CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

Benralizumab (Fasenra)

(AstraZeneca Canada Inc.)

Indication: An add-on maintenance treatment of adult patients with severe eosinophilic asthma.

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

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Abbreviations

ACMA	Asthma Canada Member Alliance
ACQ	Asthma Control Questionnaire
ACQ-5	five-question Asthma Control Questionnaire
ACQ-6	six-question Asthma Control Questionnaire
ACQ-7	seven-question Asthma Control Questionnaire
AE	adverse event
ALWC	at least well-controlled
AQLQ	Asthma Quality of Life Questionnaire
AQLQ12+	Asthma Quality of Life Questionnaire for 12 years and older
AQLQ(S)	Standardized Asthma Quality of Life Questionnaire
CI	confidence interval
CIQ	Classroom Impairment Questions
CDR	CADTH Common Drug Review
DB	double blind
DRMI	dropout reason-based multiple imputation
EQ-5D	EuroQoL 5-Dimensions questionnaire
EQ-5D-5L	EuroQoL 5-Dimensions 5-Levels questionnaire
ER	Emergency room
FAS	full analysis set
FEV1	forced expiratory volume in one second
ICC	intraclass correlation coefficient
ICS	inhaled corticosteroid
IDC	indirect comparison
IL-5	Interleukin-5
IgE	immunoglobin E
ITT	intention-to-treat
LABA	long-acting beta2 agonist
LAMA	long-acting muscarinic agonist
LS	least squares
MD	mean difference
MCID	minimal clinically important difference
MPPI	minimal patient perceivable improvement
NWC	not well-controlled
OCS	oral corticosteroid
PEF	peak expiratory flow
Q4W	every four weeks
Q8W	every eight weeks
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
SF-36	Short Form (36) Health Survey
SHP	Specific Health Problem
TASS	total asthma symptom score
WPAI	Work Productivity and Activity Impairment Questionnaire
WPAI-GH	Work Productivity and Activity Impairment Questionnaire–General Health

Drug	Benralizumab (Fasenra)
Indication	As an add-on maintenance treatment of adult patients with severe eosinophilic asthma.
Reimbursement Request	As an add-on maintenance treatment for adult patients with severe eosinophilic asthma who are inadequately controlled with high-dose inhaled corticosteroids and one or more additional asthma controller(s) (e.g., long-acting beta2 agonist), if one of the following clinical criteria are met: 1. Blood eosinophil count of ≥ 300 cells/μL and have experienced two or more clinically significant asthma exacerbations in the past 12 months, or 2. Blood eosinophil count of ≥ 150 cells/μL and are treated chronically with an oral corticosteroid.
Dosage Form(s)	30 mg subcutaneous injection
NOC Date	February 22, 2018
Manufacturer	AstraZeneca Canada Inc.

Executive Summary

Introduction

Asthma is a chronic respiratory disorder characterized by reversible airway obstruction, inflammation of the airways, airway hyper-responsiveness, and remodelling. Symptoms may include wheezing, dyspnea, chest tightness, sputum production, and cough associated with airway limitation and hyper-responsiveness to exogenous and endogenous stimuli. Onset can occur at any time, including in young children. It is estimated that 2.4 million Canadians aged 12 years and older have a diagnosis of asthma. Severe eosinophilic asthma is an asthma phenotype characterized by the presence of eosinophils in the airways and sputum despite conventional asthma therapy, and it affects 5% to 10% of all asthma patients. The prevalence of severe uncontrolled eosinophilic asthma is likely lower. Eosinophils are involved in the pathogenesis of asthma through the release of pro-inflammatory mediators at the airways, which contribute to epithelial cell damage, airway hyper-responsiveness, mucus hypersecretion, and airway remodelling.

The goal of asthma management is to maintain long-term asthma control with the least amount of medication using a stepwise approach to pharmacological therapy. Patients are started with a low-dose inhaled corticosteroid (ICS) before the addition of second-line drugs such as long-acting beta2 agonists (LABA), with an increase in ICS dose if symptoms remain uncontrolled. Long-term use of an OCS (oral corticosteroid) would be considered a last resort due to the significant harms associated with this class. Benralizumab is an interleukin-5 (IL-5) inhibitor, a monoclonal antibody that binds to the alpha subunit of the IL-5 receptor. The IL-5 alpha receptor is found on eosinophils and basophils. Binding of the monoclonal antibody facilitates the interaction of these cells with natural killer cells, resulting in the death of eosinophils. Eosinophils mediate inflammation in asthma, and thus inhibiting eosinophils has an anti-inflammatory effect. Benralizumab is administered by subcutaneous injection, 30 mg once every four weeks for the first three doses, then once every eight weeks thereafter. Injections should be administered into the upper arm, thigh, or abdomen. Benralizumab is indicated as an add-on maintenance treatment of adult patients with severe eosinophilic asthma.

The objective of this review is to perform a systematic review of the beneficial and harmful effects of benralizumab as an add-on maintenance treatment of adult patients with severe eosinophilic asthma.

Results and Interpretation

Included Studies

Three manufacturer-sponsored multinational double-blind randomized controlled trials, each comparing two different regimens of benralizumab, administered every four and eight weeks, met the inclusion criteria for this systematic review. Only the Health Canada–approved Q8W regimen was of interest for this review. CALIMA (N = 1,306, 56 weeks) and SIROCCO (N = 1,206, 48 weeks) were similarly designed trials that enrolled patients with poor asthma control (at least two exacerbations in the past year) despite high-dose ICS (SIROCCO) or medium- to high-dose ICS (CALIMA). In both studies, two-thirds of patients had high eosinophil counts (≥ 300 cells/μL), and these patients, as well as patients on high-dose ICS (> 500 mcg fluticasone equivalents daily), were the focus of the primary analysis. The primary outcome in both studies was the annualized relapse rate. Key secondary outcomes included change from baseline in forced expiratory volume in one second (FEV1) and total asthma symptom score (TASS). ZONDA was a smaller and shorter study (N = 220; 28 weeks) that enrolled patients with severe asthma who required chronic use (at least six months) of oral corticosteroids to maintain asthma control. The primary outcome in ZONDA was the per cent reduction in OCS dose. There were no multiplicity-controlled secondary outcomes.

Critical appraisal issues included the lack of an active comparator in the included studies, including existing IL-5 inhibitors reslizumab and mepolizumab. Only exacerbations, FEV1, and TASS were controlled for multiple comparisons in CALIMA and SIROCCO, while key efficacy outcomes for this review such as health-related quality of life and exacerbations resulting in hospitalizations and emergency room visits were not adjusted for multiplicity. The included studies all had a relatively short follow-up in which to assess the longer-term safety of this relatively novel pharmacological target.

Efficacy

The annualized exacerbation rate was lower for benralizumab versus placebo in both CALIMA over 56 weeks (rate ratio of 0.72; 95% confidence interval [CI], 0.54 to 0.95; P = 0.019) and SIROCCO over 48 weeks (rate ratio of 0.49; 95% CI, 0.37 to 0.64; P < 0.001), and these differences were statistically significant. The statistically significant reductions in exacerbations are likely clinically significant in a population of patients who were having regular exacerbations at baseline despite high-dose ICS. The annualized exacerbation rate ratio of benralizumab versus placebo over 28 weeks in ZONDA was 0.30 (95% CI, 0.17 to 0.53; P < 0.001). This outcome was not adjusted for multiple comparisons in ZONDA. The percentage of benralizumab patients versus placebo patients who had at least one exacerbation over the course of 56 weeks in CALIMA was 40% versus 51% of patients, respectively; over 48 weeks in SIROCCO it was 35% versus 51% of patients, respectively; and over 28 weeks in ZONDA it was 23% versus 52% of patients, respectively. No statistical analyses were reported for this outcome. Exacerbations associated with hospitalizations or emergency room visits occurred in 8% of patients in each of the benralizumab and placebo groups over 56 weeks in CALIMA, 7% of benralizumab versus 14% of placebo patients over

48 weeks in SIROCCO, and in 1% of benralizumab patients versus 12% of placebo patients over 28 weeks in ZONDA.

In ZONDA, the per cent reduction in OCS dose was the primary outcome — there was a greater reduction in corticosteroid dose with benralizumab than with placebo, and this difference was statistically significant (estimate for difference between groups of 37.5%; 95% CI, 20.8% to 50.0%; $P < 0.001$). The proportion of patients able to reduce their dose by different percentages was also reported, and 30% of benralizumab patients (11% in placebo) were able to reduce their OCS dose by 100%. For these patients who were able to discontinue their OCS, the benefit of benralizumab is clear. However, for those who remained on OCS, it has not been established whether there is a threshold dose for elevated risk of OCS-related systemic adverse effects. Exacerbations associated with the use of OCS was a secondary outcome in both CALIMA and SIROCCO, although no statistical analyses were planned or provided for these outcomes.

Health-related quality of life, assessed by the change from baseline in Asthma Quality of Life Questionnaire for 12 years and older (AQLQ12+) score, benralizumab versus placebo, was reported in CALIMA after 56 weeks (least squares [LS] mean difference [MD] of 0.24; 95% CI, 0.04 to 0.45; $P = 0.019$), in SIROCCO after 48 weeks (LS MD of 0.30; 95% CI, 0.10 to 0.50; $P = 0.004$), and after 28 weeks in ZONDA (LS MD of 0.45; 95% CI, 0.14 to 0.76; $P = 0.004$). Increases in scores from baseline denote improvement in health-related quality of life on this scale. Note that none of these statistical analyses were adjusted for multiple comparisons and should be considered hypothesis-generating. Given the importance of health-related quality of life in a disease such as asthma, controlling for multiple comparisons would have allowed for a more definitive assessment of the impact of benralizumab on this outcome. Although a minimal clinically important difference exists for the Asthma Quality of Life Questionnaire (AQLQ), none has been established for the AQLQ12+, thus both the statistical and clinical significance of health-related quality of life findings in the included studies is unknown.

Pre-bronchodilator change from baseline in FEV1 was an outcome that was controlled for multiplicity in CALIMA and SIROCCO. In both studies the FEV1 was improved versus placebo, and these differences were statistically significant in CALIMA (LS MD of 0.116; 95% CI, 0.028 to 0.204; $P = 0.010$) and in SIROCCO (0.159; 95% CI, 0.068 to 0.249; $P = 0.001$). Change from baseline in FEV1 of benralizumab versus placebo was also reported after 28 weeks in ZONDA (0.112; 95% CI, −0.033 to 0.258; $P = 0.129$). However, no adjustments were made for multiple comparisons for this outcome in ZONDA. The minimal clinically important difference for FEV1 is not well-established and these differences may not be clinically significant. Peak expiratory flow (PEF), assessed in the morning and evening in CALIMA, SIROCCO, and ZONDA was not adjusted for multiplicity. Morning values for PEF, benralizumab versus placebo, after 56 weeks in CALIMA was (LS MD) 15.27 L/minute; 95% CI, 0.90 to 29.64; $P = 0.037$, and after 48 weeks in SIROCCO, 16.46 L/minute; 95% CI, 2.08 to 30.83; $P = 0.025$, and after 28 weeks in ZONDA, 30.01; 95% CI, 4.26 to 55.76; $P = 0.023$. Evening PEF values after 56 weeks in CALIMA were 21.22 L/minute (95% CI, 6.65 to 35.79; $P = 0.004$) and after 48 weeks in SIROCCO were 19.18 (95% CI, 5.09 to 33.28; $P = 0.008$) and after 28 weeks in ZONDA were 31.52 (95% CI, 6.32 to 56.71; $P = 0.014$).

The change from baseline in TASS was a key secondary outcome in both CALIMA and SIROCCO, and thus was controlled for multiple comparisons. TASS was reduced (improved) for benralizumab versus placebo in both studies and these differences were statistically significant in both CALIMA (LS MD of −0.23; 95% CI, −0.43 to −0.04; $P = 0.019$)

and SIROCCO (LS MD of −0.25; 95% CI, −0.45 to −0.06; *P* = 0.012). The six-question Asthma Control Questionnaire (ACQ-6) was also used to assess symptoms in both CALIMA and SIROCCO, but adjustments were not made for multiple comparisons for this outcome. The total ACQ-6 change from baseline, benralizumab versus placebo, was reported after 56 weeks in CALIMA (LS MD of −0.25; 95% CI, −0.44 to −0.07; *P* = 0.008), after 48 weeks in SIROCCO (LS MD of −0.29; 95% CI, −0.48 to −0.10; *P* = 0.003) and after 28 weeks in ZONDA (LS MD of −0.55; 95% CI, −0.86 to −0.23; *P* = 0.001). A decrease from baseline denotes improvement in symptoms on this scale.

Change in rescue medication use, measured as puffs/day of salbutamol, was reported in all three studies. Mean (standard deviation [SD]) change in rescue medication use over the course of 56 weeks in CALIMA was [redacted] puffs/day with benralizumab and [redacted] puffs/day with placebo and over 48 weeks in SIROCCO was [redacted] puffs/day with benralizumab and [redacted] puffs/day with placebo, and over 28 weeks in ZONDA was [redacted] puffs/day with benralizumab and [redacted] puffs/day with placebo. The proportion of nights with nocturnal awakenings was also reported in all three studies. The LS MD from baseline in proportion of nights with nocturnal awakenings over 56 weeks in CALIMA for benralizumab versus placebo was [redacted], over 48 weeks in SIROCCO was [redacted], and over 28 weeks in ZONDA was [redacted]. None of these analyses were adjusted for multiple statistical comparisons. All three studies reported the change from baseline in eosinophil counts, benralizumab versus placebo, after 56 weeks in CALIMA (LS MD in per cent change from baseline of 105.0) (95% CI, −115.1 to −94.96; *P* < 0.001), after 48 weeks in SIROCCO (LS MD in per cent change from baseline of −99.59 (95% CI, −113.6 to −85.59; *P* < 0.001), and after 28 weeks in ZONDA (LS MD in per cent change from baseline of −159.4 (95% CI, −217.9 to −100.9; *P* < 0.001).

The manufacturer submitted an indirect comparison that was reviewed and critically appraised by CADTH Common Drug Review (CDR) (see Appendix 7). The objective of the indirect comparison was to compare benralizumab with other monoclonal antibodies in patients with severe uncontrolled asthma. The network meta-analysis included [redacted] studies, but only [redacted] studies were included in the match-adjusted indirect comparison [redacted] of benralizumab (SIROCCO, CALIMA, ZONDA). reslizumab, and mepolizumab, and [redacted] of omalizumab. [redacted]

Harms

The proportion of patients with an adverse event was 76% with benralizumab and 79% placebo after 56 weeks in CALIMA, 72% versus 77%, respectively, after 48 weeks in SIROCCO, and after 28 weeks in ZONDA, 75% versus 83%, respectively. The most common adverse events in all three studies were nasopharyngitis (CALIMA: 19% benralizumab versus 21% placebo; SIROCCO: 12% in each group; ZONDA: 15% with benralizumab and 20% placebo) and asthma (CALIMA: 11% with benralizumab versus 16% placebo; SIROCCO: 11% benralizumab versus 20% placebo; ZONDA: 3% benralizumab versus 24% placebo).

The proportion of patients with a serious adverse event was 10% of benralizumab and 14% of placebo patients over 56 weeks in CALIMA, 14% in each group after 48 weeks in SIROCCO, and in ZONDA 10% of benralizumab patients and 19% of placebo patients. Withdrawals due to an adverse event occurred in 2% of benralizumab versus 1% of placebo in CALIMA and in SIROCCO, and in 4% of benralizumab versus 3% of placebo patients in ZONDA.

Notable harms included infection and immune and injection-site reactions. Upper respiratory tract infections occurred in benralizumab and placebo patients in each of the three studies (CALIMA: 9% benralizumab versus 10% placebo; SIROCCO: 8% benralizumab versus 9% placebo; ZONDA: 7% in each group), while influenza occurred in 3% of benralizumab and 6% of placebo patients in CALIMA, 5% of benralizumab versus 6% of placebo patients in SIROCCO, and 1% of benralizumab versus 7% of placebo patients in ZONDA (Table 12). Serious adverse events of infection were infrequent in the case of both pneumonia (CALIMA: 0% benralizumab versus 1% placebo; SIROCCO: 1% in each group; ZONDA: 3% in benralizumab versus 4% in placebo) and influenza (CALIMA: 1% benralizumab versus 0% placebo; SIROCCO: 0% in benralizumab versus less than 1% placebo; ZONDA: 0% in benralizumab versus 3% in placebo). BORA is an extension that enrolled patients from all three of the trials included in this review, and [redacted].

Potential Place in Therapy[1]

The standard of care for asthma therapy for adults in Canada is ICS. Most patients who remain uncontrolled can be managed with a combination of non-pharmacologic strategies (e.g., asthma educator, environmental control) and pharmacologic strategies (e.g., adding a second agent such as LABA, and then further increasing the dose of ICS). Despite optimal management, the 5% to 10% of the overall asthma population who remain uncontrolled drive the majority of health care costs.[1] Besides benralizumab, there is also mepolizumab or reslizumab, which target a population of patients with severe asthma who have allergic or non-allergic eosinophilic airway inflammation for which anti-IL-5 therapy is the only current option to achieve control.[2] Without anti-IL-5 therapy, this population can suffer from the side effects of long-term OCS therapy or from worsened quality of life due to uncontrolled asthma.

Benralizumab is effective at achieving asthma control in patients with eosinophilic airway inflammation who remain uncontrolled despite high-dose ICS with a second controller added or who require an OCS to maintain control.[3] These patients should be the ones to receive benralizumab. Some patients who are non-compliant with inhaled therapies, who continue to smoke, or who have ongoing environmental exposures (e.g., pets or occupation) may otherwise appear to meet criteria to receive anti-IL-5 therapy. Peripheral eosinophil levels are easily measured and are a surrogate for airway eosinophilic inflammation. Therefore, patients should meet Health Canada–approved eosinophil levels before initiating therapy.

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

Conclusions

Three manufacturer-sponsored multinational double-blind randomized controlled trials that compared benralizumab with placebo met the inclusion criteria for this review. In CALIMA and SIROCCO, benralizumab demonstrated superiority over placebo over 56 and 48 weeks, respectively, for the primary outcome, annualized exacerbation rate, in a population of patients with high eosinophil counts (≥ 300 cells/μL) and on high-dose ICS (> 500 mcg fluticasone equivalents). This effect on exacerbations is likely clinically significant in a difficult-to-treat population. However, limited inferences can be made about the effects of benralizumab on exacerbations leading to hospitalization and emergency department visits as analyses of these outcomes were not controlled for multiple statistical comparisons. In ZONDA, in a population of patients who required chronic OCS treatment to maintain asthma control, benralizumab demonstrated superiority over placebo for the primary outcome, reducing the OCS dose over 28 weeks by more than 50%. This is likely a clinically significant finding in a population that is exhibiting corticosteroid resistance. However, no conclusions can be drawn about the key clinical outcome of exacerbations, as these analyses were not adjusted for multiple comparisons, nor were any other secondary outcomes in ZONDA. Limited inferences about benralizumab's effects on health-related quality of life can be drawn from all three studies. Multiplicity-controlled secondary outcomes such as FEV1 and were improved for benralizumab versus placebo in CALIMA and SIROCCO, but the clinical significance of these differences may be limited as the treatment effect was generally modest. There were no clear or consistent safety differences between benralizumab and placebo, but given the novelty of IL-5 inhibitors, longer-term safety data are needed. Data from BORA, an extension that enrolled patients from the [redacted] included studies, suggested [redacted] A limitation of the included studies is that none compared benralizumab with an active comparator such as another IL-5 inhibitor. A manufacturer-submitted indirect comparison found the efficacy of benralizumab [redacted] from mepolizumab [redacted]. The indirect comparison also found that benralizumab [redacted]

Table 1: Summary of Results

Outcome	CALIMA		SIROCCO		ZONDA	
	Ben N = 441	Placebo N = 440	Ben N = 398	Placebo N = 407	Ben N = 73	Placebo N = 75
Mortality						
Deaths, n	2/441 (< 1%)	1/440 (< 1%)	2/398 (1%)	2/407 (< 1%)	2/73 (3%)	0
Primary analysis population for all outcomes in CALIMA, SIROCCO: blood eosinophils ≥ 300 cells/µL, on high-dose ICS	**N = 239**	**N = 248**	**N = 267**	**N = 267**		
Exacerbations						
Annual exacerbation rate, estimate (95% CI)	0.66 (NR)	0.93 (NR)	0.65 (NR)	1.33 (NR)	0.54 (0.33 to 0.87)	1.80 (1.32 to 2.46)
Rate ratio (95% CI)	0.72 (0.54 to 0.95), *P* = 0.019[a]		0.49 (0.37 to 0.64), *P* < 0.001[a]		0.30 (0.17 to 0.53) *P* < 0.001	
Hospitalization, Physician, ED Visits Due to Exacerbations						
Hospitalization, patients, n (%)	14 (5.9)	12 (4.8)	12 (4.5)	20 (7.5)	1 (1.4)	6 (8.0)
ED visit, patients, n (%)	12 (5.0)	18 (7.3)	6 (2.2)	20 (7.5)	0	4 (5.3)
HRQoL						
Mean (SD) baseline overall AQLQ12+ score	3.87 (1.05) N = 232	3.93 (1.04) N = 240	3.93 (0.97) N = 267	3.87 (0.99) N = 267	4.44 (1.3)	4.11 (1.1)
LS mean change from baseline	1.56 N = 230	1.31 N = 240	1.56 N = 252	1.26 N = 254	1.08 N = 67	0.63 N = 68
LS MD between groups (95% CI)[b]	0.24 (0.04 to 0.45) *P* = 0.019		0.30 (0.10 to 0.50) *P* = 0.004		0.45 (0.14 to 0.76) *P* = 0.004	
Oral Corticosteroid Use						
Mean baseline daily OCS dose (mg)	NR	NR	NR	NR	[redacted]	[redacted]
Mean (SD) per cent reduction in OCS dose from baseline	NR	NR	NR	NR	[redacted]	[redacted]
Estimate for difference between groups (95% CI)[c]	NR	NR	NR	NR	[redacted]	
OCS use associated with exacerbations, mean (SD) total dose per patient, grams	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Withdrawals						
Total, n (%)	51 (11.6)	38 (8.6)	40 (10.1)	40 (9.8)	4 (5.5)	3 (4.0)
Serious Adverse Events						
Total patients, n (%)	41 (9.6)	61 (13.9)	54 (13.7)	58 (14.3)	7 (9.6)	14 (18.7)
Withdrawals Due to AE						
Total, n (%)	10 (2.3)	5 (1.1)	8 (2.0)	3 (0.7)	3 (4.1)	2 (2.7)

Outcome	CALIMA		SIROCCO		ZONDA	
	Ben N = 441	Placebo N = 440	Ben N = 398	Placebo N = 407	Ben N = 73	Placebo N = 75
Notable Harms, n (%)						
Upper respiratory tract infection	38 (8.9)	42 (9.5)	32 (8.1)	37 (9.1)	5 (6.8)	5 (6.7)
Influenza	14 (3.3)	25 (5.7)	19 (4.8)	24 (5.9)	1 (1.4)	5 (6.7)
Pneumonia-SAE	0	4 (0.9)	2 (0.5)	3 (0.7)	2 (2.7)	3 (4.0)
Influenza-SAE	2 (0.5)	0	0	1 (0.2)	0	2 (2.7)
Injection-site reactions	9 (2.1)	8 (1.8)	9 (2.3)	8 (2.0)	0	2 (2.7)
Any hypersensitivity	13 (3.0)	17 (3.9)	11 (2.8)	11 (2.7)	2 (2.7)	1 (1.3)

AE = adverse event; AQLQ12+ = Asthma Quality of Life Questionnaire for 12 years and older; ben = benralizumab; CI = confidence interval; ED = emergency department; HRQoL= health-related quality of life; ICS = inhaled corticosteroid; LS = least squares; MD = mean difference; NR = not reported; OCS = oral corticosteroid; SAE = serious adverse event; SD = standard deviation.

Note: Estimate of the median per cent reduction from baseline in final OCS dose in the two treatment groups was compared with the placebo group using a Wilcoxon rank sum test, yielding the *P* value presented. The Hodges–Lehmann estimate and CIs were presented. The estimate was the median for the n1 × n2 differences between treatment groups, where n1 was the number of patients in each benralizumab-treated group, and n2 was the number of patients on placebo. This was not the same as the difference between the observed medians within each group.

[a] Primary outcome of CALIMA and SIROCCO: Statistical analysis model was a negative binomial model including covariates treatment group, region, number of exacerbations in the previous year, and use of maintenance oral corticosteroids. Total follow-up time was defined as the time from randomization to the date of week 56 visit (end of treatment) or last contact if the patient was lost to follow-up. The log of each patient's corresponding follow-up time was used as an offset variable in the model to adjust for patients having different exposure times during which the events occurred. Annual exacerbation rates were model estimated.

[b] The model was: change from baseline in AQLQ12+ score = Treatment + baseline AQLQ12+ score + region + use of maintenance oral corticosteroids + visit + treatment × visit. The number of patients in the repeated measures analysis represents all patients with baseline and at least one post-baseline assessment.

[c] Primary outcome of ZONDA: The Wilcoxon rank sum test was the primary analysis method and was used for the multiplicity-protected end point.

Source: Clinical Study Report for CALIMA,[4] SIROCCO,[5] ZONDA.[6]

Introduction

Disease Prevalence and Incidence

Asthma is a chronic respiratory disorder characterized by reversible airway obstruction, inflammation of the airways, airway hyper-responsiveness, and remodelling. Symptoms may include wheezing, dyspnea, chest tightness, sputum production, and coughing associated with airway limitation and hyper-responsiveness to exogenous and endogenous stimuli. Onset can occur at any time, including in young children. It is estimated that 2.4 million Canadians aged 12 years and older have a diagnosis of asthma. Severe eosinophilic asthma is an asthma phenotype characterized by the presence of eosinophils in the airways and sputum despite conventional asthma therapy, and it affects 5% to 10% of all asthma patients.[7] The prevalence of uncontrolled severe eosinophilic asthma is likely lower. Eosinophils are involved in the pathogenesis of asthma through the release of pro-inflammatory mediators at the airways, which contribute to epithelial cell damage, airway hyper-responsiveness, mucus hypersecretion, and airway remodelling.[7,8]

Standards of Therapy

Asthma is managed acutely, largely with the use of inhaled short-acting beta agonists, also known as “rescue” bronchodilators, and through maintenance therapies, many of which address the underlying pathophysiology of the disease. Non-pharmacological measures are considered to be critical underpinnings of good asthma management, and these include environmental control, allergen avoidance, and asthma education. The goal of maintenance therapy is to maintain control of asthma, indicated by absence of asthma exacerbations, and improvement in symptoms. The cornerstone of maintenance therapy of asthma is the use of an inhaled corticosteroid (ICS). The major drawback of ICS use, particularly at high doses, is systemic absorption of the ICS, which can lead to some of the classic side effects associated with chronic corticosteroid use, including osteoporosis. Adjunctive drugs include long-acting beta2 agonists (LABAs), which are available in fixed-dose combinations with an ICS. As long as LABAs are used in combination with an ICS, they are considered to be relatively safe and well-tolerated in asthma. Additional options, typically for asthma with an allergic phenotype, include leukotriene receptor antagonists and immunoglobin E (IgE) inhibitors. Although the leukotriene antagonists are well-tolerated, they generally have limited efficacy. IgE inhibitors, namely omalizumab, have classic drawbacks associated with monoclonal antibodies, such as hypersensitivity and injection-site reactions, and a major drawback is cost. Other bronchodilators, such as the long-acting muscarinic antagonists (LAMAs) and methylxanthines, such as theophyilline, may be considered, but are definitely not first-line options. Theophylline is associated with significant tolerability and safety issues, as well as numerous drug interactions, limiting its use. Finally, oral corticosteroids (OCSs), due to their poor tolerability and safety profile, are typically reserved for management of exacerbations, or for patients whose asthma has not been controlled on the aforementioned maintenance therapies. OCSs are associated with significant side effects, mitigated somewhat by their short-term use in managing exacerbations. Long-term use of an OCS would be considered a last resort due to the significant harms associated with this class.[9,10]

Drug

Benralizumab is an interleukin-5 (IL-5) inhibitor, a monoclonal antibody that binds to the alpha subunit of the IL-5 receptor. The IL-5 alpha receptor is found on eosinophils and basophils. Binding of the monoclonal antibody facilitates the interaction of these cells with natural killer cells, resulting in the death of eosinophils. Eosinophils mediate inflammation in asthma, and thus inhibiting eosinophils has an anti-inflammatory effect. Benralizumab is administered by subcutaneous injection, 30 mg once every four weeks (Q4W) for the first three doses, then once every eight weeks (Q8W) thereafter. Injections should be administered into the upper arm, thigh, or abdomen. Benralizumab is indicated as an add-on maintenance treatment for adult patients with severe eosinophilic asthma.

