Common Drug Review
Clinical Review Report

September 2017

Drug	Omalizumab (Xolair)
Indication	Adults and adolescents (12 years of age and above) 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 with inhaled corticosteroids.
Reimbursement Request	As per indication
Dosage Form(s)	Sterile powder for reconstitution for subcutaneous injection, 150 mg vial
NOC Date	November 18, 2004
Manufacturer	Novartis Pharmaceuticals Canada Inc.

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

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ABBREVIATIONS

ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
AE	adverse event
AQLQ	Asthma Quality of Life Questionnaire
AUS23	Study CIGE025AUS23
A2425	Study CIGE025A2425
C-ACT	Childhood Asthma Control Test
CI	confidence interval
CDEC	Canadian Drug Expert Committee
CDR	CADTH Common Drug Review
FEV_1	forced expiratory volume in one second
GETE	global evaluation of treatment effectiveness
ICAC	Inner-City Asthma Consortium
ICS	inhaled corticosteroid
IgE	immunoglobulin E
IGETE	investigator's global evaluation of treatment effectiveness
ITT	intention-to-treat
LABA	long-acting beta $_2$-agonist
LSM	least squares mean
LTRA	leukotriene receptor antagonist
LOCF	last observation carried forward
MCID	minimal clinically important difference
mITT	modified intention-to-treat
OCS	oral corticosteroids
PEF	peak expiratory flow
PROSE	Preventative Omalizumab or Step-up Therapy for Severe Fall Exacerbations
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomized controlled trial
SABA	short-acting beta agonist
SAE	serious adverse event
SCS	systemic corticosteroid
SD	standard deviation
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Asthma is a common chronic respiratory disorder characterized by reversible airway obstruction, pulmonary inflammation, airway hyper-responsiveness, and airway remodelling.[1] Patients with asthma typically present with paroxysmal or persistent symptoms of wheezing, dyspnea, chest tightness, sputum production, and coughing that are associated with airflow limitation and airway hyper-responsiveness to endogenous and exogenous stimuli (e.g., exercise; viral respiratory infections; or exposure to certain allergens, irritants, or gases).[1] Although asthma can be diagnosed at any age, it often starts in childhood. In 2015, Statistics Canada estimated that 2.4 million Canadians aged 12 years and older had a diagnosis of asthma,[2] representing 12% of all Canadian children and 8% of all Canadian adults.[2] The clinical expert involved in this review indicated that approximately 60% of adult asthma patients have allergic asthma. In children with asthma, slightly more are diagnosed with allergic asthma compared with non-allergic asthma. A small subset of cases of moderate-to-severe allergic asthma are inadequately controlled with the current stepwise approach, such as combination therapy of inhaled corticosteroids (ICS) and long-acting beta$_2$-agonist (LABA) with or without additional asthma controllers, such as a leukotriene receptor antagonist (LTRA).[1,3-5]

A previous CADTH Common Drug Review (CDR) of the use of omalizumab for allergic asthma in 2006 led to the recommendation by the Canadian Expert Drug Advisory Committee that omalizumab not be reimbursed due to: insufficient evidence that omalizumab improves exacerbations that lead to hospitalizations, emergency room (ER) visits, or physician visits; a dearth of data for patients who fail treatment with a LABA in addition to an ICS; and a low likelihood of being cost-effective. The current CDR review was undertaken in response to a request from the drug plans that participate in the CDR review process asking that the use of omalizumab in asthma be re-reviewed in light of the availability of new evidence. Therefore, for the current review, new clinical evidence that has become available since the CDR review in 2006 was considered for inclusion in a systematic review to assess the efficacy and harms of omalizumab in persistent allergic asthma in patients who are inadequately controlled by an ICS in combination with a LABA.

Results and Interpretation

Included Studies

New clinical evidence available since the previous CDR review of Xolair for asthma comprised six new randomized controlled trials (RCTs),[6-11] all of which were included in this review. Of these studies, four[6-9] were double-blinded RCTs and two[10,11] were open-label RCTs. Three[7-9] were conducted in the US, one[6] in the US and Canada, one[10] in Canada and Europe, and one[11] in Brazil. All patients had a diagnosis of persistent moderate-to-severe allergic asthma inadequately controlled by a high dose or a maximal-tolerable dose of ICS,[8,9] ICS plus a LABA,[10,11] or ICS plus a LABA with or without other medications such as LTRAs.[12,13] Patients aged 12 to 75 years were included in four of the RCTs,[6,7,10,11] while the other two studies[8,9] included patients aged 6 to 20 years. "Inadequately controlled asthma" was not defined consistently across studies but, in general, to be classified as having inadequately controlled asthma, patients were required to have one or more nighttime awakenings per week, daytime asthma symptoms requiring the use of rescue medication for two or more days per week, or at least one asthma exacerbation in the last year.

Patients were randomized to receive either 75 mg to 300 mg of add-on omalizumab subcutaneously every four weeks or 225 mg to 375 mg every two weeks, or a placebo matched to either the background asthma treatment in the double-blind trials[6-9] or to the control group without additional add-on treatment in the open-label trials.[10,11] The primary outcomes in the included studies were asthma exacerbations (in two studies[6,9]), symptom control (in three studies[7,8,10]), or quality of life (QoL) (assessed in one study using the Asthma Quality of Life Questionnaire [AQLQ]),[11] all of which were outcomes of interest for this review. Sample sizes ranged from 116[11] to 850 patients.[8] Trial duration ranged from 20 weeks[11] to 60 weeks.[8] Limitations of the included studies were: the inclusion of patients younger than 12 years old in two studies,[8,9] which could limit generalizability of findings to older patients; the potential for bias in favour of omalizumab for patient-reported outcomes in the two open-label studies;[10,11] lack of adjustment for multiplicity when assessing secondary outcomes; and no statistical comparisons between omalizumab and control/placebo in many cases.

Efficacy

Hospitalizations

Hospitalizations due to exacerbation were reported for three studies.[6,8,10] [redacted][6] [redacted]. In Study A2425,[10] 6% fewer patients in the omalizumab group experienced hospitalization compared with the placebo group. Although there was no statistical test of significance available for this metric, the clinical expert consulted for this review believed this difference between treatment groups to be clinically relevant. In the Inner-City Asthma Consortium (ICAC) study (ICAC-08),[8] statistically significantly fewer patients in the omalizumab group experienced hospitalization due to exacerbation compared with the patients in the placebo group (mean difference: –4.7%, 95% CI, –8.6 to –0.9; $P = 0.02$). In terms of the rate of hospitalization events per patient, the rate was low and similar in both the omalizumab and placebo groups in the EXTRA study.[6] In Study A2425,[10] the hospitalization rate in patients receiving omalizumab was reduced by 67% over 32 weeks compared with patients receiving placebo (rate ratio [RR] 0.33; 95% CI, 0.118 to 0.937; $P = 0.037$).

Emergency Room Visits

[redacted]

In Study A2425,[10] the ER visit rate was 60% lower in omalizumab-treated patients compared with patients who received placebo (RR, 0.40; 95% CI, 0.24 to 0.65; $P < 0.001$)(Table 8).

Physician Visits

[redacted]. Although none of the included studies was powered to assess the statistical significance of differences between groups for the rates of hospitalizations, ER visits, and medical doctor (MD) visits due to exacerbation, the aforementioned results suggest that adding omalizumab to ICS plus LABA, with or without other asthma controllers (in patients who were inadequately controlled with these combination therapies), is associated with a reduction in the rates of hospitalizations, ER visits, and MD visits due to exacerbation.[6,10] However, the precise magnitude of the effect of omalizumab on these outcomes in uncertain. Nevertheless, the aforementioned evidence

would appear to address one of the inadequacies identified in the previous CDR review of this drug in 2006.

Asthma Exacerbations

Asthma exacerbations were reported for all included studies except Study AUS23.[13] However, none of the studies was powered to evaluate the differences in the proportion of patients with asthma exacerbations between treatment groups. The exacerbation rate (the number of event per patient) was reported as the primary outcome in the EXTRA[6] and PROSE studies.[9] Overall, the results showed that adding omalizumab to existing therapy (ICS,[8,9] ICS plus LABA, with or without other asthma controllers)[6,7,10] reduced the proportion of patients with exacerbations by 5.4%[10] to 18.5%[8]) compared with placebo, and this reduction was statistically significant in Study ICAC-08[14] ($P < 0.001$) and the PROSE study[15] (relative risk 0.45; 95% CI, 0.25 to 0.92). Similarly, the exacerbation rate was statistically lower in omalizumab-treated patients in the EXTRA study[6] (25% reduction; $P = 0.006$) and in Study A2425 (43% reduction; $P < 0.001$).[10] This new evidence suggests that omalizumab reduces asthma exacerbations when added to the existing asthma therapy in patients with moderate-to-severe allergic asthma, which is consistent with the clinical findings reported in the previous CDR review of this drug in 2006.

[redacted]

in omalizumab-treated patients in the EXTRA study,[6] Study AUS23,[7] and Study A2425,[10] respectively. The statistical significance of differences between treatments for the reduction in the use of oral corticosteroids (OCS) was not reported.

Quality of Life

QoL, assessed using the AQLQ, was reported for three studies.[6,10,11] A statistically and clinically significant improvement was observed in omalizumab-treated patients compared with the placebo group in both open-label studies.[10,11] However, this finding must to be interpreted with caution due to the potential for bias in favour of omalizumab due to the open-label design of this study. Indeed, there was no clinically meaningful difference between omalizumab and placebo in the double-blind RCT[6] of omalizumab, although none of the studies was powered to detect significant differences in AQLQ scores. The absence of a consistent and significant improvement in QoL compared with placebo is consistent with the clinical findings reported in the previous CDR review of omalizumab in 2006.

Days of School or Work Missed

A small treatment effect of omalizumab on the reduction of work or school time missed was observed in all of the four studies[6-8,10] that reported this outcome. However, statistically significantly less time missed from work in omalizumab-treated patients was reported only in Study ICAC-08[8] (mean difference: –0.09 days; 95% CI, –0.18 to –0.01; $P = 0.038$).

Other Outcomes

A larger improvement in FEV_1 (forced expiratory volume in one second) was reported for omalizumab-treated patients versus placebo or controls in five RCTs. However, only one study (Rubin[11]) reported a statistically and clinically significant improvement in FEV_1 (mean difference of 0.13 L compared with the control group; $P = 0.049$). These findings regarding the effect of omalizumab on FEV_1 are consistent with the evidence reported in the previous CDR review of this drug in 2006.

Harms

Overall, the safety profile of omalizumab in terms of adverse events (AEs), serious adverse events (SAEs), and withdrawal due to adverse events (WDAEs) was similar to placebo, although the actual AEs and the incidence of AEs were variable across the included studies. AEs of special interest, such as anaphylaxis, were rare, and no patients experienced Churg–Strauss syndrome or thromboembolic events in any of the six studies. The incidence of injection-site reactions was similar in both treatment groups across studies. Therefore, the new clinical evidence did not reveal any new or notable safety concerns compared with those reported in the previous CDR review of this drug in 2006.

Conclusions

New clinical evidence identified since the previous CDR review of omalizumab in 2006 comprised six studies in which omalizumab was compared with either placebo (four double-blind RCTs) or control (two open-label studies). The results of these studies with respect to the effect of omalizumab on several key outcomes are inconsistent. There was evidence, from one double-blind RCT and one open-label RCT, that omalizumab statistically significantly reduced the proportion of patients hospitalized or the rate of hospitalization, while one double-blind RCT and one open-label RCT showed that omalizumab statistically significantly reduced the rate of ER visits. However, there was no evidence that omalizumab statistically significantly reduced the number of MD visits or the use of OCS.

Omalizumab was associated with a statistically significant reduction in the proportion of patients with exacerbations or rate of exacerbation in three of four RCTs and one of two open-label studies. However, this did not appear to be translated into an effect on QoL, which was improved statistically and clinically significantly in omalizumab-treated patients only in the two open-label studies, but not in any of the four double-blind RCTs.

There was evidence from a single RCT that omalizumab statistically significantly reduced the number of days of school or work missed. The results for other outcomes, including changes in FEV_1 (pulmonary function) and symptom reduction measured using a variety of instruments, were either inconsistent across studies or failed to demonstrate a statistically significantly treatment effect. There was also limited evidence that omalizumab had a beneficial effect on outcomes such as the frequency of nocturnal awakening, the number of symptom-free days/nights, use of ICS, and use of rescue medication (short-acting $beta_2$-agonist).

Some of the included studies had limitations that limit the generalizability of some findings to the population of interest, such as including patients younger than 12 years of age, or including patients with mild asthma who had not received ICS plus LABA treatment. In addition, lack of adjustment for multiplicity in some of the included studies limits interpreting the validity of findings based on secondary outcomes.

The open-label design of two of the included studies increases the uncertainty associated with the precise magnitude of any omalizumab-associated treatment effects, particularly with regards to the frequencies of hospitalization and ER visits, and QoL. Therefore, the available evidence is consistent with the overall conclusion that adding omalizumab to existing background treatment in patients with moderate-to-severe persistent allergic asthma who are inadequately controlled with ICS or ICS plus LABA, with or without other asthma controllers, might produce improvements in some asthma-related outcomes, although these improvements have not been demonstrated consistently or in a manner that allows for an accurate assessment of the magnitude of potential treatment effects. The inclusion of

patients who were treated with a LABA in addition to ICS in most of the newly identified studies addresses this shortcoming in the evidence that was assessed in the CDR review of omalizumab in 2006.

In addition, although inconsistent, the effects of omalizumab on the severity of asthma symptoms in the included studies are notable in light of the absence of such evidence from the previous CDR review in 2006. The results of the assessment of the efficacy of omalizumab on other outcomes in the included studies were consistent with those reported in the previous CDR review in 2006. In terms of safety, the incidence and types of AEs, SAEs, WDAEs, and notable AEs, were similar between treatment groups within studies, and no new or notable safety concerns were identified in this review compared with the safety profile reported in the previous CDR review of this drug in 2006.

TABLE 1: KEY EFFICACY OUTCOMES

Outcome	EXTRA[6,12]		AUS23[7,13]		ICAC-08[8,14]		PROSE[9,15]		A2425[10,16]		Rubin[11]	
	OMA	PLA	OMA	PLA	OMA	PLA	OMA	PLA	OMA	CTR	OMA	CTR
Hospitalization[a]												
Percentage of patients	[redacted]		0		**1.5**	**6.3**	0		[redacted]		NR	
Between-group difference, % (OMA – PLA), (95% CI)	[redacted]		-		**–4.7 (–8.6 to –0.9)**				[redacted]			
P value	[redacted]		-		**0.02**		-		NR			
Rate (number per patient)	[redacted]		0		NR		0		**0.05**	**0.14**	NR	
Rate ratio (95% CI) (OMA vs. PLA)	[redacted]		-		NR		-		**0.33 (0.118 to 0.937**		-	
P value	[redacted]								**0.037**			
ER visits[a]												
Percentage of patients	[redacted]		NR									
Between-group difference, (OMA – PLA)	[redacted]											
P value	[redacted]											
Rate per patient	[redacted]		NR						**0.35**	**0.83**	NR	
Rate ratio (95% CI) (OMA vs. PLA)	[redacted]								**0.40 (0.244 to 0.654)**			
P value	[redacted]								**< 0.001**			
MD visits[a]												
Percentage of patients	[redacted]		NR									
Between-group difference, % (OMA – PLA)	[redacted]											
P value	[redacted]											
Rate per patient	[redacted]		NR									
Rate ratio (95% CI) (OMA vs. PLA)	[redacted]											
P value	[redacted]											
Acute exacerbation												
Percentage of patients	[redacted]		NR		**30.3**	**48.8**	**11.3**	**21.0**	[redacted]		43.6	52.6
Between-group difference, % (95% CI) (OMA – PLA)	[redacted]				**–18.5 (–28.2 to –8.8)**		**–9.7**		[redacted]		–9	
Relative risk	NR				**NR**		**0.48 (0.25 to 0.92)**		NR			
P value					**< 0.001**		[redacted]					

Outcome	EXTRA[6,12]		AUS23[7,13]		ICAC-08[8,14]		PROSE[9,15]		A2425[10,16]		Rubin[11]	
	OMA	PLA	OMA	PLA	OMA	PLA	OMA	PLA	OMA	CTR	OMA	CTR
Rate per patient	[redacted]		NR						**0.55**	**0.98**	NR	
Rate ratio (95% CI) (OMA vs. PLA)	[redacted]		NR						**0.57 (0.417 to 0.778)**			
P value	[redacted]								**< 0.001**			
Use of OCS												
Percentage of patients	[redacted]		10.3	17.8	NR				[redacted]		NR	
Between-group difference, % (OMA – PLA)	[redacted]		–7.5						[redacted]			
Relative risk	NR											
P value												
Rate per patient	[redacted]		0.157	0.254	NR							
Rate ratio (95% CI) (OMA vs. PLA)			0.63 (0.26 to 1.53)									
P value			0 .307									
AQOL overall score												
N (%)	[redacted]		NR						[redacted]		77	36
Baseline, mean	[redacted]										3.1	3.1
End of study, mean	[redacted]										4.2	3.0
Change from baseline, mean	[redacted]								[redacted]		1.1	–0.1
Between-group difference of changes from baseline mean (95% CI)	[redacted]								[redacted]		1.2	
P value	[redacted]								[redacted]		NR	
Responder[b] in AQLQ, %	NR										**41.9**	**2.8**
Between-group difference, %											**39.1**	
P value	NR								[redacted]		**< 0.001**	
Days of school or work missed												
Days missed mean ± SD or %	NR				0.16 ± 0.03	0.25 ± 0.03	NR					
Days missed, % (mean change from baseline)	[redacted]		–1.13	–0.66	NR							
Between-group difference, % (95% CI) (OMA – PLA)	[redacted]		–0.47 (–5.97 to 5.03)		**–0.09 (–0.18 to –0.01)**		NR					
P value			0.866		**0.038**							
Work hours missed in past week, mean ± SD	[redacted]		NR									

Outcome	EXTRA[6,12]		AUS23[7,13]		ICAC-08[8,14]		PROSE[9,15]		A2425[10,16]		Rubin[11]	
	OMA	PLA	OMA	PLA	OMA	PLA	OMA	PLA	OMA	CTR	OMA	CTR
Work hours missed in past week, change from baseline	NR								[redacted]	[redacted]	NR	
Between-group difference, % (OMA – PLA)	[redacted]		NR						[redacted]		NR	
P value	NR											
School hours missed in past week, mean ± SD	[redacted]	[redacted]	NR									
Between-group difference, % (OMA – PLA)	[redacted]		NR									
P value	NR											

AQLQ = Asthma Quality of Life Questionnaire; CI = confidence interval; CTR = control group with no additional add-on therapy in an open-label randomized controlled trial; ER = emergency room; MD = medical doctor; NR = not reported; OCS = oral corticosteroids; OMA = omalizumab; PLA = placebo indicating a matching placebo study in a double-blind randomized controlled trial; SD = standard deviation; SE = standard error; vs. = versus.

[a] Hospitalizations, ER visits, and MD visits due to exacerbation.

[b] Defined as improvement of ≥ 1.5 in AQLQ.

Source: Clinical Study Reports[12-16] and relevant publications.[6-11]

TABLE 2: SUMMARY OF HARMS

Outcome	EXTRA[6,12]		AUS23[7,13]		ICAC-08[8,14]		PROSE[9,15]		A2425[10,16]		Rubin[11]	
	OMA N = 428	PLA N = 420	OMA N = 136	PLA N = 135	OMA N = 208	PLA N = 211	OMA N = 268	PLA N = 93	OMA N = 274	CTR N = 128	OMA N = 72	CTR N = 36
AEs, n (%)	344 (80.4)	334 (79.5)	90 (66.2)	93 (68.9)	82 (39.4)	100 (47.4)	146 (54.5)	51 (54.8)	184 (67.2)	69 (53.9)	NR	
SAEs, n (%)	40 (9.3)	44 (10.5)	[redacted]	[redacted]	13 (6.3)	35 (13.7)	[redacted]	[redacted]	23 (12.1)	21 (16.4)	3 (4.2)	0
WDAEs, n (%)	16 (3.7)	11 (2.6)	[redacted]	[redacted]	0		[redacted]	[redacted]	7 (2.5)	2 (1.5)	2 (2.6)	0 (0.0)
Deaths, n (%)	0	3 (0.7)	[redacted]		0		[redacted]	[redacted]	0	1 (0.8)	0	
Notable harms, n(%)												
Anaphylaxis	[redacted]	[redacted]	0		1 (0.5)	6 (2.8)	3 (1.1)	2 (2.2)	1 (0.4)	0	NR	
Churg–Strauss syndrome	0											
Injection-site reaction	5 (1.2)	13 (3.1)	[redacted]	[redacted]	8 (3.8)	6 (2.8)	[redacted]	[redacted]	2 (0.7)			
Thromboembolic events	0											

CTR = control group with no additional add-on therapy in an open-label randomized controlled trial; diff. = difference; NR = not reported; OMA = omalizumab; PLA = placebo indicating a matching placebo study in a double-blind randomized controlled trial.
Note: Values in red font are calculated by CDR.
Source: Clinical Study Reports[12-16] and relevant publications.[6-11]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Asthma is a common chronic respiratory disorder characterized by reversible airway obstruction, pulmonary inflammation, airway hyper-responsiveness, and airway remodelling.[1] Described by a range of heterogeneous phenotypes, symptoms may differ by presentation, etiology, and pathophysiology. Patients with asthma typically present with paroxysmal or persistent symptoms of wheezing, dyspnea, chest tightness, sputum production, and coughing that are associated with airflow limitation and airway hyper-responsiveness to endogenous and exogenous stimuli (e.g., exercise; viral respiratory infections; or exposure to certain allergens, irritants, or gases).[1] Although asthma can be diagnosed at any age, it often starts in childhood. In 2015, Statistics Canada estimated that 2.4 million Canadians aged 12 years and older had a diagnosis of asthma,[2] representing 12% of all Canadian children and 8% of all Canadian adults.[2] The clinical expert involved in this review indicated that approximately 60% of asthma patients are adults with allergic asthma. In children with asthma, slightly more are diagnosed with allergic asthma compared with non-allergic asthma. Only a small subset of cases of moderate-to-severe allergic asthma are inadequately controlled with the current guideline-recommended standard-stepwise approach, such as combination therapy of inhaled corticosteroids (ICS) and long-acting beta$_2$-agonist (LABA), with or without additional asthma controllers such as a leukotriene receptor antagonist (LTRA).[1,3-5]

1.2 Standards of Therapy

Given its heterogeneous phenotypes, the treatment for asthma is individualized for each patient's unique circumstances and customized as necessary. The primary goals of asthma management include long-term maintenance of asthma control[1] with the least amount of medication, and minimization of adverse events (AEs).[17] In the Canadian Thoracic Society guidelines, asthma control is based on several characteristics, including:

- frequency of daytime and nighttime symptoms
- frequency of exacerbations
- frequency of absences from work or school due to asthma
- ability to complete normal physical activity
- need for a short-acting beta$_2$-agonist (SABA)
- forced expiratory volume in one second (FEV_1) or peak expiratory flow (PEF)
- PEF diurnal variation
- sputum eosinophils.[1]

Asthma control may prevent or minimize the risk of short- and long-term complications, further morbidity, and death.[1] It has been reported that much of asthma-related morbidity is associated with poor management from underused or poor adherence to maintenance therapy.[18]

According to the guidelines published by the Canadian Thoracic Society, a stepwise approach to pharmacological therapy is recommended to achieve and maintain asthma control.[1] This involves escalating (i.e., stepping up) pharmacological treatment as necessary, to gain control, and then reducing (i.e., stepping down) treatment, with respect to dose and number of medications, to the minimum required for maintenance.[1] Current Canadian and international guidelines recommend that patients with asthma in all age groups be initiated with low-dose ICS.[1,19] If control is not gained or maintained, second-line drugs, such as a LABA or LTRAs, may be added, or the ICS dose can be titrated upward.[1] A Cochrane systematic review in 2011 found that the combination of ICS and LABA was superior to ICS and long-acting leukotriene antagonists on all outcomes examined (i.e., risk of exacerbation requiring oral

corticosteroids, health-related quality of life (QoL), rescue medication–free days, symptom-free days, and improvement in PEF among patients aged 12 years and over.[20] However, concerns remain with the use of LABAs, given the increased risk of asthma-related deaths and the severe exacerbations that have been reported; LABAs are not recommended as monotherapy for asthma.[1] For individuals whose asthma remains uncontrolled on ICS plus LABA, further increases in ICS dose or the addition of LTRAs or anti–immunoglobulin E (IgE) monoclonal antibody (e.g., omalizumab) for allergic asthma are recommended.

