CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

INDACATEROL ACETATE-GLYCOPYRRONIUM BROMIDE-MOMETASONE FUROATE (ENERZAIR BREEZHALER)

(Novartis Pharmaceuticals Canada Inc.)

Indication: Asthma maintenance, adults

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Abbreviations

ACQ-7	7-item Asthma Control Questionnaire
AE	adverse event
AQLQ	Asthma Quality of Life Questionnaire
CI	confidence interval
COPD	chronic obstructive pulmonary disease
e-diary	electronic diary
EQ-5D	EuroQol 5-Dimensions
ED-5D-5L	EuroQol 5-Dimensions 5-Levels
EMA	European Medicines Agency
FAS	full-analysis set
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GINA	Global Initiative for Asthma
HRQoL	health-related quality of life
ICC	intraclass correlation coefficient
ICS	inhaled corticosteroid
IRT	interactive response technology
ITC	indirect treatment comparison
LABA	long-acting beta2 agonist
LAMA	long-acting muscarinic antagonist
LOCF	last observation carried forward
LS	least squares
MID	minimal important difference
MMRM	mixed model repeated measures
MPPI	minimal patient perceivable improvement
NMA	network meta-analysis
PEF	peak expiratory flow
PPS	per-protocol set
QMF	indacaterol-mometasone furoate

QVM	indacaterol acetate-glycopyrronium bromide-mometasone furoate
RCT	randomized controlled trial
SABA	short-acting beta2 agonist
SAE	serious adverse event
SAMA	short-acting muscarinic antagonist
SD	standard deviation
SE	standard error
SF	salmeterol-fluticasone propionate
SGRQ	St. George's Respiratory Questionnaire
TIO	tiotropium
URTI	upper respiratory tract infection
VAS	Visual Analogue Survey
WDAE	withdrawal due to adverse event
WPAI	Work Productivity and Activity Impairment Questionnaire

Executive Summary

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

Table 1: Submitted for Review

Item	Description
Drug product	Indacaterol acetate-glycopyrronium bromide-mometasone furoate (Enerzair Breezhaler; 150 mcg indacaterol acetate, 50 mcg glycopyrronium bromide, and 160 mcg mometasone furoate) inhalation powder hard capsules for oral inhalation
Indication	A maintenance treatment for asthma in adult patients not adequately controlled with a maintenance combination of a LABA and a medium or high dose of an ICS who have experienced 1 or more asthma exacerbations in the previous 12 months
Reimbursement request	As per indication
Health Canada approval status	NOC received
Health Canada review pathway	Standard
NOC date	July 2, 2020
Sponsor	Novartis Pharmaceuticals Canada Inc.

ICS = inhaled corticosteroid; LABA = long-acting beta$_2$ agonist; NOC = Notice of Compliance.

Source: Enerzair product monograph.[1]

Introduction

Asthma is a common chronic respiratory disorder characterized by chronic airway inflammation.[2] Patients with asthma typically present with paroxysmal or persistent symptoms of wheezing, dyspnea, chest tightness or cough, and variable expiratory airflow that are associated with airway hyper-responsiveness to endogenous and exogenous stimuli.[2] The 2018 Canadian Community Health Survey reported that 9.4% of Canadians (excluding those residing in the territories) between the ages of 12 and 17 have been diagnosed with asthma by a health professional.[3] Pharmacological management of asthma typically involves a combination of reliever therapy and controller therapy. The reliever therapy is provided to all patients with asthma, and typically includes fast-acting versions of either a short-acting beta2 agonist (SABA) or long-acting beta2 agonist (LABA), which can be used for rapid relief of asthma symptoms but should be used concurrently with an inhaled corticosteroid (ICS). Controller therapies, predominantly ICSs, are used as maintenance therapy, and aim to reduce airway inflammation, control symptoms, and reduce future exacerbations.[2] Patients may add on additional therapies, such as long-acting muscarinic antagonists (LAMAs), as needed and tailored to the needs of individual patients.

Enerzair Breezhaler (indacaterol acetate-glycopyrronium bromide-mometasone furoate [QVM]; 150 mcg indacaterol acetate, 50 mcg glycopyrronium bromide, and 160 mcg mometasone furoate [150 mcg/50 mcg/160 mcg]) is a combination product composed of a LABA, LAMA, and an ICS. It is available as a dry powder (in hard capsules) for oral inhalation.[1] Health Canada approved QVM on July 2, 2020, for the following indication: as a maintenance treatment for asthma in adult patients not adequately controlled with a maintenance combination of a LABA and a medium or high dose of an ICS who experienced 1 or more asthma exacerbations in the previous 12 months.[1] Further, it is not indicated for the relief of acute bronchospasm. As described in the product monograph, it should be administered at the same time each day using the Breezhaler inhaler, and it is to be used regularly, even when patients are asymptomatic.

The objective of this review was to perform a systematic review of the beneficial and harmful effects of QVM (150 mcg/50 mcg/160 mcg) administered once daily by oral inhalation for the maintenance treatment of asthma in adult patients not adequately controlled with a maintenance combination of a LABA and a medium or high dose of an ICS who experienced 1 or more asthma exacerbations in the previous 12 months.

Stakeholder Engagement

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

Patient Input

Two patient groups, the Lung Health Foundation (formerly called the Ontario Lung Association) and Asthma Canada, provided input for use in this review as well as the CADTH review of indacaterol-mometasone furoate (QMF). The Lung Health Foundation gathered information for its submission through telephone interviews conducted in May 2020 with 3 patients living with asthma. In 2020, Asthma Canada gathered information for its submission through interviews (N = 24) and an online survey (N = 200) to inform a 2014 report titled "Severe Asthma: The Canadian Patient Journey."[4]

Patients reported that their daily activities and exercise were limited by asthma, and the majority of respondents stated that it should not be a reason for avoiding physical exertion. Two-thirds of respondents to the online survey indicated that asthma affects their social activities and interactions with others, and more than half of respondents specified that it affected their performance at work or school. "Asthma affects most aspects of my day-to-day life. There are days that I struggle to keep my symptoms controlled." The same sentiments were echoed in the patient input from the Lung Health Foundation. Patients also reported that living with asthma caused them to miss days of school or work in the previous year, and they expressed concern about the number of visits to the emergency department (ED) and hospitalizations related to asthma. Two-thirds of respondents to Asthma Canada's survey indicated that they felt stigmatized due to their asthma at 1 point in time.

Broadly, both patient groups expressed a desire for improved quality of life and lung function. Key outcomes identified as important to patients included those related to increased lung function, reduced exacerbations, and a reduction of symptoms such as shortness of breath, coughing, and fatigue. Additionally, patients expressed a desire for improved ability to exercise (higher energy level), and an increased ability to fight colds and infections. Asthma Canada reported that 45% of respondents wanted easier management of severe asthma through novel medications, and 29% wanted a reduction in fear and anxiety in managing their asthma. According to the Lung Health Foundation, when patients are deciding to try a new medication, they most often consider administration of medication, side effects, and financial burden.

Clinician Input

According to the clinical expert, the goals of asthma therapy can be achieved in many patients with available medications and treatments; standard treatment with an ICS or ICS-LABA can be optimized such that asthma control can be achieved. None of these therapies cure asthma, but for many patients long-term control can be achieved. The majority of patients with uncontrolled asthma can regain control with these treatments by focusing

upon medication adherence, self-management techniques, and inhaler education, and approximately 5% of patients who are poorly controlled despite such efforts will remain on and require additional pharmacological treatment. In addition, the clinical expert reported that these patients may benefit from add-on therapies to the standard ICS-LABA inhalers.

The clinical expert identified QVM for potential use for Global Initiative for Asthma (GINA) Step 5 therapy, noting that there are currently no single-inhaler combinations of an ICS/LABA/LAMA for asthma. Despite this, the clinical expert indicated that the drug under review, QVM, did not offer a paradigm shift in asthma management, but may offer increased convenience of use. The clinical expert noted that the negative aspect of this agent is the delivery device, Breezhaler, which is not a multi-dose instrument but requires a capsule inserted each day. The expert also noted that in general, a delivery device should be personalized based on patient preference and capability. Some patients might benefit from a metered-dose inhaler, and some from a multi-dose dry-powder inhaler. The clinical expert added that the patients who would be least suitable for treatment with QVM would be those who are unable or unwilling to use the delivery device, and those unwilling or unable to tolerate an ICS.