Table 2: Key Characteristics of Benralizumab, Reslizumab, Mepolizumab, and Omalizumab

	Benralizumab	Reslizumab	Mepolizumab	Omalizumab
Mechanism of action	Antibody to the alpha subunit of the IL-5 receptor	Anti-IL-5 antibody	Anti-IL-5 antibody	Anti-IgE antibody
Indication[a]	Add-on maintenance treatment of adult patients with severe eosinophilic asthma	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 treatment	Add-on maintenance treatment of adult patients with severe eosinophilic asthma who: • are inadequately controlled with high-dose inhaled corticosteroids and an additional asthma controller(s) (e.g., LABA), and • have a blood eosinophil count of ≥ 150 cells/μL at initiation of treatment with mepolizumab OR ≥ 300 cells/μL in the past 12 months.	Treatment of adults and adolescents 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 ICS
Route of administration	Subcutaneous injection	Intravenous infusion	Subcutaneous injection	Subcutaneous injection
Recommended dose	30 mg administered once every 4 weeks for the first 3 doses, and then once every 8 weeks thereafter	3 mg/kg every 4 weeks	100 mg every 4 weeks	150 mg to 375 mg every 2 or 4 weeks depending on body weight and serum IgE
Serious side effects and safety issues	Anaphylaxis, injection-site reaction, infection	Anaphylaxis, injection-site reaction, infection	Anaphylaxis, injection-site reaction, infection	Anaphylaxis, injection-site reaction, infection

ICS = inhaled corticosteroids; IgE = immunoglobulin E; IL-5 = interleukin-5; LABA = long-acting beta2 agonist.
[a] Health Canada indication.
Source: Product monographs for benralizumab,[11] reslizumab,[12] mepolizuma,[13] and omalizumab.[14]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of benralizumab as an add-on maintenance treatment of adult patients with severe eosinophilic asthma.

Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase III and IV studies were selected for inclusion based on the selection criteria presented in Table 3.

Table 3: Inclusion Criteria for the Systematic Review

Patient population	Adults with severe eosinophilic asthma Subgroups of interest: • baseline asthma control medication • baseline oral corticosteroid • baseline peripheral eosinophil count • baseline IgE levels • previous use of omalizumab or mepolizumab or resilizumab.
Intervention	Benralizumab 30 mg SC once every four weeks for the first three doses then once every eight weeks thereafter
Comparators	Inhaled corticosteroids alone or in combination with one or more of the following: • Mepolizumab • Reslizumab • Omalizumab • LABA • Leukotriene receptor antagonists • Oral corticosteroid (chronic) • LAMA • Rescue medications (e.g., SABA, SAMA) may be used for acute exacerbations
Outcomes	**Key efficacy outcomes:** • Mortality • Acute asthma exacerbations[a] • Hospitalizations, ED visits, physician visits due to asthma excabercation[a] • Use of oral corticosteroids[a] • Health-related quality of life as measured by a validated scale[a] • Days of missed school or work[a] **Other efficacy outcomes:** • Change in pulmonary function (e.g., PEF, FEV1) • Symptom reduction (e.g., ACQ)[a] • Change in number of asthma symptom-free days or nights[a] • Incidence of nocturnal awakenings[a] • Reduction in use of ICS[a] • Reduction in use of rescue medication[a] • Blood or sputum eosinophil levels

	Harms outcomes: AEs, SAEs, WDAEs Notable harms: infection, hypersensitivity reactions, local injection reactions
Study design	Published and unpublished RCTs phase III and IV

ACQ = Asthma Control Questionnaire; AE = adverse event; ED = emergency department; FEV1 = forced expiratory volume in one second; IgE = immunoglobin E; LABA = long-acting beta2 agonists; LAMA = long-acting muscarinic antagonists; PEF = peak expiratory flow; RCT = randomized controlled trial; SABA = short-acting beta2 agonists; SAE = serious adverse event; SAMA = short-acting muscarinic antagonists; SC = subcutaneous; WDAE = withdrawal due to adverse event.

[a] These outcomes were identified as important to patients in their input to CADTH Common Drug Review.

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 Fasenra and benralizumab.

No methodological filters were applied to limit by study type. 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. See Appendix 2 for the detailed search strategies.

The initial search was completed on March 28, 2018. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on September 20, 2018. 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 CADTH Common Drug Review (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 in Table 4 and excluded studies (with reasons) are presented in Appendix 3 .

Results

Findings from the Literature

A total of three studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

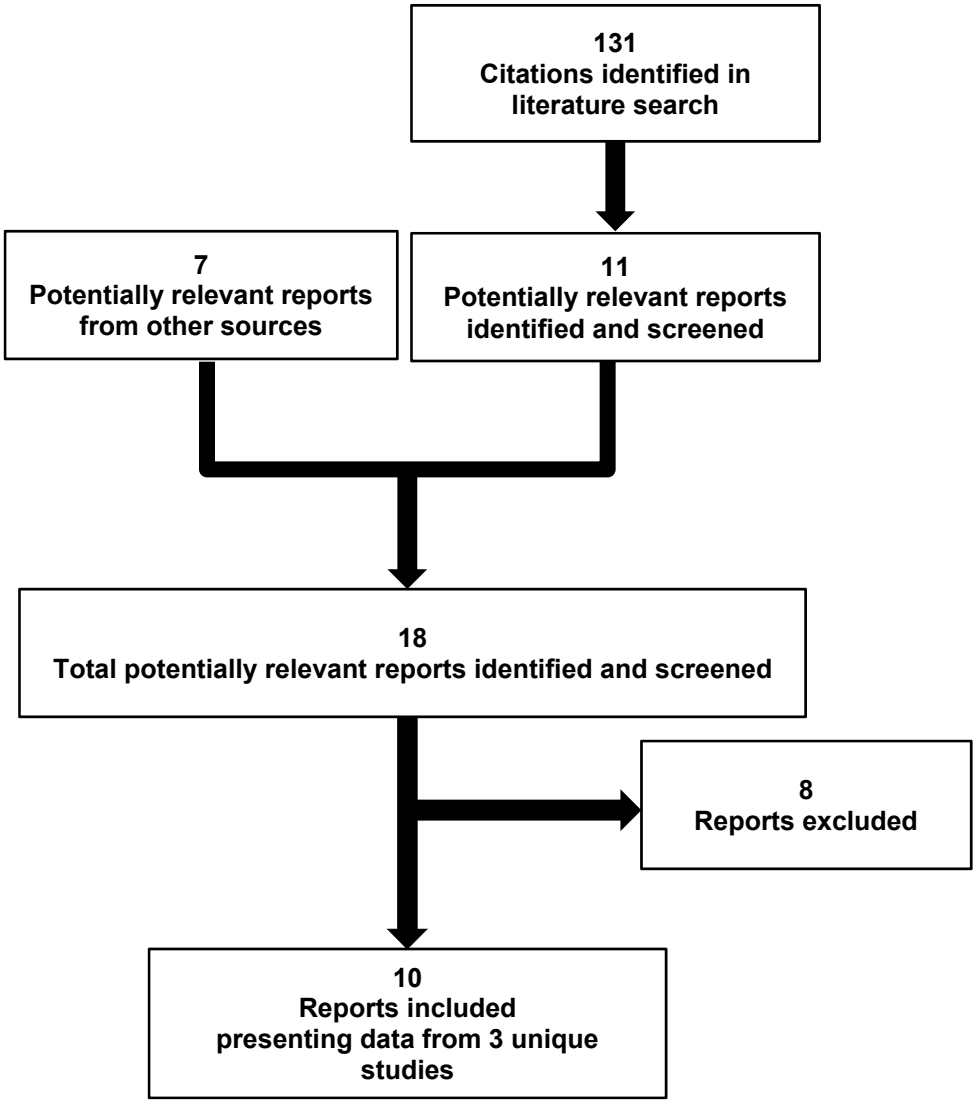


Table 4: Details of Included Studies: CALIMA and SIROCCO

		CALIMA	SIROCCO
Designs & Populations	**Study design**	DB RCT	DB RCT
	Locations	303 centres: 11 countries (Canada, USA, Europe, South America, Asia)	374 centres: 17 countries (USA, Mexico, Europe, South America, Australia, Asia)
	Randomized (N)	1,306	1,205
	Inclusion criteria (common to both trials)	Female and male aged 12 to 75 years (adolescents in Europe were not allowed to take the Q4W regimen) Weight of ≥ 40 kg Physician-diagnosed asthma requiring treatment with medium- to high-dose ICS (> 250 mcg fluticasone dry powder formulation equivalents total daily dose) and a LABA, for at least 12 months prior to visit 1 Documented treatment with ICS and LABA for at least 3 months prior to visit 1 with or without OCS and additional asthma controllers; ICS and LABA could be parts of a combination product or given by separate inhalers Pre-bronchodilator FEV1 of < 80% predicted (< 90% predicted for patients 12 to 17 years of age) at visit 2 At least 2 documented asthma exacerbations in the 12 months prior to the date of informed consent that required use of a systemic corticosteroid or a temporary increase from the patient's usual maintenance dose of OCS ACQ-6 score ≥ 1.5 at visit 1 Documented post-bronchodilator reversibility in FEV1 of > 12% and > 200 mL in FEV1 within 12 months prior to visit 1; if historical documentation was not available, reversibility had to be demonstrated and documented at visit 2 Met ≥ 1 of the following conditions over the 7 days prior to randomization: • > 2 days with a daytime or night-time symptoms score ≥ 1 • Rescue short-acting beta2 agonist use on > 2 days • ≥ 1 nocturnal awakening due to asthma Pre-bronchodilator FEV1 of < 80% (< 90% predicted for patients 12 to 17 years of age) predicted at day of randomization visit Blood eosinophils 300 cells/μL or greater and less than 300 cells/μL at screening in a ratio of approximately 2:1	
	Inclusion criteria (distinct)	Documented treatment with an ICS + LABA for at least 3 months prior to visit 1, with or without ICS: The ICS dose had to be ≥ 500 mcg/day fluticasone propionate dry powder formulation or equivalent daily	Documented treatment with an ICS + LABA for at least 3 months prior to visit 1, with or without ICS: For patients 18 years of age and older, the ICS dose had to be > 500 mcg/day fluticasone propionate dry powder formulation or equivalent daily For patients ages 12 to 17, the ICS dose had to be ≥ 500 mcg/day fluticasone propionate dry powder formulation or equivalent daily
	Exclusion criteria	Clinically important pulmonary disease other than asthma Acute upper or lower respiratory infections requiring antibiotics or antiviral medication within 30 days prior to the date of informed consent Current smokers or former smokers with a smoking history of ≥ 10 pack-years.	Clinically important pulmonary disease other than asthma Acute upper or lower respiratory infections requiring antibiotics or antiviral medication within 30 days prior Current smokers or former smokers with a smoking history of ≥ 10 pack-years

		CALIMA	SIROCCO
		Clinically significant asthma exacerbation, in the opinion of the investigator, including those requiring use of OCS, or an increase in maintenance dose of OCS 14 days prior to the date of informed consent	
DRUGS	**Intervention**	Benralizumab 30 mg once every 4 weeks or benralizumab 30 mg once every 4 weeks for the first three doses followed by once every 8 weeks for the remainder of the treatment period	Benralizumab 30 mg once every 4 weeks or benralizumab 30 mg once every 4 weeks for the first three doses followed by once every 8 weeks for the remainder of the treatment period
	Comparator(s)	Placebo	Placebo
DURATION	**Phase**		
	Run-in	2 weeks minimum	2 weeks minimum
	Double-blind	56 weeks	48 weeks
	Follow-up	4 weeks (extension available [BORA study])	4 weeks (extension [BORA study] available)
OUTCOMES	**Primary end point**	Annual asthma exacerbation rate	Annual asthma exacerbation rate
	Other end points	Pre-bronchodilator FEV1 and post-bronchodilator FEV1 Asthma symptom score (total, daytime, and night time) Rescue medication use Home lung function (morning and evening PEF) Nights with awakening due to asthma ACQ-6 Time to first asthma exacerbation and proportion of patients with ≥ 1 asthma exacerbation AQLQ12+ EQ-5D-5L Annual rate of asthma exacerbations that are associated with an ER/urgent care visit or a hospitalization WPAI+CIQ Asthma-specific resource utilization (e.g., unscheduled physician visits, unscheduled phone calls to physicians, use of other asthma medications) • Pharmacokinetic parameters • ADA • CGIC • PGIC • AEs/SAEs Blood eosinophils	
NOTES	**Publications**	Fitzgerald 2016[15]	Bleecker 2016[16]

ACQ-6 = six-question Asthma Control Questionnaire; ADA = anti-drug antibodies; AQLQ12+ = Asthma Quality of Life Questionnaire for 12 years and older; AE = adverse event; CGIC = Clinician Global Impression of Change; DB RCT = double-blind randomized controlled trial; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; ER = emergency room; FEV1 = forced expiratory volume in one second; ICS = inhaled corticosteroid; LABA = long-acting beta2 agonist; OCS = oral corticosteroid; PEF = peak expiratory flow; PGIC = Patient Global Impression of Change; Q8W = every eight weeks; SAE = serious adverse event; WPAI+CIQ = Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions.

Note: Seven additional reports were included (manufacturer's submission,[17] Clinical Study Report for CALIMA,[4] SIROCCO,[5] ZONDA,[6] FDA clinical and statistical review,[18,19] and Health Canada Reviewer's Report[20]).

Source: Clinical Study Report for CALIMA,[4] SIROCCO.[5]

Table 5: Details of Included Studies: ZONDA

		ZONDA
Designs & Populations	**Study design**	DB RCT
	Locations	64 centres: 12 countries (Canada, USA, Europe, South America, South Korea)
	Randomized (N)	220
	Inclusion criteria	Female and male aged 12 to 75 years Weight of ≥ 40 kg Peripheral blood eosinophil count of ≥ 150 cells/μL assessed by local lab at visit 1 (Week −10). Asthma requiring treatment with medium- to high-dose ICS (> 250 mcg fluticasone dry powder formulation equivalents total daily dose) and a LABA, for at least 12 months prior to visit 1 Documented treatment with high-dose ICS (> 500 mcg fluticasone propionate dry powder formulation equivalents total daily dose) and LABA for at least 6 months prior to visit 1 (Week −10). The ICS and LABA could have been contained within a combination product or given by separate inhalers • For ICS/LABA combination preparations, the highest approved maintenance dose in the local country met this ICS criterion. • Chronic OCS therapy for at least 6 continuous months directly preceding visit 1 (Week −10). Patients must have been on doses equivalent to 7.5 mg/day to 40 mg/day of prednisolone/prednisone at visit 1 and must have been on a stable dose for at least 2 weeks prior to randomization. • Patients with documented failures of OCS reduction within 6 months prior to visit 1 (Week −10) were not required to proceed through the dose optimization phase during run-in. Failed attempts at OCS dose reduction were those that resulted in documented clinical deterioration or reduced lung function attributed to asthma, defined as: o Pre-bronchodilator FEV1 < 80% of personal baseline o Morning peak expiratory flow (PEF) < 80% of personal baseline o Night-time awakenings increase of > 50% of mean personal baseline o Albuterol, salbutamol use > 4 puffs/day above mean personal baseline o Requirement for a prednisone or prednisolone burst (large temporary increase) to treat an asthma exacerbation provoked by steroid reduction Morning pre-bronchodilator FEV1 of < 80% predicted at visit 2 Evidence of asthma as documented by either: • Airway reversibility (FEV1 ≥ 12% and 200 mL) demonstrated at visit 1, visit 2, or visit 3 (Week −10, −8, or −6) using the maximum post-bronchodilator procedure or • Documented reversibility in the previous 24 months prior to Visit 1 (Week −10) or • Airway hyper-responsiveness (PC20 FEV1 methacholine concentration ≤ 8 mg/mL) documented in the previous 12 months prior to planned date of randomization OR • Airflow variability in clinic FEV1 ≥ 20% between 2 consecutive clinic visits documented in the 12 months prior to the planned date of randomization (FEV1 recorded during an exacerbation should not be considered for this criterion). At least 1 documented asthma exacerbation in the previous 12 months prior to the date informed consent was obtained **Inclusion criteria at randomization** Optimized OCS dose reached at least 2 weeks prior to randomization.
	Exclusion criteria	Clinically important pulmonary disease other than asthma Acute upper or lower respiratory infections requiring antibiotics or antiviral medication within 30 days prior Current smokers or former smokers with a smoking history of ≥ 10 pack-years.
Drugs	**Intervention**	benralizumab 30 mg once every 4 weeks benralizumab 30 mg once every 4 weeks for the first three doses followed by once every 8 weeks for the remainder of the treatment period
	Comparator(s)	Placebo

		ZONDA
DURATION	**Phase**	
	Run-in	8 weeks
	Double-blind	28 weeks
	Follow-up	8 weeks (extension [BORA study] available)
OUTCOMES	**Primary end point**	Percentage reduction in final OCS dose compared with baseline (visit 6), while maintaining asthma control
	Other end points	• Patients with ≥ 50% reduction in average daily OCS dose at visit 14 compared with baseline dose, while maintaining asthma control • Patients with ≥ 25% reduction in the final OCS dose at visit 14 compared with baseline dose, while maintaining asthma control • Patients with 100% reduction in average daily OCS dose at visit 14 compared with baseline dose, while maintaining asthma control • Patients with average final OCS dose ≤ 5.0 mg daily at visit 14, while maintaining asthma control • Patients with ≤ 5.0 mg reduction on daily OCS dose at visit 14 compared with baseline dose, while maintaining asthma control • Patients with ≥ 25% reduction in the final OCS dose at visit 14 compared with baseline dose, and with final OCS dose of ≤ 5.0 mg daily at visit 14, while maintaining asthma control • Patients with ≥ 1 asthma exacerbation after randomization • Annual rate of asthma exacerbations after randomization • Annual rate of asthma exacerbations that are associated with an emergency room (ER) visit or a hospitalization after randomization • Time to the first asthma exacerbation after randomization • Time to first exacerbation requiring hospitalization • Time to first exacerbation requiring hospitalization or ER visit • Number of days in hospital due to asthma • Mean number of days with OCS taken for exacerbations • Change from baseline in pre-bronchodilator forced expiratory volume in 1 second (FEV1) • Change from baseline in asthma symptom score (total, daytime, and night time) • Change from baseline in rescue medication use • Change from baseline in home lung function (morning and evening peak expiratory flow [PEF]) • Change from baseline in the number of nights with awakening due to asthma requiring rescue medication • Change from baseline in ACQ-6 • Change from baseline in Asthma Quality of Life Questionnaire for 12 years and older (AQLQ12+) • Change from baseline in blood eosinophils
NOTES	**Publications**	Nair 2017[21]

ACQ-6 = six-question Asthma Control Questionnaire; AQLQ12+ = Asthma Quality of Life Questionnaire for 12 years and older; DB RCT = double-blind randomized controlled trial; FEV1 = forced expiratory volume in one second; ICS = inhaled corticosteroid; LABA = long-acting beta2 agonist; OCS = oral corticosteroid; PEF = peak expiratory flow.

Note: Seven additional reports were included (manufacturer's submission,[17] Clinical Study Report for CALIMA,[4] SIROCCO,[5] ZONDA,[6] FDA clinical and statistical review,[18,19] Health Canada Reviewer's Report[20]).

Source: Clinical Study Report for ZONDA.[6]

Included Studies

Description of Studies

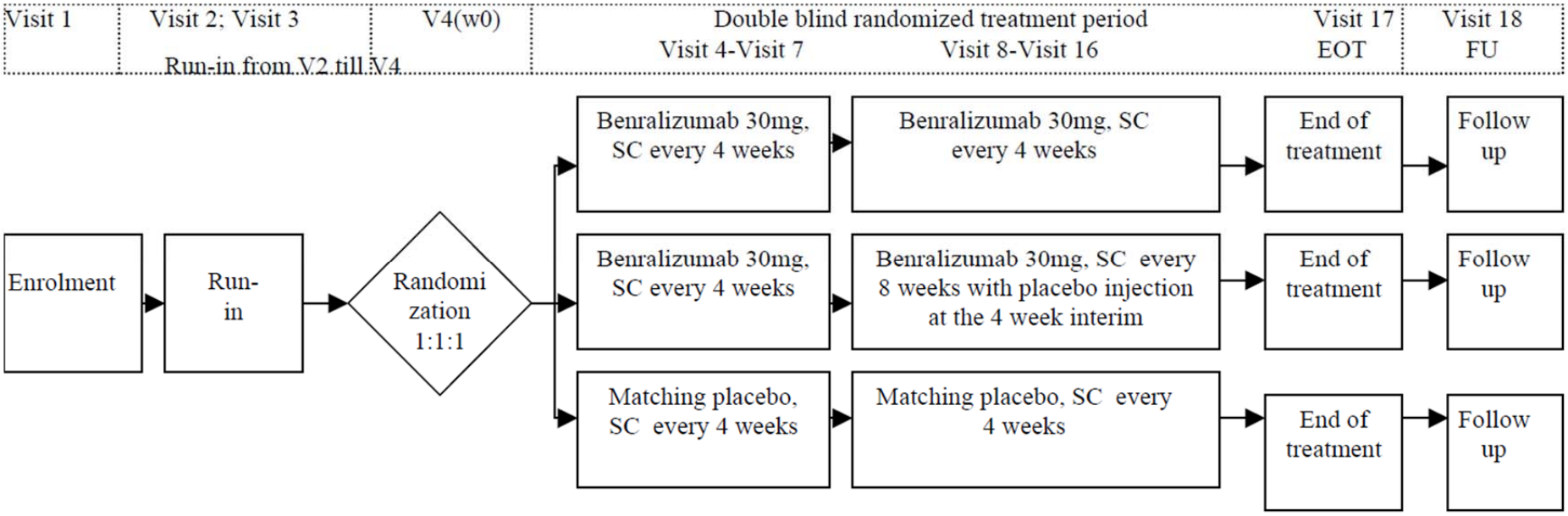
Three pivotal manufacturer-sponsored double-blind randomized controlled trials (DB RCTs) met the inclusion criteria for this systematic review. CALIMA and SIROCCO were similarly designed studies that compared two different doses of benralizumab, administered Q4W and Q8W, to placebo. ZONDA was a 28-week study that compared benralizumab Q4W or Q8W with placebo. Only the latter Q8W regimen is of interest for this review, as it is the Health Canada–approved regimen. CALIMA was a 56-week study and SIROCCO lasted 48 weeks. The population in SIROCCO was all on high-dose ICS, while CALIMA included both high- and medium-dose ICS, the latter group added as a protocol amendment. Both studies enrolled populations with high (300 cells/μL) and lower (< 300 cells/μL) eosinophil counts, in a 2:1 ratio, respectively, and the primary analysis in both focused on patients in the high eosinophil count group who were on high-dose ICS.[4-6]

Randomization was carried out using an interactive Web/voice response system. SIROCCO and CALIMA participants were stratified by age group (adult or adolescent), country (for adults) or region (within/outside EU for adolescents), and peripheral blood eosinophil count (≥ 300/μL or < 300/μL), while CALIMA also stratified by ICS dose (high/medium). Adolescents in the EU were restricted to the Q8W dosing regimen due to regulatory requirements to limit drug burden on children. ZONDA stratified by eosinophil level (≥ 150 to < 300 versus ≥ 300 cells/μL), and country or region.[4-6]

Blinding was carried out using a matching placebo injection, in what the manufacturer described as a double dummy technique. Patients on the Q8W regimen received a placebo injection in the alternating fourth week, to mirror the Q4W regimen.[4-6]

CALIMA and SIROCCO each had a two week run-in phase, followed by double-blind phases of 56 and 48 weeks, respectively, and a four-week follow-up. Patients in CALIMA, SIROOCO, or ZONDA could enter the BORA extension, in which case they did not enter into the follow-up phase. A longer run-in phase (eight weeks) in ZONDA confirmed that patients indeed required an OCS to maintain asthma control, and established a stable baseline OCS dose ("dose optimization phase"). There were patients that were considered to have been "historically" optimized coming into the study if they had already tried to reduce their OCS dose and had experienced deterioration of their asthma (evidenced by forced expiratory volume in one second [FEV1] and peak expiratory flow [PEF] below 80%, increase in night-time awakenings of more than 50%, salbutamol use of more than four puffs/day, and a need for an OCS or increased dose of an OCS). Otherwise, in this dose optimization phase patients were stepped down in their OCS dose until they experienced the clinical deterioration described above.[4-6]

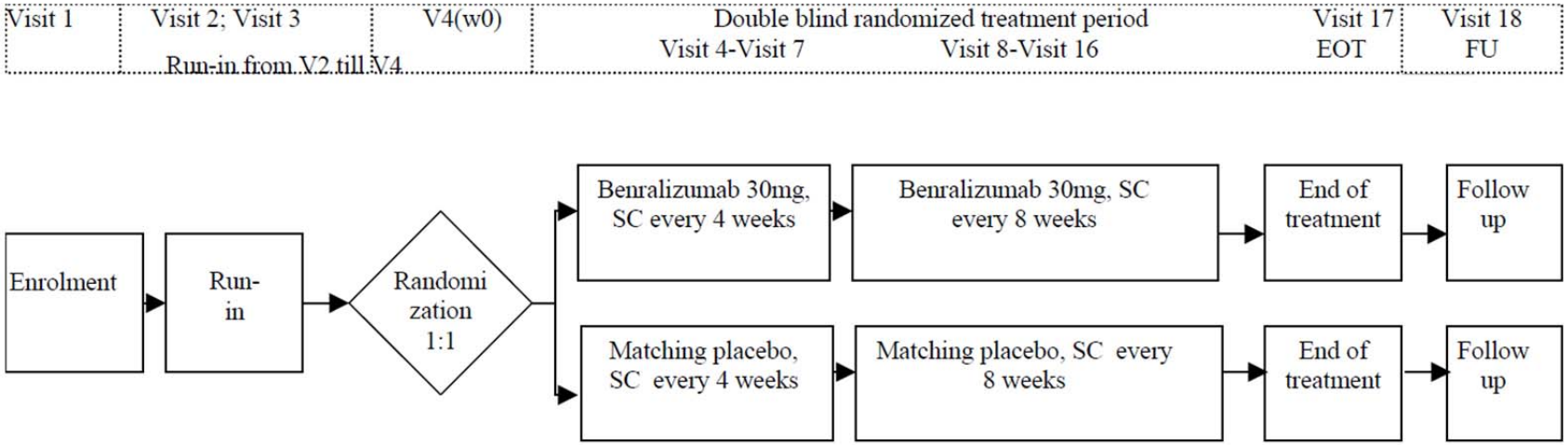
Figure 2: Study Flow Chart for CALIMA



EOT = end of treatment; FU = follow-up; SC = subcutaneous.