1.3 Drug

Omalizumab is a recombinant DNA-derived humanized monoclonal antibody to IgE. Binding of IgE to its receptor triggers an allergic inflammatory cascade. Omalizumab is indicated in adults and adolescents (12 years of age and older) 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 with ICS. It is administered by subcutaneous injection every two or four weeks, depending on the dose. The dose is based on both body weight and IgE levels (IU/mL), targeting 0.016 mg/kg/IgE (IU/mL).[14]

Indication under review
Adults and adolescents (12 years of age and above) 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 with ICS.
Reimbursement criteria requested by sponsor
As per indication

2. SUBMISSION HISTORY

The initial submission in April 2005 was suspended. The resubmission in October 2005 was considered by the Canadian Expert Drug Advisory Committee (CEDAC) in March 2006, with a recommendation of "do not reimburse" for treatment in adults and adolescents (≥ 12 years of age) 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 with ICS.[21]

2.1 Reasons for the Recommendation

1. The committee considered five double-blind, placebo-controlled, randomized controlled trials (RCTs), and one open-label RCT. Three of the four blinded RCTs reported no statistically significant improvement in acute asthma exacerbations leading to hospitalizations, emergency department visits, or physician visits. One trial reported statistically significant improvement in the rates of hospitalization and physician visits.
2. Current recommended therapy for patients with severe persistent asthma includes at least the use of an inhaled steroid plus a LABA, if symptoms persist despite the use of an inhaled steroid alone. Only one of the RCTs required that patients be on both of these therapies and this trial did not find that omalizumab decreased acute asthma exacerbations leading to hospitalizations, emergency department visits, or physician visits.
3. All trials reported that omalizumab improved QoL, as assessed by the Asthma Quality of Life Questionnaire (AQLQ).
4. The rate of SAEs was not increased by omalizumab compared with placebo; however, close monitoring for anaphylaxis at the time of injection is recommended.

5. Omalizumab costs approximately $1,200 per patient per month. The pharmacoeconomic model submitted by the manufacturer reported a mean incremental cost-effectiveness ratio of approximately $63,000 per quality-adjusted life-year (QALY), with a sensitivity analysis range of $35,000 to $219,000 per QALY. However, the pharmacoeconomic model, which was based on rates of asthma exacerbation, overstated the benefits of omalizumab by using the number of exacerbations for all patients rather than the number of patients who experienced an exacerbation. CEDAC felt this significantly overestimated the clinical effectiveness of omalizumab and that the true cost-effectiveness of omalizumab is likely to be much less favourable. CEDAC felt that omalizumab was not cost-effective at the submitted price.[21]

2.2 Basis of Resubmission

The basis of the resubmission, as indicated by the Drug Policy Advisory Committee Formulary Working Group (DPAC-FWG), is the new clinical information (systematic reviews, RCTs, and observational studies) that has become available since the original 2006 CDR review of omalizumab for the treatment of moderate-to-severe persistent allergic asthma.

The CDR-participating drug plans expressed the need for an updated review of the best available evidence and a formulary drug reimbursement recommendation from the Canadian Drug Expert Committee (CDEC) to address the use of omalizumab for the treatment of asthma. The DPAC-FWG subsequently made a formal request to Novartis Pharmaceuticals Canada, the manufacturer of the drug, to file a resubmission for the review of omalizumab through the CDR process. In response, the manufacturer indicated they did not plan to file a resubmission. As a result, the DPAC-FWG requested that CADTH undertake a review of omalizumab through the CDR process. The CDR-participating drug plans then submitted the resubmission for the review of omalizumab (Xolair) for the following Health Canada–approved indication:

> Adults and adolescents (12 years of age and above) 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 with ICS.

3. OBJECTIVES AND METHODS

3.1 Objectives

To perform a systematic review of the beneficial and harmful effects of omalizumab (150 mg vial) for the treatment of adult and adolescent (≥ 12 years of age) patients 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 with ICS.

3.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase 3 studies were selected for inclusion based on the selection criteria presented in Table 3. After consulting the CDR clinical expert involved in this review, the order of the outcomes listed in the original review (mainly, mortality, infection, and malignancy) has been slightly changed to focus relevant clinically important outcomes in order to address the issues discussed in CDEC's 2006 recommendation.

Any studies included in the previous (2006) CDR review were not included in the body of new evidence summarized in the current review. Fourteen observational studies[22-35] and six systematic reviews[36-41] provided by the manufacturer as new evidence were excluded because they did not meet the inclusion

criteria (study design not of interest); however, the conclusions drawn by the authors of those observational studies and systematic reviews are briefly summarized in Appendix 6.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adults and adolescents (≥ 12 years of age) with moderate-to-severe persistent allergic asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with ICS. Subgroup: Baseline asthma control medication (ICS, ICS + LABA, ICS + LABA + LAMA, ICS + LABA + LTRA)
Intervention	150 mg to 375 mg SC every 2 or 4 weeks Doses (mg) and dosing frequency determined by serum total IgE level (IU/mL) (used as an add-on therapy to the background treatment, such as ICS + LABA)
Comparators	ICS + LABA ICS + LABA + LAMA ICS + LABA + LTRA (i.e., zafirlukast and montelukast) Mepolizumab Chronic oral CS Placebo Control without additional add-on therapy Note: ICS could be used alone or in combination with all of the aforementioned maintenance (controller) medications, with or without rescue (reliever) medications (SABA or SAMA)
Outcomes	**Key Efficacy Outcomes** • Hospitalizations, ER visits, MD visits due to asthma exacerbation • Acute asthma exacerbations[a] • Use of oral CS • Quality of life[a] • Days of school or work missed[a]
	Secondary Efficacy Outcomes • Change in pulmonary function (FEV_1) • Symptom reduction (e.g., ACQ, ACT, C-ACT)[a] • Change in number of asthma symptom–free days/nights[a] • Incidence of nocturnal awakenings[a] • Reduction in use of ICS • Reduction in use of rescue medications (SABA or SAMA)[a] • Mortality **Harms Outcomes** • AEs • SAEs • WDAE • Notable AEs/AEs of special interest: anaphylaxis, Churg–Strauss syndrome, injection-site reaction, thromboembolic events
Study Design	Published and unpublished phase 3 RCTs

ACQ = Asthma Control Questionnaire; ACT = Asthma Control Test; AE = adverse event; AQLQ = Asthma Quality of Life Questionnaire; C-ACT = Childhood Asthma Control Test; CS = corticosteroids; ER = emergency room; FEV_1 = forced expiratory volume in one second; IgE = immunoglobulin E; ICS = inhaled corticosteroids; LABA = long-acting $beta_2$-agonist; LAMA = long-acting muscarinic antagonist; LTRA = leukotriene receptor antagonist; MD = medical doctor; QoL = quality of life; RCT = randomized controlled trial; SABA = short-acting $beta_2$-agonist; SAE = serious adverse event; SAMA = short-acting muscarinic antagonist; SC = subcutaneous; WDAE = withdrawal due to adverse event.
[a] Important outcomes indicated by patient groups.

The literature search was performed by an information specialist using a peer-reviewed search strategy. Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Xolair (omalizumab) and asthma.

Methodological filters were applied to limit retrieval to RCTs and controlled clinical trials. 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.

The initial search was completed on December 16, 2015. Regular alerts were established to update the search until the meeting of CDEC on April 20, 2016. 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 (www.cadth.ca/en/resources/finding-evidence-is/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Databases (free), Internet Search, and Open Access Journals. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

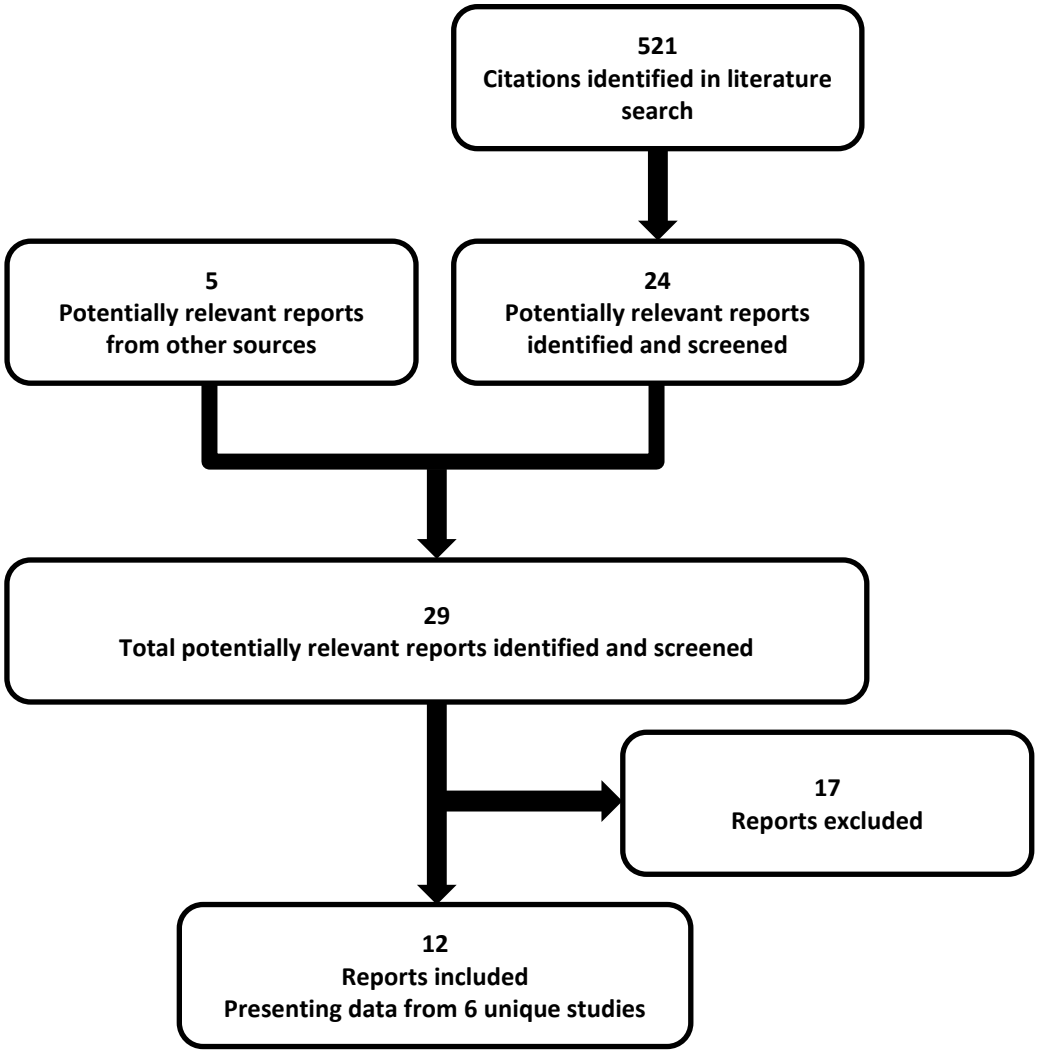
Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4 and Table 5. The excluded studies (with reasons) are presented in Appendix 3.

4. RESULTS

4.1 Findings from the Literature

A total of six studies[11-16] presented in seven reports[6-11,42] were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4 for double-blind RCTs, in Table 5 for open-label RCTs, and described in section 3.2. A list of excluded studies is presented in Appendix 3.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES



QUOROM = Quality of Reporting of Meta-analyses.

TABLE 4: DETAILS OF INCLUDED DOUBLE-BLIND, RANDOMIZED CONTROLLED TRIALS

		EXTRA[12]	AUS23[13]	ICAC-08[14]	PROSE[15]
DESIGNS AND POPULATIONS	**Study Design**	DB RCT	DB RCT	DB RCT	DB RCT
	Locations	Multiple centres, US and Canada	Multiple US centres	Multiple US centres	Multiple US centres
	Randomized (N)	850	271	419	513

	Inclusion Criteria	• 12 to 75 years of age with severe allergic asthma for ≥ 1 year
		• Persistent asthma inadequately controlled despite treatment with high-dose ICS + LABAs, with or without other controllers (including OCS)
		• Inadequately controlled defined as an average of ≥ 1 nighttime awakenings per week and requiring the use of rescue medication for ≥ 2 days per week
		• Having ≥ 1 exacerbation in past year[a]
			• ≥ 12 years of age with inadequately controlled, persistent, allergic asthma treated with medium-dose ICS plus a LABA or a medium-dose ICS plus an LTRA, theophylline, or zileuton[b]
			• Inadequately controlled asthma was defined as an ACT total score of ≤ 19 and one or more of the following within 4 weeks of entering the screening phase:
			  • symptoms for > 2 days/week, nighttime awakenings 1 time/week, use of a SABA > 2 days/week, or FEV_1 ≤ 80% predicted
			  • positive skin test for a perennial allergen
				• 6 to 20 years of age
				• Persistent allergic asthma for ≥ 1 year
				• Receiving long-term therapy for asthma control
				• Uncontrolled asthma indicated by hospitalization or unscheduled urgent care for 6 to 12 months
				• Skin test for a perennial allergen
				• Body weight between 20 kg and 150 kg, and total serum IgE levels of between 30 IU/mL and 1,300 IU/mL
					• 6 to 17 years of age
					• Asthma diagnosis or symptoms for ≥ 1 year
					• ≥ 1 exacerbations requiring SCS or hospitalization within the prior 19 months
					• A positive skin test
					• Body weight and serum IgE levels suitable for OMA dosing as indicated in Study ICAC-08[8]
					• Requiring the equivalent of 200 mg per day or greater of fluticasone propionate (< 500 mg per day)

	Exclusion Criteria	• Asthma exacerbation requiring intubation in the 12 months before screening or an exacerbation requiring treatment with SCS • An increase in the baseline dose of OCS in the 30 days before screening • Elevated serum IgE levels for reasons other than allergy • Smoking history of 10 or more pack-years	• History of intubation for asthma or anaphylaxis • SCS treatment, ER visits for asthma exacerbation within 4 weeks to 3 months • Elevated serum IgE levels for reasons other than allergy • Combination of IgE level and weight that required an OMA dose greater than 750 mg per 4 weeks	• Significant medical illnesses other than asthma, such as any infectious illness • Known hypersensitivity to any ingredients of the study medication or drugs related to OMA	• Not reported

		EXTRA[12]	AUS23[13]	ICAC-08[14]	PROSE[15]
DRUGS	**Intervention**	As add-on to "ICS + LABA, etc.": • OMA (SC) either ≥ 0.008 mg/kg/IgE (IU/mL) every 2 weeks or ≥ 0.016 mg/kg/IgE (IU/mL) every 4 weeks • Background therapy: high-dose ICS plus LABAs, OCS, or any other controller medications were permitted during the study except for SCS used to treat asthma exacerbation	As add-on to "ICS + LABA, etc.": • OMA (SC) either 150 mg or 300 mg every 4 weeks or 225 mg, 300 mg, or 375 mg every 2 weeks according to the approved US product labelling	As add-on therapy:[c] • OMA (SC) q2w or q4w for 60 weeks (15 or 30 injections) • OMA dose: 75 mg to 375 mg, calculated based on body weight and total serum IgE level to ensure a minimum monthly dose of 0.016 mg/kg/IU (IgE/mL)	As add-on to at least ICS:[c] • OMA (SC) every 2 or 4 weeks • OMA dose: same as Study ICAC-08[8]
	Comparator(s)	Placebo (SC), given at the same volume and frequency as OMA	Placebo (SC), given as the same volume and frequency as OMA	Placebo (SC), given at the same volume and frequency as OMA	Placebo (SC), given at the same volume and frequency as OMA
	Phase				
	Run-in	2 to 4 weeks	(Screen) 2 weeks	4 weeks	4 to 9 months
	Double-blind	48 weeks	24 weeks	60 weeks	4 months
	Open-label	NA	NA	17–22 weeks	NA
	Follow-up	NA	NA	NA	NA
OUTCOMES	**Primary End Point**	The rate of asthma exacerbations during the 48 weeks[d]	The primary efficacy variable was change from baseline in ACT total score	The number of days with symptoms during the previous 2 weeks	Asthma exacerbation[e]
	Other End Points	Secondary efficacy: • asthma symptom severity score • use of mean puffs per day of salbutamol • AQLQ(S)	Secondary outcomes: • IGETE exploratory efficacy • WPAI-A • FEV_1 • use of rescue SCS to treat asthma exacerbations	Exacerbations[f]	Not reported

		EXTRA[12]	AUS23[13]	ICAC-08[14]	PROSE[15]
NOTES	**Publications**	Hanania (2011)[6] Hanania (2013)[42]	Bardelas[7]	Busse (2011)[8]	Teach (2015)[9]

ACQ = Asthma Control Questionnaire; ACT = asthma control test; AQLQ = Asthma Quality of Life Questionnaire; AUS23 = study CIGE025AUS23; DB = double blind; FEV_1 = forced expiratory volume in one second; GETE = global evaluation of treatment effectiveness; ICS = inhaled corticosteroid; IgE = immunoglobulin E; IGETE = investigator's global evaluation of treatment effectiveness; LABA = long-acting $beta_2$-agonist; LTRA = leukotriene receptor antagonist; OMA = omalizumab; q2w = every 2 weeks**;** q4w = every 4 weeks; RCT = randomized controlled trial; SCS = systemic corticosteroid; SABA = short-acting $beta_2$-agonist; WPAI-A = Work Productivity and Activity Impairment Questionnaire — Asthma.

[a] Refers to an exacerbation that required systemic corticosteroid rescue in the 12 months prior to the screening visit while receiving treatment with high-dose ICS, defined as a minimum of fluticasone DPI 500 mcg twice daily or its comparable ex-valve dose.

[b] The inclusion criteria (in terms of age and background therapy) and the outcome measurement were not consistently reported in the Clinical Study Report[13] and the publication by Berdelas.[7] The information in this table was extracted mainly from the publication by Berdelas.[7]

[c] No details of background treatment (such as ICS or LABA) at baseline were reported: 25% to 28% on step 1 or 2 medication, 53% to 55% on steps 4 to 6 medication.[8]

[d] A protocol-defined asthma exacerbation was worsening asthma symptoms requiring treatment with SCS for three or more days. For patients receiving long-term OCS, an exacerbation was an increase of 20 mg or more in the average daily dose of oral prednisone (or a comparable dose of another systemic corticosteroid).

[e] Defined by a worsening of asthma control requiring SCS or hospitalization in the 90-day period beginning on the first day of each participant's school year.

[f] Defined as a need for SCS, hospitalization, or both.

Source: Clinical Study Reports[12-15] and Bardelas,[7] Hanania,[6,42] Busse,[8] and Teach.[9]

TABLE 5: DETAILS OF INCLUDED OPEN-LABEL RANDOMIZED CONTROLLED TRIALS

		A2425[16]	Rubin (2012)[11]
DESIGNS AND POPULATIONS	**Study Design**	OL RCT	OL RCT
	Locations	Multiple centres in 14 countries (Canada, Europe, Israel)	Multiple centres in Brazil
	Randomized (N)	404	116
	Inclusion Criteria	• 12–75 years of age • Allergic asthma for ≥ 1 year • ATS or GINA step 3 or 4 clinical features • Body weight of ≥ 20 kg and ≤ 150 kg and with a total serum IgE level of ≥ 30 IU/mL to ≤ 700 IU/mL • A positive skin-prick test for a perennial allergen within the past 2 years • A ≥ 12% increase in FEV_1 reversibility test • An FEV_1 of ≥ 40% and ≤ 80% of the predicted normal • Receiving ICS ≥ 800 mcg BDP or equivalent and a regular inhaled LABA for at least 3 months prior to screening and > 1,000 mcg BDP and a LABA for the last 4 weeks during the run-in and at randomization	• 12 and 75 years of age • Severe persistent asthma uncontrolled despite treatment with ICS (of at least 500 mcg/day of fluticasone equivalent) + LABA • 150 kg body weight and IgE levels of between 30 IU/mL and 700 IU/mL • Positive skin test for a perennial allergen
	Exclusion Criteria	• Patients being treated for an asthma exacerbation during the 4 weeks immediately prior to randomization • Patients with significant underlying medical conditions	• History of allergy or hypersensitivity to OMA • Use of SCS for any reason other than asthma
DRUGS	**Intervention**	As an add-on to ICS + LABA: • OMA (SC) 75 mg to 300 mg q4w or 225 mg to 375 mg q2w based on body weight and baseline serum IgE level	As an add-on to ICS + LABA: • OMA (SC) 150 mg to 375 mg every 2 or 4 weeks • doses (mg) and dosing frequency were determined based on total serum IgE level (IU/mL) and body weight (kg) • doses of > 150 mg were achieved by administering injections at multiple sites to ensure that no more than 150 mg of OMA was administered per site
	Comparator(s)	Control (ICS + LABA; none was added)	Control (LABA + ICS; none was added)
	Phase		
	Run-in	8 weeks	NA
	Double-blind	NA	NA
	Open label	32 weeks	20 weeks
	Follow-up	NA	NA

		A2425[16]	Rubin (2012)[11]
OUTCOMES	Primary End Point	The persistency rate (%) of response in patients receiving OMA based on the investigator's (physician's) GETE	AQLQ scores
	Other End Points	• Patient's GETE • FEV_1 • Asthma exacerbations • Hospitalizations, ER visits, and unscheduled outpatient clinical visits due to asthma exacerbation • Reduction in maintenance OCS • ACQ	• Increase of > 1.5 on AQLQ • Exacerbation • Rescue medication use • Clinical symptoms scores • FEV_1 • GETE
NOTES	Publications	Bousquet (2011) [10]	Rubin (2012) [11]

A2425 = study CIGE025A2425;[16] ACQ = Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; ATS = American Thoracic Society; BDP = beclomethasone dipropionate; FEV_1 = forced expiratory volume in one second; GETE = global evaluation of treatment effectiveness; GINA = Global Initiative for Asthma; ICS = inhaled corticosteroid; IgE = immunoglobulin E; IGETE = investigator's global evaluation of treatment effectiveness; LABA = long-acting $beta_2$-agonist; OL = open label; OMA = omalizumab; q2w = every 2 weeks; q4w = every 4 weeks.
Source: Clinical Study Report,[16] Bousquet,[10] and Rubin.[11]

4.2 Included Studies

4.2.1 Description of Studies

Six new RCTs (the EXTRA study,[6,12,42] study CIGE025AUS23[7,13] (known as AUS23 in this review), In the Inner-City Asthma Consortium study (ICAC-08),[8,14] the PROSE study,[9,15] Study CIGE025A2425,[10,16] (known as A2425 in this review) and the study by Rubin,[11] were included in this review. Of these six studies, four[6-9] were double-blinded RCTs, two[10,11] were open-label RCTs. Two[8,9] of the four double-blinded RCTs were conducted mainly in children (from 6 to 20 years old). Three[7-9] were conducted in the US only, one[6] in both the US and Canada, one in Canada and Europe,[10] and one[11] in Brazil. Sample sizes were from 116[11] to 850.[6] Trial duration ranged from 20 weeks[11] to 60 weeks.[6] The baseline or background treatment was "ICS plus LABA with or without other asthma controller" in two double-blinded RCTs;[6,7] and "ICS plus LABA" in two open-label RCTs.[10,11] The baseline treatment in the two pediatric studies was "at least ICS." Eligible patients were randomized to receive omalizumab subcutaneously (either 75 mg to 300 mg every four weeks, or 225 mg to 375 mg every two weeks), or matching placebo, which was added to the background asthma treatment (in the double-blind trial),[6-9] or they were randomized to a control group without additional add-on treatment (in the open-label trial[10,11]). All trials except Rubin[11] involved a run-in period of two to eight weeks. The purpose of the run-in period was to ensure and document the patient's inadequate asthma control with the background therapy (e.g., ICS plus LABA with or without other asthma controllers prior to entering the RCT. The run-in duration was four to nine months in PROSE,[9] before randomization. During the run-in period, patients maintained on a stable-dose ICS with or without other asthma control medications. The primary outcomes in the included studies were asthma exacerbation in two studies[6,9] or symptom control in three studies,[7,8,10] or QoL (AQLQ) in one study.[11]

4.2.2 Populations

a) Inclusion and Exclusion Criteria

All patients had a diagnosis of persistent moderate-to-severe allergic asthma inadequately controlled at least by the treatment of high dose or maximal-tolerable dose of ICS,[14,15] or ICS plus LABA,[11,16] or ICS plus

LABA with or without other medications such as LTRAs.[12,13] Patients' background therapy (such as ICS or ICS plus LABA) prior to the study was not consistently clearly reported across studies. Patients from 12 to 75 years of age were included in four RCTs.[11-13,16] However, two other studies[14,15] included patients from 6 to 20 years old, which is inconsistent with the approved indication. In those two studies, there was no detailed information about the percentage of patients aged 12 years and younger. A patient body weight of between 20 kg and 150 kg, and a total serum IgE level of between 30 IU/mL and 1,300 IU/mL were specified as inclusion criteria in four studies.[11,14-16] Inadequately controlled asthma was not consistently defined across studies; however, one or more nighttime awakenings per week, daytime asthma symptoms requiring the use of rescue medication for two or more days per week, or at least one asthma exacerbation in the last year were generally required.