Regarding the assessment of response to treatment, the clinical expert reported that the clinical response as measured by gaining asthma control and improving lung function best determines who should continue to receive this medication, noting that this can be done with tools such as the 7-item Asthma Control Questionnaire (ACQ-7), but it is more often assessed less rigorously by non-validated, clinical questioning. How often treatment response should be assessed varies with disease severity, as per feedback from the clinical expert. Regarding discontinuation of treatment, the clinical expert noted that asthma therapies should not be discontinued as it is a life-long disease for adults. Treatment can be escalated or de-escalated based on symptoms and lung function measurements. Lastly, the clinical expert suggested that patients who are unstable, who require frequent courses of oral corticosteroids, who require ED treatment, or who do not respond to standard therapy should be seen by specialists.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

Two randomized controlled trials (RCTs) conducted by the sponsor, IRIDIUM (N = 3,092) and ARGON (N = 1,425), met the inclusion criteria for the CADTH systematic review. The IRIDIUM study was a phase III, multi-centre, randomized, double-blind, double-dummy, parallel-group study with a 52-week treatment period; however, the primary outcome assessment was conducted at week 26. Patients were randomized at a ratio of 1:1:1:1:1 to 1 of 5 treatment groups: QVM 150 mcg/50 mcg/160 mcg once daily, QVM 150 mcg/50 mcg/80 mcg once daily, QMF 150 mcg indacaterol and 320 mcg mometasone furoate (150 mcg/320 mcg) once daily, QMF 150 mcg indacaterol and 160 mcg mometasone furoate (150 mcg/160 mcg) once daily, or salmeterol-fluticasone propionate (SF) 50 mcg salmeterol and 500 mcg fluticasone propionate (50 mcg/500 mcg) twice daily. The ARGON study was a phase IIIb, multi-centre, randomized, partially blinded, parallel-group, noninferiority, open-label, active-controlled study with a 24-week treatment period. Patients were randomized at a 1:1:1 ratio to 1 of the 3 treatment arms: QVM 150 mcg/50 mcg/160 mcg once daily, QVM 150 mcg/50 mcg/80 mcg once daily, or SF 50 mcg/500 mcg twice daily plus tiotropium (TIO) 5 mcg once daily (SF + TIO). The 2 trials evaluated the efficacy and safety of QVM

(150 mcg/50mcg/80 mcg and 150 mcg/50mcg/160 mcg) via Breezhaler in adults (≥ 18 years of age) with asthma compared to the active comparators described above. The 150 mcg/50 mcg/80 mcg dose of QVM was not summarized in this review as it *was not* aligned with the approved Health Canada indication.

Patients included in the 2 trials were required to have a diagnosis of asthma that was inadequately controlled (ACQ-7 score ≥ 1.5 at baseline), a pre-bronchodilator forced expiratory volume in 1 second (FEV_1) of at least 60% but less than 80% (IRIDIUM trial) or less than 85% (ARGON trial) of the predicted normal, and demonstrate bronchodilator reversibility. Patients also had at least 3 months of experience using a medium- or high-dose LABA-ICS that was stable for at least 1 month prior to screening. The primary and key secondary objectives of the IRIDIUM trial were to demonstrate superiority of QVM 150 mcg/50 mcg/160 mcg to QMF 150 mcg/320 mcg, both delivered by the Breezhaler device, in terms of FEV_1 and the ACQ-7, respectively, after 26 weeks of treatment in patients with asthma. The primary objective of the ARGON trial was to demonstrate noninferiority (using a noninferiority margin of 0.25 points) of QVM 150 mcg/50 mcg/160 mcg to SF + TIO in terms of the Asthma Quality of Life Questionnaire (AQLQ) after 24 weeks of treatment. Other outcomes such as asthma exacerbations as measured by the annual rate of exacerbations by exacerbation category, health-related quality of life (HRQoL), rescue medication use, and other measures of lung function (forced vital capacity [FVC] and mean morning and evening peak expiratory flow [PEF]) were also reported in the 2 studies. In addition, nocturnal awakening, days of missed work (IRIDIUM trial only), and health care resource utilization were reported, as well as safety results.

Efficacy Results

Key efficacy results are summarized in Table 2. In the IRIDIUM study, between 40.2% and 50.5% of patients experienced an asthma exacerbation and 21.8% to 23.2% experienced a severe exacerbation over 52 weeks. A numerically greater proportion of patients in the SF treatment group experienced exacerbations (all severities, 50.5%) and severe exacerbations (29.7%) compared to patients in the QVM group (40.2% overall, 21.8% severe). In the ARGON study, 24.2% to 26.5% of patients experienced an asthma exacerbation; 12.4% to 13.4% were severe. No more than 2% of patients in any treatment group required hospitalization in the 2 studies. In the IRIDIUM study, the rate ratio at a 95% confidence interval (CI) for all exacerbations was 0.79 (95% CI, 0.66 to 0.96; P = 0.016) for QVM compared to QMF, and 0.60 (95% CI, 0.50 to 0.72; P < 0.001) for QVM compared to SF. The rate ratio for severe exacerbations was 0.78 (95% CI, 0.61 to 1.00; P = 0.050) and 0.58 (95% CI, 0.45 to 0.73; P < 0.001) for QVM compared to QMF and SF, respectively. In the ARGON study, the rate ratio for all exacerbations was 0.81 (95% CI, 0.62 to 1.06; P = 0.123) for QVM compared to SF + TIO. The rate ratio for severe exacerbations was 1.14 (95% CI, 0.79 to 1.64; P = 0.494) for QVM compared to SF + TIO.

The primary outcome in the IRIDIUM study, change from baseline in trough FEV_1 at week 26, demonstrated an improvement with QVM that was statistically significant, with a treatment difference of 0.07 L (95% CI, 0.03 to 0.10; P < 0.001) versus QMF, and 0.12 L (95% CI, 0.09 to 0.15; P < 0.001) versus SF. The treatment effect was maintained at week 52 (data not shown). In the ARGON study, QVM was superior to SF + TIO for the change from baseline in trough FEV_1, with a treatment difference of 0.10 L (95% CI, 0.05 to 0.15; P < 0.001) at week 24. Only the comparison to QMF in the IRIDIUM study at week 26 controlled for multiplicity for these outcomes. The clinical significance of these differences is uncertain because of the lack of data for the between-group minimally important difference (MID) for FEV_1 in asthma when an active comparator is studied.

The primary outcome in the ARGON study, change from baseline on the AQLQ total score at week 24, demonstrated noninferiority of QVM to SF + TIO based on a treatment-group difference of 0.07 (95% CI, −0.03 to infinity; P < 0.001). In the IRIDIUM study, the least squares (LS) mean (standard error change from baseline in AQLQ total core at end of treatment (week 52) ranged from 0.81 (standard error [SE] = 0.04) to 0.87 (SE = 0.04) across treatment groups; no treatment-group differences were observed between QVM and either QMF or SF.

The key secondary outcome in the IRIDIUM study was the change from baseline in the ACQ-7 score at week 26. The treatment difference at week 26 between QVM and QMF was 0.01 points (95% CI, –0.07 to 0.09; P = 0.729) and between QVM and SF it was −0.09 points (95% CI, −0.17 to −0.01; P = 0.034). A numerically greater treatment-group difference was reported for both comparisons at week 52. In the ARGON study, the change from baseline ACQ-7 score at week 24 was −0.12 points (95% CI, −0.22 to −0.03; P = 0.004) between QVM and SF + TIO, in favour of QVM. As with trough FEV_1, the only comparison that controlled for multiplicity was the ACQ-7 score at week 26 in the IRIDIUM study.

The following outcomes were also reported in the 2 studies, but they were not included in the statistical testing procedure. The results for the proportion of patients with a change of at least 0.5 points in the ACQ-7, rescue medication use (mean daily number of puffs used and percentage of rescue medication–free days), and nocturnal awakening were aligned with the results for HRQoL and ACQ-7; no difference between treatment groups was observed. [redacted], which were only reported in the IRIDIUM study. [redacted] QVM and SF + TIO for the St. George's Respiratory Questionnaire (SGRQ) in the ARGON study. [redacted] for QVM versus SF in the IRIDIUM study corresponded to [redacted].

