. Each question is scored on a seven-point scale, which ranges from 7 (no impairment) to 1 (severe impairment). The overall score is calculated as the mean of all questions, and the four domain scores are the means of the scores for the questions in the respective domains. Patients recall their relevant experiences during the previous two weeks.

Overall, the AQLQs and AQLQ are well correlated (r = 0.99).[38] With regard to construct validity, the AQLQs has also been observed to have cross-sectional and longitudinal correlations sufficiently similar to those of the original AQLQ.[38] In addition, both instruments are responsive to within-subject changes both in patients whose asthma was stable and whose asthma changed (responsiveness indices of 1.35 and 1.34 for AQLQ and AQLQs, respectively).[38] The MCID for the AQLQs has been determined to be a cut point of 0.5.[26-28]

Forced Expiratory Volume

FEV_1 is the maximal amount of air forcefully exhaled in one second. The measured volume can be converted to a percentage of predicted normal value, which is adjusted based on height, weight, and race. The percentage of predicted FEV_1 is one of the most commonly reported pulmonary function tests.[39] Health Canada recommends FEV_1 as a secondary clinical end point (but also considers it an acceptable primary end point),[40] and it is widely used in clinical trials to evaluate the effectiveness of asthma treatments.

Clinically, the percentage of predicted FEV_1 appears to be a valid marker for the degree of airway obstruction with asthma and other respiratory conditions, including chronic obstructive pulmonary disease. Together with measures of asthma symptoms and use of inhaled short-acting beta-agonists, FEV_1 is used to classify the severity of asthma.[41,42] However, the extent to which FEV_1 values are associated with quality of life is uncertain, as researchers have reported variable correlations among adults and children with asthma, ranging from no association to strong associations.[43-46] Conversely, FEV_1 values appear to correlate well with certain final clinical outcomes, such as the likelihood of hospitalization.[47] Furthermore, FEV_1 values demonstrated high within-session repeatability: in a study of 18,526 adult patients, of whom 11% gave a history of physician-diagnosed asthma, 90% were able to reproduce FEV_1 within 120 mL.[48]

There appears to be limited published evidence relating to an MCID for FEV_1 among adult patients with asthma. In one study of 281 adult patients (baseline mean FEV_1: 2.30 L/s [SD 0.66 L/s]), the authors calculated the minimal patient-perceivable improvement (MPPI) for FEV_1 by comparing the average baseline FEV_1 scores with patient global ratings of change in asthma. Across all patients, the MPPI for FEV_1 was 230 mL, or 10.38% change from baseline. Males and females showed similar MPPI values, but older patients had a lower MPPI (170 mL) than younger ones (280 mL) for FEV_1.[24]

Asthma Control Questionnaire 7

ACQ-7[32] was developed to evaluate asthma control in patients with asthma[32,49] and is one of the most commonly used instruments measuring asthma control.[32] The questionnaire comprises seven questions, the responses to which are scored on a seven-point scale. Patients answer questions regarding six aspects of the patient's previous week's experiences, including questions on activity limitation, nocturnal waking, shortness of breath, wheezing, symptoms on waking, and the use of short-acting beta-agonists.[49] In addition, the seventh item includes calculations performed by clinical staff with regard to pre-bronchodilator FEV_1 or peak expiratory flow (percentage of predicted).[32,49] The ACQ-7 score is defined as the mean of the seven questions (as all questions are equally weighted), with scores at 0 defined as well controlled and those at 6 defined as extremely poorly controlled.[32,33,49] The ACQ-7 is used extensively in clinical trials to measure clinically meaningful change in asthma control.[32] The ACQ also exists in abbreviated versions, with the ACQ-5 focusing only on the symptoms (exclusion of the FEV_1 and bronchodilator use), while the ACQ-6 includes everything except the FEV_1 aspect.[32,35]

The ACQ is a multidimensional and standardized tool[34] that has been observed to be both highly reliable (intraclass correlation coefficient of 0.90) and responsive to change in asthma control in adults with asthma.[33] In addition, evidence for longitudinal and cross-sectional construct validity has been provided by correlations between the ACQ and other asthma health-status measures.[33] In addition, a score of 1.5 on the ACQ is the most appropriate discriminator between "well-controlled" and "not well-controlled" asthma.[50] There is also evidence of the construct validity, test–retest reliability, and responsiveness of the ACQ in children with asthma aged six to 16 years old.[51]

The ACQ MCID has been well established and accepted as 0.5 points for within-person change.[32,34] However, Bateman et al. questioned its use as a measure between groups or between patients, further speculating that patient-reported outcomes should be presented as a responder rate comparison or a net treatment benefit analysis.[25]

Asthma Symptom Utility Index

ASUI was developed by Revicki et al.[36] in 1998 to assess the frequency and severity of asthma symptoms. The ASUI is an 11-item questionnaire self-administered by patients, with four questions on asthma symptoms (wheeze, shortness of breath, cough, and awakening at night) and one question about the adverse effects of asthma medications. For each symptom, there are two dimensions: frequency and severity. [36] Patients recall their relevant experiences during the previous two weeks.[36] The frequency and severity of each symptom are measured on four-point Likert scales: "not at all," "one to three days," "four to seven days," and "eight to 14 days" during a two-week period for frequency, and "not applicable," "mild," "moderate," and "severe" for severity. An additional open-ended item asks patients to list adverse effects of asthma medications. Responses to this item serve as qualitative anchors for the two items addressing frequency and severity of adverse effects but do not contribute to the scoring of the ASUI.[36] The summary score of ASUI is a continuous scale from 0 to 1, with lower scores indicating worse asthma symptoms.[36] One study suggests that the ASUI may be a complementary patient-reported outcome for clinical studies and may be useful for applications in cost-effectiveness studies comparing different asthma treatments. However, the authors of this study pointed out that the findings should be interpreted in light of several study limitations, such as sample size and measures of disease severity that differed somewhat between the European and US samples.[52]