Patient who had significant medical illnesses other than asthma were excluded. Patients who, due to a combination of IgE level and body weight, required an omalizumab dose of more than 750 mg every four weeks were excluded in Study AUS23.[13]

b) Baseline Characteristics

The baseline characteristics of the included studies are summarized in Table 6 for the double-blinded RCTs, and in Table 7 for the open-label RCTs. Overall, the baseline characteristics were balanced between the two treatment groups in each study with minor exceptions; there were numerically more female patients included in the omalizumab group than in the placebo group in the EXTRA study, but in Study A2425, numerically more female patients were included in the placebo group than in the omalizumab group. Four of the six studies recruited patients between 12 years old to 75 years (mean: 41 to 46 years) with predominantly fewer male patients (range: 32% to 40%). In contrast, more male patients (range: 59% to 67%) were included in the two pediatric studies.[8,9] In Study ICAC-08,[8] patients from 6 to 17 years of age (mean: 11) were included and, in the PROSE study, patients from 6 to 20 years of age (mean: 10) were included.[9] Body weight ranged from 84 kg to 88 kg in two studies.[6,7] No information about body weight was reported in the remaining four studies.[8-11] Mean serum IgE levels were 175 IU/mL to 183 IU/mL in both the EXTRA study[12] and Study AUS23.[13] No IgE level information was reported in the other four studies. The majority of patients were Caucasian (range: 58% to 98%), with the exception of two pediatric studies, in which 57% to 67% of the patients were black. The mean duration of asthma ranged from 21 to 33 years. In the two pediatric studies, the mean duration of asthma was 7 to 8 years. The baseline asthma control medications (background therapy) were not consistently clearly reported across studies. In the two pediatric studies,[8,9] it was required that patients receive at least ICS. ICS plus LABA was reported in two studies,[10,11] and ICS plus LABA and/or other medications such as LTRAs was reported in two studies.[6,7] Baseline FEV_1 (predicted percentage value) ranged from 61% to 93%, with the smallest percentages recorded in Study A2425,[10] and the highest in Study ICAC-08.[8] The majority of studies did not report information on exacerbations or hospitalizations, emergency room (ER) visits, physician (MD) visits, and use of systemic corticosteroids due to exacerbations in the past year before the trial. In Study ICAC-08, 25% of patients experienced hospitalization and 78% reported unscheduled MD visits due to asthma in the past year.

TABLE 6: BASELINE CHARACTERISTICS IN DOUBLE-BLIND STUDIES

	EXTRA[6]		AUS23[7]		ICAC-08[8]		PROSE[9]	
	OMA (n = 427)	**PLA (n = 421)**	**OMA (n = 136)**	**PLA (n = 135)**	**OMA (N = 208)**	**PLA (N = 211)**	**OMA (n = 259)**	**PLA (n = 89)**
Age (years), mean (SD)	43.7 (14.3)	45.3 (13.9)	41.9 (14.6)	40.7 (14.9)	10.9 (3.6)	10.8 (3.4)	10.3 (2.99)	10.1 (3.06)
Range (years)	12 to 75		18 to 59		6 to 20		6 to 17	
Male, number (%)	165 (38.6)	126 (29.9)	43 (31.6)	48 (35.6)	122 (59)	120 (57)	174 (67.2)	59 (66.3)
Background treatment, number (%)								
ICS alone	NR	NR	14 (10.3)	21 (15.6)	Yes[a]	Yes[a]	YES	YES
ICS + LABA	**YES**	**YES**	92 (67.6)	78 (57.8)	NR	NR	NR	NR
ICS + other	NR	NR	6 (4.4)	10 (7.4)	NR	NR	NR	NR
ICS + LABA + other	NR	NR	24 (17.6)	26 (19.3)	NR	NR	NR	NR
Step level equal to 1 or 2[b]	NR	NR	NR	NR	53 (25)	60 (28)	NR	NR
Step level equal to 4 to 6[b]	NR	NR	NR	NR	115 (55)	111 (53)	NR	NR
SCS, n (%) (IV and OCS)	30 (7.0)	30 (7.1)	NR	NR	NR	NR	NR	NR
ICS dose, mg/day (prednisolone equivalent), mean (SD)	NR	NR	NR	NR	NR	NR	NR	NR
Mean asthma exacerbations requiring SCS in the 12 mo before baseline (SD), n	2.0 (2.2)	1.9 (1.5)	NR	NR	NR	NR	NR	NR
Asthma exacerbation ≥ 1	NR	NR	NR	NR	NR	NR	106 (40.9)	35 (39.3)
Duration of asthma, mean number of years ± SD	22.8 ± 15.4	24.7 ± 15.8	NR	NR	7.5 ± 4.0	7.0 ± 3.8	7.72 ± 3.56	7.24 ±3.56
Mean AQLQ(S) score ± SD	4.0 ± 1.1	3.9 ± 1.1	NR	NR	NR	NR	NR	NR
Nighttime sleep disruptions[c]	NR	NR	NR	NR	1.03 ± 2.22	0.84 ± 1.96	0.88 ± 1.84	0.90 ± 1.98
Missed school, no. of days ± SD	NR	NR	NR	NR	0.23 ± 0.76	0.25 ± 0.63		
FEV_1 reversibility (%)	NR	NR	NR	NR	NR	NR	NR	NR
FEV_1, L, mean ± SD	NR	NR	2.4 ± 0.8	2.5 ± 0.7	NR	NR	NR	NR
FEV_1, % of predicted value ± SD	65.4 ± 15.2	64.4 ± 13.9	74.5 ± 17.5	76.5 ± 17.0	92.9 ± 18.7	92.2 ± 7.6	88.7 ± 15.4	89.3 ± 21.2
Asthma-related health care use in previous year, no. (%)	NR	NR	NR	NR	NR	NR	NR	NR
≥ 1 hospitalizations	NR	NR	NR	NR	52 (25)	52 (25)	NR	NR
≥ 1 unscheduled visits	NR	NR	NR	NR	165 (79)	163 (77)	NR	NR
Mean body weight, kg (SD)	87.9 (21.2)	86.2 (21.1)	84.4 (20.3)	84.0 (20.7)	NR	NR	NR	NR
Serum IgE (IU/mL), mean (SD)	179 ± 135	175 ± 134	183 ± 126	181 ± 135	NR	NR	NR	NR
Mean puffs of rescue medication per day, n (SD)	4.0 (2.9)	4.1 (3.2)	NR	NR	NR	NR	NR	NR

	EXTRA[6]		AUS23[7]		ICAC-08[8]		PROSE[9]	
	OMA (n = 427)	**PLA (n = 421)**	**OMA (n = 136)**	**PLA (n = 135)**	**OMA (N = 208)**	**PLA (N = 211)**	**OMA (n = 259)**	**PLA (n = 89)**
OMA dosing regimen, n (%)								
Every 2 weeks	191 (44.7)	187 (44.4)	64 (47.1)	60 (44.4)	[redacted]	[redacted]	NR	NR
Every 4 weeks	236 (55.3)	234 (55.6)	72 (52.9)	75 (55.6)	[redacted]	[redacted]	NR	NR

AQLQ = Asthma Quality of Life Questionnaire; AQLQ(S) = Standardized Asthma Quality of Life Questionnaire; FEV_1 = forced expiratory volume in one second; ICS = inhaled corticosteroid; IgE = immunoglobulin E; IV = intravenous; LABA = long-acting $beta_2$-agonist;; NR = not reported; OCS = oral corticosteroid; OMA = omalizumab; PLA = placebo; RCT = randomized controlled trial; SCS = systemic corticosteroid; SD = standard deviation.

[a] The background treatment was not clearly reported in Study ICAC-08;[8,14] it was described as "long-term guidelines-based therapy for disease control." It was reported that at least 25% to 28% patients were on ICS treatment (step 1 or step 2) only.

[b] Six treatment steps were established, consistent with the National Asthma Education and Prevention Program's *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*[43] for standardizing prescribing patterns according to levels of asthma severity. Steps 1 and 2 apply to mild asthma; step 3 to moderate asthma, and steps 4 through 6 to severe asthma. At step 0, the recommendation is for no asthma control medication, or salbutamol as needed. Step 1: 180 mcg of budesonide once a day; step 2: 180 mcg of budesonide twice a day; step 3: 360 mcg of budesonide twice a day; step 4: 250 mcg of fluticasone and 50 mcg of salmeterol (Advair) twice a day; step 5: 250 mcg and 50 mcg of salmeterol twice a day plus montelukast once a day; and step 6: 500 mcg and 50 mcg of salmeterol twice a day plus montelukast once a day. (The doses for montelukast are 5 mg per day for children ≤ 14 years of age and 10 mg per day for those ≥ 15 years of age.)

[c] The number of nighttime sleep disruptions was calculated based on the numbers reported during the previous 2 weeks.

Source: Clinical Study Reports[12-15] and/or publications.[6-9,42]

TABLE 7: BASELINE CHARACTERISTICS IN OPEN-LABEL STUDIES

	A2425[16]		Rubin (2012)[11]	
	OMA (n = 272)	**CTR[a] (n = 128)**	**OMA (n = 78)**	**CTR[a] (n = 38)**
Age (years), mean (SD)	45.6 (13.04)	45.7 (12.57)	43.8 (13.1)	45.2 (12.28)
Range	14–73	18–72	13–69	20–72
Male, number (%)	89 (32.7)	52 (40.6)	18 (23.1)	9 (23.7)
Background treatment				
ICS + LABA	YES	YES	YES	YES
ICS use, n (%)	271 (99.6)	128 (100.0)	NR	NR
LABA use, n (%)	271 (99.6)	128 (100.0)	NR	NR
SABA use, n (%)	254 (93.4)	117 (91.4)	NR	NR
Duration of asthma (years), mean (SD)	21.1 (13.9)	21.0 (13.1)	31.7 (16.3)	33.1 (16.9)
Range	2–64	2–66	1–66	2–72
Mean AQLQ(S) score (SD)	NR	NR	3.1 (1.0)	3.1 (1.1)
FEV_1 reversibility, % (SD)	24.7 (13.75)	21.3 (12.44)	NR	NR
FEV_1, % of predicted value (SD)	63.0 (12.41)	61.1 (13.37)	NR	NR
≥ 1 hospitalizations	NR	NR	NR	NR
≥ 1 unscheduled visits	NR	NR	NR	NR
Mean body weight, kg (SD)	NR	NR	NR	NR
Serum IgE total (IU/mL)				
Mean (SD)	233 (153)	231 (150)	NR	NR
Range	30.7–695	30.9–675	NR	NR
Background treatment				
ICS use, n (%)	271 (99.6)	128 (100.0)	NR	NR
LABA use, n (%)	271 (99.6)	128 (100.0)	NR	NR
SABA use, n (%)	254 (93.4)	117 (91.4)	NR	NR

	A2425[16]		Rubin (2012)[11]	
	OMA (n = 272)	**CTR[a] (n = 128)**	**OMA (n = 78)**	**CTR[a] (n = 38)**
Dose, mcg/day (BDP equivalent), mean (SD)	2,049 (1,006)	1,894 (953)	NR	NR
SCS use, n (%) (IV and OCS)	61 (22.4)	27 (21.1)	NR	NR
ICS dose, mg/day (prednisolone equivalent), mean (SD)	13.0 (9)	13.3 (11)	NR	NR
OMA dosing regimen, n (%)				
Every 2 weeks	NR	NR	NR	NR
Every 4 weeks	NR	NR	NR	NR

AQLQ(S) = Standardized Asthma Quality of Life Questionnaire; BDP = beclomethasone dipropionate; CRT = control group (no additional add-on) in an open-label study; FEV_1 = forced expiratory volume in one second; ICS = inhaled corticosteroid; IV = intravenous; LABA = long-acting $beta_2$-agonist; NR = not reported; OCS = oral corticosteroids; OMA = omalizumab; q2w = every 2 weeks**;** q4w = every 4 weeks; RCT = randomized controlled trial; SCS = systemic corticosteroid; SABA = short-acting $beta_2$-agonist; SD = standard deviation.
Source: Clinical Study Report[16] and publications.[10,11]

4.2.3 Interventions

Patients were randomized to omalizumab subcutaneously (as add-on therapy to the background treatment) every two or four weeks. The injection dose of omalizumab (75 mg to 375 mg) was calculated on the basis of body weight and total serum IgE level to ensure a minimum monthly dose of either 0.008 mg/kg/IgE (IU/mL) every two weeks or 0.016 mg/kg/IgE (IU/mL) every four weeks. Otherwise, patients received matching placebo (in the double-blind RCTs);[6-9] or were randomized to the control group (in the two open-label trials) with no additional add-on to the background therapy.[10,11]

To maintain blinding, patients, parents, investigators, site personnel, and members of the sponsor's staff had no knowledge of treatment assignment. During the double-blind treatment periods, patients were not allowed to take any other asthma medication except for the fixed dose of beclomethasone dipropionate, rescue $beta_2$-agonists, and treatment for asthma exacerbations.[6-9]

4.2.4 Outcomes

a) Hospitalizations, ER Visits, and MD Visits Due to Asthma Exacerbation

While hospitalizations, ER visits, and MD visits due to asthma exacerbation were not designed as an efficacy outcome measurement in the included RCTs, this information was usually captured in health care resource utilization or in the safety outcomes, such as exacerbation requiring hospitalizations, ER visits, and MD visits. In this review, four[6-9] of the six included studies reported the information on hospitalizations, ER visits, and MD visits due to asthma exacerbation measured by event incidence (number of patients with the event) and/or event rate (number of events per patient per period). In EXTRA[6] and Study ICAC-08,[8] hospitalizations, ER visits, and MD visits were recorded during each scheduled visit; however, no specific detail was provided regarding how the data on unscheduled MD visits were collected (such as from a patient's diary or other sources not specified). None of the patients experienced hospitalization in Study AUS23[7] or PROSE.[9]

The CDR clinical expert involved in this review indicated that these outcomes, when presented as rates, more accurately reflect any changes observed with the use of omalizumab than when they are reported as the proportion of patients with the events (i.e., the incidence). The expert also emphasized that **any** statistically significant reduction in hospitalizations, ER visits, or MD visits in patients treated with omalizumab compared with those who received placebo would be considered clinically significant.

b) Acute Asthma Exacerbations

Asthma exacerbations are episodes characterized by a progressive increase in symptoms of shortness of breath, coughing, wheezing, or chest tightness, and a progressive decrease in lung function.[5] Severe exacerbations may occur in patients with mild or well-controlled asthma.[5] Frequent severe exacerbations is defined as two or more exacerbations requiring two or more bursts of systemic corticosteroids (more than three days each) in the previous year;[44] a serious exacerbation is defined as at least one hospitalization, intensive care unit stay, or mechanical ventilation in the previous year.[44] The exacerbations were defined as a need for systemic glucocorticoids, hospitalization, or both, in accordance with a recent report by the American Thoracic Society and European Respiratory Society.[44] The asthma exacerbation was reported in all studies except Study AUS23.[13] However, the definition of exacerbations or the exacerbation severity classifications were inconsistently reported across studies. In the EXTRA study, the protocol-defined asthma exacerbation was defined as a worsening of asthma symptoms requiring treatment with rescue systemic (oral or intravenous) corticosteroids for three or more days as determined by the investigator.[12] The exacerbation was defined as initiation of systemic steroid therapy or hospitalization to prevent a serious asthma outcome.[15] A clinically significant exacerbation episode was defined as a worsening of asthma requiring treatment with rescue systemic (oral or intravenous) corticosteroids.[16] Severe exacerbations were defined as exacerbations that occurred while receiving high doses of ICS (≥ 800 mcg of beclomethasone dipropionate or equivalent) plus a regular inhaled LABA and fulfilling one of the following criteria: requiring treatment with systemic (oral or intravenous) corticosteroids; resulting in hospitalization or requiring an ER visit; resulting in a greater than 30% fall from personal best in PEF on two successive days.[12] The definition of exacerbation was not defined in the study by Rubin.[11] In the included studies, asthma exacerbations were reported as the incidence of exacerbation (the number of patients with exacerbation) and/or the exacerbation rate (the number of exacerbations per patient per period). However, a review of the literature did not reveal any evidence as to what would be considered a clinically important reduction in the number of asthma exacerbations.

c) Use of Oral Corticosteroids

In clinical practice guidelines, oral corticosteroids (OCS) or systematic corticosteroids are usually recommended for acute asthma exacerbations.[1,5,44] OCS is sometimes also used for maintenance treatment for asthma. However, due to the AEs associated with long-term use of OCS, reduction of OCS use is considered an important clinical outcome when assessing new medications for asthma treatment. This outcome was reported in three [6,7,10] of the six included studies. The outcomes were reported as the number of patients who used OCS (or systematic corticosteroids) or the number of OCS used per patient per period.

d) Quality of Life

The Standardized Asthma Quality of Life Questionnaire (AQLQ[S]) is the standardized version of the AQLQ. The AQLQ(S) was used to assess the patients' asthma-related QoL. [45] The questionnaire contained four domains: activity limitations, symptoms, emotional function, and environmental stimuli. The AQLQ(S) was validated for use in this study population. The AQLQ(S) was administered to patients prior to all other assessments and before the patients received any disease status information during that assessment. The AQLQ(S) scoring manual specifies 0.5 as the minimally important difference for the AQLQ(S) overall score and the individual domains scores.[12,45] A patient was considered a responder when an AQLQ score increased by more than 1.5.[11]

The recall time for the questionnaire was two weeks and each question was answered on a 7-point scale (1 = totally limited/problems all the time; 7 = not at all limited/no problems). The adult AQLQ domain scores were calculated from the 32 individual question responses as follows: Symptoms (12 items); Activities (11 items); Emotions (5 items); Environmental Exposure (4 items). Overall score = mean of items 1 to 32 (32 items). Individual domain scores were calculated as the average of the items for each domain.

e) Days of School or Work Missed

All studies except the PROSE study[15] and Rubin[11] reported information on days of school or work missed. However, the data were not consistently reported across the studies. In Study ICAC-08, information on the days of school or work missed was collected at the screening visit (visit 1) and at monthly contacts throughout the study.[14] Asthma symptoms were collected from the caretaker/patients by questionnaire in order to calculate the number of maximum symptom days.[14] In the EXTRA study, the Work Productivity and Activity Impairment Questionnaire — Asthma covered nine questions relating to hours missed from work or school, as well as work and school productivity in the previous seven days.[12] In Study AUS23[7] (but not reported in the Clinical Study Report), it was reported as the percentage of work time missed, collected in the Work Productivity and Activity Impairment Questionnaire — Allergic Asthma (WPAI-AA). The WPAI-AA covers six questions relating to hours missed from work and work productivity in the previous 7 days.[7] In Study A2425, it was reported as the change from baseline in terms of work hours missed in the past week.[16]

f) Pulmonary Function

FEV_1 is the maximal volume of air after a full inspiration that can be forcibly exhaled in one second. It is measured electronically by spirometry. This measure can be converted to a percentage of predicted normal value that is adjusted by height, weight, and race. The percentage of predicted FEV_1 is a commonly reported pulmonary function test and is considered a valid marker for the degree of airway obstruction with asthma. However, although it is widely used in clinical trials to evaluate the effectiveness of asthma treatments, there is little literature on the minimal clinically important difference (MCID) for FEV_1-based measures. The suggested minimal patient-perceivable improvement for FEV_1 was 230 mL or a 10.38% change from baseline.[46] The clinical expert involved in this review pointed out that changes in FEV_1, while helpful and important when they can be demonstrated, should not be taken as a sole indicator of efficacy, as FEV_1 can be normal in patients with moderate-to-severe allergic asthma when they are not experiencing an exacerbation. The expert also noted that FEV_1 is not necessarily correlated with exacerbations. In addition, it is harder to see improvement in FEV_1, especially in patients with impaired FEV_1 at baseline. Therefore, while it can be considered an important outcome, it should not be taken as the sole proof of efficacy from the trials included in this review.

g) Symptom Reduction

In the included studies, the symptom reduction was reported in various symptom control questionnaires such as the Asthma Control Questionnaire (ACQ), Asthma Control Test (ACT), and global evaluation of treatment effectiveness (GETE), and in other symptom scores.

Asthma Control Questionnaire

The ACQ measures the adequacy of asthma treatment.[47] It consists of seven items (five items on symptoms, one item on rescue bronchodilator use, and one item on FEV_1 percentage of predicted normal).[47,48] The seven items were selected by 100 asthma experts from 18 countries. All seven questions are scored on a 7-point scale (0 = good control, 6 = poor control). The overall score is the mean of all seven questions, with a high score indicating poor control.[47-49] The seven items in the ACQ include: awakened by asthma at night; asthma symptoms upon waking in the morning; activity limitation because of asthma; shortness of breath; wheeze; use of short-acting bronchodilator; and FEV_1 percentage of predicted value. The ACQ is a multi-dimensional and standardized tool[50] that has been observed to be both highly reliable (intra-class correlation coefficient of 0.90) and very responsive to change in asthma control ($P < 0.0001$), with a responsiveness index of 1.35 in adults with asthma.[49] In addition, evidence for strong longitudinal and cross-sectional validity has been observed by correlations between the ACQ and other asthma heath status measures.[49] It has also been observed to be a very precise tool, with a receiver operating characteristic value of 0.843 (95% confidence interval [CI] of 0.812 to 0.874); $P < 0.0001$).[48] There is also evidence of the validity, reliability, construct validity, interpretability, and responsiveness of the ACQ in children with asthma who are six to 16 years old.[51] The ACQ MCID has been well established and is accepted as 0.5 points for within-person change.[47,50] However, Bateman et al. questioned its use as a measure between groups or between patients, further speculating that patient-reported outcomes should be presented as a responder rate comparison or a net treatment-benefit analysis.[52]

The Asthma Control Test or Childhood Asthma Control Test

The ACT is a five-item patient-reported questionnaire to measure a patient's asthma control. Items captured include the impact of asthma on work/school/home activities; shortness of breath; nocturnal awakening; use of rescue medication, and overall control.[53] Higher scores indicate better asthma control. The ACT and Childhood Asthma Control Test (C-ACT) are measured on scales of 0 to 27 and 5 to 25, respectively. A score of 19 or less on either test indicates the asthma is not well controlled.[8,53] The MCID for ACT equals 3 points;[8,54] the MCID for C-ACT is not defined.[8] The ACT (for participants aged 12 to 20 years) and the C-ACT (for participants younger than 12 years of age) were completed at monthly contacts throughout the study. These tests assessed the patient's asthma control over the previous four weeks.[14,53]

Asthma Symptom Score

In the EXTRA study,[12] asthma symptoms experienced during the study were collected using patient diaries throughout the run-in and treatment periods. These diaries (recorded twice daily) were used to record nocturnal asthma score (0 to 4 scale), morning and evening asthma symptoms (yes, no), daytime asthma symptom score (0 to 4 scale), and number of puffs of rescue medication used during the day and night. High scores indicate poorer or worse symptoms.[6] However, no validity or MCID information was identified.