Harms Results

Adverse events (AEs) were reported by 74.1% to 78.8% of patients in the IRIDIUM study and 51.6% to 52.3% of patients in the ARGON study. Between 3.8% and 9.3% of patients in treatment groups from both studies reported at least 1 serious adverse event (SAE). In the IRIDIUM study, 2.1% to 3.4% of patients withdrew from treatment due to AE, as did less than 1% of patients in treatment groups in the ARGON study. Overall, the frequency of AEs, SAEs, and withdrawals due to advents (WDAEs) did not suggest any imbalances between treatment groups in the IRIDIUM and ARGON studies. Seven deaths were reported between the 2 trials, most frequently in the QMF treatment group in the IRIDIUM study (n = 4). Two deaths were reported in the QVM treatment group in the IRIDIUM study, and 1 was reported in the SF + TIO treatment group in the ARGON study. None of the deaths were caused by asthma-related events or considered related to the study drug.

Infections (systemic and local) were the most frequently reported notable harms ([redacted] to [redacted] of patients in the IRIDIUM study and [redacted] to [redacted] of patients in the ARGON study), followed by local systemic effects (ranging from [redacted] to [redacted] across studies) and cardiac or vascular disorders (ranging from [redacted] to [redacted] across studies). Specific AEs were infrequent and did not suggest any imbalances between treatment groups.

Table 2: Summary of Key Results From Pivotal and Protocol-Selected Studies

	IRIDIUM trial			ARGON trial	
	QVM 150 mcg/ 50 mcg/160 mcg N = 619	QMF 150 mcg/ 320 mcg N = 618	SF 50 mcg/ 500 mcg N = 618	QVM 150 mcg/ 50 mcg/ 160 mcg N = 476	SF 50 mcg/ 500 mcg + TIO 5 mcg N = 476
Number of patients with asthma exacerbations during the treatment period by exacerbation category, n – FAS					
All (mild, moderate, severe)	247 (40.2)	256 (41.9)	309 (50.5)	115 (24.2)	126 (26.5)
Severe	134 (21.8)	142 (23.2)	182 (29.7)	[redacted]	[redacted]
Requiring hospitalization	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Causing permanent discontinuation of study drug	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rate of asthma exacerbations (all: mild, moderate, and severe) during the treatment period[a] – FAS					
Number contributing to analysis	615	611	612	[redacted]	[redacted]
Annualized rate (95% CI)	0.74 (0.64 to 0.85)	0.93 (0.82 to 1.06)	1.23 (1.08 to 1.39)	0.70 [redacted]	0.86 [redacted]
Rate ratio (95% CI)	0.79 (0.66 to 0.96) vs. QMF 150 mcg/320 mcg 0.60 (0.50 to 0.72) vs. SF 50 mcg/500 mcg			0.81 (0.62 to 1.06)	
P value[b]	0.016 vs. QMF 150 mcg/320 mcg < 0.001 vs. SF 50 mcg/500 mcg			0.123	
Rate of severe asthma exacerbations during the treatment period[a] – FAS					
Number contributing to analysis	615	611	612	[redacted]	[redacted]
Annualized rate (95% CI)	0.26 (0.22 to 0.31)	0.33 (0.28 to 0.39)	0.45 (0.39 to 0.53)	0.36 [redacted]	0.32 [redacted]
Rate ratio (95% CI)	0.78 (0.61 to 1.00) vs. QMF 150 mcg/320 mcg 0.58 (0.45 to 0.73) vs. SF 50 mcg/500 mcg			1.14 (0.79 to 1.64)	
P value[b]	0.050 vs. QMF 150 mcg/320 mcg < 0.001 vs. SF 50 mcg/500 mcg			0.494	
Trough FEV_1 (L), change from baseline at week 26 (IRIDIUM) or week 24 (ARGON)[c] – FAS					
Number contributing to analysis	541	527	506	385	372
Baseline, raw mean	1.72 (NR)	1.75 (NR)	1.73 (NR)	1.87 (NR)	
End-of-treatment time point (week 26), LS mean (SE)	2.05 (0.01)	1.98 (0.01)	1.93 (0.01)	NR	NR
Change from baseline, LS mean (SE)	0.32 [redacted]	0.26 [redacted]	0.20 [redacted]	0.33 [redacted]	0.24 [redacted]
Treatment-group difference vs. control (95% CI)	0.07 (0.03 to 0.10) vs. QMF 150 mcg /320 mcg 0.12 (0.09 to 0.15) vs. SF 50 mcg /500 mcg[b]			0.10 (0.05 to 0.15)	
P value	< 0.001 vs. QMF 150 mcg /320 mcg < 0.001 vs. SF 50 mcg/500 mcg[b]			< 0.001[b]	
AQLQ total score, change from baseline at week 52 (IRIDIUM)[c] or week 24 (ARGON)[d] – FAS					
Number contributing to analysis	552	547	546	453	435

	IRIDIUM trial			ARGON trial	
	QVM 150 mcg/ 50 mcg/160 mcg N = 619	QMF 150 mcg/ 320 mcg N = 618	SF 50 mcg/ 500 mcg N = 618	QVM 150 mcg/ 50 mcg/ 160 mcg N = 476	SF 50 mcg/ 500 mcg + TIO 5 mcg N = 476
Baseline, raw mean	4.67	4.71	4.71	4.67	
End-of-treatment time point (week 52), LS mean (SE)	5.56 (0.04)	5.54 (0.04)	5.50 (0.04)	0.83 (0.07)	0.75 (0.07)
Change from baseline, LS mean (SE)	0.87 (0.04)	0.85 (0.04)	0.81 (0.04)	NR	NR
Treatment-group difference vs. control (95% CI)	0.02 (−0.08 to 0.12) vs. QMF 150 mcg/320 mcg 0.06 (−0.04 to 0.16) vs. SF			NI: 0.07 (−0.03 to infinity), P < 0.001 0.07 (−0.03 to 0.17)	
P value	0.690 vs. QMF 150 mcg/320 mcg[b] 0.232 vs. SF[b]			0.152	
ACQ-7, change from baseline week 26 (IRIDIUM)[c] or week 24 (ARGON)[d] – FAS					
Number contributing to analysis	566	562	562	452	436
Baseline, raw mean	2.52			2.61	
End-of-treatment time point (week 26), LS mean (SE)	1.54 (0.03)	1.53 (0.03)	1.63 (0.03)	NR	NR
Change from baseline, LS mean (SE)	−0.98 (0.03)	−0.99 (0.03)	−0.89 (0.03)	−1.17 (0.05)	−1.05 (0.05)
Treatment-group difference vs. control (95% CI)	0.01 (−0.07 to 0.09) vs. QMF 150 mcg/320 mcg −0.09 (−0.17 to −0.01) vs. SF[b]			−0.12 (−0.22 to −0.03)	
P value	0.729 vs. QMF 150 mcg/320 mcg 0.034 vs. SF[b]			0.004[b]	
Harms, n (%) – safety set					
AEs	458 (74.4)	454 (74.1)	487 (78.8)	249 (52.3)	245 (51.6)
SAEs	46 (8.2)	52 (9.3)	39 (7.0)	18 (3.8)	19 (4.0)
WDAEs (from study treatment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deaths	2 (0.3)	4 (0.6)	0	0	1 (0.2)
Notable harms, n (%) – safety set					
Infections (systemic and local)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac and vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood glucose increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood glucose decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypoglycemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anticholinergic effects[e]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bone markers (blood alkaline phosphatase increased)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HPA axis suppression[f]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Systemic steroid effects[g]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	IRIDIUM trial			ARGON trial	
	QVM 150 mcg/ 50 mcg/160 mcg N = 619	QMF 150 mcg/ 320 mcg N = 618	SF 50 mcg/ 500 mcg N = 618	QVM 150 mcg/ 50 mcg/ 160 mcg N = 476	SF 50 mcg/ 500 mcg + TIO 5 mcg N = 476
Local systemic effects[h]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ACQ-7 = 7-item Asthma Control Questionnaire; AE = adverse event; AQLQ = Asthma Quality of Life Questionnaire; CI = confidence interval; CS = corticosteroid; CV = cardiovascular; FAS = full-analysis set; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HPA = hypothalamic-pituitary-adrenal; LAMA = long-acting muscarinic antagonist; LS = least squares; MI = myocardial infarction; MID = minimal important difference; MMRM = mixed model repeated measures; NI = noninferiority; NR = not reported; PEF = peak expiratory flow; QMF = indacaterol-mometasone furoate; QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate; SAE = serious adverse event; SABA = short-acting beta2 agonist; SAMA = short-acting muscarinic antagonist; SE = standard error; SF = salmeterol-fluticasone; SGRQ = St. George's Respiratory Questionnaire; SOB = shortness of breath; TIO = tiotropium; vs. = versus; WDAE = withdrawal due to adverse event.