Two studies (Revicki et al.[36] and Bime et al.[29]) assessed the validity of ASUI. In a cross-sectional survey study with two-week reproducibility assessment[36] (n = 161 adults with asthma), the ASUI had good reproducibility (intraclass correlation = 0.74), good construct validity (Pearson correlation coefficient with the AQLQ = 0.77), and good discriminant validity. Revicki et al. also showed that the ASUI was statistically significantly correlated with percentage of predicted FEV_1 (r = 0.27, $P < 0.001$), AQLQ (r = 0.77, $P < 0.001$), and the Health Utilities Index Mark 2 (r = 0.36, $P < 0.001$). The authors concluded that the ASUI could be a useful, complementary patient-outcome measure for clinical trials and cost-effectiveness studies in asthma.[36] In a post hoc analysis, Bime et al. (2012)[29] assessed the validity, reliability, and responsiveness to change of the ASUI in adult patients with asthma (n = 1,648) in two previously completed multi-centre randomized trials.[53,54] The minimal important difference for the ASUI was also determined in this study. Demographic information, FEV_1 results, ASUI, ACQ, and AQLQ scores were obtained at baseline and during follow-up visits. The author reported that the internal consistency reliability (Cronbach's alpha) of the ASUI was 0.74. Test–retest reliability (intraclass correlation, r) was 0.76. Construct validity was demonstrated by significant correlations between ASUI scores and ACQ scores (r = –0.79; 95% CI, –0.85 to –0.75; $P < 0.001$) and Mini-AQLQ (r = 0.59; 95% CI, 0.51 to 0.61; $P < 0.001$). Responsiveness to change was demonstrated, with significant differences between mean changes in ASUI scores across groups of participants differing by 10% in percentage of predicted FEV_1 ($P < 0.001$) and by 0.5 points in ACQ scores ($P < 0.001$). In addition, the study also showed that baseline ASUI scores predict the occurrence of episodes of poor asthma control or asthma exacerbations in the following two weeks.

Supported by anchor-based statistical methods, the suggested minimal important difference of the ASUI is 0.09.[29] As the authors pointed out, one limitation of this study is the use of percentage of predicted FEV_1, ACQ scores, and episodes of poor asthma control as anchors for determining the minimal

important difference. Data on other anchors, such as physician's global rating of asthma severity or control, were not available in this post hoc analysis.[29] Although the ASUI was reported to be statistically significantly correlated with Health Utilities Index Mark 2, the correlation coefficient is low (r = 0.36). No correlation information between ASUI and other existing widely accepted utility indices, such as the EuroQol 5-Dimensions or Short Form (36) Health Survey, was found. No studies reported that the ASUI was an acceptable proxy for utility values, with or without transformation via mapping algorithms.

Conclusion

Overall, AQLQ, FEV_1, ACQ, and ASUI appear to be validated outcomes for use in clinical trials of therapies for patients with asthma. All seem to have a well-documented MCID (or MPPI, or MID) value.

APPENDIX 6: SUMMARY OF THE EXTENSION STUDY (Study 3085)

Aim

To summarize the safety and efficacy outcomes of reslizumab in the open-label extension study of up to 24 months (Study 3085).[55]

Findings

Study 3085 (N = 1,052) was a 24-month, open-label extension study that enrolled patients who had either completed treatment in Studies 3082 and 3083 or received at least two doses of study drug treatment in Study 3081. The main inclusion criteria were male or female patients, 12 to 75 years old, with moderate to severe eosinophilic asthma. One enrolled patient did not receive the study drug. Thus, 1,051 patients were analyzed for safety and efficacy.

Patients were administered reslizumab by intravenous infusion at a dosage of 3.0 mg/kg every four weeks for up to 24 months. Patients returned to the study centre every four weeks during the open-label treatment and four weeks after the last reslizumab infusion or early termination. All patients were required to return for a follow-up evaluation 90 days after the end of treatment. The primary outcomes were safety outcomes, including adverse events, clinical laboratory tests, vital signs, and concomitant medication usage. As secondary outcomes, efficacy outcomes that were assessed included changes from baseline forced in expiratory volume in one second (FEV_1, L), percentage of predicted FEV_1, short-acting beta-agonist use, and score on the Asthma Symptoms Utility Index (ASUI), the Asthma Control Questionnaire 7 (ACQ-7), and the Asthma Quality of Life Questionnaire (AQLQ).

Patient Disposition

More than 90% of patients who completed Studies 3082 or 3083, and 85% patients who enrolled in Study 3081, entered the open-label extension (Study 3085, N = 1,052). The study was terminated early because the primary study objective, in terms of open-label events for patient exposure to study drug without confirmed benefit/risk, had been sufficiently met. Fifty patients completed the study. A total of 1,002 patients (95%) withdrew from the study. The most common reason for withdrawal was sponsor closure (N = 896; 85%), an adverse event (N = 18; 2%), or lack of efficacy (N = 9; 0.8%).

Exposure

The mean (± standard deviation [SD]) duration of reslizumab treatment phase was 347 days ± 185 (range: 36 to 863 days). Eighty-five per cent of patients enrolled in Study 3085 had received six or more reslizumab injections and 8% received 24 or more reslizumab injections.

Safety

A total of 744 (71%) patients reported an adverse event during the open-label extension study of up to 24 months (Table 23). Adverse events that occurred with a frequency greater than 5% included asthma exacerbation (most common), followed by nasopharyngitis, upper respiratory tract infection, sinusitis, bronchitis, and headache. The frequency of these events was similar, irrespective of prior treatment with reslizumab or placebo during the double-blind treatment period. There was no evidence of an increased risk of hypersensitivity reactions to reslizumab, which was assessed by reviewing immune disorders in reslizumab-naive patients compared with reslizumab-experienced patients. No cases of anaphylaxis reactions related to reslizumab were reported.

Three deaths occurred during the study, none of which were assessed as related to reslizumab. Serious adverse events were reported in 78 of patients (7%), and the frequency was similar between the reslizumab-naive and reslizumab-experienced patients. The overall rate of withdrawals from the study due to adverse events was six patients (1%) in the reslizumab-naive group and 12 (2%) patients in the reslizumab-experienced group (Table 23).

TABLE 23: HARMS IN STUDY 3085

AEs	Number (%) of Patients		
	Previous Double-Blind Treatment Group		Total
	Placebo (N = 480)	Reslizumab (N = 571)	(N = 1,051)
All AEs (including follow-up period)	[redacted]	[redacted]	[redacted]
Treatment-related AEs	[redacted]	[redacted]	[redacted]
SAEs	[redacted]	[redacted]	[redacted]
AEs leading to patient discontinuation	[redacted]	[redacted]	[redacted]
Deaths	[redacted]	[redacted]	[redacted]
AEs reported in follow-up period	[redacted]	[redacted]	[redacted]

AE = adverse event; SAE = serious adverse event.
Source: Clinical Study Report.[55]

Efficacy

A total of [redacted] reported asthma exacerbation (reported as an adverse event) during the extension period. Hospitalizations, emergency rooms visits or physician visits due to asthma exacerbation, and the days of missed school or work, were not statistically reported and summarized in the Clinical Study Report.[55] Systemic use of corticosteroids was reported in 316 (30%) patients (162 [34%] and 154 [27%] in previous reslizumab-naive and reslizumab-experienced groups, respectively).[55]

Improvement of percentage of predicted FEV_1 was observed in reslizumab-naive patients. These improvements were sustained throughout the study. Change in FEV_1 from baseline to the end of the treatment was observed in the reslizumab-naive group (Table 24).