Source: Clinical Study Report for CALIMA.[4]

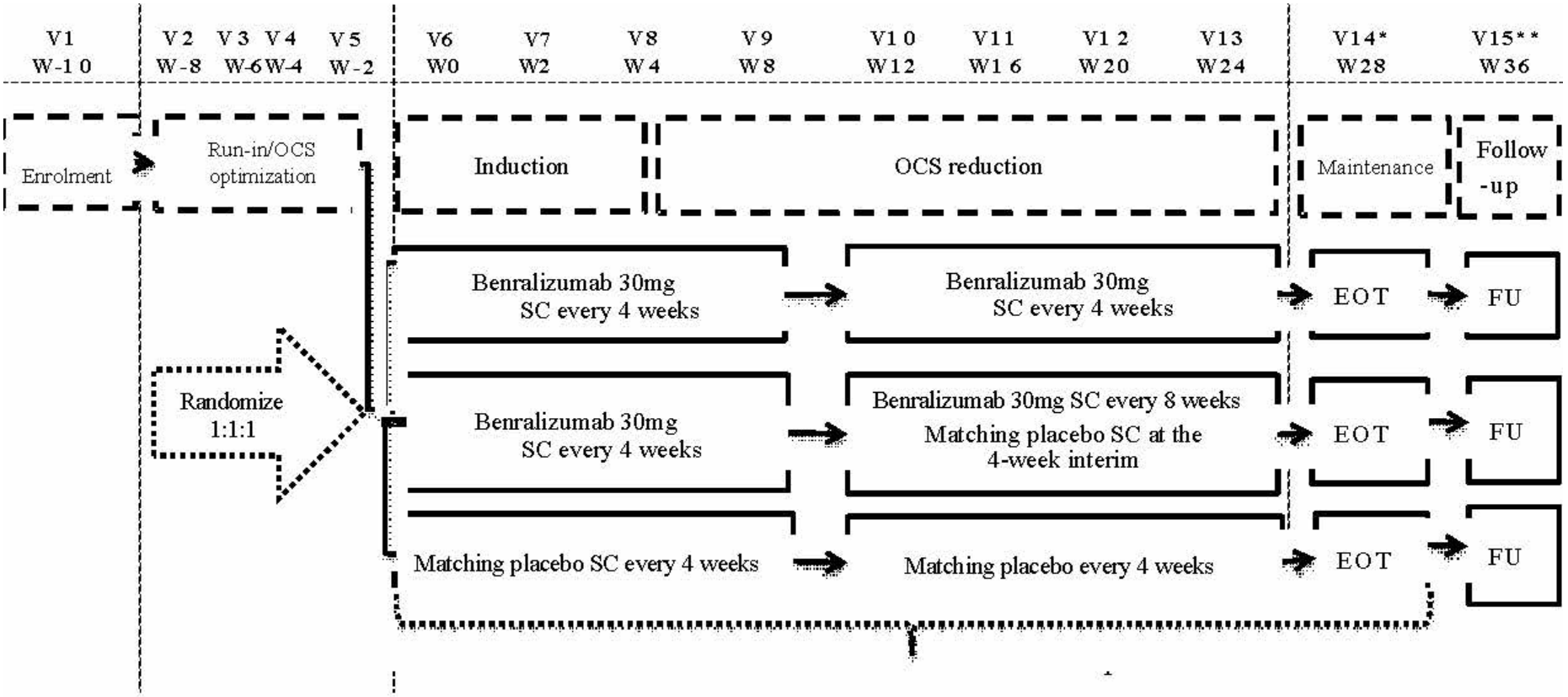
Figure 3: Study Flow Chart for SIROCCO



EOT = end of treatment; FU = follow-up; SC = subcutaneous.

Source: Clinical Study Report for SIROCCO.[5]

Figure 4: Flow Chart of Study Design for ZONDA



EOT = end of treatment; FU = follow-up; OCS = oral corticosteroid; SC = subcutaneous.

Source: Clinical Study Report for ZONDA.[6]

In ZONDA, the treatment period with respect to OCS was divided into three phases: induction, reduction, and maintenance. In the induction phase, (from week 0 to week 4) patients remained on the optimized OCS dose. In the reduction phase (from week 4 to week 24, inclusive), OCS dose reduction was initiated at week 4 with dose reduction following at four-week intervals. Patients had their doses reduced according to a set schedule, and dose reductions could only occur if patients met various criteria indicating their asthma was stable, as described previously. [6]

Populations

Inclusion and Exclusion Criteria

In CALIMA and SIROCCO, patients were to have physician-diagnosed asthma, and within three months of visit 1, patients in CALIMA were required to be on at least a medium dose of an ICS (≥ 500 mcg fluticasone dry powder equivalent) plus a LABA and in SIROCCO all patients had to be on a high dose (> 500 mcg fluticasone dry powder equivalent) plus a LABA. Patients were to have a pre-bronchodilator FEV1 of at least 80% of predicted normal, or if 12 to 17 years of age, 90% of predicted normal. Patients were to have had at least two documented asthma exacerbations within the past 12 months, requiring at least a systemic corticosteroid or an increase in dose from the patient's usual maintenance OCS. The main noteworthy exclusion criterion in all three studies, according to the clinical expert consulted by CADTH on this review, was current or former smoker. [4,5]

In ZONDA, patients had to have continuous treatment with an OCS (between 7.5 mg and 40 mg of prednisone daily) as well as documented treatment with a high-dose ICS for at least six continuous months preceding visit 1. Patients with documented failure of dose reduction were not required to enter the dose optimization phase. Documented failure was indicated by clinical deterioration, including a reduction of FEV1 and PEF below 80% of personal baseline, night-time awakenings increased by more than 50% of the mean personal baseline, salbutamol use more than four puffs daily, requirement for a large increase in prednisone or prednisolone level to treat an asthma exacerbation prompted by steroid reduction. If a patient reached an OCS dose of 5 mg prednisone equivalents or less during dose optimization they were to be screened out of the study.[6]

Baseline Characteristics

Patients in all three studies were approximately 50 years old, and the majority (approximately 60%) were female. The mean standard deviation (SD) eosinophil count was 509 ± 320 cells/μL in the benralizumab group and 656 ± 589 cells/μL with placebo in ZONDA, while mean SD eosinophil counts were 465 ± 360 cells/μL with benralizumab and 488 ± 445 cells/μL with placebo in CALIMA and 470 ± 392 cells/μL with benralizumab and 457 ± 366 cells/μL with placebo in SIROCCO. The pre-bronchodilator FEV1 was between 56% and 62% of predicted normal across all three trials. In CALIMA and SIROCCO, nearly two-thirds of patients had two exacerbations in the past 12 months, and the remainder had three or more in that time.

The mean SD of exacerbations in the past 12 months was 3.1 ± 2.8 for the benralizumab group and 2.5 ± 1.8 for placebo in ZONDA. There were no noteworthy differences in baseline characteristics between treatment groups in CALIMA or SIROCCO according to the clinical expert.

Table 6: Summary of Baseline Characteristics

Title	CALIMA		SIROCCO		ZONDA	
	Benralizumab Q8W N = 441	Placebo N = 440	Benralizumab Q8W N = 398	Placebo N = 407	Benralizumab Q8W N = 73	Placebo N = 75
Mean (SD) age, years	49.0 (14.3)	48.8 (15.1)	47.6 (14.5)	48.7 (14.9)	52.9 (10.1)	49.9 (11.7)
Male, n (%)	168 (38.1)	176 (40.0)	146 (36.7)	138 (33.9)	26 (35.6)	27 (36.0)
Race, n (%)						
White	369 (83.7)	372 (84.5)	287 (72.1)	302 (74.2)	66 (90.4)	70 (93.3)
Black	15 (3.4)	14 (3.2)	15 (3.8)	16 (3.9)	1 (1.4)	1 (1.3)
Asian	55 (12.5)	53 (12.0)	50 (12.6)	50 (12.3)	5 (6.8)	4 (5.3)
Other	2 (0.5)	1 (0.2)	46 (11.6)	39 (9.6)	1 (1.4)	0
Mean (SD) BMI (kg/m^2)	28.76 (6.535)	28.89 (6.495)	28.21 (6.178)	28.93 (7.067)	30.24 (6.534)	28.73 (5.244)
Mean (SD) local baseline eosinophil count, cells/µL	465 (359.6)	488 (444.8)	470 (392.8)	457 (366.3)	509 (320.2)	656 (589.0)
FEV1 pre-BD (% PN)	57.9 (14.9)	58.0 (14.9)	56.1 (14.6)	56.6 (15.0)	59.0 (17.9)	62.0 (16.5)
Mean reversibility, %, (SD)	24.6 (22.9)	27.3 (44.7)	27.2 (24.5)	25.5 (23.1)	25.1 (19.0)	23.2 (18.0)
Median time since asthma diagnosis, years (range)	16.81 (NR)	16.22 (NR)	14.38 (NR)	14.17 (NR)	16.34 (NR)	10.48 (NR)
Number of Exacerbations in the Last 12 Months, n (%)						
1	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	21 (28.8)	24 (32.0)
2	287 (65.1)	288 (65.5)	252 (63.3)	244 (60.0)	23 (31.5)	22 (29.3)
3	93 (21.1)	93 (21.1)	79 (19.8)	76 (18.7)	9 (12.3)	18 (24.0)
≥ 4	60 (13.6)	59 (13.4)	67 (16.8)	87 (21.4)	20 (27.4)	11 (14.7)
Mean (SD)	2.7 (1.42)	2.7 (1.63)	2.8 (1.45)	3.0 (1.81)	3.1 (2.83)	2.5 (1.77)
Number of Exacerbations in the Last 12 Months Resulting in Hospitalization						
0	363 (82.3)	368 (83.6)	298 (74.9)	300 (73.7)	53 (72.6)	49 (65.3)
Mean (SD)	0.3 (0.66)	0.3 (0.75)	0.4 (0.82)	0.4 (0.79)	0.5 (1.12)	0.5 (0.72)
Nicotine Use at Study Entry, n (%)						
Never smoked	348 (78.9)	349 (79.3)	327 (82.2)	328 (80.6)	61 (83.6)	58 (77.3)
Current smoker	3 (0.7)	2 (0.5)	1 (0.3)	5 (1.2)	0	0
Former smoker	90 (20.4)	89 (20.2)	70 (17.6)	74 (18.2)	12 (16.4)	17 (22.7)
Mean nicotine consumption in nicotine pack-years prior to study entry, n (SD)	5.0 (5.0)	4.5 (2.8)	4.9 (2.6)	4.9 (2.8)	4.7 (2.4)	5.5 (2.2)
Mean (SD) ACQ-6 score at baseline	2.75 (0.93)	2.69 (0.92)	2.80 (0.88)	2.87 (0.94)	2.42 (1.21)	2.68 (0.95)
Maintenance Asthma Medications at Baseline						
ICS, n (%)	439 (99.5)	440 (100.0)	398 (100.0)	407 (100.0)	73 (100.0)	75 (100.0)
ICS total daily dose (mcg), mean (SD)	904.517 (NR)	863.015 (NR)	902.718 (NR)	896.100 (NR)	1,191.598 (NR)	1,232.256 (NR)
LABA, n (%)	435 (98.6)	440 (100.0)	398 (100.0)	407 (100.0)	73 (100.0)	75 (100.0)
ICS/LABA, n (%)	384 (87.1)	374 (85.0)	378 (95.0)	378 (92.9)	63 (86.3)	68 (90.7)
OCS, n (%)	44 (10.0)	41 (9.3)	71 (17.8)	68 (16.7)	73 (100)	75 (100)
OCS total daily dose (mg),	9.722 (NR)	12.598 (NR)	15.176 (NR)	15.265 (NR)	14.589	15.080

Title	CALIMA		SIROCCO		ZONDA	
	Benralizumab Q8W N = 441	Placebo N = 440	Benralizumab Q8W N = 398	Placebo N = 407	Benralizumab Q8W N = 73	Placebo N = 75
Mean (SD)					(7.8397)	(6.7314)
LAMA, n (%)	39 (8.8)	36 (8.2)	33 (8.3)	34 (8.4)	21 (28.8)	21 (28.0)
LTRA, n (%)	124 (28.1)	116 (26.4)	150 (37.7)	153 (37.6)	29 (39.7)	25 (33.3)
Xanthine derivatives, n (%)	55 (12.2)	49 (11.1)	60 (15.1)	65 (16.0)	13 (17.8)	10 (13.3)
Other asthma medications, n (%)	9 (2.0)	5 (1.1)	3 (0.8)	5 (1.2)	1 (1.4)	3 (4.0)

PN = predicted normal value; ACQ-6 = six-question Asthma Control Questionnaire; BD = pre-bronchodilator; BMI = body mass index; FEV1 = forced expiratory volume in one second; ICS = inhaled corticosteroids; LABA = long-acting beta2 agonists; LAMA = long-acting muscarinic antagonists; LTRA = leukotriene receptor antagonists; NR = not reported; OCS = oral corticosteroid; SD = standard deviation.

Note: ICS doses were converted to their fluticasone propionate dry powder equivalent. OCS doses were converted to their prednisolone equivalent for this summary. The conversion factor was not reported.

Source: Clinical Study Report for CALIMA,[4] SIROCCO,[5] and ZONDA.[6]

Interventions

All three studies compared two different dose regimens of benralizumab with placebo: benralizumab 30 mg administered Q4W and benralizumab 30 mg Q8W. Patients in the Q8W regimens were titrated, initiated on a Q4W regimen for the first three doses before moving to the Q8W regimen. Placebo doses were matched in appearance to the benralizumab groups. In SIROCCO, all patients were on a high-dose (> 500 mcg fluticasone equivalents) ICS plus a LABA and continued on this dose after commencing the study drug. In CALIMA, patients were on either a high- or medium-dose ICS plus a LABA at randomization and remained on those doses during the study.

In ZONDA, the treatment period with respect to OCS was divided into three phases: induction, reduction, and maintenance, as described previously. The induction phase was from week 0 to 4, as patients stayed on their optimized dose. In the reduction phase, beginning at week 4 patients' dose was reduced every four weeks until their asthma deteriorated. If they met the aforementioned criteria for deterioration of their asthma, they were to be returned to their previous effective dose. Once this up-titration had occurred, they could no longer undergo dose reduction, and the dose they were on was to be maintained until the end of the treatment period. In the maintenance phase (after week 24 to week 28), the dose of OCS reached at week 24 or complete elimination of OCS was maintained. Patients were maintained on their currently prescribed high-dose ICS/LABA therapy, without change, from enrolment throughout the run-in and treatment period.

In all included trials, short-acting beta agonists (metered dose inhaler or nebulizer) were allowed as needed for rescue use and this was recorded in the Asthma Daily Diary. Administration via nebulization was to be recorded separately from metered dose inhaler inhalations.

Outcomes

The annualized rate of unadjudicated asthma exacerbations was the primary outcome of both CALIMA and SIROCCO and a secondary outcome of ZONDA. The annual exacerbation rate in each treatment group was calculated as:

*"Annual Exacerbation Rate = 365.25*Total Number of Exacerbations/Total duration of follow-up within the treatment group (days)"*[4-6]

An asthma exacerbation was defined by a worsening of asthma requiring:

- "Use of systemic corticosteroids (or a temporary increase in a stable OCS background dose) for at least 3 days (a single depo-injectable dose of corticosteroids was considered equivalent to a 3-day course of systemic corticosteroids)"
- "An emergency department/urgent care visit (defined as evaluation and treatment for < 24 hours in an emergency department or urgent care centre) due to asthma that required systemic corticosteroids (as per above)"
- "An inpatient hospitalization due to asthma (defined as an admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥24 hours)"[4-6]

Other analyses that were considered supportive of the primary analysis in CALIMA and SIROCCO included the proportion of patients with at least one exacerbation, proportion of patients with an exacerbation associated with an emergency department visit or hospitalization, the time to first asthma exacerbation, and the reduction in OCS dose associated with an exacerbation. The time to event analysis was performed using a Cox proportional hazards model with covariates for treatment group, region, number of exacerbations in the previous year, and use of maintenance OCS. The manufacturer also performed an additional post hoc analysis of the rate of exacerbations associated with hospitalizations or ED visits.[4-6]

Health-Related Quality of Life

Health-related quality of life was assessed as a secondary outcome in CALIMA and SIROCCO, using the Asthma Quality of Life Questionnaire for 12 years and older (AQLQ12+) and the EuroQoL 5-Dimensions questionnaire (EQ-5D). The AQLQ12+ was assessed as a secondary outcome in ZONDA.

The Asthma Quality of Life Questionnaire (AQLQ) is a patient-reported, disease-specific, health-related quality of life measure that was developed to assess the problems experienced by adults with asthma in their daily lives.[22] The AQLQ(S) is a standardized form of the AQLQ. The AQLQ and AQLQ(S) are made up of 32 questions grouped into four domains: symptoms (12 items), physical activities (11 items), emotional function (five items), and environmental stimuli (four items).[22] Each question is scored on a seven-point scale ranging from 1 (severe impairment) to 7 (no impairment). Patients are asked to recall their experiences in the past two weeks,[22] and in the included studies they were asked to complete assessments every four weeks. The overall score is calculated as the mean of all the individual scores, with a higher score indicating less impairment from asthma and each of the four domain scores calculated as the mean of the individual scores in that domain.[22] The AQLQ12+ version is identical to the AQLQ(S) with the exception of the wording in one of the activity questions being changed from "work-related limitations" to "work-/school-related limitations."[23] The minimal clinically important difference (MCID) is 0.5 for overall scores on the original AQLQ instrument, although the MCID for the AQLQ12+ version is unknown. The AQLQ is reviewed in Appendix 5.

EQ-5D is a generic quality-of-life instrument developed by the EuroQol Group.[24] It may be applied to a wide range of health conditions and treatments.[24] The EQ-5D 5-Levels version (EQ-5D-5L) was introduced in 2005 based on the earlier 3-Levels version.[24] It consists of an

EQ-5D descriptive system and the EQ visual analogue scale (VAS). The descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, each with five levels, ranging from level 1 ("no problems") to level 5 ("extreme problems" or "unable to perform,") which is the worst response in the dimension. Respondents are asked to choose the level that reflects their health state for each of the five dimensions. Results from the EQ-5D-5L descriptive system can be converted into a single index score using a scoring algorithm taking the local patient and population preferences into account. The range of index scores will differ according to the scoring algorithm used. However, in all scoring algorithms of the EQ-5D-5L, a score of 0 represents the health state "dead" and 1.0 reflects "perfect health." Negative scores are also possible for those health states that society (not the individual patient) considers to be "worse than dead." The EQ VAS records the respondent's self-rated health on a vertical scale on which the end points are labelled 0 ("the worst health you can imagine") and 100 ("the best health you can imagine"). The respondents are asked to mark an X on the point of the VAS that best represents their health on that day. The EQ-5D index and VAS scores can be summarized and analyzed as continuous data.[16,24] Hence, the EQ-5D produces three types of data for each respondent: a profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121 or 21143; a population preference-weighted health index score based on the descriptive system; and a self-reported assessment of health status based on the VAS. The MCID for the index score, overall (versus asthma-specific) was 0.056.[25] The EQ-5D is reviewed in Appendix 5.

Symptoms

Patients were asked to complete an Asthma Daily Diary, which included "daily recordings of morning and evening home PEF data, asthma symptoms, inhalations of rescue medication, nights with awakenings due to asthma symptoms, and background medication compliance."[4,5] The total asthma symptom score was a key secondary outcome, controlled for multiplicity, in both the CALIMA and SIROCCO studies. CDR was unable to find an MCID. There were single-item assessments of symptoms in the morning and evening, scored on a scale of 0 (no symptoms) to 3 (unable to sleep/perform normal activities). The two scores were totalled to arrive at the total asthma symptom score (TASS), and if one score was missing then the score for that day was missing. Additionally, the morning diary captured night-time awakenings (yes/no) and the use of rescue medication during these awakenings (yes/no). Asthma symptoms could include, but were not limited to, shortness of breath, wheezing, coughing, and/or chest tightness. Adherence to the Asthma Daily Diary was checked at each visit by the investigator or designate.[4,5]

The Asthma Control Questionnaire (ACQ) is a patient-reported instrument that measures the adequacy of asthma treatment and the original instrument, the ACQ-7, consists of seven items.[26] It includes five items on symptoms (night-time 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 FEV1 as percentage of predicted FEV1.[26] There are two versions of the ACQ-6: one excludes the FEV1 item and one excludes the item on bronchodilator use;[27] the version that excludes FEV1 was used in the three included studies, where it was assessed as a secondary outcome. Patients fill out the questionnaire and responses are based on the past seven days. In the included studies, patients were asked to fill out the ACQ every two weeks. Each item is scored on a seven-point ordinal scale, ranging from 0 (well-controlled) to 6 (extremely poorly controlled).[26] The ACQ score is calculated as the mean score with all items weighted equally and therefore

also ranges from 0 to 6 with higher scores indicating worse asthma control.[26] The MCID is 0.5 in adults for the ACQ-6.[27-29] The ACQ is reviewed in Appendix 5.

The Work Productivity and Activity Impairment (WPAI) questionnaire is a self-reporting instrument used to measure the impact of general health and symptom severity on work and on daily activities over the previous seven days.[30-32] The WPAI was used to gather information for secondary outcomes such as absenteeism. The General Health WPAI questionnaire has six questions from which the values of four different outcomes can be calculated.[31] The WPAI questionnaire can be adapted for a specific disease or condition by replacing the word "problem" in the Specific Health Problem (SHP) version of the WPAI with the specific disease.[33] When the Classroom Impairment Questions (CIQs) are added to create the WPAI+CIQ, there are a total of 10 questions, of which at least three are completed by patients.[34] While it appears that the WPAI+CIQ was meant to be adapted for specific diseases to yield the WPAI+CIQ:SHP, the statistical analysis plans for the CALIMA and SIROCCO trials indicated that the term "health problems" was used. The answers to the 10 questions in the WPAI+CIQ can be used to generate four types of scores: absenteeism (work missed), presenteeism (impairment at class or reduced on-the-job-effectiveness), work productivity loss (overall work impairment), and activity impairment.[31] The scores are provided as impairment percentages, with higher numbers corresponding to greater impairment and less productivity.[31] The WPAI is reviewed in Appendix 5.

Pulmonary Function

FEV1 was a key, multiplicity-controlled secondary outcome of both CALIMA and SIROCCO. FEV1 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 minimal patient perceivable improvement (MPPI) for FEV1 is 230 mL or a 10.38% change from baseline.[35] FEV1 is reviewed in Appendix 5.

PEF — sometimes referred to as PEF rate — is defined as "the maximum flow achieved during an expiration delivered with maximal force starting from the level of maximal lung inflation."[36] Morning and evening PEF were assessed as a secondary outcome in CALIMA and SIROCCO. Electronic peak flow metres automatically store and download measurements as needed, circumventing the need for patients to manually record PEF values in diaries. PEF is usually expressed in units of litres per minute (L/min) and sometimes as a percentage of the predicted normal value or as a change from baseline average values.[37] The MPPI for PEF was 18.8 L/min or a 5.39% change from baseline, with no differences in MPPI values by gender or age, although in a population with moderate to severe asthma.[35] PEF is reviewed in Appendix 5.

Statistical Analysis

Sample Size

In CALIMA and SIROCCO, power calculations were based on the high eosinophil count/high ICS population (≥ 300 cells/μL), seeking 90% power to detect a 40% reduction in exacerbations in both benralizumab dosing regimens versus placebo.[4,5] In ZONDA, 70 patients per treatment group were required to detect a difference in per cent reduction of OCS dose between each benralizumab group and placebo, with 86% power using a two-sided Wilcoxon rank sum test.[6] In CALIMA and SIROCCO, the sample size calculation assumed a two-sided alpha level of 0.04 and an annual exacerbation rate of 0.88 in placebo, an assumption based on published data and from a phase II study.[4,5] The sample size calculation for ZONDA was based on simulations using OCS reduction data from the Steroid

Reduction with Mepolizumab Study, which reported a 50% reduction in the median percentage OCS dose with mepolizumab versus zero per cent reduction with placebo.[6] In CALIMA and SIROCCO, two-thirds of the randomized population were to have high eosinophil counts (≥ 300 cells/μL) and the remaining one-third were to have eosinophil counts below 300 cells/μL.[4,5] In ZONDA, approximately 60 patients were to have eosinophil counts between 150 and 300 cells/μL, while 150 patients were to have eosinophil counts of 300 cells/μL or more.[6]

Analysis of Primary and Secondary End Points

In CALIMA and SIROCCO the exacerbation rate in each of the benralizumab groups was compared with the exacerbation rate in the placebo group using a negative binomial model for the primary analysis. The response variable in the model was the number of asthma exacerbations experienced by a patient over the double-blind treatment period. The model included the following covariates: treatment group, region, number of exacerbations in the previous year, and the use of maintenance OCS (yes/no). The logarithm of the patient's corresponding follow-up time was used as an offset variable in the model to adjust for patients having different exposure times during which the events occur. The continuous secondary efficacy end points, including change from baseline in pre-bronchodilator FEV1, asthma symptom score, ACQ-6, and AQLQ12+, were analyzed using a mixed-effect model for repeated measures analysis. For each end point, the dependent variable was the change from baseline of the parameter at post-baseline scheduled visits up to the end-of-treatment visit. The model included treatment group as the explanatory variable and fixed effects included: region, the use of maintenance oral corticosteroids (yes/no), visit, and treatment x visit interaction while the baseline value acted as a covariate.[4,5] Continuous variables were reported both as means with standard deviations and least squares means with 95% confidence intervals. Exacerbations were reported as annualized exacerbation rates in the primary analysis, with 95% confidence intervals.

In ZONDA, the primary end point (median per cent reduction from baseline in final OCS dose) in the two treatment groups was compared with the placebo group using a Wilcoxon rank sum test, and a Hodges–Lehmann estimate was used to estimate the difference in medians between groups. There were secondary outcomes identified in ZONDA, although none were controlled for multiplicity. Similar to CALIMA and SIROCCO, ZONDA used a negative binomial model to analyze asthma exacerbations. The model used the same covariates as the model in CALIMA and SIROCCO except maintenance OCS, and the same offset variable.[6] A Cochran–Mantel–Haenszel test was used in the comparison of categorical outcomes related to OCS use, such as the proportion of patients achieving 25%, 50%, 75%, and 100% reduction in OCS doses. This test controlled for region. A Cox proportional hazards model was used to analyze the time to first asthma exacerbation as well as time to first exacerbation that required a hospitalization or an emergency department visit. Continuous secondary outcomes were analyzed in a similar manner to CALIMA and SIROCCO, using a mixed-effect model for repeated measures.[6]

Sensitivity Analysis

In addition to the sensitivity analyses to account for missing data described below, the manufacturer performed a number of other sensitivity analyses. In CALIMA and SIROCCO, sensitivity analyses were performed to exclude patients with protocol deviations deemed important, as according to the manufacturer there was no per-protocol analysis in these studies. One analysis focused on patients with eosinophil counts below 300 cells/μL, a population that, despite making up one-third of the enrolled population, was not included in

the primary analysis. There was also an analysis by baseline eosinophils broken down into four categories (< 150 cells/μL, 150 to 299 cells/μL, 300 to 449 cells/μL, and ≥ 450 cells/μL), and the results of this analysis are reported as part of the subgroup analysis reported by CDR.[4,5]

In ZONDA, the manufacturer described a sensitivity analysis of the primary analysis using a proportional odds model that controlled for treatment group, region, and baseline OCS dose. The manufacturer also performed a sensitivity analysis to account for protocol violations in dose titration; this is to account for patients who, instead of having their OCS dose up-titrated to their previous dose after experiencing an exacerbation, were down-titrated in error. In this analysis, the OCS dose associated with the first post-baseline exacerbation was automatically entered into the program as being increased one level. The results of this sensitivity analysis were similar to those of the primary analysis.[6]

Subgroups

Both CALIMA and SIROCCO performed pre-specified subgroup analyses for the same factors. In SIROCCO these were performed on patients with high baseline eosinophil counts (≥ 300 cells/μL), and in CALIMA they were performed in high eosinophil counts and patients on either a high-dose ICS or medium/high-dose ICS.[4,5] The subgroups examined were: OCS use at baseline (yes/no), gender, age (< 18 years, ≥ 18 years to 65 years, and ≥ 65 years), geographic region, body mass index (BMI) (≤ 35 kg/m^2, > 35 kg/m^2), the number of exacerbations in the previous year (two, three, or four or more exacerbations), race, nasal polyps (yes/no), immunoglobulin E (IgE) (≤ 30 KU/L, > 30 KU/L to ≤ 700 KU/L, > 700 KU/L), atopic status (yes/no), and prior treatment with omalizumab (yes/no). Tests for interactions were also pre-planned. However, the threshold for declaring statistical significance was not reported, and there was no mention of any adjustments made for multiple statistical comparisons. The manufacturer noted that these studies were not powered to assess efficacy within these subgroups and should be considered exploratory analyses.[4,5] In ZONDA, subgroup analyses were performed for the following factors: age category (≥ 18 years to < 65 years and ≥ 65 years), gender, BMI (≤ 35 kg/m^2, > 35 kg/m^2), number of exacerbations in the previous year (1, 2, ≥ 3), region, and OCS dose at baseline (≤ 10 mg, > 10 mg).[6] No analyses were planned for these subgroups in ZONDA.