Global Evaluation of Treatment Effectiveness

The GETE was developed with clinical input only and is a tool used to measure treatment effectiveness in patients with moderate-to-severe allergic asthma.[55] Two GETE scales can be used to assess treatment effectiveness at the end of a treatment period, namely, the physician and patient versions.[55] Both versions rate treatment effectiveness. GETE is a five-point scale that evaluates change in asthma control/symptoms: 1 = excellent (complete control of asthma); 2 = good (marked improvement of asthma); 3 = moderate (discernible, but limited improvement of asthma); 4 = poor (no appreciable change); and 5 = worsening of asthma.[16] Response to treatment was defined as a rating of 1 or 2.[7] GETE was reported in four studies. [7,11,14,16] A good level of agreement between physician and patient GETE was

observed. In addition, the GETE has been observed to have good construct validity and inter-rater reliability.[55] However, no evidence to support test–retest reliability, MCID, or sensitivity was identified with regard to the GETE.[55]

h) Change in Number of Asthma Symptom–Free Days/Nights

Change in number of asthma symptom–free days/nights was not reported. Instead, in one included study, the number of days with asthma symptoms in the previous two-week period was reported at each visit throughout the study.[8] How this information was collected was not reported. No number of nights with or without symptoms were reported in the included studies.

i) Incidence of Nocturnal Awakenings

Three studies[7,8,10] reported nocturnal awakenings. In Study ICAC-08[8] and Study A2425,[10] it was reported at each visit throughout the study as the number of days with nighttime sleep disruptions in the previous two weeks. In Study AUS23,[7] it was reported as the change from baseline at the end of the study. The information was collected based on patients' diaries in studies AUS23[7] and A2425.[10] How the information was collected was not provided in Study ICAC-08.[8] The clinical expert involved in this review indicated that while reductions in nighttime awakenings are important, they are not as important as other key outcomes such as reductions in hospitalizations, ER visits, and exacerbations.

j) Reduction in Use of Inhaled Corticosteroids

Reduction in the use of ICS was reported in studies ICAC-08[8] and A2425.[10] The information was collected from patients' diaries in Study A2425.[10] Such information was not reported in Study ICAC-08,[8] and no information on the use of ICS was reported in the remaining four studies.[11-13,15]

k) Reduction in Use of Rescue Medications

A reduction in the use of rescue medications (SABAs or short-acting muscarinic antagonists) was reported in the EXTRA study,[6] Study AUS23,[7] and the study by Rubin.[11] The use of rescue medication was recorded daily by the patient and reviewed by the investigator at each visit.[14]

l) Mortality

All-cause mortality was reported as a safety outcome instead of as an efficacy outcome in all included studies. The clinical expert indicated that all-cause mortality was very low in each of the asthma trials.

4.2.5 Statistical Analysis

In all trials, the intention-to-treat (ITT) population[7,8,10,11] or modified ITT (mITT) population (including all patients randomized in the study who received at least one dose of the study drug[6] or at least had one study contact[9]) was the primary population investigated in the efficacy analysis, with missing data handled by the last outcome carried forward (LOCF) approach. Analyses of the primary and secondary efficacy outcomes were repeated with the per-protocol population to assess the robustness of the study in two studies.[8,10]

a) Determination of Sample Size

The EXTRA study[12] had 90% power to detect a 27% reduction in average exacerbation rates due to omalizumab, assuming 0.8 exacerbations per patient in the placebo group over a 48-week treatment period, a 20% overall dropout rate. Sample size calculations are based on a Poisson regression model and Wald test conducted at the 0.05 level (two-sided) using the Signorini method. In Study AUS23,[7] an expected mean treatment difference of two and a standard deviation of five for change from baseline in ACT total score were assumed. Using a t-test, an allocation ratio of 1:1, a two-sided significance level of

0.05, and a power of 0.90, approximately 266 patients (133 in each treatment group) were required. Study ICAC-08[8] had a power of 90% to detect a clinically meaningful difference of 30% in the number of days with symptoms during a two-week period. PROSE[9] had a power of ≥ 90% to compare the omalizumab and placebo groups (estimated effect on exacerbation of 11.8% versus 35.9%). In Study A2425,[10] the sample size was calculated based on an anticipated responder rate of 60% at week 16, with dropout rates of approximately 10% and 15% for responders and non-responders, with persistency rates of 70% to 90% for response and non-response. It was expected there would be 95% power for key secondary end points (GETE), after allowing for the previously mentioned dropout rates. In the study by Rubin,[11] no information on the sample size calculation and power was provided in the report. The author indicated that this study was not powered enough to detect differences between groups regarding the number of exacerbation episodes. Whether it was powered enough to detect the difference between groups regarding the use of rescue medication ($P > 0.05$) was not reported.[11]

b) Statistical Test

In the EXTRA study,[6] the pre-specified primary efficacy analysis was based on Poisson regression to compare the rate of asthma exacerbations between the omalizumab and placebo groups. This method accounts for differential time on study and allows for covariate procedure with a Poisson distribution, log-link function, and offset as the log of time at risk. [redacted].[12] In Study AUS23,[7] all statistical tests were conducted against a two-sided alternative hypothesis, employing a significance level of 0.05; no further information was provided.[7] In Study ICAC-08, the primary outcome was the number of days with symptoms during the previous two weeks. The analysis was performed with the use of linear mixed-effects models with random intercept and slope (to account for the within-patient correlation over time) and with visit and group as fixed effects; the models were adjusted for baseline variables, site, dosing schedule, and season. Group differences in utilization outcomes were tested by means of logistic regression. Twenty-one pre-specified sub-analyses were conducted to assess the heterogeneity of treatment effects across nine characteristics, with a statistical test for interaction. In the PROSE study,[9] the primary outcome was analyzed as a dichotomous variable (occurrence or absence of exacerbations). Analysis was conducted by using a logistic regression model, adjusting for site, dosing schedule, and treatment step. The analysis of continuous secondary outcomes measured longitudinally was conducted by using a similarly adjusted linear mixed-effect model with random intercept (to account for the within-patient correlation). Sensitivity analyses were conducted to assess the effect of missing data on the results. Eleven pre-specified subgroup analyses were conducted to assess heterogeneity of treatment effects with a statistical test for interaction.[9] In Study A2425,[10] due to this selective nature, only descriptive statistics were presented for the primary outcome (the persistency rate), which was described with point estimates and 95% CIs. The 95% CIs were derived using the normal approximation to the binomial.[10] In the study by Rubin,[11] change in AQLQ domain and overall scores (using LOCF) and FEV_1 were evaluated using analysis of variance. Number of rescue medications, exacerbations, treatment perception, investigator/patient global evaluation, and combined clinical symptom scores were analyzed using a Mann–Whitney test.[11]

c) Multiplicity

None of the studies except EXTRA[6] performed multiplicity tests for secondary or exploratory outcomes to control type 1 error.

d) Subgroup Analyses

No relevant subgroup analyses specified in Table 3 were conducted in any included study.

e) Analysis Populations

Intention-to-Treat

The ITT population comprised all patients randomized to treatment. ITT constituted the primary population for primary outcome in four studies.[7,8,10,11]

Modified Intention-to-Treat

The mITT population comprised all randomized patients who received at least one dose of the study drug,[6] or who had at least one study contact during the study.[9]

Per Protocol

The per-protocol population comprised all patients in the ITT population who did not have any full protocol deviations. Per-protocol data were available in two studies,[6,10] but not available in the remaining studies.[7-9]

Safety Population

This included all patients who received any study drug and who had at least one post-baseline safety assessment.

4.3 Patient Disposition

Patient disposition is summarized in Table 8 and Table 9. Study completion ranged from 78% to 93% across trials. The completion rates were similar between treatment groups within each study, except Study A2425.[10] A discontinuation rate of 20% or more was reported in the placebo groups in two studies,[6,8] compared with 7% to 19% in the other studies. This is likely due to the longer study duration (48 to 60 weeks). Differential dropout was observed in several of the trials and, in general, higher discontinuation rates were found in the placebo groups. The reasons for study discontinuation varied across studies; the common reasons were protocol deviation, lost to follow-up, AE, or withdrew consent.

TABLE 8: PATIENT DISPOSITION IN DOUBLE-BLIND STUDIES

	EXTRA[6]		AUS23[7]		ICAC-08[8]		PROSE[9]	
	OMA	**PLA**	**OMA**	**PLA**	**OMA**	**PLA**	**OMA**	**PLA**
Screened, N	1,979		625		996		1,312[a]	
Randomized, N (%)	427	423	136	135	208	211	278	97
Completed, n (%)	344 (81)	329 (78)	120 (88)	122 (90)	170 (82)	169 (80)	259 (93)	89 (92)
Discontinued, N (%)	82 (19.2)	94 (22.2)	16 (11.8)	13 (9.6)	38 (18)	42 (20)	19 (7)	8 (8)
WDAE(s)	16 (3.7)	11 (2.6)	3 (2.2)	3 (2.2)	0	0	2 (0.7)	1 (1)
Withdrew consent	22 (5.2)	33 (7.8)	6 (4.4)	7 (5.2)	0	0	0	1 (1)
Protocol deviation	0	0	2 (1.5)	2 (1.5)	38 (18)	42 (20)	5 (1.8)	1 (1)
Administration	0	0	0	0	0	0	0	0
Lack of effect	0	0	0	0	0	0	0	0
Lost to follow-up	25 (5.9)	19 (4.5)	5 (3.7)	1 (0.7)	0	0	12 (4.3)	4 (4.1)
Physician's decision	15 (3.5)	22 (5.2)	0	0	0	0	NR	NR
Pregnancy	4 (0.9)	6 (1.4)	0	0	0	0	NR	NR
Other	1 (0.2)	0	0	0	0	0	0	1 (1)

	EXTRA[6]		AUS23[7]		ICAC-08[8]		PROSE[9]	
	OMA	**PLA**	**OMA**	**PLA**	**OMA**	**PLA**	**OMA**	**PLA**
Death n (%)	0	3 (0.7)	0	0	0	0	NR	NR
ITT (or mITT), N	427	420	136	135	208	211	259	89
PP, N (%)	NR	NR	NR	NR	140 (67)	132 (63)	NR	NR
Safety, N	427	420	136	135	208	211	268	93

ICS = inhaled corticosteroid; ITT = intention-to-treat; mITT = modified intention-to-treat; OMA = omalizumab; PLA = placebo; PP = per protocol; WDAE = withdrawal due to adverse event.
[a] This was a three-group study; the ICS boost group is not reported in this review because it is not relevant. The 138 patients randomized in the ICS boost group are not reported in this review.
Note: Numbers in red are not reported in the study, but calculated by CDR.
Source: Clinical Study Reports or relevant publications.[6-9,12-15]

TABLE 9: PATIENT DISPOSITION IN OPEN-LABEL STUDIES

	A2425[10]		Rubin 2012[11]	
	OMA	**CTR**	**OMA**	**CTR**
Screened, N	768		202	
Randomized, N (%)	275	131	78 (100.0)	38 (100.0)
Completed, n (%)	253 (92.0)	106 (80.9)	70 (89.7)	34 (89.4)
Discontinued, N (%)	22 (8.0)	25 (19.1)	8 (10.3)	4 (10.5)
WDAEs	7 (2.5)	2 (1.5)	2 (2.6)	0 (0.0)
Withdrew consent	7 (2.5)	11 (8.4)	0	0
Protocol deviation	5 (1.8)	3 (2.3)	0	0
Administration	2 (0.7)	0 (0.0)	1 (1.3)	0 (0.0)
Lack of effect	1 (0.4)	6 (4.6)	0	0
Lost to follow-up	0 (0.0)	2 (1.5)	4 (5.1)	1 (2.6)
Physician's decision	0 (0.0)	0 (0.0)	0	0
Pregnancy	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.3)
Death	0 (0.0)	1 (0.8)	0	0
ITT (or mITT), N	272	128	78 (100.0)	38 (100.0)
PP, N	182 (66.7)	78 (59.5)	NR	NR
Safety, N	274	128	NR	NR

CTR = control group in which there was no additional add-on therapy to background treatment in the two open-label studies; ITT = intention-to-treat; mITT = modified intention-to-treat; OMA = omalizumab; PP = per protocol; WDAE = withdrawal due to adverse event.
Source: Clinical Study Report and publications.[10,11,16]

4.4 Exposure to Study Treatments

Detailed information on medication exposure is presented in Appendix 4 (Table 10 and Table 11).

Numerically, more patients (53% to 61%) received omalizumab every four weeks rather than every two weeks, except in Study A2425, in which 52% received an omalizumab dose every two weeks. In the 60-week study, the mean number of doses received in the omalizumab group was 23 for those receiving treatment every two weeks, and 13 for those receiving treatment every four weeks.[14] [redacted].[16] The exposure information was not reported in the study by Rubin.[11]

4.5 Critical Appraisal

4.5.1 Internal Validity

The potential internal validity issues are discussed below. Firstly, methods for randomization and allocation concealment were clearly reported in two studies[6,10] where an interactive voice response system was used for treatment allocation; such information was not reported in the remaining four studies.[7-9,11] However, the demographic and baseline patient characteristics were generally balanced between treatment groups in all included studies, except that the female gender was under-represented in the EXTRA study and in Study A2425. Secondly, four study[6-9] designs were double-blind and double-dummy to preserve blinding to treatment allocation; but two studies,[10,11] which were open-label RCTs, had no add-on matching placebo in the control groups. So, the between-group difference could possibly be biased in favour of omalizumab treatment due to the potential placebo effect in the two open-label studies, especially in assessing those subjective outcomes using AQLQ, ACQ, ACT, and GETE. Thirdly, GETE was used to measure the effectiveness of omalizumab treatment in four studies,[7,8,10,11] and "asthma control score" was used in the EXTRA study to assess symptom reduction; however, no validity information or MCID for GETE or "asthma control score" was identified. Therefore, the clinical significance of the findings on GETE or asthma score needs to be further addressed. Fourthly, in the EXTRA study,[6] the discontinuation rates were 19% to 22%. The dropout rates were balanced between treatment groups in all studies except A2425.[10] Such a relative high (> 20%) discontinuation rate may introduce potential bias for the results derived from ITT or mITT population analysis with the use of LOCF to handle missing data (which often biases toward no differences in treatment effect); however, the per-protocol analysis results (data not shown) are consistent with the ITT or mITT results. Therefore, the concern of the potential bias of high discontinuation rate on the findings is unlikely. Furthermore, asthma exacerbation was not designed as the primary outcome in four studies;[7,8,10,11] therefore, they were not powered to detect the treatment group difference of exacerbation. The EXTRA study[6] and PROSE study[9] were powered to detect the treatment difference of exacerbation rate (the number of exacerbations per patient per period), but not the incidence of exacerbation (the number of patients with exacerbation). The clinical expert involved in the review believed that these outcomes (such as hospitalizations, ER visits, or exacerbations) presented as rates more accurately reflect any changes observed with the use of omalizumab. Similarly, none of the included studies was designed with sufficient power to detect the difference for other the key outcomes, such as hospitalizations, ER visits, and MD visits due to exacerbation, reduction in OCS use, or days of school or work missed. Other potential limitations may include the uncertain validity of reporting health care utilization — such as the number of unexpected medical visits; use of OCS, ICS, and SABA; days missed from work or school; and days with symptoms — because all of the aforementioned outcomes were collected based on the patient's diary, or no collection method was reported. Adherence to completing diaries and the way to handle data missing from diaries were not clearly reported. Finally, in four studies,[7,9-11] no statistical methods were employed to control for multiplicity (to control the type 1 error rate) in the analyses of the secondary and exploratory outcomes. This increases the risk of finding a statistically significant difference between groups due to chance.

4.5.2 External Validity

According to the clinical expert consulted for this review, the patient population in the included studies, except in two pediatric studies, was considered representative of patients with persistent, moderate-to-severe allergic asthma seen in clinical practice in Canada. Two studies[8,9] included patients younger than 12 years old; there was no subgroup analysis data for the group of patients ≥ 12 years old. Also, no information was included in the two studies on how many patients were younger than 12 years of age. In addition, in the two pediatric studies,[8,9] about 25% to 30% of patients were diagnosed with mild asthma and received only ICS treatment before randomization. In Canada, omalizumab treatment is not

indicated for patients aged 12 years or younger; it is clinically recommended for adults and adolescents (aged ≥ 12 years) with moderate-to-severe allergic asthma uncontrolled with ICS plus LABA and other asthma controllers (such as LTRA).[1,5] The CDR clinical expert involved in this review felt that omalizumab should be used as a third-line medication in the treatment of allergic asthma. Therefore, whether the findings observed in Study ICAC-08[8] and the PROSE study[9] are generalizable to real Canadian clinical practice (i.e., used as third-line or fourth-line treatment for moderate-to-severe asthma) is unclear.

The study duration ranged from four months[9] to 60 weeks;[8] based on the clinical expert's opinion, patients should receive omalizumab for at least six months (24 weeks) before determining whether the patients have responded to omalizumab treatment. The study duration was insufficient to capture the clinically important outcomes such as exacerbations or health care utilization (hospitalizations, ER visits, and MD visits) due to asthma exacerbation. It is worth noting that a large proportion of patients were screened out in all included studies, which could have potential implications in terms of generalizability. Overall, no major generalization issue was identified across studies, except the findings from two pediatric studies.[8,9]

4.6 Efficacy

Only those efficacy outcomes identified in the review protocol (Table 3) are reported subsequently. See Appendix 4 for detail data. The key efficacy findings are presented in Table 1.

4.6.1 Hospitalizations, ER Visits, and MD Visits Due to Asthma Exacerbation

None of the included studies evaluated the hospitalizations, ER visits, or MD visits due to asthma exacerbation as an efficacy outcome. However, such information was usually reported as health care utilization or captured in the safety outcomes in three studies[6,8,10] (Table 1).

a) Hospitalization

Among the three studies[6,8,10] that reported this outcome, the incidence of hospitalization due to asthma exacerbation was [redacted] and 1.5%, in omalizumab-treated patients, and [redacted] and 6.3%, in the placebo group [redacted] and Study ICAC-08 respectively. Statistically significantly fewer omalizumab-treated patients (mean difference: –4.7%; 95% CI, –8.6 to –0.9) experienced hospitalization compared with those in the placebo group, which was only reported in Study ICAC-08.[8] In Study A2425, [redacted] statistically significantly lower hospitalization rate per patient during the study period for omalizumab-treated patients than that for placebo was reported in Study A2425,[10] with the rate ratio of 0.33 (95% CI, 0.118 to 0.937; *P* = 0.037) (Table 1 and Table 12) [redacted] (Table 1).

b) Emergency Room Visits

ER visits due to asthma exacerbation were reported in only two studies.[6,10] In the EXTRA study[6] [redacted] In Study A2425,[10] the ER visit rate was 0.35 per patient in the omalizumab group and 0.83 per patient in the placebo group during the 32-week trial period, with a rate ratio of 0.40 (95% CI, 0.24 to 0.65; *P* < 0.001)(Table 1).

c) MD Visits

MD visits due to asthma exacerbation were reported only in the EXTRA study.[6] During the 48-week [redacted]. The MD visit rates per patient [redacted] (Table 1).

4.6.2 Acute Asthma Exacerbations

Asthma exacerbations were reported in all included studies except AUS23[13] (Table 1). However, as the primary outcome, the exacerbation rate (number of exacerbations per patient) and the incidence of patients with exacerbation were reported only in the EXTRA study[6] and PROSE study,[9] respectively. Across the studies, the incidence of exacerbation ranged from 5.5%[10] to 43.6%[11] in omalizumab-treated patients and from 10.9%[10] to 52.6%[11] in the placebo group. The mean difference between treatment groups (omalizumab minus placebo) ranged from –5.4%[10] to –18.5%.[8] Study ICAC-08[8] and the PROSE study[9] reported that statistically significantly fewer patients experienced exacerbation compared with placebo. A statistically significantly lower per-patient exacerbation rate among omalizumab-treated patients was reported in the EXTRA study[6] and Study A2425,[10] with a rate ratio of 0.75 (95% CI, 0.61 to 0.92; $P = 0.006$) and 0.57 (95% CI, 0.42 to 0.78; $P < 0.001$), respectively (Table 1).

4.6.3 Use of Oral Corticosteroids

The use of OCS was reported in three studies[6,7,10] (Table 1, Table 13, and Table 14). In the EXTRA study,[6] [redacted]. In Study AUS23,[7] 10.3% of patients in the omalizumab group and 17.8% in the placebo group used OCS during the 24-week period. In Study A2425,[16] [redacted]. The mean difference between omalizumab and placebo (omalizumab minus placebo) [redacted] in the EXTRA study and studies AUS23 and A2425, respectively. All showed omalizumab-treated patients used fewer OCS compared with those who received placebo (Table 1, Table 13, and Table 14).

4.6.4 Quality of Life

QoL was measured with AQLQ in three studies[6,10,11] (Table 1, Table 15, Table 16, and Table 17). Similar baseline AQLQ total scores in both treatment groups were reported in the EXTRA study,[6] and the study by Rubin.[11] The baseline AQLQ was not reported in Study A2425.[10] By the end of treatment, the AQLQ score had improved for patients in all groups except those in the placebo group in Rubin's study (Table 1). Similarly, a relatively larger improvement was observed in omalizumab-treated patients. The between-group difference of change from baseline was [redacted] 1.2 (95% CI, interval not reported; the statistical analysis was not performed) and [redacted], study by Rubin and the EXTRA study respectively. The statistically significant improvement was reported in the EXTRA study[6] and Study A2425.[10] In Rubin's study,[11] a statistically significant proportion of patients (42%) who received omalizumab were considered responders (as rated by AQLQ and defined as achieving an improvement from baseline of ≥ 1.5 points [mean difference: 39%; $P < 0.001$]) compared with those who received placebo (3% responders) (Table 1).

4.6.5 Days of School or Work Missed

All studies except the PROSE study[9] and Rubin[11] reported the information on days of school or work missed (Table 1 and Appendix 4; Table 18, Table 19, Table 20, and Table 21). The information (unit of time missed from school or work) was reported inconsistently across studies. A small but statistically significant fewer number of times missed from work was reported in Study ICAC-08,[8] with a between-group difference (omalizumab minus placebo) of –0.09 day (95% CI, –0.18 to –0.01; $P = 0.038$). No statistically significant difference was reported in other studies (Table 1).

4.6.6 Change in Pulmonary Function

Among the studies (the EXTRA study[6] [Table 22 and Table 23], Study AUS23[7] [Table 20], Study A2425[10] [Table 24] and the Rubin[11] study [Table 25]), none showed a statistically significantly or clinically meaningful difference in FEV_1 improvement, except Rubin.[11] In Rubin's study, it was reported that the mean change from baseline in FEV_1 in the omalizumab group was 0.13 L compared with –0.003 L in the control group (i.e., a group with no additional add-on therapy in an open-label RCT) at the end of the study (omalizumab versus control group: mean difference = 0.13; 95% CI, interval not reported; *P* = 0.049 [Table 25]).