Patient-reported measures of asthma control (ACQ), quality of life (AQLQ), and symptoms (ASUI) were improved and sustained throughout the study in both previous reslizumab-naive and reslizumab-experienced groups (Table 24).

SABA use in reslizumab-experienced patients was generally stable over time, with small improvements observed for reslizumab-naive patients.[55] Reslizumab treatment produced a decrease in blood eosinophilic cell levels in reslizumab-naive patients. At the follow-up visit (90 days after end of treatment), the mean (250/µL) and median (100/µL) blood eosinophil levels for the overall population were substantially lower than the mean and median baseline values reported in the individual placebo-controlled studies (Studies 3081, 3082, and 3083).

TABLE 24: EFFICACY OUTCOMES IN STUDY 3085

Outcomes	Statistic	Previous Double-Blind Treatment Group	
		Placebo	Reslizumab
FEV_1 change from baseline to end point (L)	N	[redacted]	[redacted]
	Mean	[redacted]	[redacted]
	SD	[redacted]	[redacted]
Percentage predicted FEV_1 change from baseline to end point	N	[redacted]	[redacted]
	Mean	[redacted]	[redacted]
	SD	[redacted]	[redacted]
AQLQ change from baseline to end point	n	[redacted]	[redacted]
	Mean	[redacted]	[redacted]
	SD	[redacted]	[redacted]
ACQ-7 change from baseline to end point	n	[redacted]	[redacted]
	Mean	[redacted]	[redacted]
	SD	[redacted]	[redacted]
ASUI change from baseline to end point	n	[redacted]	[redacted]
	Mean	[redacted]	[redacted]
	SD	[redacted]	[redacted]

ACQ = Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; ASUI = Asthma Symptom Utility Index; FEV_1 = forced expiratory volume in 1 second; SD = standard deviation.
Source: Clinical Study Report.[55]

Conclusion

Study 3085 is an open-label up to 24-month extension study of Studies 3082, 3083, and 3081. The results of this study indicated that the safety profile was similar to that reported in Studies 3082, 3083, and 3081, with the most common adverse events being asthma exacerbation and nasopharyngitis. Consistent with Studies 3082, 3083, and 3081, improvement in FEV_1, ACQ-7, and AQLQ scores were observed in reslizumab-naive patients who were new to therapy. Limitations of this study were its open-label design and single arm without a control group.

APPENDIX 7: SUMMARY OF INDIRECT COMPARISONS

Introduction

Background

The manufacturer conducted a systematic review and a network meta-analysis (NMA) to estimate the relative treatment effects of reslizumab compared with its potential market competitors, mepolizumab and omalizumab.[22] No head-to-head trials of these drugs were available for direct comparisons. The primary objective of the NMA was to assess the relative efficacy and safety of reslizumab versus mepolizumab and omalizumab. The population of interest was adults and adolescents (≥ 12 years) with moderate to severe asthma that was inadequately controlled. Asthma severity was defined indirectly by defining well-controlled asthma: "[having] symptoms that occur no more than twice per week (including the need for rescue medication), normal lung function, no awakenings due to asthma, and no activity limitation due to asthma" (p. 17).[22]

Methods

One NMA was submitted by the manufacturer.[22] No additional NMAs were identified through a literature search conducted by the CADTH Common Drug Review (CDR). A summary and critical appraisal of the manufacturer-submitted NMA follows.

Review of Manufacturer's Network Meta-Analysis

Methods for Manufacturer's Network Meta-Analysis

Study Eligibility and Selection Process

The NMA was informed by a systematic search of electronic databases, limited to the English language: MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and clinicaltrials.gov. The following study-selection criteria were pre-specified to identify potentially relevant studies:

Criteria	Definition
Population	Patients ≥ 12 years of age with moderate to severe asthma that was inadequately controlled
Interventions	• Reslizumab • Mepolizumab • Omalizumab
Comparisons	Best supportive care used as maintenance therapy in all the trials with or without placebo control. That is, for placebo-controlled trials, patients received placebo treatment with best supportive care used as maintenance therapy. For open-label trials, patients received best supportive care alone.
Outcomes	• Rate and/ or number of severe asthma exacerbations • Rate and/ or number of any asthma exacerbations • Rate and/or number of moderate exacerbations [a] • Number of patients experiencing an exacerbation • Change in FEV_1 (mean or percentage of predicted) • Number of hospitalizations • Number of emergency room visits • Change in dosage of rescue medication • Change in eosinophil count • ACQ

Criteria	Definition
	• AQLQ • Time to first exacerbation • Total adverse events • Discontinuations due to adverse events • Serious adverse events
Study design	Phase II and phase III RCTs for principal analyses; well-conducted phase IV RCTs were included in sensitivity analyses; published and unpublished RCTs were included

ACQ = Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; FEV_1 = forced expiratory volume in 1 second; RCT = randomized controlled trial.
[a] NMA did not report results on moderate exacerbations because of a lack of data.

Two reviewers independently screened abstracts and full-text reports, extracted data from eligible studies, and appraised study quality using the Cochrane Collaboration risk-of-bias instrument. A third reviewer resolved discrepancies at each stage.

The final sample included 44 records representing 25 trials, of which five were for reslizumab, six for mepolizumab, and 14 for omalizumab. Four omalizumab trials were open-label, and all others were double-blind. Of the 25 trials, two were phase II (8%), 10 were phase III (40%), four were phase IV (16%), and nine were unclear (36%). Of the 44 records, 23 were published material (52%); nine were unpublished material from clinicaltrials.gov, FDA briefing documents, and clinical study reports (20%); and 12 records were unaccounted for (27%).

Data Extraction

Population — The NMA accepted trials with differing definitions of inadequately controlled asthma. All trials considered inadequate control as requiring inhaled corticosteroid (ICS). Some trials specified ICS dose (at least medium or high), and some required additional controllers to be used (i.e., long-acting beta-agonist).