Multiplicity

Multiplicity was accounted for in CALIMA and SIROCCO using a three-step gate-keeping procedure. First, two tests were conducted of the primary outcome, one for each dose regimen versus placebo, at the family-wise error rate of $P = 0.04$ using a Hochberg procedure. If $P < 0.04$ for both tests, then the two key secondary end points for both dose regimens were tested as one family at the family-wise error rate of 0.05 using a Holm procedure. However, if $P < 0.02$ for the smaller P value, then the two secondary end points for the dose associated with this smaller P value were tested at a family-wise error rate of $P = 0.01$, again using a Holm procedure.[4,5]

In ZONDA, adjustment for multiple comparisons was only made for the primary outcome (reduction in OCS dose), using the Hochberg procedure, to account for the fact that two different doses of benralizumab were being compared with placebo. Of the two P values generated, if the larger value was greater than 0.05 then the threshold for statistical significance for the smaller value became 0.025. Otherwise if both P values were below 0.05, statistical significance was declared.[6]

Missing Data

In CALIMA and SIROCCO, the manufacturer employed three different imputation methods to account for missing data. The first, and simplest, approach is referred to as missing at random. This approach assumes that the results for those patients who withdrew from a given group in the study would not differ from the patients who remained in that group. This could mean, for example, that patients who withdrew due to therapeutic failure would still be assumed to be potential responders, when clearly that is not the case. For the other two methods of imputation, dropout reason-based multiple imputation (DRMI) and partial-DRMI, the method of imputation depended on the reason for withdrawal. For partial-DRMI, for benralizumab patients who dropped out for treatment-related reasons (such as adverse event, death, and protocol-defined reasons for stopping therapy) it was assumed that their results would reflect that of the placebo group. For patients from the placebo group who withdrew, it was assumed that their results would be missing at random. DRMI added severe non-compliance to protocol as a treatment-related reason for withdrawal.[4,5]

In ZONDA, the method of imputation for missing data for the primary outcome was not specifically stated. For secondary patient-reported outcomes (ACQ-6, AQLQ12+), the manufacturer stated that no imputation for missing data was carried out, as an optional sensitivity analysis was only planned to be carried out if there was an "imbalance" in missing data between treatment groups, and this was not the case.[6]

Analysis Populations

For all included studies, the full analysis set (FAS) included all patients randomized and treated. According to the manufacturer, they followed the intention-to-treat (ITT) approach, which they defined as "Patients were analyzed according to their randomized treatment, irrespective of whether or not they had prematurely discontinued, according to the Intent-to-Treat (ITT) principle." However their definition did not appear to distinguish between patients randomized and treated and those randomized and not treated, which would be a true ITT. The safety analysis set consisted of all patients who received at least one dose of study drug, and patient data were analyzed based on the actual treatment they received, rather than the group to which they were assigned.[4-6]

Patient Disposition

The percentage of patients withdrawing from CALIMA and SIROCCO ranged between 9% and 12% and in ZONDA it was approximately 5%. There were no notable differences between groups in the proportion of patients withdrawing from any of these studies.

Table 7: Patient Disposition

	CALIMA		SIROCCO		ZONDA	
	Benralizumab Q8W	**Placebo**	**Benralizumab Q8W**	**Placebo**	**Benralizumab Q8W**	**Placebo**
Screened, N	2,505		2,681		369	
Did not enter screening/run-in	324		449		98	
Eligibility criteria not fulfilled	213		302		84	
Development of study-specific withdrawal criteria	70		114		6	
Patient decision	26		24		4	
Other	12		2		2	

	CALIMA		SIROCCO		ZONDA	
	Benralizumab Q8W	Placebo	Benralizumab Q8W	Placebo	Benralizumab Q8W	Placebo
Patient lost to follow-up	2		4		0	
Severe non-compliance to protocol	1		0		0	
Adverse event	0		3		2	
Entered	2,181		2,232		271	
Non-randomized	875		1,027		51	
Eligibility criteria not fulfilled	634		749		35	
Development of study-specific withdrawal criteria	166		188		14	
Patient decision	45		46		1	
Adverse event	16		21		0	
Other	7		17		0	
Severe non-compliance to protocol	4		1		1	
Lost to follow-up	3		3		0	
Death	0		2		0	
Randomized, N (%)	441	440	398	407	73	75
Randomized and treated	441	440	398	407	73	75
Discontinued study, N (%)	51 (11.6)	38 (8.6)	40 (10.1)	40 (9.8)	4 (5.5)	3 (4.0)
Patient decision	27 (6.1)	19 (4.3)	15 (3.8)	17 (4.2)	1 (1.4)	0 (0.0)
Other	9 (2.0)	4 (0.9)	9 (2.3)	14 (3.4)	0 (0.0)	0 (0.0)
Adverse event	3 (0.7)	4 (0.9)	5 (1.3)	1 (0.2)	0 (0.0)	1 (1.3)
Severe non-compliance to protocol	1 (0.2)	2 (0.5)	2 (0.5)	2 (0.5)	0 (0.0)	0 (0.0)
Death	2 (0.5)	1 (0.2)	2 (0.5)	2 (0.5)	2 (2.7)	0 (0.0)
Development of study-specific withdrawal criteria	1 (0.2)	0 (0.0)	1 (0.3)	1 (0.2)	1 (1.4)	1 (1.3)
Lost to follow-up	8 (1.8)	6 (1.4)	6 (1.5)	3 (0.7)	0 (0.0)	1 (1.3)
Eligibility criteria not fulfilled	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Full analysis set, N	441	440	398	407	73	75
Per protocol, N	NR	NR	NR	NR	NR	NR
Safety, N	441	440	398	407	73	75

NR = not reported; Q8W = every eight weeks.

Source: Clinical Study Report for CALIMA,[4] SIROCCO,[5] and ZONDA.[6]

Exposure to Study Treatments

In ZONDA, the mean durations of exposure were 159.77 days (range 1.0 to 190.0 days), and 167.05 days (range 113.0 to 177.0 days) in the benralizumab 30 mg Q8W, and placebo groups, respectively. In CALIMA, the mean durations of exposure were 331.64 days (range: 1 to 399 days), and 336.69 days (range: 1 to 400 days) in the benralizumab 30 mg Q8W, and placebo groups, respectively. In SIROCCO, the mean durations of exposure were 288.02 days (range: 1 to 330 days), and 289.38 days (range: 1 to 343 days) in the benralizumab 30 mg Q8W, and placebo groups, respectively.

Use of asthma-related drugs was allowed as concomitant therapy during the included studies. Use of leukotriene receptor antagonists was most common (31% of patients in CALIMA, 41% in SIROCCO, 38% in ZONDA) followed by methylxanthines (15% in CALIMA, 20% in SIROCCO, 19% IN ZONDA), and anticholinergics (12% in CALIMA, 14% in

SIROCCO, 25% IN ZONDA). There were no notable differences in use of these drugs between studies.

Critical Appraisal

Internal Validity

All included studies used appropriate methods to randomize and allocated patients. All trials were double-blinded, and blinding was facilitated by the use of a matched placebo. Injection-site reactions would be expected to occur more frequently with benralizumab than with placebo, and this might have resulted in accidental unblinding. However the percentage of patients with injection-site reactions was low (3% or less) and the risk of an injection-site reaction did not differ between groups. Therefore, any unblinding that might have occurred due to adverse events is unlikely to have biased the results in a significant way.

The percentage of patients withdrawing from CALIMA and SIROCCO ranged between 9% and 12%, with similar proportions between groups, and withdrawals in ZONDA were low — 6% with benralizumab and 4% with placebo. Larger numbers of data were missing for some patient-reported outcomes in CALIMA and SIROCCO; the manufacturer performed post hoc analyses on these outcomes, and the results were consistent with that of the original analysis. CALIMA and SIROCCO both employed multiple imputation methods to account for missing data, and these sensitivity analyses appeared to support the findings of their original analyses. The FDA statistical reviewer also performed a tipping point analysis, and again this supported the findings of the primary analysis, although the reviewer noted that, with respect to CALIMA, “the results were not so robust to withstand a big variation of assumptions” within the analysis.[19]

Sample size calculations were performed in each of the included studies, and in CALIMA and SIROCCO these calculations were carried out in the subgroup of interest in the study (eosinophil counts of ≥ 300 cells/μL and high-dose ICS) and the minimum requirements for enrolment appear to have been met for each of the subgroups. ZONDA planned a relatively small sample size compared with the other two studies, and this may have been due to the fact that the phenotype they were looking for is quite uncommon, according to the clinical expert consulted for this review.

The manufacturer employed a hierarchical testing procedure to control for multiple statistical comparisons in both CALIMA and SIROCCO. The hierarchy included the following outcomes: annualized exacerbation rate, FEV1, and TASS. The remaining outcomes, including other key outcomes for this CDR review, namely health-related quality of life and exacerbations resulting in hospitalizations and emergency room (ER) visits, were not controlled for multiplicity, which increases the risk of making a type I error. In ZONDA there was no accounting for multiplicity for any of the secondary efficacy outcomes.

A number of subgroup analyses were performed, with interaction *P* values reported, and a number of these subgroups were of interest for this review. However, no adjustments were made for multiple comparisons involving these subgroups. Also, the subgroups did not maintain the strata upon which randomization was based, and this is a limitation as it compromises randomization and introduces the potential for bias, both known and unknown.

The FDA statistical reviewer noted errors in dose titration with some patients in ZONDA. Specifically, 4.5% of patients had their OCS dose down-titrated despite not meeting the criteria for down-titration, while 5% of patients failed to have their dose down-titrated despite

meeting the criteria. The manufacturer assumed that the fact that the errors in dosing occurred in roughly equivalent percentages of patients in either direction, thereby cancelling the effects of each other out. The FDA reviewer agreed with the manufacturer's assessment, but expressed concern that such an error could happen in a pivotal trial and leading the reviewer to "doubt the overall quality of data generated from this trial."[19] Concerned with the overall high proportion of protocol deviations, the FDA reviewer performed an independent per-protocol analysis that supported the results of the primary analysis.[19]

The included studies defined the FAS as including all patients who were randomized and treated, and therefore this is not reflective of a true ITT analysis, in which all patients randomized are included, regardless of whether they were treated. However, all randomized patients appear to have been treated, and therefore the use of the FAS for assessment of efficacy outcomes is not expected to influence the treatment effect.

External Validity

There were no active comparators in each of the included studies, most notably other biologics such as omalizumab, mepolizumab, and reslizumab, the latter two drugs being IL-5 inhibitors. Omalizumab is a monoclonal antibody to IgE, and is approved for moderate to severe persistent asthma in patients with allergy-induced phenotype.

The populations enrolled in the included studies generally reflected the populations that would be candidates for benralizumab, according to the clinical expert consulted for this review. Between 9% and 18% of patients across groups in CALIMA and SIROCCO were identified as taking OCS at baseline, under maintenance therapy. If this range represents patients requiring chronic OCS to manage their asthma, it would be higher than the estimate of approximately 5% provided by the clinical expert consulted by CADTH on this review. However, it is unclear whether these patients were using OCS on a chronic basis, as in ZONDA, or whether they were simply on short-term OCS when baseline assessments were performed. In ZONDA, all patients were required to be on chronic OCS at baseline, and there was a run-in phase where their reliance on OCS to maintain control of their asthma was confirmed. Such a run-in phase to determine OCS use was not part of the design of CALIMA or SIROCCO, so even if patients were taking OCS chronically there was no way of determining whether they needed the drug to maintain asthma control, as was established in ZONDA. The expert noted that current smokers were excluded from the studies, despite the fact that there are a number of patients with asthma who smoke; this is therefore a potential generalizability issue. The populations of both CALIMA and SIROCCO were enriched with patients with high eosinophil counts — patients that would most be expected to respond to a drug that targets eosinophils. It is noteworthy that a relatively large proportion of patients were screened out of the included studies, and it is not clear why the numbers were so large.

The primary outcomes of all the included studies were relevant in assessing the efficacy of asthma drugs in these populations, according to the clinical expert consulted by CDR on this review. Exacerbations are an important contributor to the pathophysiology of asthma, as they are believed to accelerate and entrench remodelling of the airways, and the definitions used in the included trials ensured that the exacerbations were associated with cost drivers within the health care system, such as hospitalizations and ER and physician visits, or with OCS use, which has important adverse effects. ZONDA focused on patients whose asthma was severe enough to require chronic OSC use, and the primary outcome focused on the reduction of OCS dose. In CALIMA and in SIROCCO, the primary analysis focused on patients with high eosinophil counts (at or above 300 cells/μL), while the indication for

benralizumab merely states that patients should have eosinophilic asthma, without defining a minimum eosinophil count. The manufacturer has proposed reimbursement criteria that more precisely follow the design and findings of the pivotal trials.

None of the included studies were of sufficient duration to assess long-term safety. Benralizumab and other IL-5 inhibitors employ a novel mechanism of action and thus it will be important to monitor for safety issues as their use becomes more widespread and as the length of time they are on the market increases. As these drugs modulate immune/inflammatory responses, one of the potential long-term concerns is development of malignancies. There are longer- term extension trials that are designed to assess the safety of benralizumab, and these are summarized in Appendix 6.

Eosinophil counts for inclusion in all studies relied on peripheral (blood) sampling versus induced sputum, despite the fact that sputum is considered to be a more accurate method for assessing eosinophil levels. The clinical expert consulted by CADTH on this review noted that sputum sampling is much more time-consuming to carry out and this is likely the reason that the manufacturer used blood for sampling. The clinical expert also noted that there are limitations in sampling for eosinophils in general, such as cost, patient discomfort, and lack of sensitivity and specificity, and there is no ideal method for measuring eosinophils.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Table 3). See Table 8 and Table 9 for detailed efficacy data. The primary analyses for all efficacy outcomes in CALIMA and ZONDA were carried out in the population of patients with eosinophil counts ≥ 300 cells/μL and on high-dose ICS.

Mortality

Across the studies there were six deaths (1% of patients) in the benralizumab group and three (< 1%) with placebo. Only one death in a benralizumab-treated patient was respiratory-related (pneumonia, in ZONDA) (Table 8).

Exacerbations

The primary outcome of both CALIMA and SIROCCO was the annualized exacerbation rate. The primary analysis in CALIMA and SIROCCO was based on the population with eosinophils ≥ 300 cells/μL and on high-dose ICS. The annualized exacerbation rate was lower for benralizumab versus placebo in both CALIMA over 56 weeks (rate ratio of 0.72; 95% confidence interval [CI], 0.54 to 0.95; $P = 0.019$) and SIROCCO over 48 weeks (rate ratio of 0.49; 95% CI, 0.37 to 0.64; $P < 0.001$), and these differences were statistically significant (Table 8). In response to a request from CDR, the manufacturer also provided data for the FAS for both studies. It should be noted that this was a post hoc analysis, and the full data are summarized in Appendix 4 (Table 15). The results for the FAS are consistent with that of the primary analysis.

The rate ratio for the annualized exacerbation rate for benralizumab versus placebo over 28 weeks in ZONDA was 0.30 (95% CI, 0.17 to 0.53; $P < 0.001$) (Table 9). This outcome does not appear to have been adjusted for multiple comparisons in ZONDA.

The time to first asthma exacerbation was also reported, with a hazard ratio for benralizumab to placebo of 0.73 (95% CI, 0.55 to 0.95; $P \leq 0.018$) in CALIMA, 0.60 (95% CI,

0.46 to 0.78; *P* < 0.001) in SIROCCO, and 0.32 (95% CI, 0.17 to 0.57; *P* < 0.001) in ZONDA.

A total of 40% of benralizumab patients and 51% of placebo patients had at least one exacerbation over the course of 56 weeks in CALIMA and 35% of benralizumab and 51% of placebo patients over 48 weeks in SIROCCO. In ZONDA, 23% of benralizumab and 52% of placebo patients had at least one exacerbation over 28 weeks. No statistical analyses were reported for this outcome in the Clinical Study Report.

Subgroups

Analyses were reported in CALIMA and SIROCCO for subgroups of interest to this review: baseline use of OCS, baseline eosinophils, baseline IgE, and prior use of omalizumab (Table 14). Baseline use of asthma controller medication was already stratified in the design of the studies, as all patients in SIROCCO were on high-dose ICS, and both studies reported the primary analysis in this population. Eosinophil counts were also part of the primary analysis, as it focused on patients with eosinophil counts ≥ 300 cells/μL. Only interactions with *P* values below 0.05 will be noted here; the remaining are found in Table 14. Results were compared in SIROCCO for the subgroup of patients who were on baseline OCS (rate ratio of 0.31; 95% CI, 0.16 to 0.60; *P* < 0.001) versus those not on OCS (0.54; (95% CI, 0.40 to 0.73; *P* < 0.001) and the *P* value for the interaction by baseline OCS use was 0.039. Also in SIROCCO, there was an interaction *P* value of 0.008 based on IgE, with the largest treatment effect found in those with the highest baseline IgE (> 700 KU/L), with a rate ratio of 0.41 (95% CI, 0.20 to 0.81; *P* = 0.011), followed by those with an IgE between 30 KU/L and 700 KU/L (rate ratio of 0.49; 95% CI, 0.36 to 0.67; *P* < 0.001).

Hospitalizations, MD, Emergency Department Visits Due to Exacerbations

In CALIMA, the percentage of patients with exacerbations leading to hospitalizations or emergency department visits was 8.4% with benralizumab and 8.1% with placebo groups over 56 weeks, while in SIROCCO the percentages were 6.7% with benralizumab and 13.9% with placebo groups over 48 weeks and in ZONDA the percentages were 1.4% with benralizumab and 12.0% with placebo groups over 28 weeks (Table 8 and Table 9). As a post hoc analysis, the manufacturer also presented data on the annual exacerbation rate leading to emergency department visits or hospitalizations. In CALIMA the rate ratio for benralizumab versus placebo was 1.23 (95% CI, 0.64 to 2.35; *P* = 0.538); in SIROCCO, the rate ratio was 0.37 (95% CI, 0.20 to 0.67; *P* < 0.001) and in ZONDA the rate ratio for benralizumab versus placebo was 0.07 (95% CI, 0.01 to 0.63; *P* = 0.018).

Health-Related Quality of Life

The primary analysis in CALIMA and SIROCCO was based on the population with eosinophils ≥ 300 cells/μL and on high-dose ICS. In CALIMA, mean (SD) increase (improvement) in AQLQ12+ score was 1.61 (1.24) for benralizumab and 1.32 (1.19) for placebo groups after 56 weeks (least squares [LS] mean difference [MD] of 0.24; 95% CI, 0.04 to 0.45; *P* = 0.019). In SIROCCO mean (SD) increase (improvement) in AQLQ12+ score was 1.56 (1.17) for benralizumab and 1.25 (1.18) for placebo after 48 weeks (LS MD of 0.30; 95% CI, 0.10 to 0.50; *P* = 0.004) (Table 8). The results in the FAS population, provided by the manufacturer in a post hoc analysis, were consistent with the results from the primary analysis (Table 15). Change from baseline in the EQ-5D was reported but no statistical comparisons were provided.

In ZONDA, mean (SD) increase (improvement) in AQLQ12+ score was 1.05 (1.0) for benralizumab and 0.67 (1.1) for placebo after 28 weeks (LS MD of 0.45; 95% CI, 0.14 to 0.76; *P* = 0.004) (Table 9). Note that none of these statistical analyses were adjusted for multiple comparisons and should be considered hypothesis-generating.

Oral Corticosteroid Use

In ZONDA, the per cent reduction in OCS dose was the primary outcome, there was a greater reduction in corticosteroid dose with benralizumab than with placebo, and this difference was statistically significant (estimate for difference between groups of 37.5%; 95% CI, 20.8% to 50.0%; *P* < 0.001) (Table 9). The percentage of patients able to reduce their dose by different percentages (25%, 50%, 75%, and 100%) was also reported. In total, 30% of patients treated with benralizumab and 11% of patients treated with placebo were able to reduce their dose by 100%.

Use of an OCS associated with exacerbations was a secondary outcome in both CALIMA and SIROCCO, although no statistical analyses were planned or provided for these outcomes (Table 8). In CALIMA, the mean (SD) total OCS dose per patient associated with an exacerbation was [redacted] grams with benralizumab and [redacted] grams with placebo. In SIROCCO, the mean (SD) total OCS dose per patient associated with an exacerbation was [redacted] with benralizumab and [redacted] with placebo. In CALIMA the mean (SD) number of OCS treatment days was [redacted] with benralizumab and [redacted] with placebo. In SIROCCO, the mean (SD) number of OCS treatment days was [redacted] with benralizumab and [redacted] days with placebo.

Days Missed from Work/School

Absenteeism was reported as per cent of hours missed. However, no statistical analysis was planned in either CALIMA or SIROCCO (Table 8, Table 9). In CALIMA, the mean (SD) percentage of hours missed from work was [redacted] with benralizumab versus [redacted] and the mean (SD) percentage of hours missed from school was [redacted] with benralizumab and [redacted] with placebo. In SIROCCO, the mean (SD) percentage of hours missed from work was [redacted] with benralizumab and [redacted] with placebo and of hours missed from work was [redacted]) with benralizumab and [redacted] with placebo.

Other Efficacy Outcomes

The primary analysis population for other efficacy outcomes in CALIMA and SIROCCO were those patients with high baseline eosinophils (≥ 300 cells/μL) and on high-dose ICS.

Pulmonary Function

Pre-bronchodilator change from baseline in FEV1 was an outcome that was controlled for multiplicity in CALIMA and SIROCCO. In both studies FEV1 was improved versus placebo, and these differences were statistically significant in CALIMA (LS MD of 0.116; 95% CI, 0.028 to 0.204; *P* = 0.010) and in SIROCCO (0.159; 95% CI, 0.068 to 0.249; *P* = 0.001) (Table 10). In the FAS population, in a post hoc analysis provided by the manufacturer, results for FEV1 were not consistent with the primary analysis in CALIMA, but were consistent with the primary analysis in SIROCCO (Table 16).

Changes in PEF were reported in both morning and afternoon, for benralizumab versus placebo, in both studies. PEF was not adjusted for multiplicity.

Symptoms

The change from baseline in TASS was a key secondary outcome in both CALIMA and SIROCCO, and thus was controlled for multiple comparisons. TASS was reduced (improved) for benralizumab versus placebo in both studies and these differences were statistically significant in both CALIMA (LS MD of −0.23; 95% CI, −0.43 to −0.04; *P* = 0.019) and SIROCCO (−0.25; 95% CI, −0.45 to −0.06; *P* = 0.012) (Table 8). Results for the TASS in the FAS population were provided by the manufacturer as a post hoc analysis, and the results were not consistent with the primary analysis for CALIMA but were consistent with the primary analysis for SIROCCO (Table 16).

The ACQ-6 was also used to assess symptoms in both CALIMA and SIROCCO. The total ACQ-6 score was decreased (improved) from baseline for benralizumab versus placebo in both CALIMA (LS MD of -0.25; 95% CI, −0.44 to −0.07; *P* = 0.008) and SIROCCO (LS MD of −0.29; 95%CI, −0.48 to −0.10; *P* = 0.003).

Mean (SD) change in rescue medication use over the course of 56 weeks in CALIMA was [redacted]puffs/day with benralizumab and [redacted]puffs/day with placebo and over 48 weeks in SIROCCO was [redacted]puffs/day with benralizumab and [redacted] puffs/day with placebo, and over 28 weeks in ZONDA was [redacted]puffs/day with benralizumab and [redacted]puffs/day with placebo.

Nocturnal Awakenings

The least squares mean change from baseline in percentage of nights with nocturnal awakenings over 56 weeks in CALIMA for benralizumab versus placebo was [redacted], over 48 weeks in SIROCCO was [redacted], and over 28 weeks in ZONDA was [redacted]. None of these analyses were adjusted for multiple statistical comparisons.

Eosinophil Counts

Eosinophil counts, LS MD, benralizumab versus placebo group, after 56 weeks in CALIMA were 105.0% (95% CI, −115.1 to −94.96; *P* < 0.001), after 48 weeks in SIROCCO they were −99.59% (95% CI, −113.6 to −85.59; *P* < 0.001), and after 28 weeks in ZONDA they were −159.4% (95% CI, −217.9 to −100.9; *P* < 0.001). None of these outcomes were adjusted for multiple statistical comparisons.

Two other efficacy outcomes that were not studied in the included trials were the percentage of asthma symptom-free days or nights and the reduction in use of ICS. Regarding the latter outcome, patients in the included studies were required to continue on their current ICS dose during the study.

Table 8: Key Efficacy Outcomes for CALIMA, SIROCCO

	CALIMA		SIROCCO	
	Benralizumab Q8W	**Placebo**	**Benralizumab Q8W**	**Placebo**
Mortality				
Deaths, n	2/441 (< 1%)	1/440 (< 1%)	2/398 (1%)	2/407 (< 1%)
Primary analysis population for all outcomes: blood eosinophils ≥ 300 cells/μL, on high-dose ICS	**N = 239**	**N = 248**	**N = 267**	**N = 267**
Exacerbations				
Annual exacerbation rate, estimate after 56 weeks in CALIMA and 48 weeks in SIROCCO	0.66	0.93	0.65	1.33
Rate ratio (95% CI)[a]	0.72 (0.54 to 0.95), *P* = 0.019		0.49 (0.37 to 0.64), *P* < 0.001	
Patients with ≥ 1 exacerbation after 56 weeks in CALIMA and 48 weeks in SIROCCO, n (%)	95 (39.7)	126 (50.8)	93/267 (34.8)	135/267 (50.6)
Time to first exacerbation, hazard ratio (95% CI)[b,c]	0.73 (0.55 to 0.95), *P* ≤ 0.018		0.60 (0.46 to 0.78), *P* < 0.001	
Hospitalization, Physician, ED Visits Due to Exacerbations	N = 239	N = 248	N = 267	N = 267
Patients with ≥ 1 exacerbation associated with hospitalization or ED visit, adjudicated events, n (%): after 56 weeks for CALIMA; after 48 weeks for SIROCCO				
Hospitalization or ED visit, n (%)	20 (8.4)	20 (8.1)	18 (6.7)	37 (13.9)
Hospitalization, n (%)	14 (5.9)	12 (4.8)	12 (4.5)	20 (7.5)
ED visit, n (%)	12 (5.0)	18 (7.3)	6 (2.2)	20 (7.5)
Annual exacerbation rate associated with an adjudicated ER visit or hospitalization (95% CI)	0.05 (0.03 to 0.08)	0.04 (0.02 to 0.07)	0.06 (0.04 to 0.11)	0.18 (0.13 to 0.25)
Rate ratio [95% CI][a,c]	1.23 (0.64 to 2.35), *P* = 0.538		0.37 (0.20 to 0.67), *P* < 0.001	
HRQoL				
Mean (SD) baseline overall AQLQ12+ score	3.87 (1.05) N = 232	3.93 (1.04) N = 240	3.93 (0.97) N = 267	3.87 (0.99) N = 267
Mean (SD) Change from baseline in overall AQLQ12+ score at week 56 in CALIMA and week 48 in SIROCCO	1.61 (1.24) N = 180	1.32 (1.19) N = 191	1.56 (1.17) N = 187	1.25 (1.18) N = 180
Repeated measures analysis for change from baseline in overall AQLQ12+ score at week 56 in CALIMA and week 48 in SIROCCO	1.56 N = 230	1.31 N = 240	1.56 N = 252	1.26 N = 254
LS MD (95%CI)[c,d]	0.24 (0.04, 0.45), *P* =0.019		0.30 (0.10, 0.50), *P* = 0.004	
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

	CALIMA		SIROCCO	
	Benralizumab Q8W	Placebo	Benralizumab Q8W	Placebo
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ACQ-6 = Asthma Control Questionnaire-6; AQLQ12+ = Asthma Quality of Life Questionnaire for 12 years and older; CI = confidence interval; ED = emergency department; EQ-5D-5L = EuroQol 5-Dimensions 5-Level questionnaire; ER = emergency room; ICS = inhaled corticosteroids; LS = least squares MD = mean difference; MI = myocardial infarction; OCS = oral corticosteroid; PE = pulmonary embolism; Q8W = every eight weeks; SD = standard deviation.