[a] Generalized linear model assuming a negative binomial distribution with the following covariates: FEV_1 prior to inhalation and FEV_1 15 to 30 minutes post-inhalation of salbutamol-albuterol (components of SABA reversibility).

[b] P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

[c] MMRM with the following covariates: baseline value for the outcome analyzed (e.g., FEV_1, AQLQ, ACQ-7), baseline-by-visit interaction, FEV_1 prior to inhalation and FEV_1 within 15 to 30 minutes post-inhalation of salbutamol-albuterol (components of SABA reversibility).

[d] MMRM with corresponding baseline value for the outcome analyzed as the covariate.

[e] Includes dry mouth, constipation, urinary retention, bowel obstruction, dilated pupils, blurred vision, increased heart rate, and decreased sweating.

[f] Includes secondary glucocorticoid insufficiency and adrenal hypercorticism (Cushing disease, hyperglycemia, glycosuria).

[g] Includes glaucoma, loss of vision, cataracts, osteoporosis, increased appetite, insomnia, and adrenal insufficiency.

[h] Includes cough, oral thrush, nosebleeds, oropharyngeal pain and discomfort, dysphonia, and larynx irritation.

Source: Clinical Study Reports for IRIDIUM[5] and ARGON.[6]

Critical Appraisal

Several of the outcomes identified in the CADTH systematic review protocol were reported in the studies that were analyzed outside of the statistical testing procedure and therefore need to be interpreted with consideration of type I error. This includes outcomes related to asthma exacerbations and HRQoL (except for AQLQ in the ARGON study), both of which were outcomes that were noted in this review as important to patients and clinically relevant for clinicians. Further, the use of trough FEV_1 as the primary outcome in the IRIDIUM study is not considered a sufficient measure of efficacy when used alone for a new controller treatment for asthma.[7] The design of the IRIDIUM study included change in ACQ-7 score, a measure of asthma control, as a key secondary outcome, which increases the clinical relevance of the study's design. Study duration and time points for outcome assessment have an important impact on the results of drug trials in asthma. Such trials would ideally be designed for at least 12 months, in part because of the seasonal variation in the condition. The primary and key secondary outcomes were assessed at 26 weeks of treatment in the IRIDIUM study, which may be too short to comprehensively assess asthma control in patients; the study was designed to assess outcomes at week 52 as well. The ARGON study was designed as a 24-week trial.

The partially blinded design of the ARGON study was a limitation given the primary outcome measure, HRQoL via the AQLQ, is more subjective in nature and vulnerable to potential bias due to knowledge of treatment allocation and open-label use of the active comparator. The study design poses the same issues on the other reported outcomes, as well as reporting of harms in the ARGON study.

The 2 trials were limited in their generalizability to clinical practice in Canada. First, only the IRIDIUM trial included study sites in Canada. Although the inclusion and exclusion criteria

of the trials were generally consistent with other asthma clinical trials, patients enrolled in the IRIDIUM and ARGON studies were not representative of patients in Canadian clinical practice, according to the clinical expert consulted for this review. The requirement of having to demonstrate bronchodilator reversibility for inclusion in both of the clinical trials would, in the opinion of the clinical expert, also exclude a significant portion of patients who would be candidates for treatment with an ICS-LABA-LAMA combination product. Lastly, the clinical expert consulted on this review noted that FEV_1 is generally not useful for making decisions regarding the selection of treatments for asthma, and the ACQ-7 is generally not used in clinical practice, particularly by family physicians, who would be expected to be prescribing QVM in clinical practice.

Indirect Comparisons

The sponsor provided a feasibility report for the purposes of assessing the viability of conducting a network meta-analysis (NMA) for indirect treatment comparisons (ITCs) among QVM, QMF, and other dual and triple asthma therapies for the treatment of patients with uncontrolled asthma. The sponsor concluded that it was not feasible due to extensive heterogeneity in the literature, specifically study populations, study duration, and varying definitions of exacerbation. The CADTH assessment of the feasibility report likewise noted the degree of clinical, methodological, and statistical heterogeneity that would make conducting an NMA challenging.

Other Relevant Evidence

Description of Studies

Study 1304 (N = 94) is a multi-centre, open-label, single-arm, 52-week treatment study designed to assess the safety and tolerability of once-daily QVM administered at 150 mcg/50 mcg/160 mcg in Japanese patients with inadequately controlled asthma. Patients were required to have had a diagnosis of persistent asthma for 1 year prior to study initiation based on the GINA 2016 guidelines. A key difference from the IRIDIUM and ARGON studies was that patients were not required to have a history of asthma exacerbations in the past year.

At baseline, approximately [redacted] of patients had not had an asthma exacerbation in the previous year, [redacted] of patients had never smoked, and the mean (standard deviation [SD]) baseline ACQ-7 score was [redacted]. Almost all patients [redacted] reported prior use of an ICS-LABA combination other than at a low-dose strength. Further, the mean (SD) reversibility at baseline was [redacted] as a percentage increase or [redacted] as an increase in litres.

Efficacy Results

Study 1304 was not designed to evaluate efficacy, although lung function (pre-dose FEV_1), asthma control (ACQ-7), and the proportion of patients with an asthma exacerbation were reported.

Harms Results

The incidence and severity of treatment-emergent AEs was the primary outcome of Study 1304; statistical testing was not conducted. Briefly, [redacted] of patients experienced an AE, and [redacted] patients experienced an SAE, with [redacted] patients [redacted] which withdrew from the study due to an AE. Overall, once-daily QVM therapy appeared to be well tolerated

up to 52 weeks; however, a large proportion of patients [redacted] experienced a local infection.

Critical Appraisal

The main limitations of Study 1304 include the open-label and single-arm study design.

Conclusions

Treatment with QVM 150 mcg/50 mcg/160 mcg demonstrated superiority to treatment with high-dose ICS-LABA comparators, QMF 150 mcg/320 mcg, and SF 50 mcg/500 mcg, in terms of the change from baseline in trough FEV_1 after 26 weeks of treatment and other measures of lung function; however, it failed to demonstrate superiority in terms of asthma control based on the ACQ-7 after 26 weeks. The corresponding results of the noninferiority trial, which compared QVM 150 mcg/50 mcg/160 mcg to a loose triple ICS-LABA + LAMA combination and SF 50 mcg/500 mcg + TIO 5 mcg, were aligned with the IRIDIUM study in terms of these outcomes. Treatment with QVM 150 mcg/50 mcg/160 mcg was noninferior to SF 50 mcg/500 mcg + TIO 5 mcg in terms of HRQoL based on the change from baseline measured with the AQLQ after 24 weeks of treatment. The results of the other HRQoL outcomes included in both trials were aligned with this finding in that no treatment differences in HRQoL were observed. In terms of asthma-related exacerbations, QVM appears to offer a benefit compared to ICS-LABA combinations, and no difference in benefit to SF 50 mcg/500 mcg + TIO 5 mcg; however, the results related to exacerbations in the 2 trials are subject to uncertainty due to a lack of statistical testing or control for multiplicity. There were insufficient data to determine whether the combination of QVM delivered via the Breezhaler device provides superior adherence to treatment or fewer critical errors in drug administration compared with other ICS-LABA + LAMA comparators administered separately.

Serious adverse events and WDAEs were reported infrequently in all treatment groups. Seven deaths were reported between the 2 trials, most of which were caused by cardiovascular events, and none were adjudicated as asthma-related or related to the study drug. No new safety signals were identified in the 52-week, open-label, safety-extension study.