The reviewers extracted study characteristics and patient baseline characteristics as part of a feasibility assessment for conducting an NMA. The transitivity assumption was assessed to ensure included trials were reasonably similar in terms of study and patient characteristics. These characteristics may be potential effect modifiers. Distributions of baseline age, sex, disease duration, body weight, forced expiratory volume in one second (FEV_1), ICS use, and immunoglobulin E (IgE) levels were provided as histograms and summary statistics.

The mean proportion of female patients in reslizumab studies (60.4%) was similar to the proportion in mepolizumab and omalizumab studies (54.8% and 63.6%, respectively). Mean age in reslizumab studies (45.4 years) was similar to mean ages in mepolizumab and omalizumab studies (47.9 years and 43.8 years, respectively). Variations were due, in part, to recruitment, as some trials included adults only and others included adults and adolescents. However, recruitment of adolescents was not summarized by the manufacturer. A check of the 15 trials that included adolescents found the proportion of adolescents for four studies, in which it ranged from 1% to 5%.[5-7,56]

There was heterogeneity in disease phenotype and severity among the drug trials. The biological mechanism of reslizumab and mepolizumab targets eosinophilic asthma mediated by interleukin-5, whereas omalizumab targets allergic asthma mediated by IgE. Allergic asthma mediated by IgE can have

an eosinophilic component, thus creating an "overlap" population eligible for either IgE or interleukin-5 agents. The "overlap" population was not established in the trials. Only reslizumab and mepolizumab trials reported baseline eosinophil counts. Reslizumab trials had a mean count of 547 cells/µL (range 277 cells/µL to 696 cells/µL), and mepolizumab had a mean of 400 cells/µL (range 320 cells/µL to 664 cells/µL). Variations may be due to recruitment, as four of five reslizumab studies required eosinophil counts ≥ 400 cells/ µL during screening, and three of five mepolizumab studies required eosinophil counts ≥ 300 cells/ µL in the previous year. Reslizumab trials did not report IgE levels. Inclusion criteria also differed in terms of number of exacerbations in the last year: mepolizumab and most omalizumab studies required two or more exacerbations, whereas reslizumab studies and one omalizumab study required one or more. The reported mean number of exacerbations per patient for reslizumab, mepolizumab, and omalizumab trials was 2.0, 3.8, and 2.9, respectively. In terms of baseline ICS use, pivotal reslizumab trials required at least a medium dose (fluticasone propionate ≥ 440 mcg per day, or equivalent) with or without another asthma controller (some of which included oral corticosteroids [OCS]), which corresponds to moderate asthma. In contrast, mepolizumab studies required a high dose (fluticasone > 880 mcg per day, or equivalent, with or without OCS) with an additional asthma controller (long-acting beta-agonist, leukotriene inhibitor, or theophylline), which corresponds to severe asthma.

Interventions — The NMA considered the following doses and frequency of administration:

Intervention	Administration
Reslizumab	3.0 mg/kg every 4 weeks
Mepolizumab	75 mg every 4 weeks [a] 100 mg every 4 weeks 250 mg every 4 weeks 750 mg every 4 weeks
Omalizumab	Licenced dose based on immunoglobulin E levels or body weight (0.016 mg/kg)

[a] The mepolizumab 75 mg dose was included in the evidence network to show all possible comparators, but its results were not presented. No explanation was provided for why the dose was excluded. Specifically for safety outcomes, the 75 mg dose was removed from the evidence networks as part of sensitivity analyses.

In this summary, only the 100 mg Health Canada–approved dose for mepolizumab is discussed.

Comparators

The comparator was best supportive care, used as maintenance therapy in all the trials with or without placebo control. This was referred to as "placebo" by the manufacturers. In this appendix, the same terminology is followed, despite the comparator being maintenance therapy alone in open-label studies. Best supportive care was based on standard of care recommendations from the Global Initiative for Asthma (GINA) or the National Heart, Lung, and Blood Institute. Given that reslizumab, mepolizumab, and omalizumab are add-on therapies, maintenance therapy comparators are appropriate.

Outcomes

Primary measures of efficacy were asthma exacerbations: defined variously as any exacerbation reported as clinically significant in the trial; severe exacerbation; exacerbation requiring hospitalization; exacerbation requiring hospitalization and/or emergency visit; patients with any exacerbation at 16 weeks (or within two weeks of that time); patients with any exacerbation at 12 months (or within two weeks); patients with exacerbations requiring systemic corticosteroids at 12 months (or within two weeks); or time to first exacerbation. To minimize variability in how trials defined clinically significant exacerbations, the reviewers reclassified outcomes according to international clinical practice guidelines

(GINA, British Guideline on the Management of Asthma, European Respiratory Society/ American Thoracic Society) and expert opinion:

> *Severe exacerbation* — "Study specific definition required use of systemic corticosteroids or use of oral corticosteroids for ≥ 3 days, or the need for asthma-related emergency treatment (emergency room visit, hospital admission, or unscheduled physician's office visit for nebulizer or other urgent treatment)" (p. 22)[22]
>
> *Moderate exacerbation* — "Study specific definition required temporary change in treatment e.g., increased use of short-acting β-agonist but not be severe enough to warrant systemic corticosteroid use and/or hospitalization or emergency visits for asthma" (p. 23)[22]

Quality of life (e.g., score on the Asthma Quality of Life Questionnaire [AQLQ]) was also considered a primary outcome by the CADTH clinical review team. Other measures of efficacy, reported as secondary outcomes, were FEV_1, changes in symptom scores (e.g., score on the Asthma Control Questionnaire 7 [ACQ-7]), eosinophil counts, and dosage of rescue medication. Safety was measured as total number of adverse events at end of study, discontinuations due to adverse events, and severe adverse events at end of study. These outcomes were analyzed at four weeks, 16 weeks (or within two weeks), 26 weeks (or within two weeks) and/ or 52 weeks (or within two weeks).

The following outcomes were deemed important according to patient input received by CADTH, but were not examined in the NMA: use of oral corticosteroids, days of missed school or work, change in number of asthma-symptom–free days or nights, and frequency of nocturnal awakenings. Similarly, mortality was deemed important by the clinical expert, but was not examined.

Quality Assessment of Included Studies

Two reviewers independently used the Cochrane Collaboration risk-of-bias instrument to assess the included trials. Twelve of the 25 studies did not state the method used to generate an allocation sequence. Four studies were open-label randomized controlled trials (RCTs), of which two did not blind outcomes assessors. Four studies did not describe their patient population or study attrition.