[a] Statistical analysis model: a negative binomial model including covariates treatment group, region, number of exacerbations in the previous year, and use of maintenance oral corticosteroids. Total follow-up time was defined as the time from randomization to the date of week 56 visit (end of treatment) or last contact if the patient was lost to follow-up. The log of each patient's corresponding follow-up time was used as an offset variable in the model to adjust for patients having different exposure times during which the events occurred. Annual exacerbation rates were model estimated.

[b] Cox proportional hazards model, which included covariates of treatment group, region, number of exacerbations in previous year, and use of maintenance OCS.

[c] This analysis was not adjusted for multiplicity.

[d] The model was: change from baseline in AQLQ12+ score = treatment + baseline AQLQ12+ score + region + use of maintenance oral corticosteroids + visit + treatment × visit. The number of patients in the repeated measures analysis represents all patients with baseline and at least one post-baseline assessment. A positive change in score denotes improvement.

[e] For the EQ-5D a positive change in score denotes improvement.

Source: Clinical Study Report for CALIMA and SIROCCO.[4,5]

Table 9: Key Efficacy Outcomes for ZONDA

	ZONDA	
	Benralizumab Q8W N = 73	Placebo N = 75
Mortality		
Deaths, n	2/73 (3%)	0
OCS Dose		
Mean (SD) baseline daily OCS dose (mg)	14.28 (7.756)	14.15 (6.353)
Mean (SD) per cent reduction from baseline to week 28	57.75 (43.561)	20.48 (54.446)
Analysis for % reduction from baseline in final OCS dose at week 28 while maintaining asthma control Estimate for difference (95% CI)[a]	37.50 (20.80 to 50.00), $P < 0.001$	
Patients with ≥ 25% reduction from baseline in final OCS dose at week 28, n (%)	57 (78.1)	38 (50.7)
Odds ratio (95% CI)	3.25 (1.62 to 6.52), $P < 0.001$	
≥ 50% reduction in dose, n (%)	48 (65.8)	28 (37.3)
Odds ratio (95% CI)	3.03 (1.57 to 5.86), $P < 0.001$	
100% reduction in dose, n (%)	22 (30.1)	8 (10.7)
Odds ratio (95% CI)	3.63 (1.47 to 9.00), $P = 0.004$	
Exacerbations		
Annual exacerbation rate, estimate (95% CI)	0.54 (0.33 to 0.87)	1.80 (1.32 to 2.46)

	ZONDA	
	Benralizumab Q8W N = 73	**Placebo N = 75**
Rate ratio (95% CI)[b,c]	0.30 (0.17 to 0.53), *P* < 0.001	
Patients with ≥ 1 exacerbation, n (%)	17 (23.3)	39 (52.0)
Time to first exacerbation, hazard ratio (95% CI)[d]	0.32 (0.17 to 0.57), *P* < 0.001	
Total number of exacerbations/follow-up years	0.55	1.80
Hospitalization, Physician, ER Visits Due to Exacerbations		
Patients with ≥ 1 exacerbation associated with hospitalization or ER visit, investigator assessment, n	1	14
Hospitalization or ER visit, n (%)	1 (1.4)	9 (12.0)
Hospitalization, n (%)	1 (1.4)	6 (8.0)
ER visit, n (%)	0	4 (5.3)
Annual exacerbation rate associated with ER/hospitalization, estimate (95% CI)	0.01 (0.00 to 0.08)	0.12 (0.04 to 0.35)
Rate ratio (95% CI)[e]	0.07 (0.01 to 0.63), *P* = 0.018	
HRQoL		
Mean (SD) baseline overall AQLQ12+ score	4.44 (1.3)	4.11 (1.1)
Mean (SD) change from baseline week 28	1.05 (1.0)	0.67 (1.1)
Mean (SD) change from baseline overall	0.80 (0.9)	0.51 (0.8)
Repeated measures analysis for change from baseline in overall AQLQ12+ score at week 28, estimate for difference (95% CI)[f]	0.45 (0.14 to 0.76), *P* = 0.004	

AQLQ12+ = Asthma Quality of Life Questionnaire for 12 years and older; CI = confidence interval; ER = emergency room; OCS = oral corticosteroid; Q8W = every eight weeks; SD = standard deviation.

[a] The Wilcoxon rank sum test was the primary analysis method and was used for the multiplicity-protected end point. Estimate of the median per cent reduction from baseline in final OCS dose in the two treatment groups was compared with the placebo group using a Wilcoxon rank sum test, yielding the *P* value presented.

[b] Statistical analysis model: a negative binomial model including covariates treatment group, region, and number of exacerbations in the previous year. Total follow-up time was defined as the time from randomization to the date of week 28 visit (end of treatment) or last contact if the patient was lost to follow-up. The log of each patient's corresponding follow-up time was used as an offset variable in the model to adjust for patients having different exposure times during which the events occurred.

[c] This analyses was not controlled for multiplicity.

[d] Cox proportional hazards model, which included covariates of treatment group, region, number of exacerbations in previous year, and use of maintenance OCS.

[e] Statistical analysis model: a negative binomial model including covariates treatment group, region, and any exacerbations in the previous year requiring hospitalization or ER visit. Total follow-up time was defined as the time from randomization to the date of week 28 visit (end of treatment) or last contact if the patient was lost to follow-up. The log of each patient's corresponding follow-up time was used as an offset variable in the model to adjust for patients having different exposure times during which the events occurred.

[f] Estimates are least squares means. The model is: change from baseline in AQLQ12+ score = treatment + baseline AQLQ12+ score + region+ visit + treatment × visit. An increase from baseline denotes improvement.

Source: Clinical Study Report for ZONDA.[6]

Table 10: Other Efficacy Outcomes (CALIMA, SIROCCO)

	CALIMA		SIROCCO	
	BEN Q8W	PLACEBO	BEN Q8W	PLACEBO
Primary analysis population for all outcomes: blood eosinophils ≥ 300 cells/µL, on high-dose ICS	N = 239	N = 248	N = 267	N = 267
FEV1				
Mean (SD) baseline FEV1, litres	1.758 (0.622) N = 239	1.815 (0.648) N = 245	1.660 (0.574) N = 267	1.654 (0.580) N = 267
Pre-bronchodilator mean (SD) change from baseline in FEV1 at week 56 in CALIMA and week 48 in SIROCCO, litres	0.332 (0.518) N = 211	0.206 (0.471) N = 221	0.398 (0.546) N = 235	0.237 (0.508) N = 233
Repeated measures analysis for pre-bronchodilator change from baseline in FEV1 at week 56 in CALIMA and week 48 in SIROCCO, litres, LS mean change	0.330 N = 238	0.215 N = 244	0.398 N = 264	0.239 N = 261
LS mean difference (95% CI)[a]	0.116 (0.028 to 0.204), *P* = 0.010		0.159 (0.068 to 0.249), *P* = 0.001	
Peak Expiratory Flow				
Mean (SD) baseline PEF, L/minute – a.m.	246.422 (118.859) N = 236	250.123 (118.155) N = 246	230.074 (112.487) N = 261	230.025 (107.021) N = 264
Mean (SD) change from baseline in PEF at week 56 in CALIMA and week 48 in SIROCCO, L/minute	43.375 (91.865) N = 193	23.961 (71.509) N = 197	36.994 (72.002) N = 181	22.059 (74.434) N = 189
Repeated measures analysis for change from baseline in PEF at week 56 in CALIMA and week 48 in SIROCCO, L/minute, LS mean change	38.13 N = 235	22.86 N = 246	38.96 N = 260	22.51 N = 264
LS mean difference (95% CI)[b]	15.27 (0.90 to 29.64), *P* = 0.037		16.46 (2.08 to 30.83), *P* = 0.025	
Mean (SD) baseline PEF, L/minute – p.m.	257.116 (117.253) N = 236	263.998 (121.090) N = 248	241.989 (113.409) N = 262	239.750 (106.080) N = 264
Mean (SD) change from baseline in PEF at week 56 in CALIMA and week 48 in SIROCCO, L/minute	39.270 (89.772) N = 192	15.448 (78.341) N = 197	33.460 (74.017) N = 187	14.784 (68.799) N = 189
Repeated measures analysis for change from baseline in PEF at week 56 in CALIMA and week 48 in SIROCCO, L/minute, LS mean change	33.59 N = 236	12.37 N = 246	34.91 N = 261	15.73 N = 264
LS mean difference (95% CI)[b]	21.22 (6.65 to 35.79), *P* = 0.004		19.18 (5.09 to 33.28), *P* = 0.008	
Symptoms				
Mean (SD) baseline total asthma symptom score	2.76 (1.06) N = 238	2.71 (1.06) N = 247	2.68 (1.09) N = 265	2.74 (1.08) N = 267
Mean (SD) change from baseline in total asthma symptom score at Week 56 in CALIMA and week 48 in SIROCCO	−1.40 (1.17) N = 185	−1.20 (1.19) N = 187	−1.34 (1.27) N = 178	−1.03 (1.07) N = 180
Repeated measures analysis for change from baseline in total asthma symptom score at week 56 in CALIMA and week 48 in SIROCCO, LS mean change	−1.40 N = 237	−1.16 N = 247	−1.30 N = 263	−1.04 N = 267
LS mean difference (95% CI)[c]	−0.23 (−0.43 to −0.04), *P* = 0.019		−0.25 (−0.45 to -0.06), *P* = 0.012	
Baseline ACQ-6 score mean (SD)	2.80 (0.95) N = 239	2.75 (0.94) N = 248	2.81 (0.89) N = 267	2.90 (0.95) N = 267
Mean (SD) change from baseline in ACQ-6 score at week 56 in CALIMA and week 48 in SIROCCO	−1.49 (1.13) N = 185	−1.21 (1.12) N = 197	−1.47 (1.05) N = 191	−1.12 (1.15) N = 186
Repeated measures analysis for change from baseline in ACQ-6 score at week 56 in CALIMA and week 48 in SIROCCO	−1.44 N = 239	−1.19 N = 247	−1.46 N = 263	−1.17 N = 267
LS mean difference (95% CI)[d]	−0.25 (−0.44 to −0.07), *P* = 0.008		−0.29 (−0.48 to −0.10), *P* = 0.003	

	CALIMA		SIROCCO	
	BEN Q8W	PLACEBO	BEN Q8W	PLACEBO
Rescue Medication Use				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]	−0.03 (−0.08 to 0.01), *P* = 0.146		−0.06 (−0.11 to −0.01), *P* = 0.012	
Eosinophil Counts				
Mean (SD) baseline blood eosinophil counts, cells/μL	576.9 (386.84) N = 239	583.1 (460.17) N = 248	551.2 (432.66) N = 276	566.6 (360.93) N = 265
Mean (SD) % change from baseline in blood eosinophil counts at week 56 in CALIMA and week 48 in SIROCCO	−92.2 (27.65) N = 193	26.5 (435.72) N = 200	−92.2 (31.98) N = 208	6.4 (126.90) N = 201
Repeated measures analysis for per cent change from baseline in blood eosinophil counts at week 56 in CALIMA and week 48 in SIROCCO	−89.0 N = 238	17.72 N = 245	−92.7 N = 264	6.85 N = 263
LS mean difference (95% CI)[g]	−106.8 (−149.7 to −63.88), *P* < 0.001		−99.59 (−113.6 to −85.59), *P* < 0.001	

ACQ-6 = six-question Asthma Control Questionnaire; BEN = benralizumab; CI = confidence interval; FEV1 = forced expiratory volume in one second; ICS = inhaled corticosteroid; LS = least squares; PEF = peak expiratory flow; Q8W = every eight weeks; SD = standard deviation.

[a] The model was: change from baseline in pre-bronchodilator FEV1 = treatment + baseline pre-bronchodilator FEV1 + region + use of maintenance oral corticosteroids + visit + treatment × visit. The number of patients in the repeated measures analysis represents all patients with baseline and at least one post-baseline assessment.

[b] The model was: change from baseline in morning/evening PEF = treatment + baseline morning/evening PEF + region + use of maintenance oral corticosteroids + visit + treatment × visit. The number of patients in the repeated measures analysis represents all patients with baseline and at least one post-baseline assessment.

[c] The model was: change from baseline in asthma symptom score = treatment + baseline asthma symptom score + region + use of maintenance oral corticosteroids + visit + treatment × visit. The number of patients in the repeated measures analysis represents all patients with baseline and at least one post-baseline assessment.

[d] The model was: change from baseline in ACQ-6 score = treatment + baseline ACQ-6 score + region + use of maintenance oral corticosteroids + visit + treatment × visit. The number of patients in the repeated measures analysis represents all patients with baseline and at least one post-baseline assessment.

[e] The model was: change from baseline in total asthma rescue medication use = treatment + baseline total asthma rescue medication use + region + use of maintenance oral corticosteroids + visit + treatment × visit. The number of patients in the repeated measures analysis represents all patients with baseline and at least one post-baseline assessment.

[f] The model was: change from baseline in proportion of nights with nocturnal awakenings = treatment + baseline proportion of nights with nocturnal awakenings + region + use of maintenance oral corticosteroids + visit + treatment × visit. The number of patients in the repeated measures analysis represents all patients with baseline and at least one post-baseline assessment.

[g] The model was: per cent change from baseline in blood eosinophil count = treatment group + baseline eosinophil count + region + use of maintenance oral corticosteroids + visit + treatment × visit. The number of patients in the repeated measures analysis represents all patients with baseline and at least one post-baseline assessment.

Source: Clinical Study Report for CALIMA, SIROCCO.[4,5]

Table 11: Other Efficacy Outcomes (ZONDA)

	ZONDA	
	BEN Q8W N = 73	**PLACEBO N = 75**
FEV1		
Mean (SD) baseline FEV1, L	1.754 (0.635)	1.931 (0.662)
Pre-bronchodilator mean (SD) change from baseline in FEV1 at week 28, litres	0.255 (0.508)	0.114 (0.401)
Repeated measures analysis for pre-bronchodilator change from baseline in FEV1 at week 28 LS mean change, litres	0.239	0.126
LS mean difference (95% CI)[a]	0.112 (−0.033 to 0.258), *P* = 0.129	
Peak Expiratory Flow		
Mean (SD) baseline PEF (L/minute) – a.m.	246.4 (130.2)	262.3 (114.9)
Repeated measures analysis for change from baseline in PEF at week 56 (L/minute) LS mean change	39.78	9.77
LS mean difference (95% CI)[a]	30.01 (4.26 to 55.76), *P* = 0.023	
Mean (SD) baseline PEF (L/minute) – p.m.	263.3 (133.9)	286.1 (125.2)
Repeated measures analysis for change from baseline in PEF at week 56 (L/minute) LS mean change	32.33	0.81
LS mean difference (95% CI)[a]	31.52 (6.32 to 56.71), *P* = 0.014	
Symptoms		
Mean (SD) baseline total asthma symptom score	2.34 (1.09)	2.43 (0.99)
Total asthma symptom score mean (SD) change from baseline at week 28	−0.77 (1.03)	−0.58 (1.03)
Difference in LS means (95% CI)[b]	−0.18 (−0.51 to 0.16), *P* = 0.291	
Mean (SD) baseline ACQ-6 score	2.42 (1.21)	2.68 (0.95)
Mean (SD) change from baseline in ACQ-6 score at week 28	−1.09 (1.09)	−0.68 (1.10)
LS mean difference (95% CI)[c]	−0.55 (−0.86 to −0.23), *P* = 0.001	
Rescue Medication Use		
Mean (SD) baseline asthma rescue medication use (puffs/day)	4.30 (5.62)	4.05 (5.43)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
Eosinophil Counts		
Mean (SD) baseline blood eosinophil counts, cells/μL	434.9 (324.73)	464.3 (315.74)
Mean (SD) blood eosinophil counts at week 28, cells/μL	12.2 (56.47)	467.4 (476.10)
Mean (SD) % change from baseline in blood eosinophil counts at week 28 (%)	−94.9 (16.54)	45.5 (239.51)
LS mean difference (95% CI)[f]	−159.4 (−217.0 to −100.9), *P* < 0.001	

ACQ-6 = six-question Asthma Control Questionnaire; BEN = benralizumab; CI = confidence interval; FEV1 = forced expiratory volume in one second; LS = least squares; PEF = peak expiratory flow; Q8W = every eight weeks; SD = standard deviation.

Note: Estimate of the mean change from baseline at each week in the treatment group is compared with the placebo group using a repeated measures analysis. Estimates are least squares means. The number of patients in the repeated measures analysis represents all patients with baseline and at least one post-baseline assessment.

[a] The model was: change from baseline in pre-bronchodilator FEV1 = treatment + baseline pre-bronchodilator FEV1 + region + visit + treatment × visit.

[b] The model was: change from baseline in asthma symptom score = treatment + baseline asthma symptom score + region + visit + treatment × visit.

[c] The model was: change from baseline in ACQ-6 score = treatment + baseline ACQ-6 score + region + visit + treatment × visit.

[d] The model was: change from baseline in total asthma rescue medication use = treatment + baseline total asthma rescue medication use + region + visit + treatment × visit.

[e] The model was: change from baseline in proportion of nights with nocturnal awakenings = treatment + baseline proportion of nights with nocturnal awakenings + region + visit + treatment × visit.

[f] The model was: per cent change from baseline in blood eosinophil count = treatment group + baseline eosinophil count + region + visit + treatment × visit.

Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). See Table 12 for detailed harms data.

Adverse Events

The percentage of patients with an adverse event was 76% with benralizumab and 79% with placebo in CALIMA, 72% with benralizumab and 77% with placebo in SIROCCO, and 75% with benralizumab and 83% with placebo in ZONDA (Table 12). The most common adverse events in all three studies were nasopharyngitis (CALIMA: 19% benralizumab versus 21% placebo; SIROCCO: 12% in each group; ZONDA: 15% with benralizumab and 20% placebo) and asthma (CALIMA: 11% with benralizumab versus 16% placebo; SIROCCO: 11% benralizumab versus 20%.placebo; and ZONDA: 3% benralizumab versus 24% placebo).

Serious Adverse Events

The percentage of patients with a serious adverse event was 14% in each group in SIROCCO and 10% of benralizumab and 14% of placebo patients in CALIMA. In ZONDA, 10% of benralizumab patients and 19% of placebo patients had a serious adverse event (Table 12).

Withdrawals Due to Adverse Events

Withdrawals due to an adverse event occurred in 2% of benralizumab versus 1% of placebo in CALIMA and SIROCCO, and in 4% of benralizumab versus 3% of placebo patients in ZONDA (Table 12).

Notable Harms

Notable harms included infection and immune and injection-site reactions. Upper respiratory tract infections occurred in benralizumab and placebo patients in each of the three studies (CALIMA: 9% benralizumab versus 10% placebo; SIROCCO: 8% benralizumab versus 9% placebo; ZONDA: 7% in each group), while influenza occurred in 3% of benralizumab and 6% of placebo patients in CALIMA, 5% of benralizumab versus 6% of placebo patients in SIROCCO, and 1% of benralizumab versus 7% of placebo patients in ZONDA (Table 12). Serious adverse events of infection were infrequent, such as pneumonia (CALIMA: 0% benralizumab versus 1% placebo; SIROCCO: 1% in each group; ZONDA: 3% in benralizumab versus 4% in placebo) and influenza (CALIMA:1% benralizumab versus 0% placebo; SIROCCO: 0% in benralizumab versus < 1% placebo; ZONDA: 0% in benralizumab versus 3% in placebo.

Table 12: Harms

	CALIMA		SIROCCO		ZONDA	
AEs	**BEN Q8W N = 428**	**PLA N = 440**	**BEN Q8W N = 394**	**PLA N = 407**	**BEN Q8W N = 73**	**PLA N = 75**
Subjects with > 0 AEs, N (%)	323 (75.5)	348 (79.1)	282 (71.6)	313 (76.9)	55 (75.3)	62 (82.7)
Most common AEs (10% in any group)						
Nasopharyngitis	82 (19.2)	92 (20.9)	47 (11.9)	49 (12.0)	11 (15.1)	15 (20.0)
Asthma	48 (11.2)	69 (15.7)	47 (11.0)	82 (20.1)	2 (2.7)	18 (24.0)
Bronchitis	46 (10.7)	54 (12.3)	19 (4.8)	30 (7.4)	7 (9.6)	12 (16.0)
SAEs						
Subjects with > 0 SAEs, N (%)	41 (9.6)	61 (13.9)	54 (13.7)	58 (14.3)	7 (9.6)	14 (18.7)
Most common SAEs						
Asthma	21 (4.8)	19 (4.4)	24 (6.1)	32 (7.9)	1 (1.4)	4 (5.3)
WDAEs						
WDAEs, N (%)	10 (2.3)	5 (1.1)	8 (2.0)	3 (0.7)	3 (4.1)	2 (2.7)
Notable Harms						
Patients, N (%)						
Upper respiratory tract infection	38 (8.9)	42 (9.5)	32 (8.1)	37 (9.1)	5 (6.8)	5 (6.7)
Influenza	14 (3.3)	25 (5.7)	19 (4.8)	24 (5.9)	1 (1.4)	5 (6.7)
Pneumonia – SAE	0	4 (0.9)	2 (0.5)	3 (0.7)	2 (2.7)	3 (4.0)
Pneumonia bacterial – SAE	0	3 (0.7)	1 (0.3)	0	NR	NR
Influenza – SAE	2 (0.5)	0	0	1 (0.2)	0	2 (2.7)
UTI – SAE	1 (0.2)	0	NR	NR	NR	NR
UTI bacterial – SAE	NR	NR	0	2 (0.5)	NR	NR
Any hypersensitivity	13 (3.0)	17 (3.9)	11 (2.8)	11 (2.7)	2 (2.7)	1 (1.3)
Injection-site reactions	9 (2.1)	8 (1.8)	9 (2.3)	8 (2.0)	0	2 (2.7)

AE = adverse event; BEN = benralizumab; NR = not reported; Q8W = every eight weeks; NR = not reported; PLA = placebo; SAE = serious adverse event; UTI = urinary tract infection; WDAE = withdrawal due to adverse event.

Note: Adverse events are reported for the on-study period, which includes the treatment period and the follow-up period.
Source: Clinical Study Report for CALIMA, SIROCCO, ZONDA.[4-6]

Discussion

Summary of Available Evidence

Three manufacturer-sponsored multinational pivotal phase III DB RCTs are included in this systematic review. CALIMA (N = 1,306) and SIROCCO (N = 1,205) were similarly designed trials that compared benralizumab with placebo. The studies enrolled patients with high or lower eosinophil counts in a 2:1 ratio, respectively, and patients on medium- (CALIMA) or high-dose ICS (CALIMA and SIROCCO) with poor asthma control (two exacerbations in the past year), over a treatment course of 56 weeks (CALIMA) and 48 weeks (SIROCCO). The primary analysis in both studies focused on patients with high eosinophil counts (≥ 300 cells/μL) and on high-dose ICS. The primary outcome of both of these studies was the annualized exacerbation rate, and key secondary outcomes, controlled for multiplicity, included FEV1 and asthma symptom scores. Other outcomes not controlled for multiplicity included health-related quality of life, assessed by the AQLQ12+ and the EQ-5D-5L, exacerbations associated with hospitalizations or emergency department visits, symptoms using the ACQ-6, OCS use associated with exacerbations, absenteeism, PEF, rescue medication use, nocturnal awakenings, and eosinophil counts. ZONDA (N = 220) was a 28-week study that compared benralizumab with placebo in patients with severe asthma who required chronic use of oral corticosteroids. The primary outcome of ZONDA was the reduction in OCS dose from baseline. Secondary outcomes, not controlled for multiplicity, included annualized exacerbation rate, exacerbations associated with hospitalizations or emergency department visits, health-related quality of life assessed on the AQLQ12+, symptoms assessed using the ACQ-6, rescue medications, FEV1, PEF, and nocturnal awakenings.

Key limitations of these studies included the lack of an active comparator, including comparisons with other IL-5 inhibitors (mepolizumab and resolizumab) or omalizumab, lack of adjustments for multiple statistical testing across end points other than the primary and key secondary, subgroups and sensitivity analyses. Given the novelty of this therapeutic target, these studies were of relatively short duration to assess long-term safety of benralizumab.

Interpretation of Results

Efficacy

The annualized rate of asthma exacerbations was the primary outcome of both CALIMA and SIROCCO, and the primary analysis in both studies focused on the population of patients with high (≥ 300 cells/μL) eosinophil counts. However, the Health Canada indication does not specify a particular eosinophil count that patients must meet to be eligible for therapy. The manufacturer has requested reimbursement criteria that are more in line with the objectives and findings of the pivotal trials, namely patients with high eosinophil counts (≥ 300 cells/μL) or with eosinophil counts ≥ 150 cells/μL and on chronic high-dose OCS. The clinical expert consulted by CDR on this review noted that the population of patients treated with high-dose ICS and who remain with high eosinophil counts, though uncommon, represents an important unmet clinical need in asthma. Therefore the results demonstrating superiority of benralizumab to placebo for reduction in exacerbations in this population are likely to be clinically significant. However, it is noteworthy that exacerbations associated with ER visits and hospitalizations were not part of the statistical hierarchy and therefore limited

conclusions can be drawn about this data, despite the fact that these events are important cost drivers. Results from the BORA extension (reviewed in Appendix 6), which enrolled patients who had been in CALIMA, SIROCCO, or ZONDA, suggest that the effect of benralizumab on [redacted].

Patients in ZONDA represent the most "steroid resistant" population in asthma, i.e., patients who are reliant on OCSs to maintain control of their asthma, and despite chronic use of OCSs and high-dose ICS, still have high eosinophil counts. The clinical expert consulted by CDR on this review noted how uncommon these patients were in clinical practice. However, the expert indicated that they are a challenging population to treat, and thus any drugs that can effectively treat this population would be filling an important gap. ZONDA demonstrated a steroid-sparing effect for benralizumab, reducing the mean OCS dose by greater than 50% compared with placebo, from a baseline of 14 mg daily prednisone equivalents. Long-term use of an OCS has been associated with several serious adverse effects, including osteoporosis, but the minimum dose and duration of therapy required to significantly elevate the risk of osteoporosis has not been established. A meta-analysis by Amiche et al. found that chronic OCS users were at increased risk of vertebral and non-vertebral fractures, although they noted that the risk, though still elevated, seemed to decline somewhat with time. They concluded that the risk of fracture among OCS users may be higher than previously thought.[38] Ideally, a study like ZONDA would have not only recorded a reduction in OCS dose with use of benralizumab, but would have gone further and demonstrated a corresponding improvement in bone mineral density, and, optimally, fractures. This would have required a longer follow-up than 28 weeks and this longer follow-up would have perhaps provided more information about the impact of OCS dose reduction on the risk of side effects. Chronic OCS use is associated with significant adverse effects, though approximately 30% of patients treated with benralizumab (versus 11% with placebo) were able to achieve a 100% reduction in OCS dose. Therefore, the remaining question is: how much benefit is derived by the remaining patients who continue on OCS but at a significantly reduced dose?

Benralizumab improved lung function, measured by FEV1 and PEF, in both CALIMA and SIROCCO, in which FEV1 was a secondary outcome that was controlled for multiplicity. However, the improvement versus placebo fell short of what is considered to be a clinically important difference that can be perceived by patients, and there are limited data available upon which to ascertain a minimally important improvement from a patient perspective (See Appendix 5 for detailed review). Improvement in PEF versus placebo was also less than what is considered to be a clinically important difference as perceived by patients.

Symptom scores were assessed using the TASS, which is a scoring system based on the completion of one item twice daily on the asthma symptom diary, and the ACQ-6. The TASS was statistically significantly improved for benralizumab versus placebo in CALIMA and SIROCCO; however no MCID was found for this instrument, which basically consists of two similar questions, one asked in the morning and one in the evening, and the clinical significance of this finding is questionable. The difference versus placebo in ACQ-6 scores did not meet the MCID in either study. Therefore, there is some agreement between the pulmonary function tests and the symptom scales suggesting that, although there may have been statistically significant improvement for benralizumab versus placebo, these improvements may be of questionable clinical significance. One possible explanation for this observation is that the populations in CALIMA and SIROCCO had asthma that was well-established (mean time since diagnosis of approximately 15 years) and if their asthma has

been poorly controlled, they have likely experienced significant remodelling, and this cannot be reversed.