The included evidence on the effectiveness and safety of QVM compared to other alternative combination therapies is limited to the 2 RCTs that have been described, compromising the ability to sufficiently assess the advantages and disadvantages of QVM in the broader context of currently available treatments for asthma. The available evidence suggests that QVM 150 mcg/50 mcg/160 mcg is an option for patients with poorly controlled severe asthma (GINA Steps 4 to 5) who require a LAMA added to ICS-LABA therapy.

Introduction

Disease Background

Asthma is a common chronic respiratory disorder characterized by chronic airway inflammation.[2] The disease is described by a range of heterogeneous phenotypes, and symptoms that may differ by presentation, etiology, and pathophysiology. Patients with asthma typically present with paroxysmal or persistent symptoms of wheezing, dyspnea, chest tightness or cough, and variable expiratory airflow that are associated with airway hyper-responsiveness to endogenous and exogenous stimuli (e.g., exercise; viral respiratory infections; or exposure to certain allergens, irritants, or gases).[2] Patients describe impacts on their ability to work or go to school, exercise, and socialize, as well as fatigue due to interrupted sleep.

Based on data from the 2018 Canadian Community Health Survey, a total of 211,100 (9.4%) Canadians (excluding those residing in the territories) between the ages of 12 years and 17 years reported being diagnosed by a health professional as having asthma.[3] The estimated number of persons 12 years and older living with asthma was 2.6 million (8.3%).[3] According to the 2019 Annual Asthma Survey Report by Asthma Canada more than 3.8 million Canadians (approximately 10.8% of the population) currently live with asthma.[8]

A diagnosis of asthma is based on presentation of respiratory symptoms typical of asthma (previously described), a detailed patient history or examination for asthma, and spirometry/PEF with a reversibility test. The severity of asthma is assessed retrospectively, following at least 2 to 3 months of treatment.[2] In clinical practice, disease severity may be classified as mild, moderate, or severe, depending on the therapies needed to achieve control of asthma, and may change over time. In clinical trials, severity is typically based on a prescribed treatment step. A summary of the GINA steps is provided in Table 3.

Table 3: Summary of Asthma Management (GINA Steps)

GINA step	Preferred controller	Preferred reliever
Step 1	As-needed low-dose ICS-formoterol	As-needed low-dose ICS-formoterol
Step 2	Daily low-dose ICS or as-needed low-dose ICS-formoterol	
Step 3	Low-dose ICS-LABA Option: medium-dose ICS, or low-dose ICS + LTRA	As-needed low-dose ICS-formoterol for patients prescribed maintenance and reliever therapy
Step 4	Medium-dose ICS-LABA Option: High-dose ICS, add-on TIO, or add-on LTRA	
Step 5	High-dose ICS-LABA Option: add low-dose OCS, but consider side effects	

GINA = Global Initiative for Asthma; ICS = inhaled corticosteroid; LABA = long-acting beta2 agonist; LTRA = leukotriene receptor antagonist; OCS = oral corticosteroid; TIO = tiotropium.

Source: Global Strategy for Asthma Management and Prevention.[2]

Standards of Therapy

The primary goals of asthma management are to achieve control of asthma symptoms and minimize future risk, such as asthma exacerbations, morbidity, mortality, and adverse effects related to treatment.[2,9,10] Given the heterogeneous phenotypes of the disease, treatment for asthma is individualized to suit the needs of each patient's circumstances.

The Canadian Thoracic Society guidelines for asthma management describe asthma control in terms of the following characteristics:

- frequency of daytime and nighttime symptoms
- frequency of exacerbations
- frequency of absences from work or school due to asthma
- ability to complete normal physical activity
- need for a fast-acting beta2-agonist
- FEV_1 or PEF
- PEF diurnal variation.[9]

Pharmacological management of asthma typically involves a combination of reliever therapy and controller therapy, with an option to add on additional therapies tailored to the needs of individual patients. Reliever therapy is provided to all patients with asthma, and typically includes fast-acting SABAs or LABAs, which can be used for rapid relief of asthma symptoms but should be used concurrently with an ICS. Controller therapies, predominantly ICSs, are used as maintenance therapies, and aim to reduce airway inflammation, control symptoms, and reduce future exacerbations.[2] The choice of an appropriate controller therapy is based on the individual's current asthma control. According to guidelines published by the Canadian Thoracic Society, a stepwise approach to pharmacological therapy is recommended to achieve and maintain asthma control.[9] This involves escalating pharmacological treatment, as necessary, to gain control (i.e., step up) and reduce treatment (i.e., step down) to the minimum dose and number of medications required for maintenance when possible.[9]

The use of ICSs has been and remains the cornerstone of pharmacotherapy for the maintenance of asthma. Current Canadian and international guidelines recommend that patients with asthma in all age groups be initiated with a low-dose ICS.[2,9] If control is not gained or maintained, second-line agents may be added, such as a LABA or leukotriene receptor antagonist, or the ICS dose can be titrated upward.[2,9] A LAMA may also be used as add-on therapy for patients with asthma that is not well-controlled with a combination of an ICS and LABA.[2] Prior to the availability of QVM, TIO was the only available LAMA with an indication for asthma. Additional information about TIO is provided in Table 4. The most severely affected patients can be prescribed oral corticosteroids or immunomodulatory therapies.[5] The specific choice of medication takes the following factors into consideration: age of the patient, symptoms, lung function, risk factors for exacerbations, patient preference, and practical issues such as those related to administration and accessibility of medication. Table 4 provides a list of ICS-LABA combinations and LAMAs available in Canada.

Much asthma-related morbidity is reportedly associated with poor management from under-used or poor adherence to maintenance therapy.[11] As a result, non-pharmacological therapy such as patient education serves an essential role in the management of asthma. Additional non-pharmacological therapies include control of asthma triggers through identification and avoidance, and monitoring for changes in symptoms or lung function.[10]

Drug

Enerzair Breezhaler (QVM, 150 mcg/50 mcg/160 mcg) is a combination product composed of a LABA, LAMA, and ICS. It is available as a dry powder (in hard capsules) for oral inhalation.[1] It is indicated as a maintenance treatment for asthma in adult patients not adequately controlled with a maintenance combination of a LABA and a medium or high dose of an ICS who experienced 1 or more asthma exacerbations in the previous 12 months.[1] Further, it is not indicated for the relief of acute bronchospasms. As described in the product monograph, it should be administered at the same time each day using the Breezhaler inhaler, and it is to be used regularly, even when patients are asymptomatic.

Regarding the mechanism of action, indacaterol is a LABA that stimulates an enzyme (adenyl cyclase) that catalyzes the conversion of adenosine triphosphate to cyclic-3′,5′-adenosine monophosphate, an increase in which causes relaxation of bronchial smooth muscle. When inhaled, indacaterol acts locally in the lung as a bronchodilator and has a rapid onset and long duration of action.[1]

Glycopyrronium is a LAMA or anti-cholinergic with high affinity for muscarinic receptors M1, M2, and M3. It allows the airways to dilate by blocking bronchoconstriction via acetylcholine on smooth muscle cells of the airways. Glycopyrronium has a rapid onset of action and a long duration of action, the latter partly due to sustained drug concentrations in the lungs.[1]

Mometasone furoate is a synthetic corticosteroid with high affinity for glucocorticoid receptors. Although the mechanism of action is not completely understood, it is likely that the effects of mometasone furoate inhibit the release of mediators of the inflammatory cascade, thus providing local anti-inflammatory properties.[1]

The sponsor requested that QVM be reimbursed as per the Health Canada–approved indication. A Notice of Compliance from Health Canada was received on July 2, 2020.