Reporting bias was also assessed by comparing outcomes identified in the protocol or methodology section of the publication with outcomes reported in the results section. Studies were not excluded based on quality. The authors concluded that the risk of reporting bias was generally low.

Evidence Network

FIGURE 6: OVERALL EVIDENCE NETWORK FOR NMA

Figure redacted upon request by manufacturer

MEPO = mepolizumab; OMA = omalizumab; RES = reslizumab.
Note: Numerical values represent the dose in milligrams.
Source: Manufacturer-submitted network meta-analysis.[22]

Indirect Comparison Methods

NMA analyses were conducted under a Bayesian framework using OpenBUGS and JAGS software packages. There were 50,000 iterations used for burn-in and for sampling each. Convergence criteria were met.

Random-effects models were considered when possible, but fixed-effects models were used in networks informed by only one study in which inter-trial variance could not be properly estimated. When the data were sparse, informative priors obtained from a review of meta-analyses were used instead of non-informative priors to stabilize the random-effects models. The review from which the informative priors were taken from was referenced; however, information on the priors themselves was not provided (i.e., type of distribution, parameters of distribution). Deviance information criterion guided model selection. Estimates from the NMA's final model selection were extracted for this appendix.

Exacerbation rates were modelled by Poisson regression analysis instead of negative binomial regression analysis. The rationale for this choice was that the model was unable to estimate over-dispersion from summary data. Continuous outcomes were modelled by linear regression analysis, and safety was modelled by a generalized linear model.

The NMA reported outcomes at multiple time points, when available: end of study, 12 months, six months, 16 weeks, and four weeks. The end of the study varied among studies, ranging from four to 18 months. Specifically, 22 trials had more than six months of follow-up, including four of five reslizumab trials, all six mepolizumab trials, and 12 of 14 omalizumab trials. In this supplement, only the latest time point is discussed.

Subgroup Analyses

Patient subgroups were determined a priori, but only two were sufficiently reported by the trials for NMA analyses:

1. GINA 4/5 patients with two or more exacerbations
2. GINA 4/5 patients with two or more exacerbations and age 18 years or older

Because trials implemented different recruitment criteria, subgroups allowed for comparisons of drug efficacy and safety among patients who should have greater similarities. They represented a population with severe asthma. For both subgroup analyses, the reslizumab data were taken from pooled post hoc analyses of two pivotal reslizumab studies (Study 3082 and Study 3083).

Sensitivity Analyses

Base-case analyses included only phase II and phase III studies, while sensitivity analyses included phase IV studies, all of which were omalizumab trials. Base-case analyses examined safety using all doses of

mepolizumab, while sensitivity analyses removed the 75 mg dose. Rationales were not provided for the choice of sensitivity analyses.

Results

Results represent the relative efficacy and safety of reslizumab (3.0 mg/kg) versus mepolizumab and omalizumab. Results are presented as the median of the posterior distributions with credible intervals (CrIs) constructed from the 2.5th and 97.5th percentiles. Estimates are relative risks (RRs) for binomial data and mean differences in change from baseline for continuous data. The term "significance" refers to statistical significance rather than clinical significance in this section of results.

Primary Outcomes — Exacerbations

Evidence Network

Most exacerbation outcomes were measured at the end of study: any, severe, exacerbations requiring hospitalization, and exacerbations requiring hospitalization and/or emergency visit. The evidence networks were informed by 13, 10, four, and four trials, respectively. Number of patients with any exacerbation and number of patients with exacerbations requiring systemic corticosteroids were measured at 12 months, and were informed by four and three trials, respectively.

Base-Case Analysis

Compared with omalizumab, reslizumab only significantly reduced time to exacerbation (Table 25). Reslizumab was not statistically significantly different than mepolizumab 100 mg for any type of exacerbation.

TABLE 25: BASE-CASE ANALYSIS OF EXACERBATIONS FOR RESLIZUMAB VERSUS MEPOLIZUMAB AND OMALIZUMAB

	Rate Ratio/ Hazard Ratio	95% Credible Interval
Any exacerbation at end of study (RE)		
Omalizumab	[redacted]	[redacted]
Mepolizumab 100 mg	[redacted]	[redacted]
Severe exacerbations at end of study (RE)		
Omalizumab	[redacted]	[redacted]
Mepolizumab 100 mg	[redacted]	[redacted]
Exacerbations requiring hospitalization at end of study (FE)		
Omalizumab	[redacted]	
Mepolizumab 100 mg	[redacted]	[redacted]
Exacerbations requiring hospitalization and/or emergency visit at end of study (FE)		
Omalizumab	[redacted]	
Mepolizumab 100 mg	[redacted]	[redacted]
Patients with any exacerbation at 12 months (RE with informative priors)		
Omalizumab	[redacted]	[redacted]
Mepolizumab 100 mg	[redacted]	
Patients with exacerbations requiring systemic corticosteroids at 12 months (RE with informative priors)		
Omalizumab	[redacted]	[redacted]
Mepolizumab 100 mg	[redacted]	
Time to first exacerbation (FE)		
Omalizumab	[redacted]	[redacted]
Mepolizumab 100 mg	[redacted]	[redacted]

FE = fixed-effects model; NMA = network meta-analysis; NR = not reported; RE = random-effects model.
Note: Bolded estimates show statistical significance.
Source: Manufacturer-submitted NMA.[22]

Subgroup Analyses

In both subgroup 1 (GINA 4/5 patients with two or more exacerbations) and subgroup 2 (GINA 4/5 patients with two or more exacerbations and age 18 years or older), outcomes were measured at the end of the study, and modelled using fixed effects. Findings were similar to the base case. In subgroup 1, reslizumab significantly reduced severe exacerbations compared with omalizumab (RR 0.48; 95% CrI, 0.33 to 0.68), but not mepolizumab 100 mg (RR 0.74; 95% CrI, 0.56 to 1.01). In subgroup 2, reslizumab significantly reduced severe exacerbations compared with mepolizumab 100 mg (RR 0.70; 95% CrI, 0.52 to 0.96). No data were available for mepolizumab 100 mg.

Sensitivity Analyses

Sensitivity analyses included additional omalizumab phase IV studies and examined any exacerbations and severe exacerbations at the end of study. Compared with omalizumab, reslizumab significantly reduced any exacerbations (RR 0.80; 95% CrI, 0.68 to 0.94) and severe exacerbations (RR 0.78; 95% CrI, 0.67 to 0.92) under fixed-effects models. Compared with mepolizumab 100 mg, reslizumab was not significantly different.