4.6.7 Symptom Reduction

a) Asthma Control Questionnaire

The ACQ was reported in the open-label Study A2425.[10,16] The ACQ overall score showed a significantly greater reduction from baseline for the omalizumab group compared with the control group at the end of the study. The mean change from baseline (standard error) was –0.91 (0.081) in patients with omalizumab and –0.04 (0.110) in patients with placebo, respectively. The treatment group difference (least squares mean [LSM]) was –0.87; 95% CI, –1.09 to –0.65; *P* < 0.001 (Table 26).

b) The Asthma Control Test

ACT results were reported in two studies.[7,8] No statistically significant difference between the omalizumab and placebo groups was observed at week 60 in Study ICAC-08,[8] (*P* = 0.54) (Table 18) or at week 24 (*P* = 0.178) in Study AUS23.[7] Based on the post-hoc analysis, in patients with very poorly controlled asthma (ACT ≤ 15 at baseline), treatment with omalizumab resulted in significantly greater improvement on the ACT total score at week 24 compared with placebo (LSM change from baseline: 6.66 and 5.27, respectively; LSM treatment difference: 1.39; 95% CI, 0.11 to 2.66; *P* = 0 .033)

c) Childhood Asthma Control Test

C-ACT results were reported for patients younger than 12 years old in Study ICAC-08.[8] A small but statistically significant difference between treatment groups was reported. The C-ACT score was reported as 23.0 for patients in the omalizumab group, and 22.2 for patients in the placebo group (mean difference: 0.78; 95% CI, 0.21 to 1.35; *P* = 0.007) (Table 18).

d) Global Evaluation of Treatment Effectiveness

GETE results were reported in four studies.[6,7,10,11] In the EXTRA study and Rubin's study, more omalizumab-treated patients responded as "excellent" or "good" in both physicians' and patients' GETE[6] (Table 27, Table 28, and Table 30). Similarly, more patients reported as "excellent" and "good" and in physicians' GETE in Study A2425[10] (Table 29). However, based on the post-hoc analysis, statistical significance between treatment groups (*P* = 0.032) in terms of investigator's GETE (IGETE) were reported only in patients with a baseline ACT score of ≤ 15 in Study AUS23.[7]

e) Asthma Symptom Score

In the EXTRA study,[6] the total symptom score showed a statistically significantly larger improvement in the omalizumab group compared with the placebo group. The LSM of change from baseline [redacted] respectively. The mean treatment group difference of LSM of change from baseline was –0.25 (95% CI, −0.49 to −0.01; *P* = 0.038) (Table 31 and Table 32).

4.6.8 Change in Number of Asthma Symptom–Free Days/Nights

Changes in the number of days with symptoms was reported in Study ICAC-08.[8] It was reported that, for patients treated with omalizumab, the mean number of days with symptoms was reduced from 1.96 to

1.48 over a two-week period, with a reduction of 24.5% ($P < 0.001$) in omalizumab-treated patients (Table 18). The PROSE study also reported a significantly decreased mean number of days with symptoms in patients treated with omalizumab compared with those in the placebo group (data not shown).[9]

4.6.9 Incidence of Nocturnal Awakenings

Three studies[7,8,10] reported the incidence of nocturnal awakenings. In Study ICAC-08,[8] it was reported that patients treated with omalizumab experienced statistically significantly fewer nocturnal awakenings (mean LSM difference: −0.17; 95% CI, −0.31 to –0.03; $P = 0.02$) over a two-week period compared with those who received placebo (Table 18). Similar treatment effect was reported in Study AUS23[7] (mean difference: –0.39; 95% CI, –0.71 to –0.07; $P = 0.019$) (Table 20). In Study A2425,[10] omalizumab-treated patients also experienced statistically fewer nocturnal awakenings compared with those who received [redacted])(Table 33).

4.6.10 Reduction in Use of Inhaled Corticosteroids

Reduction in use of ICS was reported in Study ICAC-08[8] and Study A2425.[10] In Study ICAC-08,[8] compared with placebo, omalizumab-treated patients reported a statistically significantly lower prescribed ICS dose (budesonide-equivalent dose between-group difference: −109 mcg/day; 95% CI, −172 to −45; $P < 0.001$) during the 48-week study period (Table 18). In Study A2425,[10] the mean dose of ICS showed a decrease from baseline at week 32 for the [redacted][16] [redacted](Table 34).

4.6.11 Reduction in Use of Rescue Medications (Short-Acting Beta$_2$ Agonists)

Reduction in the use of rescue medications (SABA) was reported in the EXTRA study,[6] Study AUS23,[7] and in the study by Rubin.[11] The use of rescue medication was recorded daily by the patient and reviewed by the investigator at each visit.[6] In the EXTRA study,[6] patients in the omalizumab group received fewer daily salbutamol puffs (mean difference: –0.27 puff/day; 95% CI, –0.49 to –0.04; $P = 0.09$), compared with the placebo group, during the 48-week study period (Table 35).

No statistically significant differences between treatment groups was observed in SABA use ($P = 0.374$) in either Study AUS23[7] (Table 20) or in the study by Rubin ($P > 0.05$).[11]

4.6.12 Mortality

In the EXTRA study,[6] three deaths (0.7%) were reported. All three were reported in the placebo group. Of the three deaths, one (cardiac arrest) was considered treatment-emergent because it occurred during the study; the other two deaths occurred more than six weeks after study discontinuation.[6]
In Study A2425,[10] one death was reported in the placebo group. No death was reported in the remaining four studies (Table 8 and Table 9).

4.7 Harms

Only those harms identified in the review protocol are reported subsequently (see 2.2.1, Protocol) (Table 3).

4.7.1 Adverse Events

The percentage of patients experiencing an AE ranged from 40%[8] to 80%[6] across all included studies, except the study by Rubin,[11] which did not report on AEs (Table 2 and Table 36 to Table 42).

The incidence of patients with AEs was similar in both treatment groups, except more were reported in the placebo group in Study ICAC-08,[8] and more AEs were reported in the omalizumab group in Study A2425.[10] The common AEs reported were gastrointestinal AEs,[8,9] respiratory AEs,[8,9] skin AEs,[7-9] nervous system AEs,[9] infection,[8-10] asthma and injection-site reaction,[7] bleeding-related AEs,[6] headache,[10] and hypersensitivity reaction[10] (Table 36 to Table 43).

4.7.2 Severe Adverse Events

Across all included studies, the incidence of patients with a serious adverse event (SAE) ranged from 0.7% in omalizumab-treated patients[9] to 16.4% in the placebo group in Study A2425.[10] The reported incidence of patients with SAEs was similar in all studies, except more SAEs were reported in the placebo group in Study ICAC-08, and in the omalizumab-treated group in the study by Rubin[11] (Table 2 and Table 37).

4.7.3 Withdrawal Due to Adverse Events

The proportion of patients who withdrew due to an adverse event (WDAE) ranged from 0% to 3.7% across studies. Two patients in an omalizumab-treated group and three in a placebo group discontinued the study because of asthma exacerbation.[10] The non–asthma-related AEs leading to discontinuation across the studies were cardiac disorder,[6] gastrointestinal disorder,[6,9] respiratory disorder,[9] urticaria,[7] anaphylactic reaction,[9] arthralgia,[10] and infection[6] (Table 2 and Table 37).

4.7.4 Notable Harms

As indicated in the protocol, the notable harms identified in this report are anaphylaxis, Churg–Strauss syndrome, injection-site reaction, and thromboembolic events (Table 3). During the treatment period, the incidence of anaphylaxis ranged from 0% in Study AUS23,[7] to 2.8% in the placebo group in Study ICAC-08[8] across studies. The proportion of patients with an injection-site reaction [redacted], [7] [redacted][9] [redacted].[10] No patients experienced Churg–Strauss syndrome or thromboembolic events in any studies (Table 2, Table 37, Table 42, and Table 43).

5. DISCUSSION

5.1 Summary of Available Evidence

A previous review in 2006 by CDR on the use of omalizumab in persistent allergic asthma led to the recommendation by CDAC that omalizumab not be reimbursed due to:

- insufficient evidence that omalizumab improves exacerbations that lead to hospitalizations, ER visits, or physician visits
- a dearth of data for patients who fail treatment with a LABA in addition to an ICS
- a low likelihood of being cost-effective.

The CDR review of omalizumab in 2006 included six RCTs,[56-61] of which five[56-58,60,61] were double-blind RCTs and one was an open-label RCT.[59] The current CDR review was undertaken in response to a resubmission to CDR from the drug plans that participate in the CDR review process. This resubmission requested that the use of omalizumab in asthma be re-reviewed in light of the availability of "new evidence . . . for the treatment of moderate-to-severe persistent asthma with omalizumab." Therefore, for the current review, new clinical evidence that has become available since the CDR review in 2006 was considered for inclusion in a systematic review to assess the efficacy and harms of omalizumab in persistent allergic asthma in patients who are inadequately controlled by an ICS in combination with a LABA.

5.1.1 New Evidence Identified in the Current Review

Six new RCTs were included in this review, namely EXTRA,[6,12,42] AUS23,[7,13] ICAC-08,[8,14] PROSE,[9,15] A2425,[10,16] and Rubin.[11] Of these studies, four[12-15] were double-blinded and two[11,16] were open-label. Two of the four double-blind RCTs[6,7] were conducted in patients ≥ 12 years old with moderate-to-severe persistent allergic asthma who were inadequately control with ICS plus LABA, with or without other asthma controllers. The other two double-blind RCTs[8,9] were conducted in pediatric patients (aged 12 to 20 years) with mild or moderate-to-severe persistent allergic asthma who were inadequately controlled with at least an ICS. According to a clinical expert consulted by CDR for the purpose of this review, the populations studied in the included studies generally reflect the patient population in Canada with moderate-to-severe allergic asthma who likely would fit the indication for treatment with omalizumab. Moreover, the inclusion of patients who were treated with a LABA in addition to ICS in most of the included studies addresses this shortcoming in the evidence that was assessed in the CDR review of omalizumab in 2006. Nevertheless, in some of the included studies in the current review, the inclusion of patients younger than 12 years old, as well as patients with mild asthma who did not receive ICS plus LABA treatment, somewhat limits generalizability.

The primary outcomes in the included studies were related to the effects of omalizumab on exacerbations,[12,15] symptom control,[13,14,16] or QoL.[11] None of the studies was powered to assess other outcomes that were identified as important in the review protocol, including: changes in the frequency of hospitalizations, ER visits, and MD visits due to asthma exacerbation; OCS use; and work or school absences. Furthermore, in most studies,[11,13,15,16] no statistical methods were employed to control for multiplicity (i.e., to control the type 1 error rate) in the analyses of secondary and exploratory outcomes. Therefore, the statistical significance associated with treatment effects on these outcomes was either not reported (due to statistical testing not being applicable or feasible), or was of uncertain rigour when reported.

5.2 Interpretation of Results

5.2.1 Efficacy

The frequencies of hospitalization as well as the number of ER visits and MD visits due to the exacerbation of asthma symptoms were identified as being outcomes that are important to patients with asthma (Appendix 1). In EXTRA,[6] [redacted] in A2425. While statistical significance was not demonstrated for either of the aforementioned differences, in ICAC-08, 4.7% fewer omalizumab-treated patients were hospitalized due to exacerbation than placebo-treated patients, a difference that was statistically significant ($P = 0.02$). Results were similar for the overall rates of hospitalization events per patient. In EXTRA,[6,12] [redacted] Similarly, omalizumab-treated patients experienced a 60% reduction in the rate of ER visits in A2425.[16] In EXTRA,[12] [redacted] omalizumab-treated patients visited an MD due to exacerbation compared with placebo-treated patients. The statistical significance of the aforementioned differences in visits to the ER or an MD due to exacerbation are not known for the reasons noted earlier. While the clinical expert suggested that **any** reduction in these outcomes would be beneficial and of clinical relevance to patients, the absence of a consistently statistically significant effect of omalizumab in the aforementioned studies increases uncertainty regarding the true effect of omalizumab on these outcomes, and it is not possible to assess the true magnitude of the treatment effect.

Input received by CADTH from patient groups for the purpose of informing this review indicated that effective treatment of asthma should reduce asthma exacerbations. In the included studies, fewer omalizumab-treated patients appeared to experience acute exacerbations compared with placebo treatment (the average reduction in the incidence of patients with exacerbation was [redacted][10] to 18.5%[8] across studies), and this effect was statistically significant in ICAC-08[14] ($P < 0.001$) and PROSE,[15] (relative risk = 0.45; 95% CI, 0.25 to 0.92). Similarly, omalizumab treatment was associated with a statistically significant reduction in the rate of exacerbations (i.e., the number of exacerbations per patient per period) in EXTRA[6,12] and A2425.[10,16] These findings comprise evidence that omalizumab treatment is associated with a reduction in the occurrence of acute asthma exacerbations in patients who are inadequately controlled by an ICS with or without other asthma treatments, including a LABA, which is consistent with the findings reported in the 2006 review of omalizumab.

Three of the included studies (EXTRA,[6,12] AUS23,[7,13] and A2425[10,16]) provided evidence that omalizumab treatment is associated with a reduction in OCS use of 4% to 8% compared with placebo, but none of these differences was determined to be statistically significant.

Omalizumab-treated patients appeared to report relatively greater improvements in QoL assessed using the AQLQ in the included studies. The inter-treatment differences (omalizumab versus placebo/control) [redacted] and 1.2 in EXTRA,[6] A2425,[10] and Rubin,[11] respectively. Considering that the MCID for changes in the AQLQ is 0.5 (Appendix 5), the improvements observed in two of the aforementioned studies (A2425 and Rubin) would appear to be clinically meaningful. However, it is important to note that both of these studies had an open-label design, which increases the potential for biasing the outcome in favour of omalizumab, particularly when the outcome includes subjective assessments of health (such as QoL questionnaires), rather than hard outcomes. Therefore, there is considerable uncertainty associated with the apparent improvement in QoL due to omalizumab treatment. Moreover, this effect was not demonstrated in other studies, and is therefore inconsistent across the included studies, with most failing to demonstrate a significant effect of omalizumab on QoL.

The evidence available to evaluate the effect of omalizumab on absences from school or work was as similarly inconsistent as for the outcomes discussed above. Specifically, omalizumab was associated with a small reduction in the number of days of school or work missed in those studies that reported this outcome, but there was statistically significantly less time absent from work in omalizumab-treated patients only in one study (ICAC-08[14]). However, this difference was small (mean difference between treatment of 0.09 days over 60 weeks; $P = 0.038$) and of unknown clinical relevance.

A larger improvement in FEV_1 was reported for omalizumab-treated patients versus placebo or controls in five RCTs. However, only one study (Rubin[11]) reported a statistically and clinically significant improvement in FEV_1 (mean difference compared with the control group: 0.13 L; $P = 0.049$). These findings regarding the effect of omalizumab on FEV_1 are consistent with the evidence reported in the previous CDR review of this drug in 2006. The clinical expert noted that if an improvement in FEV_1 can be demonstrated, then this is a helpful readout of efficacy, but changes in FEV_1 are not a critical outcome, as FEV_1 can be normal in patients with moderate-to-severe allergic asthma when they are not experiencing an exacerbation.

Changes in the severity of asthma symptoms were assessed in the included studies using a variety of instruments. Omalizumab treatment was associated with a statistically significant improvement in the severity of asthma symptoms in both open-label studies.[10,11] In A2425,[10] omalizumab treatment was associated with a statistically significant improvement in the severity of asthma symptoms compared with the control group. However, as discussed earlier, these findings should be viewed as uncertain due to the open-label design of this study. Other results related to symptom severity were inconsistent across studies, both with respect to the significance of treatment effects and the measurement instruments used. In EXTRA,[6] statistically significantly more omalizumab-treated patients were rated as treatment-responders using the GETE, whereas another study (AUS23[7]) failed to demonstrate such an effect of omalizumab treatment. Similarly, symptom severity measured using the ACT or C-ACT revealed no improvement in omalizumab-treated patients compared with placebo treatment in ICAC-08[8] and AUS23,[7] respectively. When the number of symptom-free days was used to assess severity, the results were somewhat more consistent. For instance, omalizumab was associated with a significant reduction in the number of days with asthma symptoms in two studies,[8,9] although the effect sizes were relatively small. Similarly, omalizumab-treated patients had statistically significantly fewer nocturnal awakenings due to asthma in three studies.[6,7,10] The latter findings are notable in light of the absence of such evidence from the previous CDR review in 2006.

Several of the included studies assessed whether omalizumab treatment led to a reduction in the use of other asthma medications. In the study of pediatric patients (ICAC-08[8]), omalizumab-treated patients used statistically significantly lower doses of ICS compared with the placebo group. The results of Study A2425[10] were similar in demonstrating a reduction in the mean dose of ICS used by omalizumab-treated patients compared with the baseline dose, although the statistical significance of this effect was not assessed. The use of SABA was assessed in three studies, but none demonstrated a statistically significant reduction in SABA use in omalizumab-treated patients compared with placebo. The aforementioned evidence is consistent with that reported in the previous CDR review of omalizumab in 2006.

5.2.2 Harms

In all of the included studies, the overall safety profile in terms of the frequencies and types of AEs, SAEs, and WDAE was similar in omalizumab-treated patients and placebo-treated or control patients within studies. The occurrence of potential harms of special interest for this review was either rare (e.g., anaphylaxis), absent (Churg–Strauss syndrome and thromboembolic events), or balanced between treatment groups (e.g., injection-site reactions). Overall, no new safety concerns were noted in the included studies compared with the safety information reviewed previously by CDR in 2006.

5.3 Potential Place in Therapy[1]

ICS suppresses inflammation generally, long-acting bronchodilators are helpful to open airways, and LTRAs are helpful in a minority of patients who are responders to the drug. Despite these available treatments, there remains a small subset of allergic asthmatic patients who remain symptomatic, with exacerbations, hospitalizations, ER visits, and the need for OCS (either frequently for exacerbations, or chronically for long-term control), despite adhering to standards of care. In those patients who remain symptomatic despite moderate-to-high doses of combination ICS/LABA inhalers (with or without other add-on therapies such as tiotropium bromide or montelukast), omalizumab would be an appropriate therapy. Therefore, an unmet need in the treatment of moderate-to-severe allergic asthma is access to biologic therapies that target the immune mediators of the disease.

Omalizumab should not be considered a first-line therapy for allergic asthma, but should be reserved for those patients with moderate-to-severe persistent allergic asthma who remain symptomatic despite ICS/LABA treatment (or who are intolerant of the side effects of ICS/LABA) and have also not responded to less expensive add-on options such as montelukast or tiotropium bromide. It is anticipated that suitable patients could be identified readily in practice, because access to total IgE levels and spirometry with bronchodilator responses are not ultra-specialized tests restricted to tertiary or quaternary care centres.[1,62]

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

6. CONCLUSIONS

New clinical evidence identified since the previous CDR review of omalizumab in 2006 comprised six studies in which omalizumab was compared with either placebo (four double-blind RCTs) or control (two open-label studies). The results of these studies with respect to the effect of omalizumab on several key outcomes are inconsistent. There was evidence from one double-blind RCT and one open-label RCT that omalizumab statistically significantly reduced the proportion of patients hospitalized or the rate of hospitalization, while one double-blind RCT and one open-label RCT showed that omalizumab statistically significantly reduced the rate of ER visits. However, there was no evidence that omalizumab statistically significantly reduced the number of MD visits or the use of OCS.

Omalizumab was associated with a statistically significant reduction in the proportion of patients with exacerbation or rate of exacerbation in three of four RCTs and one of two open-label studies. However, this did not appear to be translated into an effect on QoL, which was improved statistically and clinically significantly in omalizumab-treated patients only in the two open-label studies, but not in any of the four double-blind RCTs.

There was evidence from a single RCT that omalizumab statistically significantly reduced the number of days of school or work missed. The results for other outcomes, including changes in FEV_1 (pulmonary function) and symptom reduction measured using a variety of instruments, were either inconsistent across studies or failed to demonstrate a statistically significantly treatment effect. There was also limited evidence that omalizumab had a beneficial effect on outcomes such as the frequency of nocturnal awakening, the number of symptom-free days/nights, use of ICS, and use of rescue medication (SABA).

Some of the included studies had limitations that limit the generalizability of some findings to the population of interest, such as including patients younger than 12 years old or including patients with mild asthma who had not received ICS plus LABA treatment. In addition, lack of adjustment for multiplicity in some of the included studies limits interpreting the validity of findings based on secondary outcomes.

The open-label design of two of the included studies increases the uncertainty associated with the precise magnitude of any omalizumab-associated treatment effects, particularly with regard to the frequencies of hospitalization and ER visits and QoL. Therefore, the available evidence is consistent with the overall conclusion that adding omalizumab to existing background treatment in patients with moderate-to-severe persistent allergic asthma who are inadequately controlled with ICS or ICS plus LABA, with or without other asthma controllers, might produce improvements in some asthma-related outcomes, although these improvements have not been demonstrated consistently or in a manner that allows for an accurate assessment of the magnitude of potential treatment effects. The inclusion of patients who were treated with a LABA in addition to ICS in most of the newly identified studies addresses this shortcoming in the evidence that was assessed in the CDR review of omalizumab in 2006.

In addition, although inconsistent, the effects of omalizumab on the severity of asthma symptoms in the included studies are notable in light of the absence of such evidence from the previous CDR review in 2006. The results of the assessment of the efficacy of omalizumab on other outcomes in the included studies were consistent with those reported in the previous CDR review in 2006. In terms of safety, the incidence and types of AEs, SAEs, WDAEs, and notable AEs were similar between treatment groups within studies, and no new or notable safety concerns were identified in this review compared with the safety profile reported in the previous CDR review of this drug in 2006.

APPENDIX 1: PATIENT INPUT SUMMARY

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

1. Brief Description of Patient Groups Supplying Input

The Asthma Society of Canada (ASC) is a national charitable volunteer-supported organization committed to enhancing the quality of life and health of people living with asthma and associated allergies. The ASC (and its patient advocacy group, the National Asthma Patient Alliance) provides health education services, advocates on behalf of Canadians with asthma, and engages in research to improve asthma prevention and management strategies. The ASC receives approximately 20% of its funding from pharmaceutical companies through unrestricted grants, consulting fees, or other fee-for-service contracts. These companies include AstraZeneca, Boehringer Ingelheim International, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis, Roche Canada, Sanofi, Sanofi Pasteur, Takeda, and Teva Canada Innovation.

The British Columbia Lung Association (BCLA) is a charitable organization whose mission is to improve lung health and to lead lung health initiatives. Its areas of interest and expertise include the entire scope of respiratory diseases. It works together with the Canadian Lung Association and other partners to help people with breathing disorders. The BCLA has received unrestricted educational grants from a number of pharmaceutical companies, including AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Grifols, InterMune, Merck, Novartis, and Pfizer.

The Ontario Lung Association (OLA) is a charitable organization that assists and empowers people living with or caring for others with lung disease, including asthma. The OLA works closely with nine other provincial lung associations and the Canadian Lung Association. The OLA has received sponsorships and grants to support educational and research initiatives from a number of pharmaceutical companies, including AstraZeneca, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis, Roche, Canada's Research-Based Pharmaceutical Companies (RX&D), and Pfizer, as well as the Ontario Home Respiratory Services Association.

No conflicts of interest were declared by any of the aforementioned patient groups with regard to their patient input submissions.

2. Condition-Related Information

Information for this submission was obtained through the ASC's *Severe Asthma: The Canadian Patient Journey*. It is the first patient study (both qualitative and quantitative through research, best practices, guidelines, direct patient involvement, certified respiratory educators, and five online surveys) to consider the impacts on everyday lives of those suffering from severe asthma.

Asthma is a chronic respiratory disease affecting between 1% and 18% of the population. Eight per cent of patients with asthma believe their asthma is not controlled at all and the disease is poorly controlled in up to 53% of patients with asthma. Asthma is characterized by variable symptoms: wheezing, shortness of breath, chest tightness, coughing (with our without mucus), and limitations in expiratory airflow, all of which can vary over time and in severity. In addition, patients experience difficulty fighting infections, difficulties sleeping, and fatigue. Their reduced ability to engage in physical activities (such as going or playing outdoors and biking and other sports); everyday activities (including home care, work, and school); and social and leisure activities can lead to a diminished sense of self-worth and a decline in

health. One patient noted, "It can limit or restrict activities, interfere with work (both in terms of attendance and concentration and performance while at work) and make daily activities more difficult." Unpredictable flare-ups or exacerbations can further impede physical and social activities, thus leading to an increase in isolation — something the patient with asthma already experiences due to the symptomatology and social barriers associated with the disease. Patients reported that because of their decreased ability to perform physical activities, their ability to perform a sufficient amount of exercise is inhibited, which can further lead to deterioration in fitness levels and the body's ability to use oxygen effectively. In addition, patients reported experiencing a loss of productivity due to missed days of school or work. For those patients who are of working age, this loss in time at work, time spent at doctor's appointments, and costs associated with treatment all reinforce the stress and strain they feel due to the financial burden of their condition and associated treatment. These financial repercussions can subsequently trickle down and affect both caregivers and the family as a whole. As another patient stated, "Asthma is very expensive. People don't realize how much the asthma drugs cost. When you are on a disability pension, even when insurance covers three-quarters, the other 25% kills you." Patients indicated that the most important aspects of their asthma they would like to control are their ability to sleep without nighttime symptoms, reduce daytime exacerbations, and improve their overall health and well-being.