Table 4: Key Characteristics of Drug Under Review and Comparators

	QVM (Enerzair Breezhaler)[1]	Budesonide-formoterol fumarate dihydrate (Symbicort)[12]	Fluticasone furoate-vilanterol (Breo Ellipta)[13]	SF (Advair pMDI and Advair Diskus)[14]	Mometasone-formoterol fumarate dihydrate (Zenhale)[15]	TIO (Spiriva Respimat)[16]
Mechanism of action	Indacaterol and glycopyrronium: bronchodilation by separate mechanisms; mometasone furoate: anti-inflammatory	ICS: anti-inflammatory effects LABA: stimulation of beta2 in the lungs leads to bronchodilation				Relaxation of the airways causing bronchodilation
Indication[a]	Proposed: once-daily maintenance treatment for asthma, and to reduce asthma exacerbations, in adults not adequately controlled with a maintenance combination of a LABA and an ICS	Treatment of asthma in patients 12 years and older with reversible obstructive airways disease	Indicated for the once-daily maintenance treatment of asthma in patients aged 18 years and older with reversible obstructive airways disease	Maintenance treatment of asthma in patients with reversible obstructive airways disease	Treatment of asthma in patients 12 years and older with reversible obstructive airway disease	Add-on maintenance treatment in adult patients with asthma who remain symptomatic on a combination of an ICS (equivalent to, but not limited to ≥ 500 mcg fluticasone per day or ≥ 800 mcg budesonide per day) and a LABA and who experienced ≥ 1 severe exacerbation in the previous year
Route of administration	Oral inhalation					
Recommended dose	150 mcg/50 mcg/ 160 mcg once-daily	100 mcg/6 mcg, 200 mcg/6 mcg, or 400 mcg/12 mcg, twice daily	100 mcg/25 mcg or 200 mcg/25 mcg, once daily	25 mcg/125 mcg or 25 mcg/250 mcg, twice daily	50 mcg/5 mcg, 100 mcg/5 mcg, or 200 mcg/5 mcg, twice daily	2.5 mcg/actuation: 2 actuations inhaled once daily
Serious adverse effects or safety issues	Contraindicated in patients hypersensitive to this drug or any ingredient in the formulation	Can cause sore mouth, sore throat, dysphonia, or oral thrush (can be reduced by rinsing	Use with caution in patients with cardiovascular disorders; can cause sore mouth, sore	Can cause sore mouth, sore throat, dysphonia, or oral thrush (can be reduced by rinsing	Contraindicated in patients with cardiac tachyarrhythmia. Can cause dysphonia, oral thrush, tremor,	Contraindicated in patients hypersensitive to this drug or any ingredient in the formulation;

	QVM (Enerzair Breezhaler)[1]	Budesonide-formoterol fumarate dihydrate (Symbicort)[12]	Fluticasone furoate-vilanterol (Breo Ellipta)[13]	SF (Advair pMDI and Advair Diskus)[14]	Mometasone-formoterol fumarate dihydrate (Zenhale)[15]	TIO (Spiriva Respimat)[16]
	Warnings: deterioration of disease; should not be used to treat acute asthma symptoms; asthma-related AEs and exacerbations may occur; anticholinergic effect related to glycopyrronium; can also cause cardiovascular effects, hyperglycemia, hypokalemia, and bronchospasms	mouth or using a spacer), nervousness, tremor, tachycardia, palpitations	throat, dysphonia, or oral thrush (can be reduced by rinsing mouth or using a spacer); nervousness, tremor, tachycardia, or palpitations	mouth or using a spacer); nervousness, tremor, tachycardia, or palpitations	tachycardia, or palpitations	should not be used as rescue medication for the relief of acute bronchospasm; can cause: dry mouth, metallic taste; mydriasis and glaucoma if released into eye

AE = adverse event; ICS = inhaled corticosteroid; LABA = long-acting beta2 agonist; pMDI = pressurized metered-dose inhaler; QVM =indacaterol acetate-glycopyrronium bromide-mometasone furoate; SF = salmeterol-fluticasone propionate; TIO = tiotropium.

[a] Health Canada–approved indication.

Source: Product monographs.[1,12-17]

Stakeholder Engagement

Patient Group Input

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

About the Patient Groups and Information Gathered

CADTH presented a joint patient input call for the review of QVM and indacaterol-mometasone furoate. Two patient groups provided input for use in both reviews: the Lung Health Foundation (formerly the Ontario Lung Association) and Asthma Canada.

Both patient groups are registered charities that support research and provide programs and services to patients and their caregivers. The Lung Health Foundation aims to help fill the gaps in prevention and diagnosis of lung disease in Canada, while Asthma Canada aims to educate and advocate for Canadians living with asthma. Furthermore, Asthma Canada provides support to the Asthma Canada Member Alliance, an organization that reaches more than 7,000 people living with asthma and allergies, caregivers, health care providers, and other interested participants from all regions of Canada. A disclosure of any conflicts of interest for both organizations is available on the CADTH website.

The Lung Health Foundation gathered information for its submission through 3 telephone interviews with patients living with asthma completed in May 2020. The 3 patients were females over the age of 30 and residing in Ontario. The Lung Health Foundation commissioned a certified respiratory educator to review the sections related to experience living with asthma, available treatments, and outcomes. Asthma Canada gathered information for its submission through interviews and an online survey, which was conducted to inform a report in 2014 titled “Severe Asthma: The Canadian Patient Journey.”[4] A total of 24 patients participated in interviews, 75% of whom were between 30 and 60 years old, and the majority (81%) were female. The online survey had 200 respondents from across Canada. Nearly half (47%) of the respondents were employed on a full-time basis, and 9% said a disability prevented them from working. In addition, Asthma Canada conducted an online survey specifically to provide evidence for this patient evidence submission (available April 27, 2020, to May 8, 2020). This resulted in 192 respondents, 171 (89%) of whom were asthma patients and 21 (11%) of whom were caregivers. The majority of the respondents were female (86%), and half (50%) of the respondents resided in Ontario. Other respondents resided in British Columbia (15%), Alberta (13%), Quebec (7%), Nova Scotia (4%), Manitoba (3%), Saskatchewan (3%), New Brunswick (3%), Newfoundland and Labrador (2%), and Yukon (1%). Two of the respondents were from outside of Canada.

Disease Experience

Both patient groups described the following symptoms and challenges associated with asthma: wheezing, coughing, shortness of breath, a tight sensation in the chest, fatigue, and difficulty fighting colds and infections. It was also noted that symptoms can occur in a chronic manner and during an acute severe attack, typically called an exacerbation.

More than 70% of the respondents to Asthma Canada’s online survey (associated with its 2014 report) reported that their daily activities and exercise were limited by asthma, although 89% of patients expected that asthma should not prevent them from participating in daily activities. Two-thirds of respondents indicated that asthma affects their social activities and

interactions with others, and more than half of respondents specified that it affected their performance at work or school. “Asthma affects most aspects of my day-to-day life. There are days that I struggle to keep my symptoms controlled.” The same sentiments were echoed in the patient input from the Lung Health Foundation. Asthma Canada indicated that approximately 40% of respondents said their asthma affected them a “great deal,” 30% said that asthma caused them to miss days of school or work in the previous year, with two-thirds missing 5 days or more and one-third missing more than 10 days. “I must monitor my triggers and adjust my routine accordingly.” Furthermore, half of respondents had to visit the ED in the previous year due to asthma, with one-third of respondents visiting more than once, and one-fifth needing hospitalization. Lastly, asthma can take a psychological and emotional toll on patients, with two-thirds of respondents to Asthma Canada’s survey indicating that they felt stigmatized due to their asthma at 1 point in time.

Experience With Treatment

The Lung Health Foundation reported that respondents in telephone interviews have had experience with budesonide/formoterol (Symbicort), albuterol (Ventolin), fluticasone/salmeterol (Advair), TIO (Spiriva), prednisone, and montelukast (Singular). Respondents had also tried mometasone (Nasonex), cetirizine (Reactine), and other antihistamines for allergies as needed. The respondents indicated that these treatments provide some relief for fatigue, shortness of breath, wheezing, coughing, and reduced energy. Both of the patient groups reported side effects of medications experienced by patients, including dry mouth or thrush, hoarseness, appetite loss, impact on mood, difficulty sleeping, increased heart rate, and “feeling jittery/shaky.” Patients with severe asthma are often dependent on long-term oral corticosteroids to provide some symptom relief. However, these medications come with an array of systemic side effects, including cataracts, bone density variations, adrenal suppressions, and emotional or psychological side effects such as irritability, agitation, and insomnia. Asthma Canada indicated that HRQoL improves in the severe asthma population when patients add a supplementary non-oral corticosteroid medication.

When patients interviewed by the Lung Health Foundation were asked whether their current asthma medication affected their life in any other way, 1 respondent indicated cost burden was an issue, and another reported lack of sleep due to uncontrolled asthma affecting their ability to perform well at work. All respondents expressed dissatisfaction with the ability of their current treatments to improve their ability to exercise.