Although health-related quality of life was a key efficacy outcome in this review, it was not adjusted for multiplicity in the included trials. It is clear from patient input to CDR that asthma takes a significant toll on patients' health-related quality of life. Symptoms such as shortness of breath are frequently cited by patients as affecting quality of life, as are the impacts of the disease on their sleep patterns, and the need for urgent visits to physicians, emergency departments, and hospitalizations. Not adjusting the AQLQ for multiple comparisons thus limits the conclusions that one can draw from the included studies regarding the impact of benralizumab on this important outcome. The AQLQ-12 was the specific instrument used in the included trials, and although it is closely related to the AQLQ, it is not the same, and therefore no MCID was available for this instrument, either.

There were no active comparator trials of benralizumab included in this systematic review, though the manufacturer submitted an indirect comparison (IDC) that was reviewed and critically appraised by CDR (see Appendix 7). No published IDCs were found by CDR. The objective of the IDC was to compare benralizumab with other monoclonal antibodies in patients with severe uncontrolled asthma. The manufacturer employed a matching-adjusted indirect comparison, a form of population-based IDC that used patient-level data to adjust for cross-trial differences in distribution of variables that influence outcomes. [redacted] studies were included in the matching-adjusted indirect comparison: [redacted] benralizumab (SIROCCO, CALIMA, ZONDA), reslizumab, and mepolizumab, and [redacted] omalizumab. Overall the IDC found [redacted] between benralizumab and mepolizumab for [redacted] There was [redacted] between benralizumab and omalizumab for [redacted].

The manufacturer's primary analysis for CALIMA and SIROCCO focused on the two-thirds of patients enrolled in each study who had high eosinophil counts (≥ 300 cells/μL) at baseline. After a request from CDR, the manufacturer provided a post hoc analysis of data for the FAS (i.e., regardless of eosinophil count). The results for the primary outcome for the FAS were consistent with that of the primary analysis. However, some secondary outcomes such as FEV1 and change in total asthma symptom score were not statistically significantly improved for benralizumab versus placebo in the FAS, particularly in CALIMA. It should be noted however that CALIMA also included patients on a medium-dose ICS, and these patients would have also been included in this FAS analysis. The FAS also included adolescent patients, and the indication for benralizumab is currently restricted to adults. The findings from the FAS analysis serve to highlight the fact that the treatment effect was not as large in CALIMA as it was in SIROCCO in the primary analysis. There are no obvious reasons as to why this might be so, and there are limitations to making such comparisons, as these studies were of similar, but not identical design.

Harms

IL-5 inhibitors represent a novel mechanism in the treatment of asthma, with the first IL-5 inhibitor, mepolizumab, having only a few years of additional market experience compared with benralizumab. Fundamentally, blocking the effects of IL-5 would be expected to have an inhibitory effect on the immune system. Therefore, as with many immune modulators that have come before, infections, particularly serious opportunistic infections, were notable harms of interest. There were no clear indications of an increased risk of infections with benralizumab. Monoclonal antibodies are also known for hypersensitivity and injection-site reactions, and these also did not occur more frequently with benralizumab than with placebo. An extension to all three included studies, BORA, found [redacted] in patients who continued on benralizumab for an additional year, [redacted] placebo in CALIMA, SIROCO, or ZONDA to benralizumab in BORA.

Potential Place in Therapy[2]

The standard of care for asthma therapy for adults in Canada is an ICS. Most patients who remain uncontrolled can be managed with a combination of non-pharmacologic strategies (e.g., asthma educator, environmental control) and pharmacologic strategies (e.g., adding a second agent, such as a LABA, and then further increasing the ICS dose). Despite optimal management, 5% to 10% of the overall asthma population remain uncontrolled and drive the majority of health care costs.[1] Besides benralizumab, there is also mepolizumab and reslizumab, which target a population of patients with severe asthma who have allergic or non-allergic eosinophilic airway inflammation and for whom anti-IL5 therapy is the only current option to achieve control.[2] Without anti-IL5 therapy, this population can suffer from the side effects of long-term OCS therapy or from worsened quality of life due to uncontrolled asthma.

Benralizumab is effective at achieving asthma control in patients with eosinophilic airway inflammation who remain uncontrolled despite high-dose ICS with a second controller added or who require an OCS to maintain control.[3] These patients should be the ones to receive benralizumab. Some patients who are non-complaint with inhaled therapies, who continue to smoke, or who have ongoing environmental exposures (e.g., pets or occupation) may otherwise appear to meet criteria to receive anti-IL5 therapy. Peripheral eosinophil levels are easily measured and are a surrogate for airway eosinophilic inflammation. Therefore, patients should meet Health Canada–approved eosinophil levels before initiating therapy.

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

Conclusions

Three manufacturer-sponsored multinational DB RCTs that compared benralizumab with placebo met the inclusion criteria for this review. In CALIMA and SIROCCO, benralizumab demonstrated superiority over placebo over 56 and 48 weeks, respectively, for the primary outcome, annualized exacerbation rate, in a population of patients with high eosinophil counts (≥ 300 cells/μL) and on a high-dose ICS (> 500 mcg fluticasone equivalents). While this effect on exacerbations is likely clinically significant in a difficult-to-treat population, limited inferences can be made about the effects of benralizumab on exacerbations leading to hospitalization and emergency department visits as analyses of these outcomes were not controlled for multiple statistical comparisons. In ZONDA, in a population of patients who required chronic OCS to maintain asthma control, benralizumab demonstrated superiority to placebo for the primary outcome, reducing the OCS dose over 28 weeks by more than 50%. This is likely a clinically significant finding in a population that is exhibiting corticosteroid resistance. However, no conclusions can be drawn about the key clinical outcome of exacerbations, as these analyses were not adjusted for multiple comparisons, nor were any other secondary outcomes in ZONDA. Limited inferences about benralizumab's effects on health-related quality of life can be drawn from all three studies. Multiplicity-controlled secondary outcomes such as FEV1 were improved for benralizumab versus placebo in CALIMA and SIROCCO, but the clinical significance of these differences may be limited as the treatment effect was generally modest. There were no clear or consistent safety differences between benralizumab and placebo. However, given the novelty of IL-5 inhibitors, longer-term safety data are needed. Data from BORA, an extension that enrolled patients from the [redacted] included studies, suggested [redacted]. A limitation of the included studies is that none compared benralizumab to an active comparator such as another IL-5 inhibitor. A manufacturer-submitted IDC found the efficacy of benralizumab [redacted] mepolizumab [redacted]. The IDC also found that benralizumab [redacted].

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, Asthma Canada and the British Columbia Lung Groups, provided input for this summary.

Asthma Canada is a nationally registered charitable organization that provides support to all Canadians affected by asthma. Members aim to advocate for people living with asthma and respiratory allergies. The Asthma Canada Member Alliance (ACMA) is the patient arm and voice of Asthma Canada. Created in 2007, it serves in an advisory capacity with active volunteers to further the purpose of Asthma Canada's programs and initiatives and increase awareness and education about asthma within Canada.

The British Columbia Lung Groups (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.

Asthma Canada has received funding in excess of $50,000 from AstraZeneca in the past two years, and requested and received a medical briefing from AstraZeneca with regard to this product. Asthma Canada also received funding in excess of $50,000 from GlaxoSmithKline, Novartis, and Teva in the past two years. The BCLG has received educational grants from AstraZeneca totalling $2,000; in addition the BCLG received educational grants from GlaxoSmithKline and Boehringer Ingelheim.

2. Condition-Related Information

The information provided in the submission from Asthma Canada was a summary of: an Asthma Canada online survey sent to ACMA members with respect to the use of medications, daily management of asthma and the impact of severe asthma on quality of life, as well as interviews with six participants involved in the Canadian benralizumab clinical trials (SIROCCO and CALIMA); information from a study conducted by the Asthma Society of Canada in 2014, titled "Severe Asthma: The Canadian Patient Journey"; and peer-reviewed studies sourced for the purposes of this submission. The online survey was sent to ACMA members in November 2017 and 55 responses were received. A total of 87% of respondents had received a diagnosis of asthma and 9% identified themselves as caregivers of an individual with asthma. The information provided in the submission from BCLG was obtained from telephone interviews with seven female and three male patients who are on the medication.

According to information provided by Asthma Canada, eosinophilic asthma is a subtype of asthma characterized by the presence of eosinophils in the inflamed tissues, which can be detected through examination of sputum. In contrast to more classic forms of asthma that tend to be linked to a particular allergic trigger and diagnosed earlier in life, many cases of eosinophilic asthma only appears in adulthood, in patients with few or no allergies. It was also indicated that severe asthma has many different effects and consequences that can impair patients' quality of life, and that patients living with asthma have experienced a wide range of symptoms relating to the severity and control of their disease, including limitations on daily activities and exercise due to their asthma, increased emergency room visits, and hospitalizations.

It is estimated that 3.8 million Canadians live with asthma. Approximately 5% of Canadians with asthma have severe asthma. The Canadian Thoracic Society classifies severe asthma

as a subset of asthma that remains poorly controlled despite adherence to best practices in terms of self-management and pharmacologic strategies. According to information from Asthma Canada, patients with severe asthma have found there to be restrictions on social and physical activities, and progression can further deteriorate personal health. Patients say their condition prevents them from regularly participating in social activities due to a fear of flare-ups. As a result, staying active on a regular basis can be challenging for some, and depression and anxiety around this condition can develop. Patients will often say that the condition has put a strain and burden on their family and their personal and work life.

In the ACMA survey, 79% of respondents reported that they restrict the type or amount of physical activity they engage in because of their asthma, 36% of respondents reported missing either school or work due to their illness, and 29% of respondents said that it has an impact on family and caregivers. In regards to stigma surrounding the disease, 14% claimed to have felt a negative stigma with their disease. Additional responses included experiencing anxiety and other mental health issues, decreased social life, and inability to work. Avoiding physical activities such as exercising and spending time outdoors was cited by 80% of respondents. Avoiding social activities was cited by 32% of respondents, and when asked about sleeping habits, 41% of respondents claimed that asthma interfered with their sleep.

These sentiments were echoed in the BCLG submission, in which respondents indicated that symptoms experienced as a result of asthma were shortness of breath, chronic cough, wheezing, shortness of breath or tightness on the chest, and fatigue. Other symptoms were depression and frustration as a result of not able to be active and do things that they were once able to do. Depression also plays a factor, given that they are restricted from doing things or face limits on their activities.

When asked about what aspect of asthma is most important to control, 52% of respondents to the ACMA survey said day-to-day symptoms were the most important to control, while 36% identified asthma exacerbations or attacks, and 5% cited cost of medication. The BCLG indicated that reducing or stopping the progression of the disease and subsequent hospitalizations is of critical importance to the treatment of severe asthma.

3. Current Therapy-Related Information

Among the 55 respondents in the ACMA survey to questions about therapy, 88% indicated that they used a combination of inhaled corticosteroids (ICSs) and long-acting beta2 agonists (LABAs), while 83% reported usage of reliever inhalers. Use of an ICS was reported by 30% of respondents, 25% said that they use oral corticosteroids, 18% reported use of leukotriene receptor antagonists, and 3% reported the use of a LABA. Another 5% of respondents said they use anti-immunoglobin E biologics and 13% indicated using an anti-interleukin-5 biologic.

When evaluating the effectiveness of current treatments to control asthma, 38% ACMA respondents reported they are only somewhat effective, indicating they do not maintain adequate disease control. The individuals interviewed with severe asthma by the BCLG indicated that there is no cure for asthma but it can be controlled and they do understand that drugs can slow the progression and relieve their symptoms. Statements from most of the patients interviewed said “it gives them a chance to work again and have less admission to hospital.” They can sleep better and feels less tired. According to “Severe Asthma: The Canadian Patient Journey,” many patients report several years of trying different medications before finding the right medication or combination to maintain symptom control. Some participants have spent up to seven years experimenting before finding the right treatment, while others have not yet achieved this.

The most difficult adverse event reported by ACMA respondents was an increase in weight due to medication, increased heart rate, and hoarseness, each at (43%), followed by headache (37%), dry throat (34%); difficulty sleeping (31%) and mood or behavioural changes (29%). One patient indicated, "[I experience] mood swings, depression, tiredness, hand tremors, insomnia … all thanks to prednisone." Another patient wrote, "My weight has been steadily increasing despite diet and whatever limited exercise I'm able to do." Other side effects that patients complained of included upset stomach (20%), thrush (17%), bad taste (14%), and acne (6%).

In regards to difficulties accessing current treatments, 53% of ACMA respondents reported cost as a main concern. Lack of awareness of new treatments was the second most-reported obstacle (47%). An equal number of respondents (9%) reported inability to locate an asthma specialist, and a doctor being unwilling to prescribe treatment. An example of this was expanded: *"At this point, when my asthma is controlled I don't have financial difficulties. I work full time. Before my [benralizumab] clinical trial I had to take extra time off because I had daily symptoms and was not able to sleep. It resulted in decreased income."* Another patient wrote, *"Sometimes I cannot afford [medication] and ask if doctor might have a sample or I go without."* A third patient indicated that *"The most effective inhaler I tried isn't covered by my health plan so I am using something that isn't as effective."* Another response stated, *"[Asthma] caused me to not be able to work, then not have insurance, but cost of medications keeps rising, while income diminishes."*

When asked about needs not being met by current asthma treatments, 49% of ACMA respondents said that they continued to experience poor symptom control, 29% reported that many doses were needed daily, making it difficult to manage their asthma on a day-to-day basis, and 26% indicated that they continued to require frequent hospitalization and doctors' visits. The lack of affordability of current treatment, resulting in limited access to available medications, was cited by 17% of respondents. One respondent reported "*Moderate symptom control, but still limitations day to day."* Another patient stated, *"Severe attacks during colds. Constant coughing up of phlegm."*

Asthma effects on caregivers were also captured. A total of 71% of ACMA respondents who were caregivers reported worrying about or fear of exacerbation/attack in their loved ones, and 57% indicated missed work/school days was challenging. About half of respondents (51%) said potential hospital admissions were a substantial concern. About 46% indicated cost and financial burden was a considerable challenge. In terms of the burden that asthma treatments impose on the daily routine or lifestyle of caregivers, 66% stated lack of sleep, 59% mentioned frequent doctor's appointments, and 50% cited managing multiple medications. One respondent stated, "*Drugs are costly, as is the cost of having to give up a full-time career to be available 24/7 to care for my child.*" Another respondent indicated *"[Caregivers] never get a chance to do what they want. Lack of sport and social activities and worry about sick person can be very depressing."*

4. Expectations About the Drug Being Reviewed

Asthma Canada interviewed six participants involved in the Canadian benralizumab clinical trials (SIROCCO and CALIMA) in December 2017, and BCLG interviewed 10 patients who are on benralizumab.

The feedback received by Asthma Canada was positive, with patients indicating that they experience no negative effects from the drug and that their asthma symptoms were negligible, with no need to use their rescue inhaler. Benralizumab was successful in reducing asthma. One patient stated, *"I have tried every asthma medication available in*

Ontario. Benralizumab is the only drug that has worked long-term, without any side effects… The only disadvantage is that I have to travel to Hamilton every month from Wasaga Beach [2.5 hours] to receive my injection … It is difficult to describe the impact that this drug has had. For anyone who has a disease or chronic condition of any kind, living with the symptoms, fear, sickness, depression, etc. is as debilitating to family and friends as it is to the individual. To have a condition, that gradually worsened with age, virtually disappear is literally a miracle to me and my family. My life is no longer limited in any capacity by asthma. I literally almost died in 2011, and would have left behind my husband and 2 small children. Knowing that my life is no longer impacted by my asthma is like having a new lease on life." Another patient wrote, *"My current therapy is benralizumab, I have no adverse effects and I am fully happy. My life is back to normal."* A third patient indicated *"Benra[lizumab] was amazing, it was like I didn't have asthma. And the adverse effects were minimal if anything. It's not like prednisone which have crippling side effect… Having Benra[lizumab] would make my life easier. I cannot explain what it was like not having asthma for the first time in my life. Not always worrying where my inhaler was, not needing to plan my life around avoiding triggers. A wonderful secondary effect was my nasal polyps shrunk and I got my sense of smell back. I want benra[lizimab] back."* A fourth patient mentioned *"The asthma study I participated in was benralizumab. I wish with all my heart that I could afford it when it comes to market, as my severe asthma was noticeably better while I was on the injectable drug, but I can't afford."*

These sentiments were echoed in the submission from BCLG, in which patients indicated that while using benralizumab they experienced fewer side effects, were able to live a normal life, absence of shortness of breath and chronic coughing, reduced flare-ups with asthma, and fewer admissions to hospital. The BCLG also indicated that patients who were using oral prednisone for a long time had a significant reduction or discontinued the use of oral corticosteroids while on benralizumab. It was also mentioned that patients who used benralizumab had better asthma control and their exacerbation rate was lower.

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:	March 28, 2018
Alerts:	Bi-weekly search updates until September 20, 2018
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
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Adjacency within # number of words (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)
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
medall	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	
Line #	**Search strategy**
1	(Fasenra* or benralizumab* or BIW 8405 or BIW8405 or medi563 or medi 563 or 71492GE1FX).ti,ab,kf,ot,hw,rn,nm.
2	1 use medall
3	*benralizumab/
4	(Fasenra* or benralizumab* or BIW 8405 or BIW8405 or medi563 or medi 563).ti,ab,kw,dq.
5	3 or 4
6	5 use oemezd
7	conference abstract.pt.
8	6 not 7
9	2 or 8
10	remove duplicates from 9

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:	March 2018
Keywords:	Fasenra, benralizumab, 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

Table 13: Excluded Studies

Reference	Reason for Exclusion
SEHMI et al. J Allergy Clin Immunol 2018;2018 Jan 31	Letter
NAIR et al. N Engl J Med 2017;377(12):1205, 2017	
KHORASANIZADEH et al. Acta Med Iran 2017;55(5):352-3	
CHIPPS et al. Ann Allergy Asthma Immunol 2018;2018 Jan 31	Pooled
FITZGERALD et al. Lancet Respir Med 2018;6(1):51-64	
FERGUSON et al. Lancet Respir Med 2017;5(7):568-76	Wrong comparator (placebo)
MENZELLA et al. Multidiscip Respir Med 2015;10(1) :1	Review

Appendix 4: Detailed Outcome Data

Table 14: Subgroups (High-Dose Inhaled Corticosteroid)

CI = confidence interval; IgE = immunoglobulin E.

Source: Clinical Study Report for CALIMA, SIROCCO.[4,5]

Table 15: Key Efficacy Outcomes (Full Analysis Set Population)

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ACQ-6 = six-question Asthma Control Questionnaire; AQLQ12+ = Asthma Quality of Life Questionnaire for 12 years and older; CI = confidence interval; ED = emergency department; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; LS = least squares; MD = mean difference; SD = standard deviation.

Source: Response to information request.[39]

Table 16: Other Efficacy Outcomes (Full Analysis Set Population)

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ACQ-6 = six-question Asthma Control Questionnaire; BEN = benralizumab; CI = confidence interval; FEV1 = Forced expiratory volume in one second; LS = least squares; MD = mean difference; PEF = peak expiratory flow; Q8W = every eight weeks; SD = standard deviation.

Source: Response to information request.[39]

Appendix 5: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- forced expiratory volume in one second (FEV1)
- peak expiratory flow (PEF)
- Asthma Control Questionnaire 6 (ACQ-6)
- Asthma Quality of Life Questionnaire for 12 years and older (AQLQ12+)
- Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions (WPAI+CIQ)
- EuroQol 5-Dimensions 5-Levels questionnaire (EQ-5D-5L).

Findings

Table 17: Validity and Minimal Clinically Important Difference of Outcome Measures

Instrument	Type	Evidence of Validity	MCID	References
FEV1	FEV1 is the volume of air that can be forcibly expired in one second after a full inspiration.	Yes	MPPI: 0.23 L or 10.4% change from baseline	Santanello (1999)[35]
PEF	PEF is the maximum flow rate achieved during a maximal forceful exhalation, starting from full lung inflation.	Yes	MPPI: 18.8 L/minute or 5.39% change from baseline	Santanello (1999)[35]
ACQ-6	ACQ-6 is a shortened version of the original 7-item ACQ. It is a patient-reported questionnaire for assessing the adequacy of asthma treatment.	Yes	0.5 points in adult patients	Juniper (2001)[29] Juniper (2005)[27] Wyrwich (2011)[28]
AQLQ12+	AQLQ12+ is a patient-reported questionnaire for assessing problems experienced by patients with asthma in their daily lives.	Yes	Unknown 0.5 points for the original AQLQ	Juniper (1994)[40] Juniper (2005)[23] Wyrwich (2011)[41]
WPAI+CIQ	WPAI+CIQ is a patient-reported questionnaire for assessing the impact of a disease on work or school as well as daily activities.	Limited	Unknown	Demoly (2012)[42] Chen (2008)[43]
EQ-5D-5L	EQ-5D-5L is a general, non–disease-specific health-related quality-of-life questionnaire.	Limited	Summarized mean index score of 0.056 (SD 0.011) and summarized median index score of 0.056 (IQR 0.049 to 0.063) for general use	McClure (2017)[25] Hernandez (2016)[44]

ACQ-6 = six-question Asthma Control Questionnaire; AQLQ12+ = Asthma Quality of Life Questionnaire for 12 years and older; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; FEV1 = forced expiratory volume in one second; IQR = interquartile range; MPPI = minimal patient perceivable improvement; PEF = peak expiratory flow; SD = standard deviation; WPAI+CIQ = Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions.

Forced Expiratory Volume in One Second

Forced expiratory volume in one second (FEV1) 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 FEV1 is one of the most commonly reported pulmonary function tests.[45]

Clinically, the percentage of predicted FEV1 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, FEV1 is used to classify the severity of asthma.[46,47] However, the extent to which FEV1 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.[48-51] Conversely, FEV1 values appear to correlate well with certain final clinical outcomes, such as the likelihood of hospitalization.[52] Furthermore, FEV1 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 FEV1 within 120 mL.[53]

There appears to be limited published evidence relating to a minimal clinically important difference (MCID) for FEV1 among adult patients with asthma. In one study of 281 adult patients with mild to moderate asthma symptoms (baseline mean FEV1: 2.30 L/s [standard deviation of 0.66 L/s]), the authors calculated the minimal patient perceivable improvement (MPPI) for FEV1 as the mean change in FEV1 in patients rating themselves as “a little better” (n = 86) on the global rating of change in asthma.[35] Across all patients, the MPPI for FEV1 was 230 mL or a 10.38% change from baseline. Male and female patients showed similar MPPI values, but older patients had a lower MPPI (170 mL) than younger ones (280 mL) for FEV1.[35]

Peak Expiratory Flow

PEF — sometimes referred to as PEF rate — is defined as “the maximum flow achieved during an expiration delivered with maximal force starting from the level of maximal lung inflation.”[36] Electronic peak flow meters automatically store and download measurements as needed, circumventing the need for patients to manually record PEF values in diaries. PEF is usually expressed in units of litres per minute (L/min) and sometimes as a percentage of the predicted normal value or as a change from baseline average values.[37]

PEF values appear to discriminate between patients with reversible and irreversible airflow obstruction.[54] PEF values also appear to be a valid clinical marker of airway responsiveness and asthma severity.[37] In addition, they seem to correlate well with other measures of lung function, including FEV1,[55] although evidence that directly links PEF with quality of life is lacking.

Some trialists have used a value of 25 L/min as an MCID for PEF values among patients with asthma.[56,57] However, no research seems to support the use of this MCID. In one study of 281 adult patients with mild to moderate asthma symptoms, researchers calculated the MPPI for PEF as the mean change in PEF in patients rating themselves as “a little better” (n = 86) on the global rating of change in asthma. The MPPI for PEF was 18.8 L/min, or a 5.39% change from baseline, with no differences in MPPI values by gender or age.[35] In another study, researchers noted a predicted PEF of about 12% to be a minimal clinically

significant improvement among patients presenting to the emergency department with acute asthma exacerbation.[58]

Asthma Control Questionnaire 6 (ACQ-6)

The Asthma Control Questionnaire (ACQ) is a patient-reported instrument that measures the adequacy of asthma treatment. The original instrument, the ACQ-7, consists of seven items:[26] five on symptoms (night-time awakenings, symptom severity upon awakening, activity limitation due to asthma, shortness of breath due to asthma, and wheezing), one on rescue bronchodilator use, and one on FEV1 as percentage of predicted FEV1.[26] Aside from the item on FEV1, patients fill out the questionnaire and responses are based on the past seven days. Each item is scored on a seven-point ordinal scale, ranging from 0 (well-controlled) to 6 (extremely poorly controlled).[26] The ACQ-7 score is calculated as the mean score with all items weighted equally and therefore also ranges from 0 to 6 with higher scores indicating worse asthma control.[26] There are two versions of the ACQ-6: one excludes the FEV1 item and one excludes the item on bronchodilator use.[27] The ACQ-5 omits both the FEV1 item and the item on bronchodilator use.[27]

In a study of 50 adults with symptomatic asthma, convergent validity of the ACQ-7 was assessed and a positive association with the Asthma Quality of Life Questionnaire (AQLQ) was demonstrated (Pearson correlation coefficient [*r*] = 0.76).[26] Although high scores represent poorly controlled asthma in the ACQ and no impairment from asthma in the AQLQ, the convention used to assess construct validity was that positive correlation coefficients indicated the association between the two measures was consistent with validity. The change in ACQ-7 and the change in AQLQ were also associated with each other in 36 patients with unstable asthma ($r = 0.73$).[26] The predicted range of strengths of association for both comparisons was 0.4 to 0.8.[26] In the same study, acceptable (≥ 0.7[59]) test-retest reliability of the ACQ-7 was demonstrated in 36 patients whose asthma was stable between clinic visits (intraclass correlation coefficient [ICC] = 0.90).[26] The ACQ-7 was also responsive to change in the patients with unstable asthma (mean change of 0.73, standard deviation [SD] = 0.54, $P < 0.0001$).[26]

Validation and agreement across the shortened versions of the ACQ (ACQ-5 and ACQ-6) has also been investigated.[27-29] In a re-analysis of the aforementioned ACQ-7 validation study, all three shortened versions of the ACQ had strong associations with the AQLQ (*r* ranging from 0.77 to 0.85) and acceptable test-retest reliability (ICCs of 0.89 to 0.90).[29] Responsiveness in patients with unstable asthma for the shortened versions were similar to that for the full version.[29] These findings were corroborated by two subsequent validation studies based on samples from a 26-week randomized controlled trial (RCT, N = 552) and a post hoc analysis of two larger RCTs (N = 737 and N = 772).[27,28] In the 26-week RCT in 552 adults with asthma requiring inhaled steroids, the ACQ-6 omitting the FEV1 item had acceptable (≥ 0.7[59]) internal consistency reliability (Cronbach's alpha = 0.98), acceptable test-retest reliability (ICC = 0.82), and a strong positive association with the mini AQLQ ($r = 0.76$).[27] The MCIDs for all versions of the ACQ were found by regressing the changes in ACQ score on changes in mini AQLQ score using a geometric mean regression model.[27] Using an MCID of 0.5 for the mini AQLQ, the results indicated an MCID of approximately 0.5 for all versions of the ACQ.[27] However, it is not clear how the MCID for the mini AQLQ was determined.[60] A separate study determined the MCID for the ACQ-7 to be 0.53 using an anchor-based approach with a global rating, although the conference abstract in which it is cited was not available at the time of this review.[61] Studies in pediatric patients with asthma have found an MCID of 0.63 for the ACQ-6 using an anchor-based approach with global

rating of change,[62] an MCID of 0.375 for the ACQ-7 using a distribution-based approach,[63] and MCIDs ranging from 0.4 to 0.5 for the ACQ-7 using an anchor-based approach.[63]