Caregivers of patients with asthma generally tend to include parents, spouses, and siblings. Often, with the continually declining health and declining physical abilities of the patient, caregivers must take on additional activities around the house, transport patients to medical appointments, and deal with exacerbations, which can be life-threatening medical emergencies. Caregivers also experience emotional and financial burdens associated with the care of the patients with asthma and their exacerbations, and cost of treatment/appointments, respectively. Often, their lives and their sleep are also affected, which can negatively affect the caregiver and lead to additional stress.

3. Current Therapy-Related Information

Current therapy for patients with asthma includes corticosteroids and long-acting beta$_2$ agonists (Symbicort), long-acting anticholinergics (Spiriva Respimat), antihistamines (Reactine), antileukotrienes (Singulair), and short-acting beta$_2$-agonists (Ventolin), and a few patients have received Xolair.

From the ASC submissions, it is apparent that patients often journeyed through experimentation with a multitude of treatments before finding one drug or a combination of drugs that worked well. In some cases, upwards of 10 prescriptions were tried before finding the right treatment, and this coincided with a diagnosis of severe asthma in many cases.

Patients reported that current treatments provide relief for shortness of breath, cough, poor appetite, and the inability to fight infections, although they were associated with low energy.

4. Expectations About the Drug Being Reviewed

Patients would like more asthma treatment options along with more affordable and timely treatment. Patients indicated their desire for an increased improvement associated with their symptoms and an overall goal of less medication burden. In addition, many patients felt that, in terms of medications, dosing frequency, better and more options, convenience, ability to work quickly, and affordability were all important aspects associated with treatment. There appeared to be a consensus among patients that treatments and, in particular, Xolair, need to be covered by drug formularies and made more accessible, especially for low-income families.

When compared with other treatments in the ASC study, many patients who had experience with Xolair indicated they had no visits to the emergency department in the last 12 months, had no hospital admissions, and had missed fewer days of school or work. Patients varied in how they felt about the once-a-month injections, with 50% in favour, 33% neither liking nor disliking, and 17% disliking. In the OLA submission, one patient had experience with Xolair. That patient indicated that administering the treatment and the time needed to accommodate the treatment were worse than other drugs; yet, the cost burden, side effects (with the exception of impact on mood), and treatment efficacy were the same as other comparative treatments. Concerns were also expressed concerning treatment accessibility. As one patient noted, "Xolair injections are hard to access; they must be done in a trained clinic during office hours. For me, this is over an hour from my home and I work full time. Injections must be booked monthly with fairly limited flexibility. All other medications are more easily accessed."

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:	December 16, 2015
Alerts:	Weekly search updates until April 20, 2016
Study types:	randomized controlled trials; controlled clinical trials
Limits:	No language or date limits 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
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
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
#	**Searches**
1	(Xolair* or omalizumab* or olizumab* or rhuMab-E25 or rhu MAB-E25 or rhu MADE25 or rhuMabE25 or HSDB 5742 or HSDB5742 or 2P471X1Z11 or UNII2P471X1Z11 or hu 901 or hu901 or HSDB8176 or HSDB 8176).ti,ab,ot,kw,hw,rn,nm.
2	(monoclonal adj2 antibod* adj2 (E25 or E 25)).ti,ab,ot,kw,hw,rn,nm.
3	(humanized anti IgE Mab or humanised anti IgE Mab or humanized antiIgE Mab or humanised antiIgE Mab).ti,ab,ot,kw,hw,rn,nm.
4	("242138 07 4" or "242138074" or 24213807 4 or "242318 074" or 2421380 74).rn,nm.
5	1 or 2 or 3 or 4
6	exp Asthma/
7	Asthma*.ti,ab,kf.
8	(bronchi* adj2 spasm*).ti,ab,kf.

MULTI-DATABASE STRATEGY	
#	**Searches**
9	6 or 7 or 8
10	5 and 9
11	10 use pmez
12	exp *omalizumab/
13	(Xolair* or omalizumab* or olizumab* or rhuMab-E25 or rhu MAB-E25 or rhu MADE25 or rhuMabE25 or HSDB 5742 or HSDB5742 or 2P471X1Z11 or UNII2P471X1Z11 or hu 901 or hu901 or HSDB8176 or HSDB 8176).ti,ab,kw.
14	(monoclonal adj3 antibod* adj3 (E25 or E 25)).ti,ab,kw.
15	(humanized anti IgE Mab or humanised anti IgE Mab or humanized antiIgE Mab or humanised antiIgE Mab).ti,ab,kw.
16	12 or 13 or 14 or 15
17	exp asthma/
18	Asthma*.ti,ab,kw.
19	(bronchi* adj2 spasm*).ti,ab,kw.
20	17 or 18 or 19
21	16 and 20
22	21 use oemezd
23	11 or 22
24	exp animals/
25	exp animal experimentation/ or exp animal experiment/
26	exp models animal/
27	nonhuman/
28	exp vertebrate/ or exp vertebrates/
29	animal.po.
30	or/24-29
31	exp humans/
32	exp human experimentation/ or exp human experiment/
33	human.po.
34	or/31-33
35	30 not 34
36	23 not 35
37	(Randomized Controlled Trial or Controlled Clinical Trial).pt.
38	Randomized Controlled Trial/
39	Randomized Controlled Trials as Topic/
40	"Randomized Controlled Trial (topic)"/
41	Controlled Clinical Trial/
42	Controlled Clinical Trials as Topic/
43	"Controlled Clinical Trial (topic)"/
44	Randomization/
45	Random Allocation/

MULTI-DATABASE STRATEGY	
#	**Searches**
46	Double-Blind Method/
47	Double Blind Procedure/
48	Double-Blind Studies/
49	Single-Blind Method/
50	Single Blind Procedure/
51	Single-Blind Studies/
52	Placebos/
53	Placebo/
54	Control Groups/
55	Control Group/
56	(random* or sham or placebo*).ti,ab,hw.
57	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
58	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
59	(control* adj3 (study or studies or trial*)).ti,ab.
60	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw.
61	allocated.ti,ab,hw.
62	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.
63	or/37-62
64	36 and 63
65	64 not conference abstract.pt.
66	remove duplicates from 65

OTHER DATABASES	
PubMed	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:	December 8–10, 2015
Keywords:	Drug name (Xolair, omalizumab), Indication (asthma)
Limits:	No language or date limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

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

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Niven[27]	Duplicate data: Post-hoc analysis of a study (Ayres[59]), which was included in previous CDR review in 2006
Siergiejko et al.[30]	Duplicate data: subgroup analysis of the included Study A2425[10]
Mumm et al.[63]	Review comments
Newbrough et al.[64]	Review comments
Walker et al.[65]	Review comments
Thien et al.[66]	Review comments
Garcia et al.[67]	Population not of interest
Zielen et al.[68]	Population not of interest
Massanari et al.[69]	Outcome not of interest
Prieto et al.[70]	Population not of interest
Silkoff et al.[71]	Population not of interest
Lemanske et al.[72]	Population not of interest
Milgrom et al.[73]	Intervention not of interest
Busse et al.[74]	Pooled analysis
Humbert et al.[75]	Outcome not of interest
Massanari et al.[76]	Pooled analysis
PACEet al.[77]	Observational study without control group

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 10: STUDY DRUG EXPOSURE IN DOUBLE-BLIND STUDIES

	EXTRA[6,12]		AUS23[7,13]		ICAC-08[8,14]		PROSE[9,15]	
	OMA	PLA	OMA	PLA	OMA	PLA	OMA	PLA
Randomized, N								
Dose q2w, n of patients (%)								
225 mg								
300 mg								
375 mg								
Dose q4w, n of patients (%)								
150 mg								
300 mg								
Dose q2w, n of doses								
Mean (SD)								
Range								
Dose q4w, n of doses								
Mean (SD)								
Range								

OMA = omalizumab; PLA = placebo indicating a matching placebo study in a double-blind, randomized controlled trial; q2w = every two weeks; q4w = every 4 weeks; SD = standard deviation.
Source: Clinical Study Reports[12-15] and relevant publications.[6-9]

TABLE 11: STUDY DRUG EXPOSURE IN OPEN-LABEL STUDIES

	A2425[16]		Rubin (2012)[11]	
	OMA	CTR	OMA	CTR
Randomized, N (%)				
Dose q2w, n of patients (%)				
225 mg				
300 mg				
375 mg				
Dose q4w, n of patients (%)				
150 mg				
225 mg				
300 mg				
Dose q2w, n of doses				
Mean (SD)				
Range				
Dose q4w, n of doses				
Mean (SD)				
Range				

CTR = control group with no additional add-on therapy in an open-label randomized controlled trial; OMA = omalizumab; q2w = every two weeks; q4w = every 4 weeks; SD = standard deviation.
Source: Clinical Study Reports[12-16] and relevant publications.[6-11]

TABLE 12: NUMBER OF HOSPITALIZATIONS DUE TO AN ASTHMA EXACERBATION IN STUDY A2425 (MITT)

	OMA (N = 272)	CRT (N = 128)
Number of hospital admissions due to asthma exacerbation, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
≥ 4	[redacted]	[redacted]
P value (OMA versus CTR)[a]	[redacted]	
Total number of hospital admissions for asthma exacerbation	[redacted]	[redacted]
Mean number of hospital admissions per 32-week period	[redacted]	[redacted]
Ratio of hospital admission rates[b]		
Rate ratio (95% CI), *P* value	[redacted]	

CI = confidence interval, CTR = control group with no additional add-on therapy in an open-label randomized controlled trial; mITT = modified intention-to-treat; OMA = omalizumab.
[a] Based on Cochran-Mantel-Haenszel test for 0, ≥ 1 hospital admission, stratified by maintenance oral steroid use.
[b] Poisson regression model: log (hospitalization rate) = treatment + maintenance oral steroid use + error. A ratio of rates < 1 favours OMA.
Source: Study A2425.[10,16]

TABLE 13: SUMMARY OF USE OF ORAL CORTICOSTEROIDS

Study	Use of OCS (Rate, Event/Patient)		Use of OCS (n, or % of Patients)			
	OMA	PLA	OMA	PLA	Between-Group Difference	*P*
ICAC-08[14]	[redacted]					
EXTRA[12]	[redacted]					
AUS23[13]	[redacted]					
PROSE[15]	[redacted]					
A2425[16]	[redacted]					
Rubin 2012[11]	[redacted]					

OCS = oral corticosteroids; OMA = omalizumab; PLA = placebo indicating a matching placebo study in a double-blind randomized controlled trial.
Source: Clinical Study Reports[12-16] and publications.[6-9,11,42]

TABLE 14: CHANGE IN DOSE OF MAINTENANCE SYSTEMIC CORTICOSTEROID AT WEEK 32 IN STUDY A2425 (MITT)

	OMA (N = 59)			CTR (N = 23)		
	Baseline	End of the Study	Change (%)	Baseline	End of the Study	Change (%)
SCS dose (prednisolone equivalent, mg/day)						
Mean	[redacted]					
SD						
Median						
Range						
P value[a]						

CTR = control group with no additional add-on therapy in an open-label randomized controlled trial; mITT = modified intention-to-treat; OMA = omalizumab; SCS = systemic corticosteroid; SD = standard deviation.
[a] Based on the Wilcoxon rank-sum test comparing OMA with CTR.
Note: Patients with SCS at baseline were defined as those who used SCS throughout the entire run-in period. Patients who were removed from SCS during treatment were included with a dose of 0 mg/day.
Source: Study 2425, Clinical Study Report.[16]

TABLE 15: SUMMARY OF CHANGE FROM BASELINE AQLQ(S) AT WEEK 48 IN EXTRA (MITT)

Domain	Treat	N[a]	Baseline	Week 48	Change from Baseline		
			Mean	Mean	Mean	SD	Range
Activities	[redacted]						
Emotions							
Symptoms							
Environment							
Overall							

AQLQ(S) = Standardized Asthma Quality of Life Questionnaire; mITT = modified intention−to−treat population; OMA = omalizumab; PLA = placebo indicating a matching placebo study in a double-blind randomized controlled trial; SD = standard deviation.
[a] Number of patients with both baseline and visit values.
Source: EXTRA study Clinical Study Report.[6,12]

TABLE 16: CHANGE FROM BASELINE IN AQLQ(S) SCORES AT WEEK 31 IN STUDY A2425 (MITT)

Domain	Treatment	n	Change from Baseline (LSM)	95% CI	*P* Value
Overall score	[redacted]				
Symptoms score					
Activities score					
Emotions score					

Domain	Treatment	n	Change from Baseline (LSM)	95% CI	*P* Value
Environmental exposure score					

ANCOVA = analysis of covariance; AQLQ(S) = Standardized Asthma Quality of Life Questionnaire; CI = confidence interval; LOCF = last observation carried forward; LSM = least squares mean; mITT = modified intention−to−treat population; OCS = oral corticosteroid; OMA = omalizumab.
Note: LOCF was used for missing week 31 data (only week 15 data could be carried forward). ANCOVA model: treatment + country + maintenance OCS use + baseline AQLQ.
Note: Score: 1 = totally limited/problems all the time, 7 = not at all limited/no problems.
Source: Study A2425 Clinical Study Report.[16]

TABLE 17: CHANGE FROM BASELINE IN AQLQ(S)-SPECIFIC DOMAIN SCORES AT WEEK 20 IN RUBIN'S STUDY

Domain	Change from Baseline in AQLQ at Week 20, (Mean ± SE)	
AQLQ(s)-specific domains	**OMA (n = 77)**	**CTR (n = 36)**
Activity limitation score	1.3 ± 0.1 (*P* < 0 .001)	–0.2 ± 0.1 (*P* = 0 .490)
Symptoms score	1.2 ± 0.2 (*P* < 0 .001)	–0.2 ± 0.2 (*P* = 0 .469)
Emotional function score	1.3 ± 0.2 (*P* < 0.001)	0 ± 0.1 (*P* = 0 .877)
Environmental stimuli score	1.2 ± 0.2 (*P* < 0 .001)	0 ± 0.2 (*P* = 0 .844)

AQLQ(s) = Standardized Asthma Quality of Life Questionnaire; CTR = control group with no additional add-on therapy in an open-label randomized controlled trial; OMA = omalizumab; SE = standard error.
Source: Rubin, 2012.[11]

TABLE 18: ADJUSTED TREATMENT EFFECT ON ASTHMA SYMPTOMS AND HEALTH CARE USE IN STUDY ICAC-08

Outcomes	OMA (N = 208)	PLA (N = 211)	Difference (95% CI)	*P* Value
	Mean ± SE	**Mean ± SE**	**Mean (95% CI)**	
Asthma-related symptoms, no. of days in 2 wks preceding visit	1.48 ± 0.10	1.96 ± 0.10	−0.48 (−0.77 to −0.20)	< 0.001
Nighttime sleep disruption	0.42 ± 0.05	0.59 ± 0.05	−0.17 (−0.31 to –0.03)	0.02
Missed school, no. of days	0.16 ± 0.03	0.25 ± 0.03	−0.09 (−0.18 to –0.01)	0.038
ACT				
C-ACT score in previous month, age 4 to 11 yrs	23.0 ± 0.21	22.2 ± 0.21	0.78 (0.21 to 1.35)	0.007
ACT score in previous month, age 12 yrs or older	22.5 ± 0.22	22.3 ± 0.22	0.19 (−0.42 to 0.79)	0.54
FEV_1, % of predicted value	92.6 ± 0.60	91.7 ± 0.64	0.92 (−0.81 to 2.64)	0.30
Medication				
Adherence, %	84.6 ± 1.78	88.6 ± 1.80	−3.96 (−8.95 to 1.02)	0.12
Step level equal to 1 or 2,[a] %	43.6 ± 4.0	26.7 ± 3.3	16.9 (6.6 to 27.1)	0.001
Step level equal to 4 to 6,[a] %	31.2 ± 3.5	50.8 ± 4.0	−19.6 (−30.1 to −9.1)	< 0.001
ICS dose[b] prescribed, mcg/day	663 ± 23.3	771 ± 23.5	−109 (−172 to −45)	< 0.001
LABA prescribed, %	55.4 ± 2.44	65.5 ± 2.47	−10.1 (−16.8 to −3.4)	0.003
Asthma-related health care use,[c] %				

Outcomes	OMA (N = 208)	PLA (N = 211)	Difference (95% CI)	*P* Value
	Mean ± SE	Mean ± SE	Mean (95% CI)	
≥ 1 hospitalization	1.5 ± 0.9	6.3 ± 1.8	−4.7 (−8.6 to −0.9)	0.02
≥ 1 exacerbation[d]	30.3 ± 3.3	48.8 ± 3.7	−18.5 (−28.2 to −8.8)	< 0.001

ACT = Asthma Control Test; C-ACT = Childhood Asthma Control Test; CI = confidence interval; ICS = inhaled corticosteroids; FEV_1 = forced expiratory volume in one second; LABA =long-acting $beta_2$-agonist; mITT = modified intention−to−treat population; OMA = omalizumab; PLA = placebo indicating a matching placebo study in a double-blind randomized controlled trial; SE = standard error; wks = weeks; yrs = years.

[a] Six treatment steps were established, consistent with the National Asthma Education and Prevention Program's *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*[43] for standardizing prescribing patterns according to levels of asthma severity. Steps 1 and 2 apply to mild asthma; step 3 to moderate asthma, and steps 4 through 6 to severe asthma. At step 0, the recommendation is for no asthma control medication, or salbutamol as needed. Step 1: 180 mcg of budesonide once a day; step 2: 180 mcg of budesonide twice a day; step 3: 360 mcg of budesonide twice a day; step 4: 250 mcg of fluticasone and 50 mcg of salmeterol (Advair) twice a day; step 5: 250 mcg and 50 mcg of salmeterol twice a day plus montelukast once a day; and step 6: 500 mcg and 50 mcg of salmeterol twice a day plus montelukast once a day. (The doses for montelukast are 5 mg per day for children ≤ 14 years of age and 10 mg per day for those ≥ 15 years of age.)

[b] The dose of ICS was converted to the budesonide-equivalent dose.

[c] Asthma-related health care use was adjusted for study site and dosing because of the scarce data for baseline levels.

[d] An exacerbation was defined as a prednisone burst (a minimum of 20 mg per day of prednisone, or the equivalent, taken for any three of five consecutive days) or a hospitalization.

Source: Study ICAC-08.[8]

TABLE 19: WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT QUESTIONNAIRE — ASTHMA AT WEEK 48 (MITT) IN THE EXTRA STUDY

	OMA	PLA
	(n = 427)	(n = 421)
Currently employed		
N	[redacted]	[redacted]
Yes, n (%)	[redacted]	[redacted]
No, n (%)	[redacted]	[redacted]
Hours usually work per week		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Hours missed from work due to asthma during the past 7 days		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Currently a student		
N	[redacted]	[redacted]
Yes, n (%)	[redacted]	[redacted]
No, n (%)	[redacted]	[redacted]
Hours usually attend class per week		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Hours class time missed due to asthma during the past 7 days		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]

	OMA	PLA
	(n = 427)	(n = 421)
Per cent of work time missed due to asthma during the past 7 days		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Per cent of class time missed due to asthma during the past 7 days		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]

mITT = modified intent−to−treat population; OMA = omalizumab; PLA = placebo indicating a matching placebo study in a double-blind randomized controlled trial; SD = standard deviation.

TABLE 20: ANALYSES OF EXPLORATORY EFFICACY OUTCOMES AT WEEK 24 IN STUDY AUS23 (FULL ANALYSIS SET)

	OMA (n = 136)[a]	PLA (n = 135)[a]	Mean Difference (95% CI)	*P* Value
	WPAI-A (LSM Change From Baseline at Week 24)			
Work time missed, percentage	–1.13	–0.66	–0.47 (–5.97 to 5.03)	0.866
	LSM Change From Baseline at Week 24			
Average number of days per week with any daytime asthma symptoms	–2.16	–1.77	–0.39 (–0.99 to 0.21)	0.202
Average number of nighttime awakenings per week due to asthma	–1.45	–1.06	**–0.39** (–0.71 to –0.07)	**0.019**
Average number of days per week of SABA use for symptom control	–1.74	–1.49	–0.25 (–0.81 to 0.31)	0.374
LSM change from baseline in FEV_1	0.08	0.16	–0.08 (–0.19 to 0.02)	0.123

CI = confidence interval; FEV_1 = forced expiratory volume in one second; LSM = least squares mean; OMA = omalizumab; PLA = placebo; SABA = short-acting $beta_2$-agonist; WPAI-A = Work Productivity and Activity Impairment Questionnaire — Asthma.
[a] Sample sizes vary across exploratory variables.
Note: No actual between-group difference was analyzed and reported except 95% CI. The treatment group differences of change from baseline (in red font) were calculated by CDR.
Source: Study AUS23.[7]

TABLE 21: WPAI-AA — NUMBER OF HOURS MISSED FROM WORK AT WEEK 31 IN STUDY A2425 (MITT)

	OMA (N = 272)			CTR (N = 128)		
	Baseline	**Week 31**	**Change**	**Baseline**	**Week 31**	**Change**
Number of hours missed from work because of allergic asthma problems in the past 7 days at week 31						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean, no. of hours (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CTR = control group with no additional add-on therapy in an open-label randomized controlled trial; mITT = modified intention-to-treat; no. = number; SD = standard deviation; WPAI-AA = Work Productivity and Activity Impairment Questionnaire — Allergic Asthma.
Note: No between-group difference was analyzed or reported.
Source: Study A2425 Clinical Study Report.[16]

TABLE 22: FEV_1 IN THE EXTRA STUDY (MITT)

At Week 48	Treatment	N[a]	Baseline	Week 48	Change from Baseline		
			Mean	Mean	Mean	SD	Range
FEV_1 (L)	OMA	424	2.105	2.291	0.186	0.463	−1.480 to 3.490
	PLA	418	2.001	2.130	0.128	0.428	−2.020 to 1.960
FEV_1 % predicted[b]	OMA	424	65.35	71.27	5.92	14.42	−44.70 to 80.84
	PLA	418	64.40	68.76	4.36	13.88	−46.60 to 84.42

FEV_1 = forced expiratory volume in one second; mITT = modified intention−to−treat; OMA = omalizumab; PLA = placebo; SD = standard deviation.
[a] Number of patients with both baseline and visit values.
[b] FEV_1 per cent predicted: Crapo's formula was used for patients who were at least 18 years old. Plogar's formula was used for patients who were less than 18 years old.
Source: EXTRA study.[12]

TABLE 23: ADJUSTED CHANGE FROM BASELINE IN FEV_1 IN THE EXTRA STUDY (MITT)

	OMA		PLA		OMA Versus PLA		
Week 48	N	LSM	N	LSM	LSM difference	95% CI	*P* Value[a]
FEV_1 (L)	424	0.189	418	0.131	0.058	(−0.003 to 0.118)	0.061
FEV_1 % predicted	424	5.99	418	4.44	1.55	(−0.36 to 3.47)	0.112

ANOVA = analysis of variance; CI = confidence interval; FEV_1 = forced expiratory volume in one second; LSM = least squares mean; mITT = modified intention-to-treat; OMA = omalizumab; PLA = placebo.
[a] ANOVA: LSM was adjusted for treatment, concomitant asthma medication strata, and dosing regimen.
Source: EXTRA study.[6,12]

TABLE 24: FEV_1 PERCENTAGE OF PREDICTED IN STUDY A2425 (MODIFIED INTENTION-TO-TREAT)

Week 32	N	LSM ± SE	95% CI	*P* Value[a]
OMA	[redacted]	[redacted]	[redacted]	[redacted]
CTR	[redacted]	[redacted]	[redacted]	[redacted]
OMA minus CTR	[redacted]	[redacted]	[redacted]	[redacted]

ANCOVA = analysis of covariance; CI = confidence interval; CTR = control group with no additional add-on therapy in an open-label randomized controlled trial; FEV_1 = forced expiratory volume in one second; LSM = least squares mean; OMA = omalizumab; SE = standard error.
[a] ANCOVA model: Adjusted with treatment, country, maintenance oral steroid use, sex, and baseline FEV_1.
Source: Study A2425.[10,16]

TABLE 25: FEV_1 IN STUDY BY RUBIN

FEV_1	OMA	CTR
Change from baseline at week 20	**n = 76**	**n = 37**
Mean (95% CI), L	0.13 (0.06 to 0.21)	–0.003 (–0.12 to 0.12)
Between-group difference of the changes	0.13	
P value (treatment)	*P* = 0.049	