Three main challenges with the currently available treatments were identified in the 2014 report published by Asthma Canada: patient adherence, financial burden, and side effects.[4] Regarding patient adherence, many (number not available) of the respondents do not carry their short-acting reliever with them, and more than half of respondents do not regularly take their long-term controller medication. Asthma Canada reported that patients often believe they do not need to continue taking their medications when they are asymptomatic. Other reasons for nonadherence included lack of efficacy (continued exacerbations) and side effects. Regarding the financial burden, approximately one-third of patients had skipped filling a prescription because they were unable to afford it. More than one-third of survey respondents had household incomes of less than $50,000, or were unable to work due to their asthma, thus even having to pay a small percentage of the medication can be a significant financial concern. “My doctors help me with the cost by giving me samples of most of my inhalers, but when I have to pay for them…I have to take on extra work to help pay for my medication.” Regarding side effects in the severe asthma population, Asthma

Canada corroborated the fact that it is often the side effects that can regularly disrupt activity levels and social and work interactions, eventually leading to a lower HRQoL.

No patients identified by the Lung Health Foundation or Asthma Canada had experience with QVM or QMF treatments under review.

Improved Outcomes

Broadly, both patient groups expressed a desire for improved HRQoL and lung function. When asked in Asthma Canada's online survey what outcomes patients would like improved, 101 respondents (53%) indicated increased lung function, and 51% said reduced exacerbations. According to patient input received from the Lung Health Foundation, key outcomes related to asthma treatment patients would like addressed include a reduction of shortness of breath, coughing, and fatigue. Additionally, respondents from both patient groups indicated they wanted an improved ability to control day-to-day symptoms, an improved ability to exercise (higher energy level), and an increased ability to fight colds/infections.

Furthermore, 45% of respondents to Asthma Canada's survey wanted easier management of severe asthma through novel medications, and 29% indicated they want a reduction in fear and anxiety in managing their asthma. Patient input received from the Lung Health Foundation indicated that patients wanted a reduced financial burden.

Both patient groups highlighted that patients currently have to make trade-offs to manage their asthma. Asthma Canada indicated that patients typically have to trade off mild side effects to manage their asthma. For patients living with severe asthma these side effects can regularly disrupt activity levels, including social and work interactions, and can lead to a lower HRQoL. The Lung Health Foundation indicated that patients often trade off cost and likelihood of effectiveness, with one patient noting, "My doctor once said that I could try adding another medication into the mix to help with management, but noted that it was more expensive and only worked in a relatively small percentage of patients. That didn't seem worth it."

Additional Considerations

When asked how important it is to know if you have taken your medication correctly, most respondents rated this importance as 9 out of 10. Moreover, 84% of respondents agreed that being able to combine medications into 1 device safely would be very beneficial to them.

When patients are deciding whether to try a new medication, the Lung Health Foundation reported that they most often consider administration of medication, side effects, and financial burden. Two respondents expressed that "having insurance that covers the cost of medication was the key reason they were taking the medications they were taking."

Clinician Input

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

Unmet Needs

The clinical expert described the primary goals of therapy, which are to maintain control of asthma as typified by the absence of asthma exacerbations and improvement in symptoms. Achieving these treatment goals will improve HRQoL. Additionally, therapy is aimed at preventing future risks, including preventing airway remodelling and limiting complications of current therapy. Finally, effective therapy can reduce the risk of asthma-related death.[18]

According to the clinical expert, the goals of asthma therapy can be achieved in many patients with available medications and treatments. None of these therapies cure asthma but, for many patients, long-term control can be achieved. Even patients with mild disease can experience exacerbations[19] with an annualized rate of 0.11 severe exacerbations per patient-year. The clinical expert stated that treatments are therefore needed to improve the outcomes of patients with few daily symptoms but still at risk for severe exacerbations. The expert indicated that the majority of patients with uncontrolled asthma can regain control with current treatments by focusing upon medication adherence, self-management techniques, and inhaler education, and that approximately 5% of patients who are poorly controlled despite such efforts will remain on and require additional treatment. The clinical expert shared that simplified inhaler regimens may improve adherence to ICS use and thereby improve asthma control, but there is little high-quality evidence to support this contention.[20] In addition, the expert stated that these patients may benefit from add-on therapies to standard ICS-LABA inhalers. Again, there is some weak evidence[20] that reducing the numbers of different inhalers may improve adherence to therapy and thereby improve clinical outcomes.

Place in Therapy

The clinical expert reported that the GINA guidelines now recommend starting the use of low-dose ICS whenever a beta-agonist reliever is used (GINA Step 1). With increasingly persistent symptoms (GINA Step 2), treatment includes either a daily low-dose ICS or as-needed low-dose ICS-formoterol.[21,22] Pharmacologic treatment can be escalated with increasingly persistent symptoms to include a daily low-dose ICS plus LABA (ICS-LABA, GINA Step 3) or to a daily medium-dose ICS-LABA (GINA Step 4). If a daily high-dose ICS-LABA (GINA Step 5) does not achieve control then additional pharmacologic treatments could include: low-dose oral corticosteroids, inhaled TIO, and/or biologic agents (e.g., anti–immunoglobin E or anti–interleukin 5 monoclonal antibodies) targeting specific pathways of the inflammatory cascade. Other pharmacologic agents that can be used as add-on therapy include a leukotriene receptor antagonist, theophylline, and long-term macrolide therapy, the latter treatment not having Health Canada approval. Non-pharmacologic treatment for severe asthma can include bronchial thermoplasty[23] in highly select individuals.

According to the clinical expert, QVM could be used for GINA Step 5 therapy. There are currently no single-inhaler combinations of ICS-LABA-LAMA for asthma. Despite this, the clinical expert indicated that the drug under review, QVM, did not represent a paradigm shift in asthma management, but may offer increased convenience of use. The clinical expert noted that the delivery device requires the patient to insert a capsule before each use rather than containing multiple doses. The clinical expert indicated that, based on experience, patients can have trouble removing the capsule from the packaging and there is a degree of inconvenience associated with the steps required to load the capsule and inhale a dose. There is no clear evidence on how much this could negatively affect adherence. The expert also noted that, when choosing among the available inhaled treatments, the delivery device

should be personalized for patient preference and capability. Some patients may benefit from a metered-dose inhaler and some from a multi-dose dry-powder inhaler.

Patient Population

The standard approaches to the diagnosis and management of asthma as outlined in the Canadian Thoracic Society Guidelines[9] and the recent GINA recommendations[2] are sufficient for identifying patients that would be best suited for treatment QVM according to the clinical expert. The clinical expert noted that patient history, physical examination, measurements of reversibility of airway obstruction and measurement of airway hyper-reactivity, if needed, are the mainstays of diagnosis. The expert also noted that additional tests to characterize the disease phenotype more carefully are usually helpful on the more-severe patients. Response to treatment and achieving asthma control then guides the specific combination of therapies provided to individuals. The clinical expert suspected that patients who would be least suitable for treatment with QVM would be those who are unable or unwilling to use the delivery device, and those unwilling or unable to tolerate an ICS.

The clinical expert reported that response, as measured by gaining asthma control and improving lung function, best determines who should continue to receive this medication. The expert also noted that there is some evidence that more careful phenotyping with exhaled nitric oxide or measurement of inflammatory cell–induced sputum could help guide therapy, but these options are usually reserved for patients who fail standard approaches to treatment.

Assessing Response to Treatment

The clinical expert stated that the outcomes used clinically are typically measurements of achieving asthma control. This can be quantified with validated tools such as the ACQ-7. It was noted that asthma control is often assessed less rigorously with routine clinical questioning. Reduction in nocturnal symptoms, increased physical activity, and reduction of rescue medication use is often used to assess achievement of control. Measurement of PEF at home or improvement of spirometric indices in an office provide additional information regarding treatment effectiveness. Finally, reduction in exacerbation frequency is a major sign of stabilization of disease.

How often treatment response should be assessed varies with disease severity, according to the clinical expert, who noted that some patients test PEF twice daily at home to measure response. Stable, well-controlled patients could be reviewed annually for response and for adverse effects. The clinical expert also reported that patients are often provided with a written action plan to allow them to control their disease with less medical supervision.