Primary Outcome — Quality of Life

Evidence Network

Quality of life was measured using the AQLQ, which provided a score out of seven, with higher scores indicating better quality of life. Outcomes were available only at 12 months, generating an evidence network informed by six trials.

Base-Case Analysis

Reslizumab was not significantly different from omalizumab with respect to changes in AQLQ. Comparisons between reslizumab and mepolizumab 100 mg were not estimated (Table 26).

TABLE 26: BASE-CASE ANALYSIS OF ASTHMA QUALITY OF LIFE QUESTIONNAIRE FOR RESLIZUMAB VERSUS OMALIZUMAB AND MEPOLIZUMAB

	Mean Difference	95% Credible Interval
AQLQ at 12 months (FE)		
Omalizumab	0.00	–0.25 to 0.25
Mepolizumab 100 mg	NR	

AQLQ = Asthma Quality of Life Questionnaire; FE = fixed-effects model; NMA = network meta-analysis; NR = not reported.
Source: Manufacturer-submitted NMA.[22]

Subgroup Analyses

Subgroup analyses were not performed.

Sensitivity Analyses

Sensitivity analyses were not performed.

Secondary Outcome — Change in Pulmonary Function

Evidence Network

Changes in FEV_1 were measured as percentage of predicted FEV_1 and absolute volume in litres. The evidence networks at six months were informed by five and seven trials for percentage of predicted FEV_1 and absolute volume, respectively.

Base-Case Analysis

Compared with omalizumab or mepolizumab, reslizumab did not show significant lung function improvement, as measured by FEV_1 (Table 27).

TABLE 27: BASE-CASE ANALYSIS OF CHANGE IN PULMONARY FUNCTION FOR RESLIZUMAB VERSUS OMALIZUMAB AND MEPOLIZUMAB

	Mean Difference	95% Credible Interval
Change in FEV_1, per cent predicted at 6 months (FE)		
Omalizumab	–0.74	–1.65 to 15.00
Mepolizumab 100 mg	–2.07	–5.47 to 1.30
Change in FEV_1, absolute volume (in litres) at 6 months (FE)		
Omalizumab	–0.06	–0.22 to 0.10
Mepolizumab 100 mg	0.02	–0.09 to 0.12

FE = fixed-effects model; FEV_1 = forced expiratory volume in one second; NMA = network meta-analysis.
Source: Manufacturer-submitted NMA.[22]

Subgroup Analyses
Fixed-effects analyses were performed for absolute volume in subgroup 1. Change in absolute volume of FEV_1 [redacted] between reslizumab and mepolizumab 100 mg at six months. Results were not available for omalizumab. No data were provided for subgroup 2.

Sensitivity Analyses
Sensitivity analyses of percentage of predicted FEV_1 were performed at 16 weeks. The addition of omalizumab phase IV trials showed reslizumab [redacted] compared with omalizumab and mepolizumab 100 mg.

Secondary Outcome — Changes in Symptoms
Evidence Network
Changes in asthma symptoms since baseline was measured using the ACQ-7, which scores patients from 0 to 6, with higher scores representing greater impairment. The evidence network was informed by five trials at six months.

Base-Case Analysis
There was [redacted] between omalizumab and reslizumab with respect to changes in ACQ-7 scores at six months (Table 28). No data were reported for mepolizumab 100 mg.

TABLE 28: BASE-CASE ANALYSIS OF ACQ-7 SCORES FOR RESLIZUMAB VERSUS OMALIZUMAB AND MEPOLIZUMAB

	Mean Difference	95% Credible Interval
ACQ-7 at 6 months (FE)		
Omalizumab	[redacted]	[redacted]
Mepolizumab 100 mg	[redacted]	

ACQ-7 = Asthma Control Questionnaire; FE = fixed-effects model; NMA = network meta-analysis; NR = not reported.
Source: Manufacturer-submitted NMA.[22]

Subgroup Analyses
No subgroup analyses were performed.

Sensitivity Analyses
No sensitivity analyses were performed.

Secondary Outcome — Difference in Eosinophil Counts
Evidence Network
Differences in blood eosinophil counts (cells/µL) from baseline were measured. The evidence network was informed by four trials at six months.

Base-Case Analysis
At six months, reslizumab showed [redacted] in blood eosinophil counts compared with mepolizumab 100 mg by a mean 242 cells/µL reduction at six months (Table 29). No comparison was performed between reslizumab and omalizumab. None of the random-effects results was significant for any comparator.

TABLE 29: BASE-CASE ANALYSIS OF CHANGE IN BLOOD EOSINOPHIL COUNTS (CELLS/μL) FOR RESLIZUMAB VERSUS OMALIZUMAB AND MEPOLIZUMAB

	Mean Difference	95% Credible Interval
Blood eosinophil counts at 6 months (FE)		
Omalizumab	[redacted]	
Mepolizumab 100 mg	[redacted]	[redacted]

FE = fixed-effects model; NMA = network meta-analysis; NR = not reported.
Note: Bolded estimates show statistical significance.
Source: Manufacturer-submitted NMA.[22]

Subgroup Analyses
Subgroup analyses were not performed.

Sensitivity Analyses
Sensitivity analyses were not performed.

Secondary Outcome — Dosage of Rescue Medication
Evidence Network
Changes from baseline in rescue medication dosage were measured. Rescue medications included different short-acting beta-agonists, such as salbutamol, formoterol, etc. The measurement for dosage, such as frequency of administration or weight, was not defined in the NMA. The evidence network was informed by three trials at six months. Data were available for the omalizumab comparator only.

Base-Case Analysis
The NMA found [redacted] between omalizumab and reslizumab; however, given that the NMA did not define dosage of rescue medication, the results (Table 30) cannot be interpreted.

TABLE 30: BASE-CASE ANALYSIS OF CHANGE IN DOSAGE OF RESCUE MEDICATION FOR RESLIZUMAB VERSUS OMALIZUMAB AND MEPOLIZUMAB

	Mean Difference	95% Credible Interval
Dosage of rescue medication at 6 months (FE)		
Omalizumab	[redacted]	[redacted]
Mepolizumab 100 mg	[redacted]	
Dosage of rescue medication at 6 months (RE)		
Omalizumab	[redacted]	[redacted]
Mepolizumab 100 mg	[redacted]	

FE = fixed-effects model; NMA = network meta-analysis; NR = not reported; RE = random-effects model.
Note: Both fixed-effects and random-effects models were presented, given similarity in deviance information criterion.
Source: Manufacturer-submitted NMA.[22]

Subgroup Analyses
Subgroup analyses were not performed.