A systematic review of the use of the ACQ in trials of commonly used asthma drugs showed that out of 11 studies using the ACQ, none demonstrated a between-groups difference in mean change in ACQ score exceeding the 0.5.[64] The authors suggested that ACQ results should be presented as a responder-rate comparison.[64]

Asthma Quality of Life Questionnaire for 12 Years and Older

The AQLQ is a patient-reported, disease-specific, health-related quality of life measure that was developed to assess the problems experienced by adults with asthma in their daily lives.[22] The original AQLQ includes five questions based on five activities selected by the patient in which the patient is limited by their asthma.[22] The standardized AQLQ, also known as the AQLQ(S), replaces those five patient-selected activities with five generic activities.[22] The AQLQ and AQLQ(S) are made up of 32 questions grouped into four domains: symptoms (12 items), physical activities (11 items), emotional function (five items), and environmental stimuli (four items).[22] Each question is scored on a seven-point scale ranging from 1 (severe impairment) to 7 (no impairment).[22] The overall score is calculated as the mean of all the individual scores with a higher score indicating less impairment from asthma and each of the four domain scores is calculated as the mean of the individual scores in that domain.[22] Patients recall their relevant experiences during the previous two weeks.[22] The Asthma Quality of Life Questionnaire for 12 Years and Older (AQLQ12+) is identical to the AQLQ(S) with the exception of the wording in one of the activity questions being changed from “work-related limitations” to “work-/school-related limitations”.[23]

Items for the original AQLQ were initially generated from previous work in patients with severe asthma, general health-related quality of life measures, experience of patient with chronic airflow limitation, chest physician input, and interviews with patients with asthma.[65] The number of items was reduced by selecting the most commonly identified and important troublesome items according to patients.[65] Generic activities for the AQLQ(S) were selected after reviewing the item reduction data from the original AQLQ and databases of clinical trials that used the AQLQ.[22]

The AQLQ(S) was validated in a sample of 40 adults with symptomatic asthma and the overall score was positively associated with the ACQ-7 score (r = 0.64) and the physical and mental domains of the Short Form (36) Health Survey (SF-36) (r values of 0.53 and 0.48, respectively).[22] The convention used to assess construct validity was that positive correlation coefficients indicated the association between two measures was consistent with validity. Pearson correlation coefficients varied for the domain scores of the AQLQ(S) and the ACQ-7 (0.28 to 0.72), the physical domain of the SF-36 (0.34 to 0.54), and the mental domain of the SF-36 (0.14 to 0.55).[22] Associations between the AQLQ(S) overall score and PEF, FEV1% predicted normal, and beta 2-agonist use were weaker than with the patient-reported outcomes (r values ranging from 0.01 to 0.20).[22] The overall scores of the AQLQ and AQLQ(S) were well correlated (r = 0.99).[22] Acceptable test-retest reliability was demonstrated in 35 patients with stable asthma for the AQLQ(S) overall score (ICC = 0.96) and the domain scores (ICCs of 0.82 to 0.95).[22] The responsiveness index in patients whose asthma changed, calculated by dividing change in AQLQ(S) overall score by the pooled standard deviation (SD) of the change, indicated the ability to detect within-subject changes (responsiveness index of 1.34).[22] The change in AQLQ(S) overall score was also able to differentiate between patients with stable and changed asthma (P < 0.0001).[22]

The measurement properties of the AQLQ12+ were assessed using data from two clinical trials (N = 1,770 and N = 655) in patients aged 12 years and older.[23] AQLQ12+ scores were summarized for pediatric and adults patients separately.[23] Acceptable internal consistency reliability was demonstrated for the overall and domain scores (Cronbach's alpha ≥ 0.82 in adult patients).[23] In adult patients, *r* values for AQLQ12+ scores with diary-recorded symptom score, night waking, and rescue medication use ranged from –0.50 to –0.35 for the AQLQ12+ overall score and from –0.56 to –0.22 for the AQLQ12+ domain scores.[23] Associations of the overall and domain scores of the AQLQ12+ with FEV1% predicted normal and PEF were weaker than with the patient-reported outcomes (*r* ranging from 0.06 to 0.35).[23] Construct validity and internal consistency validity of the AQLQ12+ were confirmed and acceptable test-retest reliability (ICCs of 0.84 and 0.86) was demonstrated in another analysis of trial data (N = 740 and N = 778).[41] No study appears to have formally established the MCID for AQLQ12+, although an MCID of 0.5 was established for the original AQLQ in 39 adult patients with symptomatic asthma.[40] The MCID was calculated by finding the mean AQLQ score change in patients with a minimal improvement or deterioration according to the global rating of change.[40]

Work Productivity and Activity Impairment Questionnaire Plus Classroom Impairment Questions

The Work Productivity and Activity Impairment (WPAI) questionnaire is a self-reporting instrument used to measure the impact of general health and symptom severity on work and on daily activities over the previous seven days.[30-32] The General Health WPAI questionnaire (WPAI-GH) has six questions from which the values of four different outcomes can be calculated.[31] The WPAI questionnaire can be adapted for a specific disease or condition by replacing the word "problem" in the Specific Health Problem (SHP) version of the WPAI with the specific disease.[33] When the Classroom Impairment Questions (CIQs) are added to create the WPAI+CIQ, there are a total of 10 questions, of which at least three are completed by patients.[34] While it appears that the WPAI+CIQ was meant to be adapted for specific diseases to yield the WPAI+CIQ:SHP, the statistical analysis plans for the CALIMA[4] and SIROCCO[5] trials indicated that the term "health problems" was used. The 10 questions from the WPAI+CIQ in the trials asked the patient for the following information:

Q1: Currently employed (yes/no). If the answer is "no" the patient skips to Q6.

Q2: Hours of work missed due to health problems.

Q3: Hours of work missed due to other reasons.

Q4: Hours actually worked.

Q5: Degree to which health problems affected productivity while working on an ordinal scale of 0 to 10, with 0 corresponding to "no effect."

Q6: Attends class in an academic setting (yes/no). If the answer is "no" the patients skips to Q10.

Q7: Hours of class missed due to health problems.

Q8: Hours of class actually attended.

Q9: Degree to which health problems affected productivity while attending class on an ordinal scale of 0 to 10, with 0 corresponding to "no effect."

Q10: Degree to which health problems affected regular activities other than work or class on an ordinal scale of 0 to 10, with 0 corresponding to "no effect."

The answers to the questions can be used to generate four types of scores: absenteeism (work missed), presenteeism (impairment at class or reduced on-the-job-effectiveness), work productivity loss (overall work impairment), and activity impairment.[31] The scores are provided as impairment percentages, with higher numbers corresponding to greater impairment and less productivity.[31] The scores for work-related outcomes are calculated using the responses in the following manner:[31,66]

Work absenteeism = $\frac{Q2}{Q2+Q4}$

Work presenteeism = $\frac{Q5}{10}$

Work productivity loss = $\frac{Q2}{Q2+Q4} + \left[\left(1 - \frac{Q2}{Q2+Q4}\right) \times \frac{Q5}{10}\right]$ = Work absenteeism + [(1 – Work absenteeism) × Work presenteeism]

In addition, activity impairment can be calculated for all patients (activity impairment = $\frac{Q10}{10}$).[31,66]

Although methods for scoring class-related outcomes were not found, the statistical analysis plans for the CALIMA[4] and SIROCCO[5] trials indicated that class-related outcomes were determined using analogous calculations:

For patients currently attending class in an academic setting:

Class absenteeism = $\frac{Q7}{Q7+Q8}$

Class presenteeism = $\frac{Q9}{10}$

Class productivity loss = $\frac{Q7}{Q7+Q8} + \left[\left(1 - \frac{Q7}{Q7+Q8}\right) \times \frac{Q9}{10}\right]$ = Class absenteeism + [(1 – Class absenteeism) × Class presenteeism]

In a study of adult patients with "at least well-controlled" (ALWC; N = 1,480) or "not well-controlled" (NWC; N = 1,677) asthma according to the Asthma Control Test, patients in the NWC group had significantly more work productivity and activity impairment on the WPAI-GH in terms of work absenteeism (mean ± SD: 10.4% ± 23.6% for NWC versus 7.0% ± 22.3% for ALWC; $P = 0.01$), work presenteeism (mean ± SD: 32.5% ± 27.0% for NWC versus 18.0% ± 23.3% for ALWC; $P < 0.001$), and activity impairment (mean ± SD: 48.8% ± 29.2% for NWC versus 26.4% ± 28.6% for ALWC; $P < 0.001$).[42] No information was found on the reliability or MCID of the WPAI-GH in the asthma population.

Construct validity of the asthma-specific WPAI+CIQ was assessed in 2,529 patients (1,397 patients were employed and 233 patients were in school and not employed) with severe or "difficult-to-treat" asthma.[43] However, this version of the WPAI calculates work absenteeism without asking about work missed due to other reasons.[43] Work impairment (an outcome similar to work productivity loss), school impairment (similar to class productivity loss), and activity impairment were weakly correlated with FEV1 per cent predicted (Spearman correlation coefficients of –0.11 to –0.05), moderately correlated with asthma control measured by the Asthma Therapy Assessment Questionnaire control index (Spearman correlation coefficients of 0.54, 0.37, and 0.55 for work, school, and activity impairment,

respectively), and moderately correlated with the AQLQ score (Spearman correlation coefficients of –0.65, –0.52, and –0.69 for work, school, and activity impairment, respectively).[43] No information was found on the reliability or MCID of the WPAI+CIQ in the asthma population.

EuroQol 5-Dimensions 5-Levels Questionnaire (EQ-5D-5L)

The EuroQoL 5-Dimensions questionnaire (EQ-5D) is a generic quality-of-life instrument developed by the EuroQol Group.[24] It may be applied to a wide range of health conditions and treatments.[24] As a generic measure of health-related quality of life that can capture the net effect of treatment benefits and harms, the EQ-5D provides valuable information from a patient perspective. In addition to this purpose, the EQ-5D is used in clinical trials to obtain utility weights for economic models.[16] The EuroQoL 5-Dimensions 5-levels questionnaire (EQ-5D-5L) was introduced in 2005 based on the earlier three-levels version (EQ-5D-3L).[24] It consists of an EQ-5D descriptive system and visual analogue scale (VAS). The descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, each with five levels: a level 1 response represents "no problems," level 2 "slight problems," level 3 "moderate problems," level 4 "severe problems," and level 5 "extreme problems" or "unable to perform," which is the worst response in the dimension. Respondents are asked to choose the level that reflects their health state for each of the five dimensions. In total, 3,125 possible unique health states can be defined by the EQ-5D-5L, with 11111 and 55555 representing the best and worst health states. The numerical values assigned to levels 1 to 5 for each dimension reflect rank order categories of function. In terms of measurement properties, these are ordinal data; they do not have interval properties and therefore should not be summed or averaged to, for example, produce an individual dimension "score." Results from the EQ-5D-5L descriptive system can be converted into a single index score using a scoring algorithm taking the local patient and population preferences into account. Therefore, the index score is a country-specific value and a major feature of the EQ-5D instrument.[16] The range of index scores will differ according to the scoring algorithm used; however, in all scoring algorithms of the EQ-5D-5L, a score of 0 represents the health state "dead" and 1.0 reflects "perfect health." Negative scores are also possible for those health states that society (not the individual patient) considers to be "worse than dead."

The VAS records the respondent's self-rated health on a vertical VAS scale on which the end points are labelled 0 ("the worst health you can imagine") and 100 ("the best health you can imagine"). The respondents are asked to mark an X on the point of the VAS that best represents their health on that day. The EQ-5D index and VAS scores can be summarized and analyzed as continuous data.[16,24] Hence, the EQ-5D produces three types of data for each respondent:

- a profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121 or 21143
- a population preference-weighted health index score based on the descriptive system
- a self-reported assessment of health status based on the VAS.

The EQ-5D-5L has been validated in terms of feasibility, ceiling effects, discriminatory power, and convergent validity in a diverse patient population from six countries with chronic conditions (including patients with asthma or chronic obstructive pulmonary disease).[24] MCID estimates for the index score in the general Canadian population were generated by the simulating the effects of single-level transitions in each dimension.[25] The results yielded

MCIDs with a summarized mean of 0.056 (SD = 0.011), and a summarized median of 0.056 (interquartile range, 0.049 to 0.063).[25] In a European cohort of 316 patients with asthma aged 12 to 40 years, construct validity was established using the known-groups method in groups with good, intermediate, and bad asthma control defined by the ACQ-5.[44] The EQ-5D-5L index score was significantly different between the groups with good control (mean = 0.91; 95% confidence interval (CI), 0.89 to 0.93), intermediate control (mean = 0.84; 95% CI, 0.81 to 0.87), and poor control (mean = 0.73; 95% CI, 0.69 to 0.78).[44] No information was found on the reliability or MCID of the EQ-5D-5L in the asthma population.

Conclusion

FEV1, PEF, ACQ-6, and AQLQ12+ appear to be validated outcomes for use in clinical trials of therapies for patients with asthma. Mean changes in FEV1 and PEF corresponding to MPPI in adults with mild to moderate asthma symptoms have been measured. An MCID of approximately 0.5 for the ACQ-6 was found for adults with asthma requiring inhaled steroids. An MCID for the AQLQ12+ was not found, though an MCID of 0.5 has been established for the original AQLQ on which it is based. There is some evidence for construct validity of the WPAI in adults with asthma, but information was not found in the asthma population on the reliability or MCID of the WPAI or the WPAI+CIQ. The EQ-5D-5L has been validated in a diverse patient population and an MCID of 0.056 for the index score has been calculated for general use in the Canadian population. However, information was not found in the asthma population on the reliability or MCID of the EQ-5D-5L.

Appendix 6: Summary of Other Studies

Introduction

The objective of this supplemental issue is to summarize extension studies examining the long-term safety and efficacy of benralizumab administered every eight weeks (Q8W) in adult patients with severe eosinophilic asthma.

Background

Patients who completed the treatment period of the SIROCCO, CALIMA, and ZONDA trials could enrol in the BORA study. The BORA study is an extension study in which patients who received benralizumab in the predecessor trials continued to receive the same treatment regimen and patients who received placebo in the predecessor trials were re-randomized or re-assigned to one of the benralizumab treatment arms. The treatment period was 56 weeks for adult patients and 108 weeks for adolescent patients. The clinical study report[67] for the BORA study included safety and efficacy data for adult patients for the full study period and for adolescent patients for the first 56 weeks of the study.

Some adult patients who completed 16 to 40 weeks of the BORA study subsequently enrolled in the MELTEMI study, an open-label safety extension trial. Results from the MELTEMI study were not available at the time of this report.

Table 18: Details of the BORA Extension Study

		BORA
Designs & Populations	**Study design**	DB (SB following analysis of the predecessor trial), parallel-group RCT
	Locations	447 centres in 24 countries in North America, South America, Europe, Asia, and South Africa
	Randomized (N)	[redacted]
	Inclusion criteria	• Completed the double-blind treatment period in one of the predecessor studies (SIROCCO, CALIMA, and ZONDA) on benralizumab or matching placebo
	Exclusion criteria	• Any clinically significant change in physical examination, vital signs, ECG, hematology, clinical chemistry, or urinalysis during a predecessor study which in the opinion of the investigator could have put the patient at risk because of his/her participation in the study, or could have influenced the results of the study, or interfered with the patient's ability to complete the entire duration of the study • Patients with major protocol deviations in any of the predecessor studies at the discretion of the sponsor
Drugs	**Intervention**	• Benralizumab 30 mg SC every 4 weeks or • Benralizumab 30 mg SC once every 4 weeks for three injections followed by once every 8 weeks for the remainder of the treatment period
	Comparator(s)	None
Duration	Run-in	N/A
	Double-blind	56 weeks for adults and 108 weeks for adolescents
	Follow-up	12 weeks
Outcomes	**Primary end point**	• AEs and SAEs • Laboratory variables • Physical examination
	Other end points	• Annual asthma exacerbation rate • WPAI+CIQ • Hospitalizations, ED visits, urgent care visits, and all other outpatient visits due to asthma • AQLQ12+ • EQ-5D-5L • ACQ-6 • Pre- and post-bronchodilator FEV1 • Blood eosinophils
Notes	**Publications**	N/A

ACQ-6 = six-question Asthma Control Questionnaire; AE = adverse event; AQLQ12+ = Asthma Quality of Life Questionnaire for 12 years and older; DB = double-blind; ECG = electrocardiogram; ED = emergency department; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; FEV1 = forced expiratory volume in one second; N/A = not applicable; RCT = randomized controlled trial; SAE = serious adverse event; SB = single-blind; SC = subcutaneous; WPAI+CIQ = Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions.

Source: BORA Clinical Study Report.[67]

Summary of the BORA Study

Methods

Study Design

The BORA study was a patient-blinded, parallel-group randomized controlled trial that was an extension study to the predecessor SIROCCO, CALIMA, and ZONDA trials (Table 18). Patients who received benralizumab in the predecessor trial continued to receive the same blinded treatment regimen of benralizumab every four weeks (Q4W) or Q8W for 56 weeks (or 108 weeks for adolescent patients). The first injection of study drug marked week 0 of the BORA study.

Adult patients who received placebo in the predecessor trial were randomized (1:1) to benralizumab Q4W or benralizumab Q8W for 56 weeks with the last injection of study drug at week 52. There was an end-of-therapy visit at week 56 and a follow-up visit at week 68. Some adult patients enrolled in the open-label safety extension MELTEMI study before completing the full treatment and follow-up period in the BORA study. These patients were in the BORA study for at least 16 weeks and no more than 40 weeks.

Adolescent patients at non-European Union study centres who received placebo in the predecessor trials were randomized (1:1) to benralizumab Q4W or benralizumab Q8W. All adolescent patients at study centres in the European Union who received placebo in the predecessor trials received benralizumab Q8W in the BORA study. The planned treatment period was 108 weeks with the last injection of study drug at week 104. The end-of-therapy visit was planned for week 108 and the follow-up visit was planned for week 120. Patients were categorized as adolescents or adults according to their age at baseline in the predecessor trial.

Populations

Inclusion and Exclusion Criteria

Patients in the BORA study had to have completed the double-blind treatment period in the predecessor study (SIROCCO, CALIMA, or ZONDA). Patients could be excluded if they had a major protocol deviation or a clinically significant change in safety parameters during the predecessor study.

Baseline Characteristics

Information on baseline characteristics for patients who did not enrol in the MELTEMI study are presented in Table 19 while Table 20 presents baseline characteristics for patients who enrolled in the MELTEMI study. Patients were grouped according to whether they received benralizumab Q8W or placebo in the predecessor trial (Table 19 and Table 20). Patient demographics, respiratory disease characteristics, and maintenance asthma medication use [redacted] (Table 19 and Table 20). Since benralizumab exerts its clinical effects through the reduction of eosinophilic inflammation, [redacted]. The number of asthma exacerbations in the past 12 months ranged from [redacted] for

patients whose predecessor was benralizumab Q8W and ranged from [redacted] for patients whose predecessor was placebo (Table 19 and Table 20). [redacted]

FEV1, asthma exacerbations, and the six-question Asthma Control Questionnaire (ACQ-6) score suggested that the patients at baseline in the BORA [redacted] studies (see main report). Use of maintenance asthma medications [redacted] BORA study.

Table 19: Summary of Baseline Characteristics for the BORA Study Excluding MELTEMI Patients

	[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ACQ-6 = six-question Asthma Control Questionnaire; BMI = body mass index; ICS = inhaled corticosteroid; LABA = long-acting beta-adrenoceptor agonist; LAMA = long-acting muscarinic antagonist; LTRA = leukotriene receptor antagonist; NA = not applicable; NR = not reported; Pre/BEN Q8W = received benralizumab every eight weeks in the predecessor trial; Pre/PLA = received placebo in the predecessor trial; OCS = oral corticosteroid; Q8W = every eight weeks; SD = standard deviation.

Note: All baseline values in this table reflect the values recorded at baseline in BORA.

[a] ICS doses were converted to their fluticasone propionate equivalent.

[b] OCS doses were converted to the prednisolone equivalent.

Source: BORA Clinical Study Report.[67]

Table 20: Summary of Baseline Characteristics for the BORA Study, MELTEMI Patients Only

	[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]

ACQ-6 = six-question Asthma Control Questionnaire; BMI = body mass index; ICS = inhaled corticosteroid; LABA = long-acting beta-adrenoceptor agonist; LAMA = long-acting muscarinic antagonist; LTRA = leukotriene receptor antagonist; NA = not applicable; NR = not reported; Pre/BEN Q8W = received benralizumab every eight weeks in the predecessor trial; Pre/PLA = received placebo in the predecessor trial; OCS = oral corticosteroid; Q8W = every eight weeks; SD = standard deviation.

Note: All baseline values in this table reflect the values recorded at baseline in BORA.

[a] ICS doses were converted to their fluticasone propionate equivalent.

[b] OCS doses were converted to the prednisolone equivalent.

Source: BORA Clinical Study Report.[67]

Interventions

Both patients and investigators were blinded to treatment allocation (except for allocation of adolescents in the European Union) until the blind in the predecessor studies was broken (last patient visits occurred on March 11, April 5, and August 8 of 2016 in the CALIMA, SIROCCO, and ZONDA studies). The study sponsor was no longer blinded to treatment allocation in patients who had received benralizumab in the predecessor trials after this point and the study became single-blind (last patient visit in the BORA study occurred on October 12, 2017). All patients remained blinded to treatment allocation in the predecessor trial and in the BORA study. However, study conduct and blinding at the sites continued without change and it is not clear if investigators could have been informed of treatment allocation in the predecessor trials. Administration of study medication at each visit was determined using an interactive Web or voice response system.

Benralizumab and placebo injections were administered subcutaneously at the study centre every four weeks. Placebo solution was matched in appearance with the benralizumab solution. Injections had to be administered within two or three days before and after the expected date. Patients previously randomized to the Q4W regimen of benralizumab continued injections of active drug Q4W. Patients previously randomized to the Q8W regimen received benralizumab Q8W alternating with placebo to maintain blinding.

Patients in the placebo arm of the predecessor trial randomized to benralizumab Q4W in BORA received benralizumab Q4W. Patients in the placebo arm of the predecessor trial assigned to benralizumab Q8W in BORA received the first three doses of benralizumab Q4W followed by benralizumab Q8W alternating with placebo injections to maintain blinding.

If a treatment visit could not be scheduled within the specified window, that dose of study medication was skipped. If two consecutive doses or more than two of the scheduled doses were missed during course of the study the patient was discontinued.

During the trial, patients were not allowed to use immunosuppressive medication aside from maintenance oral corticosteroids or bolus systemic steroids for treatment of an asthma exacerbation or live/attenuated vaccines.

The same medication restrictions as in the SIROCCO and CALIMA studies applied in the BORA study. Disallowed concomitant medications were taken by [redacted] of patients, the most common being other therapeutic products [redacted].

Outcomes

The results presented in this summary of the BORA study are for all adult and adolescent patients in the benralizumab Q8W treatment arm of BORA who received at least one injection of the study drug. Patients from the SIROCCO and CALIMA studies were analyzed separately from patients from the ZONDA study due to differences between the predecessor study designs. Results were summarized for the full analysis set (FAS) and grouped according to whether patients received benralizumab Q8W or placebo during the predecessor trials due to different durations of exposure to benralizumab between the two groups. The FAS consisted of all patients who received at least one dose of study medication with patients classified according to their assigned treatment. In the FAS of patients from the SIROCCO and CALIMA studies, [redacted] patients in the predecessor benralizumab Q8W group, and [redacted] patients in the predecessor placebo group were adolescents at the start of the predecessor trial. Statistical testing was not performed for any of the outcomes.

Patients who prematurely discontinued study treatment were to attend a discontinuation visit within four weeks after the last dose of study drug and a follow-up visit 16 weeks after the last dose of study drug. Study assessments were performed at both visits.

Safety

The primary objective of the BORA study was to evaluate the long-term safety and tolerability of the two dosing regimens of benralizumab. Adverse events (AEs) were recorded at every scheduled study visit, the premature treatment discontinuation visit, and unscheduled visits. AEs were considered to be on-treatment if they occurred up to four weeks after the last injection of study medication. Any AEs occurring after the end-of-therapy visit were considered to be post-treatment. On-study AEs consisted of both on-

treatment and post-treatment AEs. Differences in AE incidence between treatment groups [redacted] were also to be reported.

Efficacy

Efficacy of the two dosing regimens of benralizumab was a secondary objective of the BORA study. Similar outcomes as in the predecessor trials were assessed in the BORA study (spirometry and patient-reported outcomes). However, [redacted]. To provide information on the long-term maintenance of efficacy of benralizumab [redacted], are provided in this summary of the BORA study. A worsening of asthma requiring use of systemic corticosteroids for at least three days, in-patient hospitalization, or emergency department or urgent care visit was considered evidence of an asthma exacerbation. An asthma exacerbation occurring seven or fewer days following the last dose of systemic steroids from a prior exacerbation did not count as a separate exacerbation event. Occurrence of an asthma exacerbation did not mean that the patient had to discontinue the study. An unscheduled visit could occur to evaluate asthma worsening.

Data on asthma exacerbations were only available for patients who did not enrol in the MELTEMI study. For patients from the SIROCCO and CALIMA studies, asthma exacerbation results were reported separately for patients with predecessor trial baseline blood eosinophil counts of at least and below 300 cells/μL.

Patient Disposition

Of the patients from the SIROCCO and CALIMA studies, [redacted] of patients withdrew from the BORA study in the predecessor benralizumab Q8W and predecessor placebo groups, respectively. There was a [redacted]. The most common reasons for discontinuing treatment were [redacted].

Patients who enrolled in the MELTEMI study were considered to have completed the BORA study.

There was also an approximately [redacted] in the percentage of patients entering the MELTEMI study between predecessor treatment groups. [redacted] enrolled in the MELTEMI study regardless of predecessor study.

[redacted] was excluded from all of the analysis sets due to a breach in good clinical practice.

Table 21: Patient Disposition for the BORA Study

[redacted]

BEN Q8W = benralizumab every eight weeks; Pre/BEN Q8W = received benralizumab every eight weeks in the predecessor trial; Pre/PLA = received placebo in the predecessor trial.

[a] Includes patients who later enrolled into MELTEMI.

[b] Only adolescent patients were ongoing in BORA as of the data cut-off for the BORA draft report.

Source: BORA Clinical Study Report.[67]

Exposure to Study Treatment

Duration of exposure was defined as the time from the first dose of study medication to the last dose (plus one day). The expected duration of exposure was [redacted]. In patients who received at least one dose of study treatment and did not enroll in the MELTEMI study, mean durations of exposure ranged from [redacted] days for each group (Table 22). For adult patients who enrolled in the MELTEMI study partway through the BORA study, mean duration of exposure ranged from [redacted] for each group (Table 23).

Within each subset based on predecessor study and subsequent enrolment into the MELTEMI study, patients who had previously received placebo had shorter mean durations of exposure than patients who had previously received benralizumab. Durations of on-treatment and post-treatment follow-up were similar between predecessor treatment groups in patients from the SIROCCO and CALMA studies and were close to the expected values (Table 22). The mean durations of on-treatment follow-up were [redacted] (Table 22).

Protocol Deviations

Important protocol deviations in patients from the SIROCCO and CALIMA trials who did not enter the MELTEMI study occurred in [redacted] of patients in the predecessor benralizumab group and [redacted] of patients in the predecessor placebo group. Most of the deviations involved [redacted] (Table 22).

Important protocol deviations in patients from the ZONDA trial who did not enter the MELTEMI study occurred in [redacted] of patients in the predecessor benralizumab group and [redacted] of patients in the predecessor placebo group. [redacted] (Table 22).

According to the BORA Clinical Study Report, the profiles of important protocol deviations [redacted].