CI = confidence interval; CTR = control group with no additional add-on therapy in an open-label randomized controlled trial; FEV_1 = forced expiratory volume in one second; OMA = omalizumab.
Note: *P* = repeated measures analysis of variance; *P* 1 = two-sample student's t-test for change from baseline; *P* 2 = one-sample student's t-test (change from baseline = 0).
Source: Rubin 2012.[11]

TABLE 26: ASTHMA CONTROL QUESTIONNAIRE OVERALL SCORE AT WEEK 32 IN STUDY A2425

Week 32	LSM Changes From Baseline		LSM Difference in Changes From Baseline Mean (95% CI)	*P* Value
	OMA (n = 238)	CTR (n = 104)		
LSM change from baseline, (SE)	–0.91 (0.081)	–0.04 (0.110)	–0.87 (–1.09 to –0.65)	< 0.001

CI = confidence interval; CTR = control group with no additional add-on therapy in an open-label randomized controlled trial; LSM = least squares mean; OMA = omalizumab; SE = standard error.
Source: Study A2425.[10]

TABLE 27: GLOBAL EVALUATION OF TREATMENT EFFECTIVENESS AT WEEK 48 IN EXTRA (MITT)

Week 48	OMA (n = 427)	PLA (n = 421)	*P* Value[a]
Patient's GETE, n (%)			
Patients with non–missing evaluation (n)			
Excellent			
Good			
Moderate			
Poor			
Worsening			
Physician's GETE, n (%)			
Patients with non–missing evaluation (n)			
Excellent			
Good			
Moderate			
Poor			
Worsening			

GETE = global evaluation of treatment effectiveness; mITT = modified intention–to–treat; OMA = omalizumab; PLA = placebo.
[a] *P* value from generalized Cochran-Mantel-Haenszel (van Elteren) test using modified ridit scores, stratified by dosing regimen and concomitant asthma medication strata at baseline.
Source: EXTRA study Clinical Study Report.[12]

TABLE 28: RESPONDERS BY GLOBAL EVALUATION OF TREATMENT EFFECTIVENESS AT WEEK 48 IN EXTRA (MITT)

Week 48	OMA (n = 427)	PLA n = 421)	*P* Value[a]
Patient's GETE			
Patients with non-missing evaluation (n)			
Responder,[b] n (%)			
Physician's GETE			
Patients with non-missing evaluation (n)			
Responder,[b] n (%)			

GETE = global evaluation of treatment effectiveness; mITT = modified intention-to-treat; OMA = omalizumab; PLA = placebo.
[a] *P* value from Cochran-Mantel-Haenszel test stratified by dosing regimen and concomitant asthma medication strata at baseline.
[b] Responder included GETE categories "excellent" or "good."
Source: EXTRA study Clinical Study Report.[12]

TABLE 29: INVESTIGATOR'S GLOBAL EVALUATION OF TREATMENT EFFECTIVENESS RESPONDERS IN STUDY A2425 (MITT)

	OMA (N = 259)	CTR (N = 104)	*P* Value
Responder at week 32, n (%)[a]	199 (76.8)	25 (24.0)	< 0.001

CTR = control group with no additional add-on therapy in an open-label randomized controlled trial; GETE = global evaluation of treatment effectiveness; mITT = modified intention-to-treat; OMA = omalizumab.
[a] Responder included GETE categories "excellent" or "good." Patients with missing data at each assessment are not included.
Source: Study A2425.[10]

TABLE 30: GLOBAL EVALUATION OF TREATMENT EFFECTIVENESS AT WEEK 20 IN RUBIN'S STUDY

	OMA	CTR	*P* Value[a]
IGETE, n (%)	N = 59	N = 29	*P* < 0.001
Excellent	19 (32)	2 (7)	
Good	25 (42)	2 (7)	
Moderate	10 (17)	11 (38)	
Poor	5 (9)	13 (45)	
Worsening of asthma	0 (0.0)	1 (3)	
Patient's GETE, n (%)	N = 59	N = 29	*P* < 0.001
Excellent	28 (48)	3 (10)	
Good	20 (34)	11 (38)	
Moderate	10 (17)	7 (24)	
Poor	1 (2)	7 (24)	
Worsening of asthma	0 (0.0)	1 (3)	

CTR = control group with no additional add-on therapy in an open-label randomized controlled trial; GETE = global evaluation of treatment effectiveness; IGETE = investigator's global evaluation of treatment effectiveness; OMA = omalizumab.
[a] Mann–Whitney test.
Source: Rubin.[9]

TABLE 31: ASTHMA SYMPTOM SCORES AT WEEK 48 IN THE EXTRA STUDY (MITT)

Domains	Treatment	N	Baseline	Week 48	Change From Baseline		
			Mean	Mean[a]	Mean	SD	Range
Daytime	OMA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PLA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nocturnal	OMA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PLA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Morning	OMA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PLA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	OMA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PLA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

mITT = modified intention-to-treat; OMA = omalizumab; PLA = placebo; SD = standard deviation.
[a] Daytime, nocturnal, and morning scores at each visit were calculated as the mean of available data among the last 28 days of each visit.
Source: the EXTRA study Clinical Study Report.[12]

TABLE 32: LSM CHANGE FROM BASELINE IN ASTHMA SYMPTOM SCORES AT WEEK 48 IN EXTRA (MITT)

	OMA		PLA		OMA Versus PLA		
Domain[a]	**N**	**LSM**	**N**	**LSM**	**LSM Difference**	**95% CI**	***P* Value[b]**
Daytime	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nocturnal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Morning	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; LSM = least squares mean; mITT = modified intention-to-treat; OMA = omalizumab; PLA = placebo.
[a] Daytime, nocturnal, and morning scores at each visit were calculated as the mean of available data among the last 28 days of each visit.
[b] Analysis of covariance. LSM adjusted for treatment, concomitant asthma medication strata, dosing regimen, and baseline.
Source: EXTRA study Clinical Study Report.[12]

TABLE 33: NOCTURNAL AWAKENINGS IN TWO-WEEK PERIOD PRIOR TO WEEK 32 IN STUDY A2425

	OMA		CTR	
	Baseline	**Week 32**	**Baseline**	**Week 32**
N	264	264	111	111
Number of nocturnal awakenings over a two-week period prior to visit at week 32, n ± SD	5.8 ± 5.4	1.77 ± 3.6	6.1 ± 5.3	3.37 ± 4.5
Change from baseline at week 32 (SD)	–4.1 ± 5.5		–2.7 ± 5.4	
Between-group difference of change from baseline	–1.4[a] (*P* = 0.039)			

CI = confidence interval; CTR = control group with no additional add-on therapy in an open-label randomized controlled trial; OMA = omalizumab; SD = standard deviation.
[a] Calculated by CDR; no 95% CI was provided.
Source: Study A2425.[10]

TABLE 34: SUMMARY OF REDUCTION IN USE OF INHALED CORTICOSTEROIDS (%) IN STUDY A2425

Study	OMA			PLA		
	Baseline	**At the End**	**% Change**	**Baseline**	**At the End**	**% Change**
ICS dose[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICS = inhaled corticosteroids; OMA = omalizumab; PLA = placebo.
[a] Dose of ICS is expressed in beclomethasone dipropionate–equivalent mcg/day.
Source: Study A2425 Clinical Study Report.[16]

TABLE 35: NUMBER OF PUFFS OF SALBUTAMOL PER DAY IN EXTRA STUDY (MITT)

	N	Baseline	Week 48	Change from Baseline		
		Mean		Mean	SD	Range
OMA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PLA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
				Adjusted Change From Baseline (LSM)		
				LSM	Difference of LSMs (95% CI)	
OMA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
PLA	[redacted]	[redacted]	[redacted]	[redacted]		

CI = confidence interval; LSM = least squares mean; mITT = modified intention-to-treat; OMA = omalizumab; PLA = placebo; SD = standard deviation.
Note: Number of puffs of salbutamol per day at each visit was calculated as the mean of available data among the last 28 days of each visit.
Source: EXTRA study Clinical Study Report.[12]

TABLE 36: ADVERSE EVENTS REPORTED IN STUDY ICAC-08

	OMA (N = 208)	PLA (N = 211)
	Number of Patients With AEs	
Total n (%)	[redacted]	[redacted]
Gastrointestinal	[redacted]	[redacted]
Hematologic	[redacted]	[redacted]
Anaphylactic	[redacted]	[redacted]
Infection	[redacted]	[redacted]
Injection site	[redacted]	[redacted]
Nervous system	[redacted]	[redacted]
Respiratory	[redacted]	[redacted]
Skin	[redacted]	[redacted]
Other	[redacted]	[redacted]

AE = adverse event; OMA = omalizumab; PLA = placebo.
Source: Study ICAC-08.[8]

TABLE 37: ADVERSE EVENTS REPORTED IN THE EXTRA STUDY

	OMA	PLA
	N (%)	
N	428	420
Overall AEs		
Any AE	344 (80)	334 (80)
Deaths (considered treatment-emergent)	0	3 (0.7)
SAEs	40 (9.3)	44 (10.5)
WDAEs	16 (3.7)	10 (2.4)
Treatment-emergent AEs of special interest		
Anaphylaxis	1 (0.2)	2 (0.5)
Cancer	1 (0.2)	3 (0.7)
Urticaria	9 (2.1)	13 (3.1)
Hypersensitivity reactions	7 (1.6)	12 (2.9)
Thrombocytopenia	2 (0.5)	2 (0. 5)

	OMA	PLA
	N (%)	
Injection-site reaction	5 (1.2)	13 (3.1)
Bleeding-related adverse event	16 (3.7)	17 (4.0)

AE = adverse event; OMA = omalizumab; PLA = placebo; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
Source: EXTRA study.[6]

TABLE 38: ADVERSE EVENTS OCCURRING IN 5% OR MORE OF PATIENTS IN STUDY AUS23

	OMA	PLA
	n (%)	
Total patients	136 (100)	135 (100)
Patients with AEs	90 (66)	93 (6 9)
Asthma[a]	20 (15)	27 (20)
Upper respiratory tract infection	15 (11)	18 (13)
Sinusitis	13 (10)	9 (7)
Bronchitis	7 (5)	9 (7)
Headache	7 (5)	9 (7)
Injection-site reaction	28 (20)	20 (15)

AE = adverse event; OMA = omalizumab; PLA = placebo.
[a] Exacerbations or worsening of asthma.
Source: Study AUS23.[7]

TABLE 39: AES REPORTED IN THE PROSE STUDY

System Organ Class	OMA (N = 268)	PLA (N = 93)
	n	
Total n of patients with AEs	146	51
Gastrointestinal disorders	17	7
General disorders and administration-site conditions	41	6
Immune system disorders	5	2
Infections and infestations	50	17
Injury, poisoning, and procedural complications	28	6
Musculoskeletal and connective tissue disorders	8	1
Nervous system disorders	20	8
Psychiatric disorders	6	2
Reproductive system and breast disorders	11	1
Respiratory, thoracic, and mediastinal disorders	24	8
Skin and subcutaneous tissue disorders	36	14

AE = adverse event; OMA = omalizumab; PLA = placebo.
Source: PROSE study.[9]

TABLE 40: ADVERSE EVENTS (MORE THAN 5% IN ANY GROUP) IN STUDY A2425

	OMA (N = 274)	CTR (N = 128)
	n (%)	
Patients with AE(s)	[redacted]	[redacted]
Preferred term		
Nasopharyngitis	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Influenza	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Lower respiratory tract infection	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]

AE = adverse event; CTR = control group with no additional add-on therapy in an open-label randomized controlled trial; OMA = omalizumab.
Source: Study A2425 Clinical Study Report.[12]

TABLE 41: WITHDRAWAL DUE TO ADVERSE EVENTS (MORE THAN 5%) REPORTED IN STUDY AUS23

	OMA	PLA
	n (%)	
Number (%) of patients studied	[redacted]	[redacted]
Number (%) discontinued due to AE(s)	[redacted]	[redacted]
System organ class affected		
General disorders and administration-site disorders	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Respiratory, thoracic, and mediastinal disorders	[redacted]	[redacted]

AE = adverse event; OMA = omalizumab; PLA = placebo.
Source: Study AUS23.[13]

TABLE 42: ADVERSE EVENTS OF SPECIAL INTEREST IN STUDY 2425

	OMA (N = 274)	CTR (N = 128)
	n (%)	
Hypersensitivity reaction	[redacted]	[redacted]
Skin rash	[redacted]	[redacted]
Bleeding-related disorder	[redacted]	[redacted]
Urticaria	[redacted]	[redacted]

CTR = control group with no additional add-on therapy in an open-label randomized controlled trial; OMA = omalizumab.
Source: Study A2425 Clinical Study Report.[12]

TABLE 43: TREATMENT-EMERGENT ADVERSE EVENTS OF SPECIAL INTEREST IN EXTRA STUDY

	OMA (n = 428)	PLA (n = 420)
	N (%)	
Anaphylaxis	[redacted]	[redacted]
Malignancies	[redacted]	[redacted]
Urticaria	[redacted]	[redacted]
Hypersensitivity reaction	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Injection-site reaction	[redacted]	[redacted]
Bleeding-related adverse event	[redacted]	[redacted]

AE = adverse event; OMA = omalizumab; PLA = placebo.
Source: EXTRA Clinical Study Report.[12]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

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

- Asthma Control Test (ACT)
- Asthma Control Questionnaire (ACQ)
- Asthma Quality of Life Questionnaire for 12 Years and Older (AQLQ12+)
- forced expiratory volume in one second (FEV_1)
- global evaluation of treatment effectiveness (GETE).

Findings

The aforementioned outcome measures are summarized briefly in Table 44.

TABLE 44: VALIDITY AND MCID OF OUTCOME MEASURES

Instrument	Type	Evidence of Validity	MCID (or Similar Parameter)	References
ACT	ACT is a patient-reported tool to assess asthma control among adolescents and adults (i.e., ≥ 12 years old). It consists of five items relating to different aspects of asthma control that patients are asked to recall from the previous four weeks. Each item is scored on a five-point scale that ranges from 1 to 5, with higher scores indicating better asthma control. Scores from individual items are added together to produce an overall score that ranges from 5 to 25.	Yes	3	[54]
ACQ	ACQ is a patient-reported tool to assess asthma control in patient ≥ 6 years of age. It comprises the following seven questions, of which the mean of the results is the overall score (0 = well-controlled asthma and 6 = extremely poorly controlled asthma): • daytime symptoms • nighttime awakening/symptoms • activity limitation • rescue treatment requirements (use of SABA) • lung function (FEV_1) • shortness of breath • wheezing.	Yes	0.5	[47,49,50,78]
AQLQ	AQLQ is a patient-reported assessment of functional impairments experienced by individuals with asthma. It includes 32 questions grouped into four domains: symptoms; activity limitations; emotional function; and, environmental stimuli. Each question is scored on a seven-point Likert scale, which ranges from 7 (no impairment) to 1	Yes	0.5[a]	[45,79,80]

Instrument	Type	Evidence of Validity	MCID (or Similar Parameter)	References
	(severe impairment). The overall score is calculated as the mean of all questions, and the four domain scores are the means of the scores for the questions in the respective domains.			
FEV_1	FEV_1 is the volume of air that can be forcibly expired in one second after a full inspiration.	Yes	MPPI: 10.4% change from baseline	None
GETE	GETE is a simple tool used to measure treatment effectiveness in patients with moderate-to-severe allergic asthma (IgE-mediated). Two versions are available: the physician version and the patient version. It consists of five categorical scales, as follows: • *patient version:* "How effective has your treatment been in controlling your asthma?" • *physician version:* "How effective has the treatment been in controlling the patient's asthma?" Possible answers (same for both versions): • complete control of asthma • marked improvement of asthma • discernable but limited improvement in asthma • no appreciable change in asthma • worsening of asthma.	Yes	None	None

ACT = Asthma Control Test; ACQ = Asthma Control Questionnaire; 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; FEV_1 = forced expiratory volume in one second; MCID = minimal clinically important difference; MPPI = minimal patient-perceivable improvement; SABA = short-acting $beta_2$-agonist.
[a] Given the significant overlap between the AQLQ12+ and the original AQLQ, researchers consider a cut-point of 0.5 to indicate a clinically important difference, given this is the MCID for the AQLQ(S).

Asthma Control Test

The ACT is a patient-reported tool to assess asthma control among adolescents and adults, i.e., ≥ 12 years old. Developers of the ACT originally convened a working group, which included primary care clinicians and asthma specialists from the United States, to develop a list of 22 items that reflected the multi-dimensional nature of asthma control.[53]The researchers then recruited patients with asthma to complete the 22-item survey, and used stepwise logistic regression analyses to identify the items with the greatest validity in discriminating between patients who differed in their specialists' ratings of asthma control.[53] Based on their analyses, the investigators chose the following five items for inclusion in the ACT: shortness of breath; patient's rating of asthma control; use of rescue medication; role limitations due to asthma; and nocturnal asthma symptoms.[53] Each item is scored on a five-point scale that ranges from 1 to 5, with higher scores indicating better asthma control. Scores from the individual items are added together to produce an overall score that ranges from 5 to 25.[53] Patients recall their relevant experiences during the previous four weeks.[53]

The ACT was originally validated in a cross-sectional study of patients (n = 471) with asthma who were under the routine care of an asthma specialist.[53] In this study, researchers noted low and moderate correlation between the ACT and FEV_1 (r = 0.19; *P* = 0.0001) and specialists' ratings of asthma control (r = 0.45; *P* = 0.0001), respectively. The internal consistency reliability of the ACT was 0.84. The researchers noted that ACT scores discriminated between groups of patients who differed in their specialists' ratings of asthma control; the need for change in their therapy (i.e., step down, no change, step up in therapy); and their per cent predicted FEV_1 values. Researchers have also validated the ACT in patients not previously followed by asthma specialists,[81] as well as a version administered over the Internet,[82] the telephone,[83] and in a home setting.[84]

In a study involving four independent samples of adults with asthma (n = 4,018), researchers used a variety of distribution- and anchor-based methods to establish the MCID for the ACT.[54] In particular, their anchor-based methods assessed the relationship between mean ACT scores and the following items:

- patient self-report of asthma severity
- patient self-report of number of asthma episodes
- spirometry values
- specialist global assessment
- specialist recommended change in therapy
- patient self-report of change in asthma
- short-acting $beta_2$-agonist dispensing more than six canisters
- asthma exacerbations.

Based on their analyses, the authors proposed an MCID of three units for the ACT.[54]

Asthma Control Questionnaire

The ACQ (also called the ACQ-7)[47] was developed to evaluate asthma control in patients with asthma.[47,48] It is one of the most commonly used instruments measuring asthma control.[47] The questionnaire comprises seven questions, the responses for which are scored on a seven-point scale. Patients answer questions pertaining to six aspects of their experiences in the previous week. They include questions on activity limitation, nocturnal waking, shortness of breath, wheezing, symptoms on waking, and the use of short-acting $beta_2$-agonists.[48] In addition, the seventh item includes calculations performed by clinical staff with regard to pre-bronchodilator FEV_1 or peak expiratory flow (per cent predicted).[47,48] The ACQ score is defined as the mean of the seven questions (all questions are equally weighted), with scores at zero defined as well controlled and those at six defined as extremely poorly controlled.[47-49] The ACQ, like the ACT, is used extensively in clinical trials to measure clinically meaningful change in asthma control.[47] The ACQ also exists in abbreviated versions; the ACQ-5 focuses only on the symptoms (excluding the FEV_1 and bronchodilator use), while the ACQ-6 includes everything except the FEV_1 aspect.[47,78]

The ACQ is a multi-dimensional and standardized tool[50] that has been observed to be both highly reliable (intra-class correlation coefficient of 0.90) and responsive to change in asthma control in adults with asthma.[49] In addition, evidence for longitudinal and cross-sectional construct validity has been observed by correlations between the ACQ and other asthma heath status measures.[49] In addition, a score of 1.5 on the ACQ is the most appropriate discriminator for "well controlled" and "not well controlled" asthma patients.[85] There is also evidence of the construct validity, test–retest reliability, and responsiveness of the ACQ in children with asthma aged six to 16 years.[51]

The ACQ MCID has been well established and accepted as 0.5 points for within-person change.[47,50] However, Bateman et al. questioned its use as a measure between groups or between patients, further speculating that patient-reported outcomes should be presented as a responder rate comparison or a net treatment-benefit analysis.[52]

Asthma Quality of Life Questionnaire

The Standardized Asthma Quality of Life Questionnaire (AQLQ) is a patient-reported, disease-specific, health-related quality of life measure that was developed to evaluate asthma in the clinical trial setting.[86] The AQLQ includes 32 questions grouped into four domains: symptoms; activity limitations; emotional function; and, environmental stimuli. Each question is scored on a seven-point scale, which ranges from 7 (no impairment) to 1 (severe impairment). The overall score is calculated as the mean of all questions, and the four domain scores are the means of the answer scores for the questions in the respective domains. Patients recall their relevant experiences during the previous two weeks.

The standardized AQLQ has both good test–retest and inter-rater reliability when compared with the original AQLQ, with an overall correlation of r = 0.99 between the two versions.[87] With regard to construct validity, it has also been observed to have cross-sectional and longitudinal correlations sufficiently similar to the original AQLQ.[87] In addition, both instruments were responsive for determining both within-subject changes and identifying patients whose asthma was stable and whose asthma had changed (responsiveness indices of 1.35 and 1.34 for the AQLQ and the standardized AQLQ, respectively.[87] The MCID for the standardized AQLQ has been determined to be a cut-point of 0.5.[45,79,80]

Forced Expiratory Volume in One Second

FEV_1 is the amount of air that can be forcefully exhaled in one second. The measured volume can be converted to a percentage of predicted normal value, which is adjusted based on height, weight, and race. The percentage of predicted FEV_1 is one of the most commonly reported pulmonary function tests.[88] Considered an acceptable primary end point (although recommended as a secondary clinical end point by Health Canada),[89] FEV_1 is widely used in clinical trials to evaluate the effectiveness of asthma treatments.

Clinically, the percentage of predicted FEV_1 appears to be a valid marker for the degree of airway obstruction with asthma and other respiratory conditions, including chronic obstructive pulmonary disease and cystic fibrosis. Together with asthma symptoms and use of inhaled short-acting $beta_2$-agonists, FEV_1 is used to classify the severity of asthma.[43,90] There seems to be uncertainty, however, around the extent to which FEV_1 values are associated with quality of life, as researchers have reported variable correlations — ranging from none to strong[91,92] — among adults and children with asthma. However, FEV_1 values appear to correlate well with final clinical outcomes, such as the likelihood of hospitalization.[93] Further, FEV_1 values demonstrate high within-session repeatability: in a study of 18,526 adult patients, of whom 11% gave a history of physician-diagnosed asthma, 90% were able to reproduce FEV_1 within 120 mL.[94]

There appears to be limited evidence of an MCID for FEV_1 among individuals with asthma. In one study of 281 adult asthmatic patients (baseline mean FEV_1: 2.30 L/s ± 0.66 L/s), researchers calculated the minimal patient-perceivable improvement (MPPI) for FEV_1 by comparing the average scores from baseline for FEV_1 against patient global ratings of change in asthma. Across all patients, the MPPI for FEV_1 was 230 mL, or 10.38% change from baseline. Males and females showed similar MPPI values, but older patients had a lower MPPI (170 mL) than younger individuals (280 mL) for FEV_1.[46]

Global Evaluation of Treatment Effectiveness

The GETE was developed with clinical input only and is a tool used to measure treatment effectiveness in patients with moderate-to-severe allergic asthma (immunoglobulin E [IgE]–mediated).[55] Two GETE scales can be used to assess treatment effectiveness at the end of a treatment period, namely, the physician and patient versions.[55] Both versions rate treatment effectiveness. The patient is asked, "How effective has your treatment been in controlling your asthma?", while the physician is asked, "How effective has the treatment been in controlling the patient's asthma?"[55] The five categorical scale responses for the aforementioned questions include the following: complete control of asthma; marked improvement of asthma; discernable, but limited improvement in asthma; no appreciable change in asthma; and worsening of asthma.[55]

In a secondary post-hoc analysis of trial data, it was determined there is evidence supporting the validity of the GETE as a tool for perceived treatment effectiveness. In that trial, 1,380 patients with moderate-to-severe allergic asthma inadequately controlled on Global Initiative for Asthma step 4 therapy were treated with omalizumab for 28 weeks (INNOVATE trial).[55] A good level of agreement between physician and patient GETE was observed, indicating good convergent validity. In addition, the GETE has been observed to have good construct validity and inter-rater reliability.[55] It should be noted that the authors observed a tendency to skew toward "complete asthma control" and "marked improvement of asthma."[55] The authors were unsure whether the skew resulted from a placebo effect, a genuine treatment effect, or bias associated with doctors and patients who were assessing any change as a marked changed due to the severity of the patients' asthma.[55] The INNOVATE trial data indicated that the first three response levels of both the physician and patient versions of the GETE ("complete control of asthma," "marked improvement of asthma," and "discernible, but limited improvement of asthma") are clearly differentiated from each other. According to the authors, this clear differentiation is associated with clinically important differences in terms of clinical indices and some AQLQ subscales.[55] The authors noted it is important that the physician and patient versions of the GETE be considered separately.[55] No evidence to support test–retest reliability, MCID, or sensitivity was identified with regard to the GETE.