Sensitivity Analyses
Sensitivity analyses were not performed.

Safety Outcomes

Evidence Network

Safety was measured at the end of the study in terms of total adverse events, discontinuations due to adverse events, and serious adverse events. The evidence networks were informed by 15, 14, and 18 trials for the respective outcomes. The manufacturer submission reported safety results as RRs rather than odds ratios, per the output of a logistic regression analysis. In this supplement, safety results are reported and interpreted as odds ratios.

Base-Case Analysis

Reslizumab significantly [redacted] the risk of total adverse events at the end of study compared with omalizumab, but not compared with mepolizumab (Table 31). For discontinuations due to adverse events, significance was achieved only when compared with omalizumab. Reslizumab was associated with significantly [redacted] odds for severe adverse events compared with mepolizumab, but not versus omalizumab.

TABLE 31: BASE-CASE ANALYSIS OF SAFETY OUTCOMES FOR RESLIZUMAB VERSUS OMALIZUMAB AND MEPOLIZUMAB

	Odds Ratio	95% Credible Interval
Total adverse events at end of study (FE)		
Omalizumab	[redacted]	[redacted]
Mepolizumab 100 mg	[redacted]	[redacted]
Discontinuations due to adverse events at end of study (FE)		
Omalizumab	[redacted]	[redacted]
Mepolizumab 100 mg	[redacted]	[redacted]
Serious adverse events at end of study (FE)		
Omalizumab	[redacted]	[redacted]
Mepolizumab 100 mg	[redacted]	[redacted]

FE = fixed-effects model; NMA = network meta-analysis.
Note: Bolded estimates show statistical significance.
Source: Manufacturer-submitted NMA.[22]

Subgroup Analyses

Subgroup analyses were not performed.

Sensitivity Analyses

The sensitivity analyses for safety included phase IV omalizumab trials and removed the 75 mg dose for mepolizumab. For total adverse events, findings were consistent between the base case and sensitivity analyses, in which reslizumab [redacted] odds compared with omalizumab. For discontinuations due to adverse events, significance was achieved compared with omalizumab in both statistical models, which was inconsistent with the base case, in which only the fixed-effects model was significant. For serious adverse events, reslizumab did not appear to significantly [redacted] the odds compared with omalizumab or mepolizumab.

Critical Appraisal

The transitivity assumption was difficult to assess. On one hand, the distributions for patient sociodemographic characteristics (i.e., age and sex) appeared reasonably similar across trials. On the other hand, disease severity appeared to be heterogeneous across trials as a result of different

recruitment criteria. The inclusion criteria for mepolizumab and most omalizumab trials required patients with more exacerbations and higher ICS doses compared with reslizumab. OCS use was not reported. However, the majority of patients in the reslizumab trials were considered to have severe asthma, according to the clinical expert consulted for the CDR review (i.e., 82% to 87% were receiving ICS plus long-acting beta-agonist [LABA]). The population examined in the NMA was adults and adolescents (12 years or older) with moderate to severe asthma. Health Canada's indication is for adults (18 years or older) with severe eosinophilic asthma (blood eosinophil count ≥ 400 cells/ µL). While the included trials enrolled predominantly adults, the inclusion of adolescents in 15 trials may bias the results overall if there is evidence to believe adolescents respond to treatment differently from adults. However, the proportion of adolescents recruited may have a negligible impact on the results, given that the proportions ranged from 1% to 5% among the four trials that reported age distributions. The inclusion of omalizumab trials added heterogeneity to the NMA, as omalizumab targets asthma mediated by IgE rather than interleukin-5. An "overlap" population eligible for either IgE or interleukin-5 agents could not be established in those trials. Given that omalizumab is a clinically relevant comparator, it is justified for the NMA to include the drug.

Subgroup analyses of the NMA (GINA 4/5 patients with two or more exacerbations, and GINA 4/5 patients with two or more exacerbations and age 18 years or older) reflected the indicated population more closely — that is, patients with more severe asthma. However, data were limited, and, as a result, only four outcomes were analyzed: severe exacerbations, exacerbations requiring hospitalization and/or emergency visit, change in FEV_1 in litres, and change in ACQ-7 score. Data on reslizumab trials were also from two pivotal studies pooled post hoc, after unblinding. Because the two trials had similar patient populations and study protocols, pooling can be considered appropriate for increasing the sample size and the precision of the effect size. However, subgroup analyses were not defined a priori in study protocols.

The NMA was well informed by a systematic search of multiple databases of both the peer-reviewed literature and grey literature. Even with systematic searches, there may be publication bias, the tendency to publish positive findings. Reviewers mainly had access to published trials for omalizumab and mepolizumab, supplemented by full data results of two omalizumab trials from clinicaltrials.gov. Of the 44 records included, the NMA did not classify the source of 12 records (27%) as either from the peer-reviewed literature or grey literature. The systematic review restricted the search to English records, introducing a potential language bias.

Each step in the study-selection process and quality appraisal was done independently by two reviewers. Trials of poor or unclear quality resulting from lack of reporting were not excluded from the NMA. Four of 25 trials (16%) were open-label RCTs, and all of these trials were for omalizumab. The lack of blinding may have introduced performance bias and could have influenced the reporting of subjective outcomes and adverse events. Reviewers included a mixture of phase II trials (n = 2, 8%), phase III trials (n = 10, 40%), and trials with an unclear phase (n = 9, 36%) for the base-case analysis. No explanations were provided as to why phase II and unclear trials were included, especially when they tend to not be designed to adequately evaluate efficacy and safety and may not be sufficiently powered, compared with phase III trials. For the sensitivity analysis, "well-conducted" phase IV trials (n = 4, 16%) were added. Reviewers did not define "well-conducted," and, therefore, the selection of those four particular omalizumab trials seemed arbitrary. No rationales were provided for the choice of including phase IV trials in the sensitivity analysis.

The NMA examined an extensive list of clinical outcomes, most of which were consistent with the CDR clinical review protocol and considered important by the clinical expert consulted and patient groups who submitted information to CADTH for the reslizumab review. The reviewers made an effort to reduce heterogeneity by reclassifying exacerbations according to international clinical practice guidelines in consultation with expert opinion. For changes in dosage of rescue medication, units were not provided in the NMA. In reslizumab trials, number of puffs was used, although other drug trials may have measured dosage differently. If so, it is unclear how the dosages were converted into a common measurement. Further, a handful of outcomes, such as frequency of nocturnal awakenings or days of missed school or work, were not examined by the included trials, despite being considered important by patients according to patient input submitted to CADTH.