Table 22: Treatment Exposure and Important Protocol Deviations for the BORA Study Excluding MELTEMI Patients

[redacted]	[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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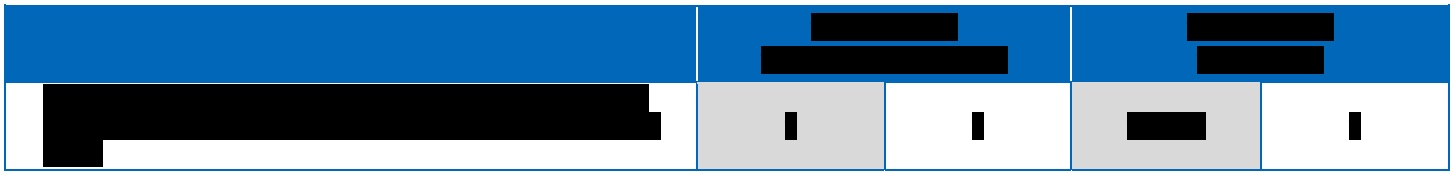

BEN Q8W = benralizumab every eight weeks; Pre/BEN Q8W = received benralizumab every eight weeks in the predecessor trial; Pre/PLA = received placebo in the predecessor trial; SD = standard deviation.

Note: Adolescent patient data were truncated at week 56 or investigational product discontinuation visit, whichever was earlier.

Source: BORA Clinical Study Report.[67]

Table 23: Treatment Exposure for the BORA Study, MELTEMI Patients Only

BEN Q8W = benralizumab every eight weeks; Pre/BEN Q8W = received benralizumab every eight weeks in the predecessor trial; Pre/PLA = received placebo in the predecessor trial.

Source: BORA Clinical Study Report.[67]

Results

Safety

Adverse Events

In patients who did not enrol in the MELTEMI study, the percentages of patients from the SIROCCO and CALIMA studies who experienced at least one AE during the on-study period were [redacted] in the predecessor benralizumab Q8W group and [redacted] in the predecessor placebo group (Table 24). The percentages of patients from the ZONDA study who experienced at least one AE during the on-treatment period were [redacted] in the predecessor benralizumab Q8W group and [redacted] in the predecessor placebo group. AEs occurring in [redacted] of any one group of patients from the SIROCCO, CALIMA, and ZONDA studies were: [redacted] (Table 24).

In patients who enrolled in the MELTEMI study and were therefore exposed to benralizumab in the BORA study for a shorter duration, the percentages of patients who experienced at least one AE during the on-study period were [redacted] for patients who had received benralizumab Q8W and placebo in the SIROCCO and CALIMA studies and [redacted] for patients who had received benralizumab Q8W and placebo in the ZONDA study (Table 25).

Serious Adverse Events

In patients who did not enroll in the MELTEMI study, [redacted] of predecessor benralizumab Q8W patents and [redacted] of predecessor placebo patients from the SIROCCO and CALIMA studies experienced at least one serious adverse event (SAE) during the on-study period. In

patients from the ZONDA study, [redacted] of predecessor benralizumab Q8W patients and [redacted] of predecessor placebo patients experienced at least one SAE during the on-treatment period (Table 24). The SAEs occurring [redacted] in any treatment group from the SIROCCO and CALIMA studies who did not enter the MELTEMI study were [redacted] (Table 24).

In patients who enrolled in the MELTEMI study, [redacted] of patients who had previously received benralizumab and [redacted] of patients who had previously received placebo in the SIROCCO and CALIMA studies experienced at least one SAE during the on-study period (Table 25). In patients from the ZONDA study, [redacted] of patients who had previously received benralizumab Q8W and [redacted] of patients who had previously received placebo experienced an SAE during the on-study period.

Withdrawals Due to Adverse Events

Percentages of patients withdrawing from the BORA study due to an AE ranged from 0% to 6.5% (Table 24).

Mortality

During the on-study period, there were [redacted] in the group that had received benralizumab in the SIROCCO and CALIMA [redacted]. The AEs leading to death in patients [redacted].

Notable Harms

[redacted] of patients, respectively; SAE of [redacted] were among the most common AEs and SAEs in patients from the SIROCCO and CALIMA studies. The other notable harms identified in the systematic review protocol of hypersensitivity and local injection-site reactions occurred in less than 3% of patients from the SIROCCO and CALIMA studies (Table 24).

Table 24: Adverse Events During On-Study Period Excluding MELTEMI Patients

	[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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AE = adverse event; BEN Q8W = benralizumab every eight weeks; Pre/BEN Q8W = received benralizumab every eight weeks in the predecessor trial; Pre/PLA = received placebo in the predecessor trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

Note: Adolescent patient data were truncated at week 56 or investigational product discontinuation visit, whichever was earlier.

[a] Identified in the systematic review protocol as a notable harm.

Source: BORA Clinical Study Report.[67]

Table 25: Adverse Events in MELTEMI Patients

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; BEN Q8W = benralizumab every eight weeks; Pre/BEN Q8W = received benralizumab every eight weeks in the predecessor trial; Pre/PLA = received placebo in the predecessor trial; SAE = serious adverse event.

Source: BORA Clinical Study Report.[67]

Efficacy

The primary efficacy end point in the SIROCCO and CALIMA studies was the annual rate of asthma exacerbations in patients with a baseline blood eosinophil count of 300 cells/μL or higher. In the BORA study, the mean number of exacerbations per follow-up years in patents from the SIROCCO and CALIMA studies with a baseline blood eosinophil count of at least 300 cells/μL was [redacted] in the group that had previously received benralizumab and [redacted] in the group that had previously received placebo (Table 26). In patients from the ZONDA

study, the number of exacerbations per follow-up years was [redacted] in the group that had previously received benralizumab and [redacted] in the group that had previously received placebo. Statistical testing was not performed for any of the outcomes in the BORA study.

Table 26: Asthma Exacerbations During the On-Treatment Period Excluding MELTEMI Patients

[redacted]

BEN Q8W = benralizumab every eight weeks; Pre/BEN Q8W = received benralizumab every eight weeks in the predecessor trial; Pre/PLA = received placebo in the predecessor trial; SD = standard deviation.

Note: Adolescent patient data were truncated at week 56 or investigational product discontinuation visit, whichever was earlier.

Source: BORA Clinical Study Report.[67]

Discussion

With patients in the benralizumab Q8W arm of the BORA study grouped by the treatment they had received in the predecessor trials, a difference between groups would suggest a difference in the safety and efficacy of benralizumab based on duration of exposure. There were [redacted] in the percentages of patients with AEs or SAEs between patients who had received benralizumab Q8W or placebo in the predecessor trial among patients from the SIROCCO and CALIMA studies and patients from the ZONDA study. The most common AEs in patients from the SIROCCO and CALIMA studies were [redacted]. In patients from the SIROCCO and CALIMA studies, there were [redacted] in the group [redacted]

Reporting of AEs could have been biased if investigators were aware of treatment allocation in the predecessor trials following breaking of the blinding of predecessor trial data for analysis. It is unclear what measures were taken to protect investigators from knowledge of treatment allocation in the predecessor trials, although most patients likely began the BORA study prior to the blinding being broken in the predecessor trials. Results were reported separately for adolescent patients but not for adult patients. Adolescent patients made up [redacted] of patients in the predecessor benralizumab Q8W group and [redacted] of patients in the predecessor placebo groups from the SIROCCO and CALIMA studies [redacted] treatment and predecessor benralizumab patients [redacted], though the between-group differences were [redacted]

[redacted]. Duration of treatment exposure was [redacted] between predecessor treatment groups from the SIROCCO and CALIMA studies and was [redacted] in patients from the benralizumab group than from the placebo group in the ZONDA study. Given [redacted] that benralizumab Q8W administered for approximately one and a half or two years [redacted] benralizumab Q8W administered for one year.

The mean number of asthma exacerbations per follow-up years was [redacted] of predecessor trial. However, no statistical testing was performed. If the reduction in asthma exacerbations with benralizumab therapy takes time to manifest after initiation of therapy, then patients newly assigned to benralizumab treatment (i.e., patients in the predecessor placebo groups) would be expected to experience more asthma exacerbations in the BORA study. There was [redacted] with continued use following the treatment periods in the predecessor studies.

Conclusions

Based on preliminary data from the BORA and MELTEMI studies, there was no evidence of a change in the safety of benralizumab Q8W with long-term administration of up to two years. The results also suggested that the efficacy of benralizumab Q8W [redacted].

Appendix 7: Summary of Indirect Comparisons

Introduction and Background

Given the absence of head-to-head studies comparing benralizumab against other biologic therapies in the study population in this CADTH Common Drug Review (CDR) report, indirect comparisons (IDCs) that include benralizumab can provide information on the comparative effectiveness of this drug to existing therapies. The objective of this Appendix is to summarize and critically appraise the evidence available regarding the comparative efficacy of any IDCs that compare benralizumab with other monoclonal antibodies for the treatment of patients with severe uncontrolled asthma.

Methods

The manufacturer submitted one IDC[68] that was reviewed, summarized, and critically appraised. CDR conducted an independent literature search for published IDCs that compared benralizumab with other relevant comparators for the treatment of adult patients with severe eosinophilic asthma; no published IDCs were identified.

Description of IDCs Identified

[redacted]

Table 27: Populations, Interventions, Comparisons, Outcomes, and Study Design Criteria for Study Inclusion

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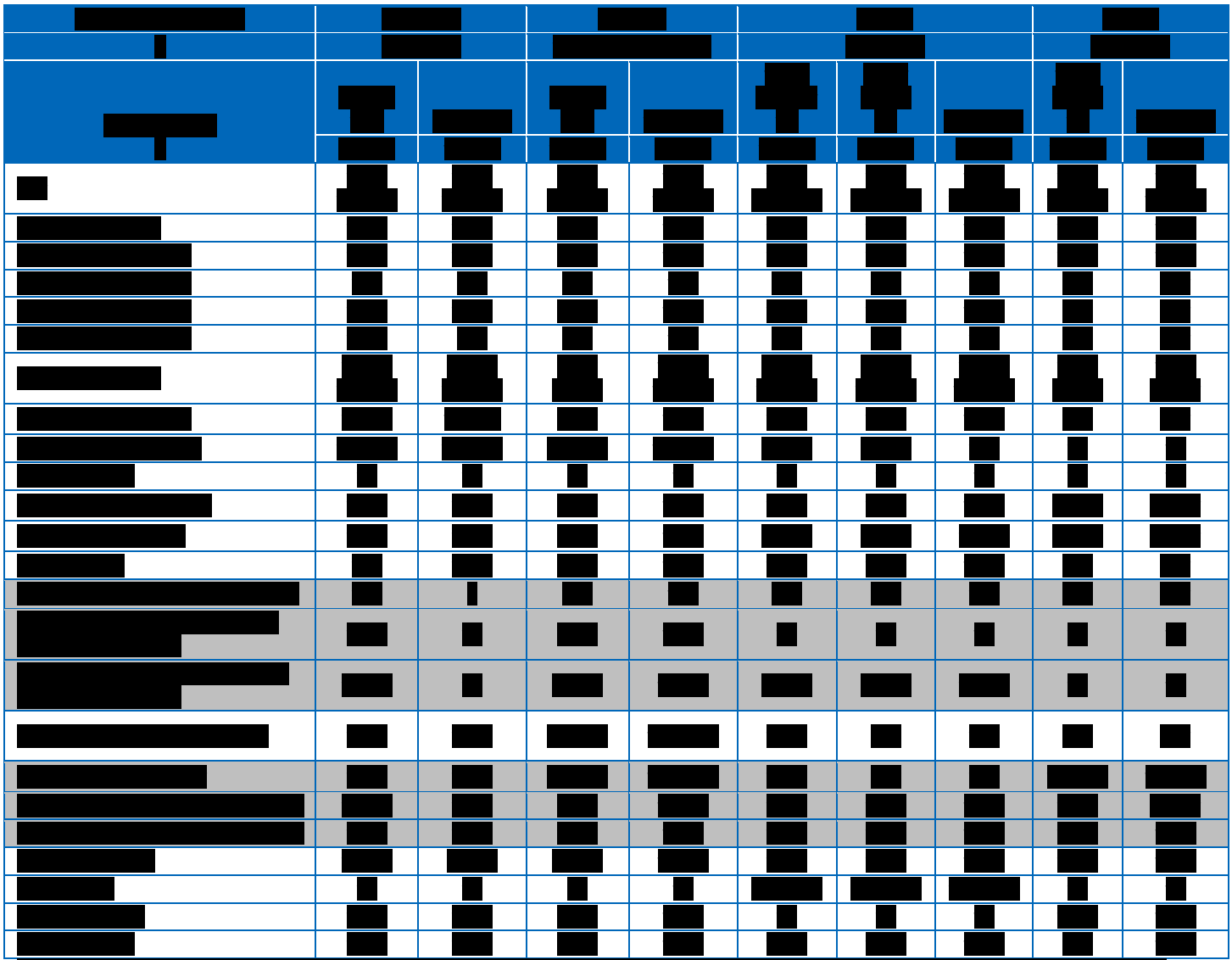

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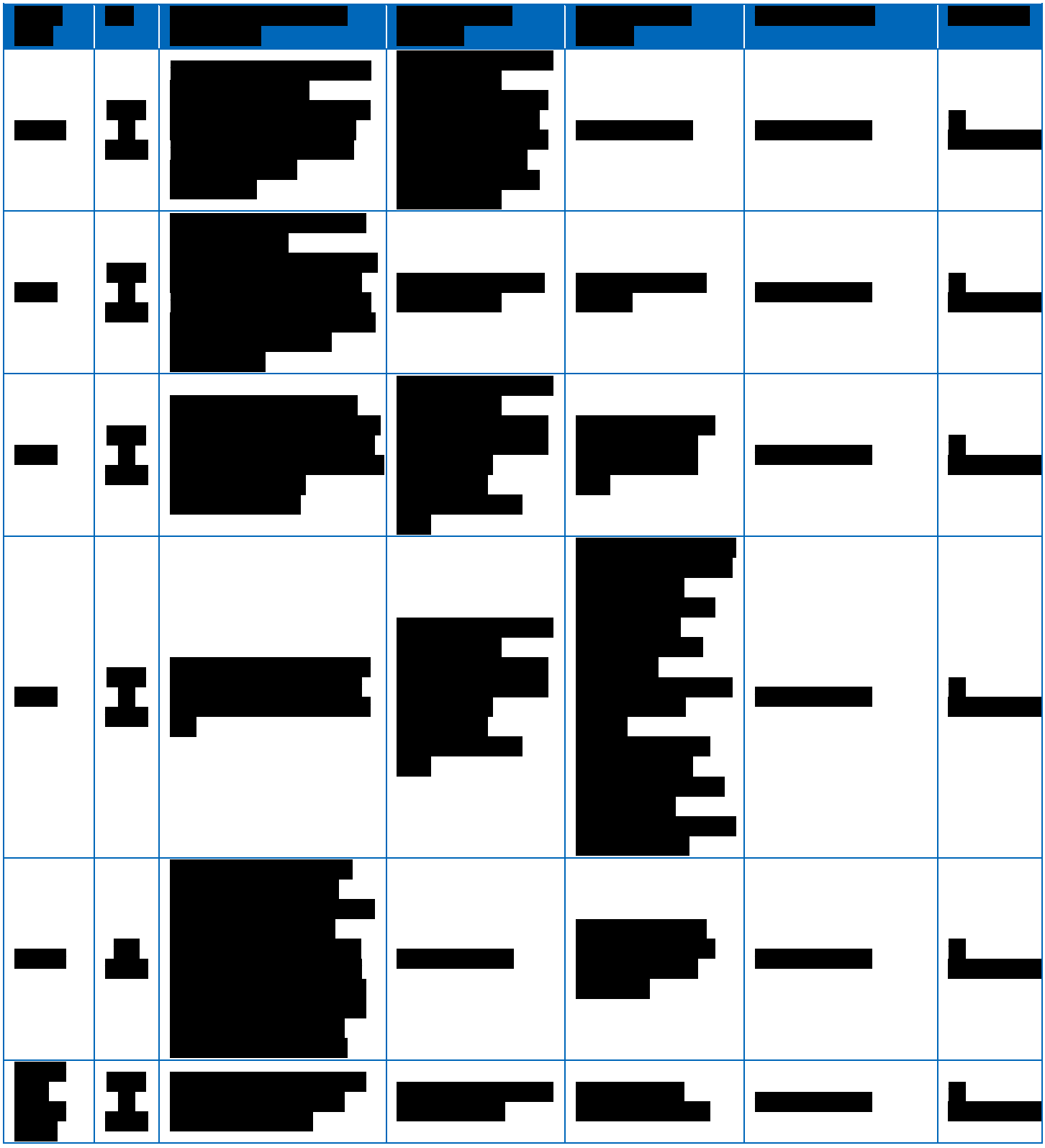

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Appendix 8: Summary of Pooled Data From SIROCCO and CALIMA

Objective

The objective of this Appendix is to summarize and critically appraise the pooled data from SIROCCO and CALIMA trials that were provided by the manufacturer. This summary will inform the pharmacoeconomic evaluation.

Methods

These two pivotal trials (SIROCCO and CALIMA) were of similar design, incorporating the same end points and frequency of assessments for efficacy and safety, and have been conducted with consistent inclusion and exclusion criteria in patients with severe asthma. The randomized treatment groups were the same in both trials (benralizumab 30 mg every four weeks [Q4W], benralizumab 30 mg Q4W for the first three doses then every eight weeks [Q8W] thereafter, or placebo). The main difference in efficacy end points between the two studies that affected this analysis was post-randomization follow-up duration: 48 weeks in SIROCCO compared with 56 weeks in CALIMA.

The following subset of the full analysis sets (FAS) was pooled from SIROCCO, CALIMA:

- ≥ 18 years at study entry
- high-dose inhaled corticosteroid (ICS)/long-acting beta2 agonist (LABA) (> 500 mcg fluticasone propionate dry powder formulation equivalents total daily dose)
- eosinophil counts ≥ 300 cells/μL
- ≥ two exacerbations in the last 12 months
- not using oral corticosteroid (OCS) at baseline.

All analysis was conducted for benralizumab 30 mg subcutaneous Q8W and standard care (placebo) treatment groups. The treatment group; benralizumab 30 mg, subcutaneous Q4W was excluded from the analysis.

A patient was considered a responder as long as one of the following criteria was met, even if data on the other conditions was missing:

- ≥ 50% reduction in annual exacerbation rate and/or
- ≥ 0.1 L change in forced expiratory volume in one second (FEV1) and/or
- ≥ 0.5 point decrease in results of the six-question Asthma Control Questionnaire (ACQ-6).

The exacerbation rate in each of the benralizumab groups was compared with the exacerbation rate in the placebo group using a negative binomial model. The response variable in the model was the number of asthma exacerbations experienced by a patient over the maximal follow-up time. The model included the following covariates: treatment group, region, and number of exacerbations in the previous year. The logarithm of the patient's corresponding follow-up time was used as an offset variable in the model to adjust for patients having different exposure times during which the events occur.

The estimated treatment effect (i.e., the rate ratio of benralizumab versus placebo), corresponding 95% confidence interval (CI), and two-sided *P* value for the rate ratio was presented. In addition, the exacerbation rate and the corresponding 95% CI within each treatment group was presented. The difference of annual rates and its 95% CI was derived from the negative binomial model.

Results

Table 28 presents the response rate for non-OCS patients in CALIMA, SIROCCO, and POOLED (CALIMA and SIROCCO).

Table 29 presents annual asthma exacerbation rate ratio treatment comparison in CALIMA, SIROCCO, and POOLED (CALIMA and SIROCCO). Table 30 presents annual asthma exacerbation rate ratio treatment comparison among responders in CALIMA, SIROCCO, and POOLED (CALIMA and SIROCCO). Table 31 presents percentage of exacerbation types by treatment group in CALIMA, SIROCCO, and POOLED (CALIMA and SIROCCO). Table 32 presents percentage of exacerbation types by treatment group among responders in CALIMA, SIROCCO, and POOLED (CALIMA and SIROCCO), and Table 33 presents summary of day-to-day utility by group, in patients with no chronic OCS use in CALIMA, SIROCCO, and POOLED (CALIMA and SIROCCO).

Table 28: Response Rate for Non-OCS Patients in CALIMA, SIROCCO, and POOLED (CALIMA and SIROCCO)

Treatment Group	N	Number of Patients Responding to Treatment	Percentage	SE
CALIMA				
Benra 30 mg every 8 weeks	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Benra = benralizumab; OCS = oral corticosteroid; SE = standard error.

Source: Manufacturer supplied.[17]

Table 29: Annual Asthma Exacerbation Rate Ratio Treatment Comparison in CALIMA, SIROCCO, and POOLED (CALIMA and SIROCCO)

Treatment Group	N	Number of Events	Total Follow-Up Time (Years)	Crude Rate	Marginal Annual Exacerbation Rate Estimate (95% CI)	Marginal Absolute Difference Estimate (95% CI)	Rate Ratio	
							Estimate (95% CI)	*P* Value
CALIMA								
Benra 30 mg every 8 weeks	208	133	216.5	0.61	0.64 (0.51 to 0.80)	−0.25 (−0.48 to −0.03)	0.72 (0.53 to 0.96)	0.027
Placebo	213	204	225.3	0.91	0.90 (0.74 to 1.09)			
SIROCCO								
Benra 30 mg every 8 weeks	206	124	180.8	0.69	0.75 (0.59 to 0.96)	−0.70 (−1.01 to −0.38)	0.52 (0.39 to 0.70)	< 0.001
Placebo	218	296	195.6	1.51	1.45 (1.20 to 1.75)			
POOLED CALIMA/SIROCCO								
Benra 30 mg every 8 weeks	414	257	397.3	0.65	0.71 (0.60 to 0.84)	−0.46 (−0.65 to −0.27)	0.61 (0.49 to 0.75)	< 0.001
Placebo	431	500	420.9	1.19	1.17 (1.02 to 1.34)			

Benra = benralizumab; CI = confidence interval.

Note: Statistical analysis model: a negative binomial model including covariates study identification, treatment group, region and number of exacerbations in the previous year. Total follow-up time was defined as the time from randomization to the date of week 48 for SIROCCO and 56 for CALIMA visit (end of treatment) or last contact if the patient was lost to follow-up. The log of each patient's corresponding follow-up time will be used as an offset variable in the model to adjust for patient's having different exposure times during which the events occur.

Rate ratio = Benralizumab treatment group/placebo.

Source: Manufacturer supplied.[17]

Table 30: Annual Asthma Exacerbation Rate Ratio Treatment Comparison Among Responders in CALIMA, SIROCCO, and POOLED (CALIMA and SIROCCO)

Treatment Group	N	Number of Events	Total Follow-Up Time (Years)	Crude Rate	Marginal Annual Exacerbation Rate Estimate (95% CI)	Marginal Absolute Difference Estimate (95% CI)	Rate Ratio	
							Estimate (95% CI)	*P* Value
CALIMA								
Benra 30 mg every 8 weeks	[redacted]							
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								

Benra = benralizumab; CI = confidence interval.

Note: Statistical analysis model: a negative binomial model including covariates study ID, treatment group, region and number of exacerbations in the previous year. Total follow-up time was defined as the time from randomization to the date of week 48 for SIROCCO and 56 for CALIMA visit (end of treatment) or last contact if the patient was lost to follow-up. The log of each patient's corresponding follow-up time will be used as an offset variable in the model to adjust for patient's having different exposure times during which the events occur.

Rate ratio = Benralizumab treatment group/placebo.

Source: Manufacturer supplied.[17]

Table 31: Percentage of Exacerbation Types by Treatment Group in CALIMA, SIROCCO, and POOLED (CALIMA and SIROCCO)

Exacerbation Type	Number of Events	Percentage	SE
CALIMA			
Benra 30 mg every 8 weeks			
Exacerbation – OCS use without ER or hospitalization	111	83.5	0.03
Exacerbation – ER or hospitalization (adjudicated)	20	15.0	0.03
Exacerbation – ER visit (adjudicated)	10	7.5	0.02
Exacerbation – Hospitalization (adjudicated)	11	8.3	0.02
Placebo			
Exacerbation – OCS use without ER or hospitalization	179	87.7	0.02
Exacerbation – ER or hospitalization (adjudicated)	18	8.8	0.02
Exacerbation – ER visit (adjudicated)	11	5.4	0.02
Exacerbation – Hospitalization (adjudicated)	7	3.4	0.01
SIROCCO			
Benra 30 mg every 8 weeks			
Exacerbation – OCS use without ER or hospitalization	107	86.3	0.03

Exacerbation Type	Number of Events	Percentage	SE
Exacerbation – ER or hospitalization (adjudicated)	16	12.9	0.03
Exacerbation – ER visit (adjudicated)	4	3.2	0.02
Exacerbation – Hospitalization (adjudicated)	12	9.7	0.03
Placebo			
Exacerbation – OCS use without ER or hospitalization	257	86.8	0.02
Exacerbation – ER or hospitalization (adjudicated)	37	12.5	0.02
Exacerbation – ER visit (adjudicated)	21	7.1	0.01
Exacerbation – Hospitalization (adjudicated)	17	5.7	0.01
POOLED CALIMA/SIROCCO			
Benra 30 mg every 8 weeks			
Exacerbation – OCS use without ER or hospitalization	218	84.8	0.02
Exacerbation – ER or hospitalization (adjudicated)	36	14	0.02
Exacerbation – ER visit (adjudicated)	14	5.4	0.01
Exacerbation – Hospitalization (adjudicated)	23	8.9	0.02
Placebo			
Exacerbation – OCS use without ER or hospitalization	436	87.2	0.01
Exacerbation – ER or hospitalization (adjudicated)	55	11	0.01
Exacerbation – ER visit (adjudicated)	32	6.4	0.01
Exacerbation – Hospitalization (adjudicated)	24	4.8	0.01

Benra = benralizumab; ER = emergency room; OCS = oral corticosteroid; SE = standard error.

Source: Manufacturer supplied.[17]

Table 32: Percentage of Exacerbation Types by Treatment Group Among Responders in CALIMA, SIROCCO, and POOLED (CALIMA and SIROCCO)

Exacerbation Type	Number of Events	Percentage	SE
CALIMA			
Benra 30 mg Every 8 Weeks			
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Exacerbation Type	Number of Events	Percentage	SE
[redacted]			

Benra = benralizumab; SE = standard error.

Source: Manufacturer supplied.[17]

Table 33: Summary of Day-to-Day Utility by Group, No Chronic OCS Use in CALIMA, SIROCCO, and POOLED (CALIMA and SIROCCO)

Utility/Group	Utility Statistics				
	n	Mean[a]	Range[a]	LS Mean[a]	SE[a]
CALIMA					
EQ-5D-5L (3L crosswalk) utility					
Benra 30 mg every 8 weeks					
[redacted]					

Utility/Group	Utility Statistics				
	n	Mean[a]	Range[a]	LS Mean[a]	SE[a]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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ACQ-6 = six-question Asthma Control Questionnaire; AQLQ(S) = Standardized Asthma Quality of Life Questionnaire; Benra = benralizumab; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels questionnaire; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; ER = emergency room; FAS = full analysis set; LS = least squares; OCS = oral corticosteriods; SE = standard error.

[a] Mean and range are based on the within patient means.

[b] LS mean and SE are evaluated from a general linear repeated measures model of utility index on-treatment group; baseline utility index; region; study; visit; type (day-to-day, OCS, ER, hospitalization); and treatment group by type interaction.

[c] Pre-assessment is based on all patients over the full follow-up period. One response is defined as a ≧ 50% reduction in the annual exacerbation rate and/or a ≧ 0.1L change in FEV1 and/or ≧ 0.5 point decrease in ACQ-6 at the end of the study.

Source: Manufacturer supplied.[17]

Critical Appraisal

The clinical expert consulted on this CDR review indicated that CALIMA and SIROCCO trials were similarly padesigned trials and enrolled patients with similar baseline characteristics, and hence pooling of individual patient-level data from these two studies is appropriate.

However, there are several weaknesses in the pooling that was done. Because it does not seem that this pooled analysis was pre-planned, it is a post hoc analysis that was unplanned and performed after the data were collected.

Results for the subpopulation included in the pooled analysis were not reported in the clinical study reports of CALIMA and SIROCCO trials provided by the manufacturer. Hence, it seems that this subpopulation was identified post hoc.

It does not seem that proper adjustment was done; instead of providing weight for each study and then performing the calculation, data from the subpopulation from both trials were combined as if these data were from one study, which is inappropriate when data are pooled. Appropriate weight should be given for each study as it is done in conventional meta-analysis; however, given the similarity in number of patients and results in each trial, it is expected that the results of weighting each study then pooling them would not substantially affect the results in this case.

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