APPENDIX 6: SUMMARY OF SYSTEMIC REVIEWS AND OBSERVATIONAL STUDIES

As new evidence, the manufacturer submitted four systemic reviews (SRs)[36,39-41] and two narrative reviews.[37,38] The main findings from the four SRs[36,39-41] and 14 observational studies[22-35] are summarized in Table 45, Table 46 and Table 47 respectively.

TABLE 45: CHARACTERISTICS OF META-ANALYSIS/SYSTEMATIC REVIEW

First Author, Publication Year, Country	Study Design	Inclusion Criteria	Patient Characteristics	Intervention/ Comparator(s)	Clinical Outcomes
Normansell R,[36] 2014, UK, Australia, Canada	SR; N = 25 RCTs (6,382 patients); 8 to 60 wks	RCTs assessing OMA in the treatment of asthma (in any manner, for any duration, with or without co-interventions, as long as they were the same in each group)	Adult and pediatric patients with asthma	• OMA + CS • CS	**Primary outcomes:** • asthma exacerbations • reduction or discontinuation of steroid (inhaled, oral) **Secondary outcomes:** • asthma symptoms • HRQoL • rescue medication use • FEV_1 and PEF • AEs
Rodrigo G,[41] 2015, Argentina	SR; N = 3 RCTs (1,381 patients); 28 to 76 wks	• RCT • Children and adolescents (aged 6–18 years) with allergic asthma • OMA, SC at any dose vs. placebo as an add-on therapy to CS (oral or parenteral) with or without co-interventions	Patients with asthma (aged 6 to 20 years)	• OMA + CS • CS	**Primary outcome:** • asthma exacerbations **Secondary outcomes** • spirometric measures • rescue medication use • asthma symptoms • HRQoL • AEs
Rodrigo G,[40] 2011, Argentina	SR; N = 8 RCTs (3,428 patients); 20 to 56 wks	• Children and adolescents/adults with allergic asthma • OMA SC at any dose versus placebo as add-on therapy to CS	Adult and pediatric patients with asthma (aged 5 to 79 years)	• OMA + CS • CS	**Primary outcomes:** • reduction of CS use (inhaled, oral) from baseline • asthma exacerbations **Secondary outcome:** • FEV_1 or PEF

First Author, Publication Year, Country	Study Design	Inclusion Criteria	Patient Characteristics	Intervention/ Comparator(s)	Clinical Outcomes
		• Patients possibly taking other treatment as long as they were the same in each group			• rescue medication use • asthma symptoms • HRQoL • AEs
Lai T,[39] 2015	SR; N = 6 RCTs (2,749 patients); 52 to 60 wks	• Adults/adolescents (aged 12 years or older) and children (aged 6 to 12 years) with a diagnosis of persistent, uncontrolled moderate-to-severe allergic asthma in spite of high-dose ICS, or ICS + LABAs • RCT on OMA SC therapy at any dose as a guidelines-based therapy and reporting the following outcomes: asthma exacerbations, ICS use, GETE), QoL, asthma symptoms, lung function, rescue medication and AEs	Adult and pediatric patients with asthma (mean age 8.4 to 68.8 years)	• OMA + CS • CS	• Asthma exacerbations • AQLQ • AEs

AE = adverse event; AQLQ = Asthma Quality of Life Questionnaire; CS = corticosteroid, including inhaled or oral; FEV_1 = forced expiratory volume in one second; GETE = global evaluation of treatment effectiveness; HRQoL = health-related quality of life; LABA = long-acting $beta_2$-agonist; ICS = inhaled corticosteroid; OMA = omalizumab; PEF = peak expiratory flow; QoL = quality of life; RCT = randomized controlled trial; SC = subcutaneous; SR = systemic review; vs. = versus; wks = weeks.

TABLE 46: MAIN STUDY FINDINGS AND AUTHORS' CONCLUSIONS OF SYSTEMIC REVIEWS

First Author, Publication Year, Country	Main Study Findings	Author's Conclusions
Normansell R et al. [36] 2014, UK, Australia, Canada	• Compared with placebo, patients with OMA likely have fewer exacerbations and a reduction of ICS, improvement of symptoms and QoL, and fewer AEs • Unfortunately, many of the trials in this review included participants with moderate asthma, and this drug is not licensed for this group. More trials need to focus on whether this drug is effective in people with the most severe asthma; evidence for efficacy in this group is poor, in spite of current guidelines	"OMA was effective in reducing asthma exacerbations and hospitalizations as an adjunctive therapy to inhaled steroids and during steroid tapering phases of clinical trials. OMA was significantly more effective than placebo in increasing the numbers of participants who were able to reduce or withdraw their inhaled steroids. OMA was generally well tolerated, although more injection-site reactions were seen with OMA. Further assessment in pediatric populations is necessary, as is direct double-dummy comparison with ICS. Although subgroup analyses suggest that participants receiving prednisolone had better asthma control when they received OMA, it remains to be tested prospectively whether the addition of OMA has a prednisolone-sparing effect. It is also not clear whether there is a threshold level of baseline serum IgE for optimum efficacy of OMA. Given the high cost of the drug, identification of biomarkers predictive of response is of major importance for future research."
Rodrigo G et al.[41] 2015, Argentina	• During the stable phase, OMA decreased the number of patients with exacerbation (26.7% vs. 40.6%, NNTB = 7; 95% CI, 5 to 11) • During the CS reduction phase, OMA reduced the number of patients with at least one exacerbation (RR = 0.48; 95% CI, 0.38 to 0.61; NNTB = 6; 95% CI, 4 to 8), and reduced the mean number of asthma exacerbations per patient (MD = 0.44; 95% CI, 0.72 to 0.17), compared with placebo • Frequency of SAEs was similar between OMA (5.2%) and placebo (5.6%)	"Data indicate that the efficacy of an add-on OMA in patients with moderate-to-severe allergic asthma uncontrolled with recommended ICS treatment is accompanied by an acceptable safety profile."
Rodrigo G et al.[40] 2011, Argentina	• At the end of the CS reduction phase, patients taking OMA were more likely to be able to withdraw from CS completely compared with those taking placebo (RR = 1.80; 95% CI, 1.42 to 2.28; *P* = 0.00001) • OMA patients showed a decreased risk of asthma exacerbations at the end of the stable phase (RR = 0.57; 95% CI, 0.48 to 0.66; *P* = 0.0001) and adjustable-steroid phase (RR = 0.55; 95% CI, 0.47–0.64; *P* = 0.0001). Post-hoc analysis suggests this effect was	"Data indicate that the efficacy of add-on OMA in patients with moderate-to-severe allergic asthma is accompanied by an acceptable safety profile."

First Author, Publication Year, Country	Main Study Findings	Author's Conclusions
	independent of duration of treatment, age, severity of asthma, and risk of bias • The frequency of SAEs was similar in the OMA (3.8%) and placebo (5.3%) groups. However, injection-site reactions were more frequent in the OMA patients (19.9% vs. 13.2%)	
Lai T,[39] 2015	• OMA was associated with significant improvements in QoL and GETE • OMA also allowed patients to completely withdraw from ICS • OMA did not increase the number of AEs. However, there was insufficient evidence that OMA reduced the incidence of exacerbations, and the cost-effectiveness of OMA varied across studies	"Our data indicated that OMA use for at least 52 weeks in patients with persistent uncontrolled allergic asthma was accompanied by an acceptable safety profile, but it lacked effect on the asthma exacerbations. Use of OMA was associated with a higher cost than conventional therapy, but these increases may be cost-effective if the medication is used in patients with severe allergic asthma."

AE = adverse event; AQLQ = Asthma Quality of Life Questionnaire; CS = corticosteroid, including or oral; FEV_1 = forced expiratory volume in one second; GETE = global evaluation of treatment effectiveness; HQOL = health-related quality of life; ICS = inhaled corticosteroid; IgE = immunoglobulin E; MD = mean difference; NNTB = number needed to treat to benefit; OMA = omalizumab; PEF = peak expiratory flow; QoL = quality of life; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event; SC = subcutaneous; vs. = versus.

TABLE 47: MAIN STUDY FINDINGS AND AUTHORS' CONCLUSIONS IN OBSERVATIONAL STUDIES

First Author, Publication Year	Main Study Findings	Author's Conclusions
Braunstahl et al. (2013)[33]	EXpeRience was a two-year, international, single-group, open-label, observational registry that evaluated real-world effectiveness, safety, and use of OMA therapy in 943 patients with uncontrolled persistent allergic asthma. Physician's GETE: 69.9% of patients were responders to OMA after 16 weeks. The proportion of patients with no clinically significant exacerbations increased from 6.8% to 54.1% and 67.3% at months 12 and 24, respectively. Symptoms and rescue medication use at month 24 were reduced by > 50% from baseline. Maintenance OCS use was lower at month 24 (14.2%) compared with month 12 (16.1%) and at baseline (28.6%). Overall, OMA had an acceptable safety profile.	"The results from eXpeRience indicate that OMA was associated with improvements in outcomes in patients with uncontrolled persistent allergic asthma; these improvements were consistent with the results of clinical trials.
Braunstahl et al. (2013)[34]	Results: A total of 943 patients (mean age: 45 years; female: 64.9%) were included in the registry; 263 of them were receiving maintenance OCS at baseline. The proportion of patients taking maintenance OCS was markedly lower at months 12 (16.1%) and 24 (14.2%) than at baseline (28.6%; intention-to-treat population). GETE: 64.2% were responders (excellent or good response); 30.7% were non-responders (moderate, poor, or worsening response); 5.1% had no assessment. The frequency of SAEs was comparable to that seen in controlled trials of OMA.	"OMA use is associated with an OCS-sparing effect in patients with uncontrolled persistent allergic asthma in the real-world setting."
Braunstahl et al. (2014)[32]	Overall, the mean (SD) number of asthma-related medical health care uses per patient decreased from 6.20 (6.97) during the pre-treatment period to 1.00 (1.96) and 0.50 (1.28) at months 12 and 24, respectively. The mean (SD) number of work or school days missed due to asthma was also lower at month 12 (3.50 [17.28] and 1.60 [4.28], respectively) and month 24 (1.00 [4.66] and 1.90 [5.46], respectively) compared with the pre-treatment period (26.40 [49.61] and 20.70 [27.49], respectively). The nature and frequency of SAEs in the eXpeRience registry were comparable to that seen in interventional clinical trials with OMA.	"The results of the eXpeRience registry indicate that OMA is associated with reductions in health care utilization, and in the number of days of absence from work or school in patients with uncontrolled persistent allergic asthma in the real-world setting."

First Author, Publication Year	Main Study Findings	Author's Conclusions
Brusselle et al. (2009)[29]	• n = 158 patients; mean age of 48.17 ± 17.18 years; female: 53.8%. Despite being treated with high-dose ICS and LABA, all patients experienced frequent symptoms and had exacerbations in the past year. • At 16 weeks, > 82% had good/excellent GETE (*P* values < 0.001), > 82% had an improvement in total AQLQ scores of ≥ 0.5 points (*P* < 0.001), and > 91% were severe exacerbation-free (*P* < 0.001). • At 52 weeks, > 72% had a good/excellent GETE rating (*P* < 0.001), > 84% had improvements in total AQLQ score of ≥ 0.5 points (*P* < 0.001), > 56% had minimally important improvements in EQ-5D utility scores (*P* = 0.012), and > 65% were severe exacerbation-free (*P* < 0.001). Significant reductions in health care utilization compared with the one year prior to treatment were noted.	"The PERSIST study shows better physician-rated effectiveness, greater improvements in quality of life, greater reductions in exacerbation rates, and greater reductions in health care utilization than previously reported in efficacy studies. Under real-life conditions, OMA is effective as add-on therapy in the treatment of patients with persistent severe allergic asthma."
Chen et al. (2013[23]	• ICS use: at baseline, mean ± SD total daily ICS doses was 680 mcg/d ± 414 mg/d in new starts, 642 mcg/d ± 431 mcg/d in established users, and 548 mcg/d ± 382 mcg/d in non-OMA patients. At year 2, total ICS dose decreased in 65% of new starts (mean ± SD change, –393 mcg/d ± 504 mcg/d), 57% of established users (–287 ± 492 mcg/d), and 54% of non-OMA patients (–232 mcg/d ± 431 mcg/d). • SABA use: at baseline, SABA use (puffs per day) for new starts, established users, and non-OMA patients was 1.9, 1.3, and 1.4, respectively. At year 2, SABA use decreased in 65% of new starts, 55% of established users, and 54% of non-OMA patients. • At year 2, LTM dose decreased in 52% of new starts, 44% of established users, and 40% of non-OMA patients.	"OMA therapy initiation was associated with decreased doses of ICS, SABA, and LT Mover 2 years of follow-up for the majority of patients in a "real-world" cohort study of moderate to-severe allergic asthma patients."
Domingo et al. (2011)[22]	• Follow-up period: the treatment benefited 83.9% (26/31) of the cohort; OCS were reduced from 7.19 mg ± 11.1 mg, to 3.29 mg ± 11.03 mg (*P* = 0.002), and withdrawn in 74.2% of patients. FEV_1 (% predicted) was 64.4% ± 22.7% at the beginning and 62.9% ± 24.3% at the end. IgE at entry was 322.2 IU/mL ± 334.2 IU/mL and increased 2.34-fold. • There were three groups of patients. The first (n = 17) had been receiving OCS at entry and their accumulated dose of OCS was progressively decreased. Another group (n = 10) included patients who had quit OCS before starting OMA, although they had not been instructed to do so, their OCS use at the end of follow-up was zero. The third group (n = 4)	"In our series, a substantial, safe decrease in OCS requirements was observed due, at least to some extent, to OMA therapy. OCS was withdrawn in three-quarters of the patients. We were unable to identify a factor able to predict which patients would benefit most from OMA treatment."

First Author, Publication Year	Main Study Findings	Author's Conclusions
	did not benefit from OMA treatment. The only relevant side effect was a flu-like syndrome that required discontinuation of treatment in one patient.	
Janson et al. (2015)[24]	N = 289 patients; of these, 83% on the two-week dosing regimen (n = 152) and 65% on the four-week dosing regimen (n = 137) missed at least one dose. More frequent dosing was associated with a larger number of missed doses. Older age (odds ratio per year 1.02; 95% CI, 1.01 to 1.03) and lower pre-bronchodilator % predicted FEV_1 (< 76; odds ratio 1.88; 95% CI, 1.09 to 3.24) were independent predictors of good adherence.	"Adherence to OMA is characterized by distinct factors. Patients receiving the four-week dosing regimen achieved better adherence than those treated every two weeks. Improved adherence could be associated with better asthma control. Age and lung function could interact with dosing frequency to affect patient adherence, thus warranting prospective planning at the time of prescribing to support long-term adherence."
Korn et al. (2010)[26]	• Compared with baseline, OMA reduced the rate of severe exacerbations in patients age 50 years or older by 68.9% ($P < 0$ .001) and in patients younger than 50 years by 75.4% ($P < 0.001$). After four months, there was a marked reduction in daily asthma symptoms and nocturnal awakenings by 67.8% and 72.6% in the older patients, and by 79.3% and 82.5% in the younger patients, respectively ($P < 0.001$, all four comparisons). • In 60% of patients aged 50 years or older, lung function improved compared with 69% of patients younger than 50 years. Efficacy of OMA was rated as "excellent" or "good" by most physicians in patients 50 years or older (68.4%), and in patients younger than 50 years (76.8%, $P = 0.05$ elderly vs. younger). • AEs were reported in 35.5% of patients aged 50 years or older and 32.1% of patients younger than 50 years. There was a higher rate of discontinuation of OMA therapy in older patients (20.9% vs. 11.1%, $P = 0.006$).	"The present study confirms the clinical efficacy of OMA in patients with severe allergic asthma irrespective of age in a real-life setting outside the OMA trial program."
Lafeuille et al. (2012)[95]	Based on a retrospective analysis of health insurance claims over a one-year period (N = 644 patients; mean age: 49.9; female: 59.2%), OMA was associated with the following: • a 48.6% reduction in the proportion of patients with one or more asthma-related ER visits (pre- vs. post-OMA: 21.4% vs. 11.0%; $P < 0.001$) • a 40.8% reduction in asthma-related hospitalizations (25.0% vs. 14.8%, respectively, $P < 0.001$)	"The current analysis showed that OMA treatment initiation was associated with significant reductions in ER visits, hospitalizations, and corticosteroid use."

First Author, Publication Year	Main Study Findings	Author's Conclusions
	• a reduction in ICS use by 41.9% of patients ($P < 0.001$) • a reduction in OCS use by 53.3% of patients ($P < 0.001$).	
Namazy et al. (2014)[25]	Of 169 pregnancies with known outcomes (median exposure during pregnancy: 8.8 months), there were 156 live births of 160 infants (4 twin pairs), 1 fetal death/stillbirth, 11 spontaneous abortions, and 1 elective termination. Among 152 singleton infants, 22 (14.5%) were born prematurely. Of 147 singleton infants with weight data, 16 (10.9%) were small for gestational age. Among 125 singleton full-term infants, 4 (3.2%) had low birth weights. Overall, of 20 infants with confirmed congenital anomalies, 7 (4.4%) had one major defect. No pattern of anomalies was observed.	"To date, proportions of major congenital anomalies, prematurity, low birth weight, and small size for gestational age observed in the EXPECT registry are not inconsistent with findings from other studies in this asthma population. Recognizing the small sample size available, no apparent increased birth prevalence of major anomalies or patterns of major anomalies has been observed."
Niven et al. (2008) [27]	In total, 164 patients (OMA, n = 115; control, n = 49) were receiving high-dose ICS plus a LABA. The annual asthma exacerbation rate was significantly reduced by 59% in the OMA group vs. control group (1.26 vs. 3.06; $P < 0.001$). The ADRI rate was significantly reduced by 40% in the OMA group compared with the control group (5.61 vs. 9.40; $P < 0.05$). Significant improvements were also seen in % predicted FEV_1 (71% vs. 60%; $P < 0.001$); change from baseline in asthma symptom scores (6.7 vs. 0.5; $P < 0.05$); and mini-AQLQ overall score (1.32 vs. 0.17; $P < 0.001$). In OMA-treated patients, 71/102 (70%) were judged to have responded to therapy. In these mini-AQLQ-assessed responders, the exacerbation rate was reduced by 64% vs. control (1.12 vs. 3.06; $P < 0.001$), and the ADRI rate was reduced by 50% vs. control (4.71 vs. 9.40; $P < 0.01$). Per cent predicted FEV_1 (73% vs. 60%; $P < 0.001$), change from baseline in asthma symptom scores (8.1 vs. 0.5; $P < 0.001$), and mini-AQLQ overall score (1.81 vs. 0.17; $P < 0.001$) were also further significantly improved vs. control.	"Adding OMA to BSC is efficacious in patients with inadequately controlled severe persistent allergic asthma despite high-dose ICS plus a LABA (EU label population), with further efficacy observed in patients judged to have responded to therapy which may more accurately illustrate the actual benefit of OMA therapy in clinical practice. The naturalistic setting of this study confirms the benefits observed in double-blind randomized clinical trials."
Nopp et al. (2010)[28]	• Three years after treatment with OMA was stopped, 12/18 patients reported improved or unchanged asthma compared with ongoing OMA treatment. • Most of the patients were in a stable clinical condition, 16/18 had not increased nightly asthma attacks, and 14/18 had little or no increase in medication. The CD-sens to cat was still significantly lower ($P < 0.02$) than untreated patients with allergic asthma and lower than expected from their serum IgE antibody levels.	"Most of the patients in this study had, still three years after closing of six years OMA treatment, a surprisingly mild and stable asthma. Interestingly, the observed, considerable, down regulation of basophil allergen sensitivity, CD-sens, most likely representing mast cell allergen sensitivity, contributed to the clinical results."

First Author, Publication Year	Main Study Findings	Author's Conclusions
Schumann et al. (2012)[31]	Measured outcome variables improved after a 16-week OMA treatment: • FEV_1: +13.7% predicted $P < 0.05$ • exacerbation rate: –74.9% $P < 0.0001$ • days of absence : –92.1% $P < 0.001$ • ACQ: –43.7% $P < 0.0001$) • IGETE: 78.8% as "excellent" or "good" (responder) Responders demonstrated better improvement of FEV_1, exacerbation rate, days of absence, ACQ and reduction of OCS compared with non-responders.	"Results of effectiveness strongly suggest that the efficacy demonstrated in RCTs can be transposed to a clinical practice-related setting."
Siergiejko et al. (2011)[30]	A total of 82 patients were receiving maintenance OCS at baseline (OMA/OAT: n = 59; OAT: n = 23). Change from baseline in mean maintenance OCS dose at week 32 was significantly greater in the OMA/OAT group compared with the OAT group (–45% vs. +18.3%; $P = 0.002$). In the OMA/OAT group, 37 patients (62.7%) reduced/stopped OCS use at week 32, compared with 7 patients (30.4%) receiving OAT ($P = 0.013$). Improvements in other efficacy outcomes were seen at week 32 in the OMA/OAT group, irrespective of OCS use.	"In this open-label study of patients with severe allergic asthma, OMA/OAT therapy reduced maintenance OCS use, compared with OAT alone. Improvements in efficacy measures were observed in the OMA/OAT group, irrespective of OCS change."
Zazalli et al. (2015)[35]	The percentage of patients with well-controlled asthma (ACT score, > 20) who were treated with OMA (n = 4,930) increased from 45% at baseline to 61% at month 60, compared with 49% (baseline) and 67% (month 60) for the non–OMA-treated cohort (n = 2,779). For new starters of OMA (n = 576), the percentage with well-controlled asthma increased from 25% at baseline to 51% at month 6, and to 60% at month 60. Patients in the OMA-treated cohort and those in the non–OMA-treated cohort experienced a reduction in asthma-related work, school, and activity impairment. The amount of improvement in asthma control achieved and the reduction in asthma-related work, school, and activity impairment were similar, regardless of asthma severity.	"Conclusion: On average, patients in the Evaluating Clinical Effectiveness and Long-Term Safety in Patients With Moderate-to-Severe Asthma observational study who initiated OMA experienced clinically significant improvement in asthma control, which was observed within six months and persisted for five years."

ACT = Asthma Control Test; ADRI = asthma deterioration–related incident; AE = adverse event; AQLQ = Asthma Quality of Life Questionnaire; BSC = best standard care; CD-sens = basophil allergen threshold sensitivity; CI = confidence interval; EQ-5D = EuroQol 5-Dimensions Questionnaire; FEV_1 = forced expiratory volume in one second; GETE = global evaluation of treatment effectiveness; ICS = inhaled corticosteroid; IgE = immunoglobulin E; IGETE = investigator's global evaluation of treatment effectiveness; LABA = long-acting $beta_2$ agonist; LT = leukotriene; LTM = leukotriene modifier; OAT = optimal asthma therapy; OCS = oral corticosteroid; OMA = omalizumab; RCT = randomized control trials; SABA = short-acting $beta_2$-agonist; SAE = serious adverse event; SC = subcutaneous; SD = standard deviation; vs. = versus.

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