In terms of reporting, the NMA correctly reported hazard ratios for time to exacerbation as well as mean differences for changes in questionnaire scores, dosage of rescue medication, and eosinophil counts. However, the NMA reported relative risks for exacerbation rates and safety outcomes instead of rate ratios and odds ratios, respectively. Rate ratio and odds ratios are the direct output of the Poisson regression and logistic regression analyses. It is unclear whether the reviewers transformed the output into relative risks without indicating this in the methods section. Further, absolute data for the comparators were not provided. For instance, knowing the placebo exacerbation rates would be informative for interpreting the rate ratio calculation between reslizumab and placebo.

Internal and External Validity

For all outcomes, different statistical models were compared: fixed-effects with non-informative priors, random-effects with non-informative priors, fixed-effects with informative priors, and random-effects with informative priors. The final model was selected based on goodness of fit and number of trials informing the evidence network. Almost all analyses used non-informative priors, which are considered objectively elicited. Two exceptions were the analyses of patients with any exacerbations, and patients with exacerbations requiring systemic corticosteroids, both of which used informative priors. The distribution and parameters of the informative priors were not provided, thus limiting reproducibility. Most NMA results were estimated from a fixed-effects model rather than random-effects. This was justified, as most connections in the evidence networks were informed by one or two studies, too few studies for a random-effects analysis. However, fixed-effects models would be expected to generate statistically significant results more frequently than random-effects models, given their tighter credible intervals. Hence, many results had inconsistent significance between the two models. For instance, reslizumab inconsistently improved rates of any exacerbation, severe exacerbation, and number of discontinuations due to adverse events at the end of the study when compared with omalizumab. Compared with mepolizumab 100 mg, reslizumab inconsistently improved the difference in eosinophil counts at six months and inconsistently increased the odds of serious adverse events at the end of the study.

Statistical significance may not equate to clinical significance. Minimal clinically important differences were not discussed in the NMA. For several statistically significant outcomes, the CrIs came close to crossing the null value (e.g., quality of life, change in FEV_1 in litres, changes in asthma symptoms, and total adverse events). Minimal clinically important differences for the following outcomes have been summarized in 0: 0.5 points for AQLQ on quality of life; 0.5 points for ACQ on symptoms; and 10.4% change from baseline, or 230 mL (range 170 mL to 280 mL) for FEV_1. The NMA results for these outcomes, both in terms of point estimates and the CrI limits, are likely not clinically meaningful.

Most outcomes were analyzed at the end of study. However, follow-up times varied across trials from four to 18 months. This would mean a constant effect size over time must be assumed. The reviewers defended the assumption by providing scatter plots of effect sizes over time for three outcomes: adverse events, serious adverse events, and discontinuations. It is unclear why the assumption was checked only for safety outcomes when other outcomes, including the primary measure of exacerbations, for which the risk over time may not be constant, were also reported at the end of the study. Further, the scatter plots provided only a qualitative check of whether the trend line appeared somewhat horizontal. No statistical tests were performed for time trends.

Several doses of mepolizumab were considered in the NMA. However, a credible rationale was not provided for excluding mepolizumab 75 mg from all reported results. On one hand, the reviewers claimed the dose was not of interest. On the other hand, the dose was used as a node in all of the networks. In the sensitivity analysis, the reviewers excluded the 75 mg dose from the reanalysis of safety outcomes only, but not other outcomes. Nonetheless, the 75 mg dose is not approved by Health Canada and is out of scope for this summary.

The reviewers checked consistency between direct comparisons and indirect comparisons in each evidence network. No formal tests were conducted. Rather, the reviewers checked whether the direct and indirect evidence both generated statistically significant results or both generated non-significant results to be considered consistent. No important inconsistencies were noted.

Exacerbation rates were modelled by Poisson regression analysis in the NMA instead of negative binomial regression analysis, which was used in the pooled analysis of reslizumab. The reviewers argued for the Poisson regression analysis because over-dispersion could not be estimated from summary statistics. However, the rationale may not be sufficient, because the reviewers tested using the negative binomial regression analysis with an over-dispersion parameter from the pooled reslizumab analysis. The reviewers argued that results were too unstable and therefore were not presented.

In terms of external validity, it is unclear whether the NMA findings are generalizable to the Canadian setting, as most of the included trials were multi-centre studies across different countries. Patient populations and guidelines for best supportive care as maintenance therapy may vary by jurisdiction.

Conclusion

The relative efficacy and safety of reslizumab 3.0 mg/kg compared with placebo, mepolizumab, and omalizumab was analyzed using NMAs. The analysis suggested that reslizumab is statistically similar to omalizumab and mepolizumab 100 mg for most efficacy outcomes, including rates of exacerbation, quality of life, lung function, and symptom control. The results of the analyses of use of short-acting beta- agonists (SABAs) cannot be interpreted because of the failure of the authors to report the definition of “SABA dosage” used to pool studies in the NMA. Reslizumab was not statistically different from omalizumab in terms of time to exacerbation, and in terms of safety. Reslizumab was not statistically different from mepolizumab 100 mg in terms of blood eosinophil counts. In one analysis, reslizumab appeared to significantly increase the odds of severe adverse events compared with mepolizumab.

The NMA relies on several strong assumptions. First, the manufacturer assumed that disease severity of the patient populations in the included trials was similar. However, inclusion criteria differed among the drug trials. In addition, heterogeneity existed in terms of asthma phenotype and exacerbation

definitions. In particular, it is unlikely that the "overlap" population between reslizumab and omalizumab was appropriately identified and compared. Without information on eosinophils and exacerbation history for omalizumab study patients, it is uncertain how many omalizumab patients would have been eligible for reslizumab. Second, the reviewers assumed that the effect sizes of all outcomes were constant over time. Consequently, outcomes were analyzed at the end of the study despite the trials having different follow-up times. This assumption was not well explored and poorly reported on.

Despite the limitations of methodology and from a lack of data, the evidence suggests that there are no substantial differences between reslizumab and mepolizumab 100 mg in terms of efficacy. Conclusions cannot be drawn between reslizumab and omalizumab because of the unknown "overlap" population.

Although the NMA of adverse events, withdrawals due to adverse events, and serious adverse events suggests some differences between treatments, these analyses are limited by the lack of blinding for omalizumab RCTs, the short-term duration of trials, and the limited number of patients enrolled. As a result of these limitations, no conclusions can be drawn with regard to the relative safety of treatments.

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