Discontinuing Treatment

According to the clinical expert, asthma therapies should not be discontinued because for adults, it is a life-long disease. Treatment can be escalated or de-escalated based upon symptoms and lung function measurements.

Prescribing Conditions

The clinical expert indicated that the majority of patients with asthma do not require input from a specialist. Patients who are unstable, who require frequent courses of oral corticosteroids, who require ED treatment, or who do not respond to standard therapy should be seen by specialists. These may include patients with GINA Step 5. The clinical expert also pointed out that QVM delivered via Breezhaler is administered at home.

Clinical Evidence

The clinical evidence included in the review of QVM is presented in 3 sections. The first section, the systematic review, includes pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those studies selected according to an a priori protocol. The second section is intended to include indirect evidence; however, no indirect evidence was submitted by the sponsor and no indirect evidence that met the selection criteria specified in the review was identified in the literature. The third section includes sponsor-submitted long-term extension studies and additional relevant studies that were considered to address important gaps in the evidence included in the systematic review.

Systematic Review (Pivotal and Protocol-Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of QVM (150 mcg/50 mcg/160 mcg) administered once daily by oral inhalation for the maintenance treatment of asthma in adult patients not adequately controlled with a maintenance combination of a LABA and a medium or high dose of an ICS who experienced 1 or more asthma exacerbations in the previous 12 months.

Methods

Studies selected for inclusion in the systematic review will include pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those meeting the selection criteria presented in Table 5.

Table 5: Inclusion Criteria for the Systematic Review

Patient population	Adults with asthma not adequately controlled with a maintenance combination of a LABA and a medium or high dose of an ICS who experienced 1 or more asthma exacerbations in the previous 12 months Subgroups: • Disease severity • Prior treatment experience • Asthma control
Intervention	Indacaterol-glycopyrronium bromide-mometasone furoate (150 mcg/50 mcg/160 mcg) for oral inhalation, administered once daily Delivered via the Enerzair Breezhaler inhalation device
Comparators	ICS + LABA ICS + LABA in combination with 1 of the following: • Tiotropium (or other LAMA) • LTRA
Outcomes	**Efficacy outcomes:** Acute asthma exacerbations[a] Change in pulmonary function[a] (i.e., FEV_1) Health-related quality of life[a] Asthma control Use of rescue medications Dyspnea[a]

	Nocturnal awakening Days of missed work or school[a] Patient adherence to regimen[a] Ease of use[a] Exercise tolerance[a] Health care resource utilization (e.g., hospitalizations, ED visits, physician visits) **Harms outcomes:** AEs,[a] SAEs, WDAEs, mortality Notable harms: infections (systemic and local), steroid effects (topical, systemic), cardiovascular events, anticholinergic effects, HPA axis suppression, bone markers, blood sugar levels
Study design	Published and unpublished phase III and IV RCTs

AE = adverse event; ED = emergency department; FEV_1 = forced expiratory volume in 1 second; HPA = hypothalamic-pituitary-adrenal; ICS = inhaled corticosteroid; LABA = long-acting beta2 agonist; LAMA = long-acting muscarinic antagonist; LTRA = leukotriene receptor antagonist; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

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

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the PRESS Peer Review of Electronic Search Strategies checklist (https://www.cadth.ca/resourceSFinding-evidence/press).[24]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's Medical Subject Headings, and keywords. The main search concepts were indacaterol glycopyrronium mometasone furoate. Clinical trial registries searched included the US National Institutes of Health's clinicaltrials.gov and the EU Clinical Trials Register.

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

The initial search was completed on June 16, 2020. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee on October 21, 2020.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters):[25] Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Clinical Trials Registries, and Databases (Free). Google was used to search for additional internet-based materials. In addition, the sponsor of the drug was contacted for information regarding unpublished studies. See Appendix 1 for more information on the grey literature search strategy.

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

Findings From the Literature

Two studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 6. A list of excluded studies is presented in Appendix 2.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

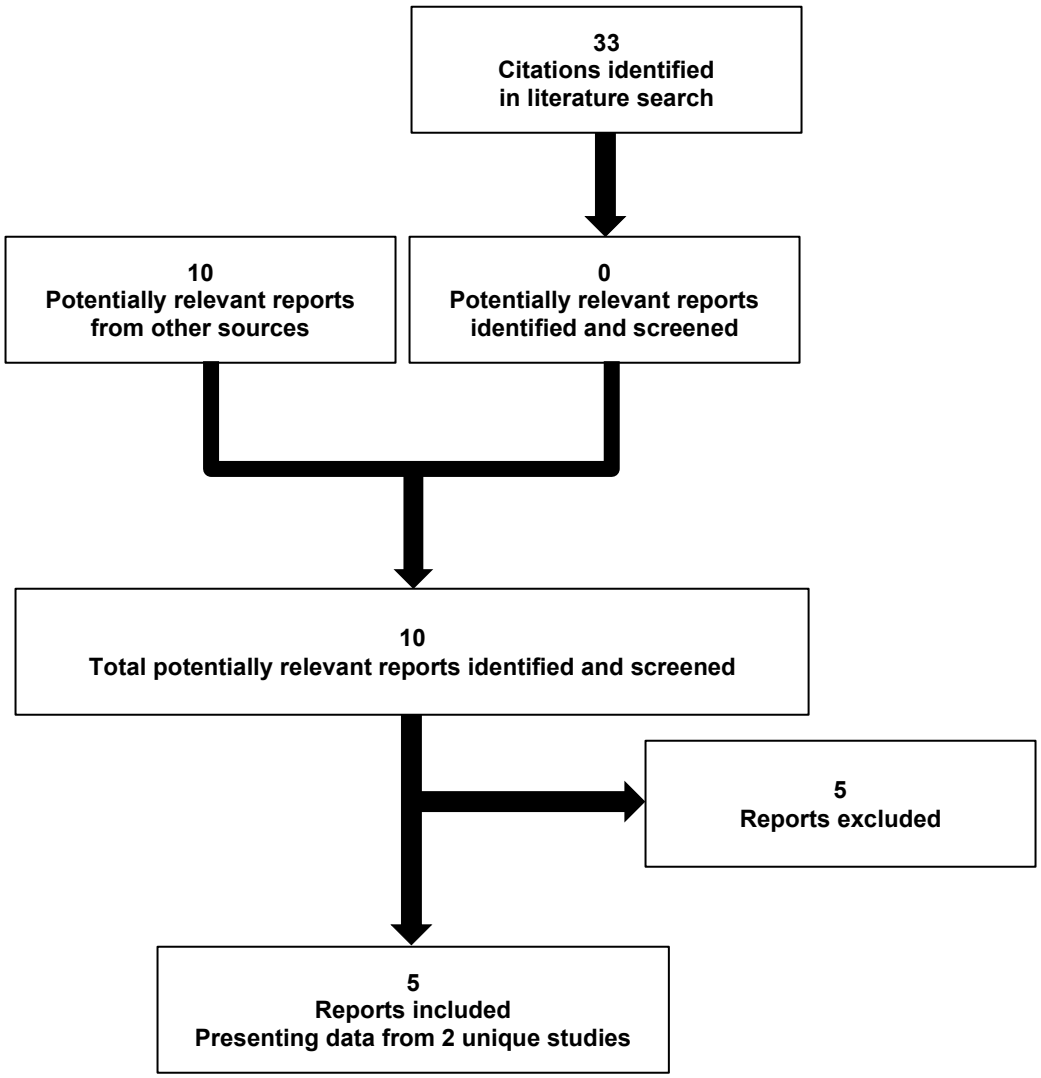


Table 6: Details of Included Studies

		IRIDIUM trial	ARGON trial
Designs and Populations	**Study design**	DB RCT, double-dummy, parallel-group, active-controlled	Phase IIIb RCT, partially blinded, parallel-group, NI, open-label, active-controlled
	Locations	415 sites in 41 countries, including: Canada, UK, Mexico, India, Europe, South America, East Asia, Africa	166 sites in 20 countries including: Central America, South America, Eastern Europe, East Asia, South Africa, Germany, Greece, Spain
	Randomized (N)	3,092	1,425
	Inclusion criteria	• Adults aged ≥ 18 years and ≤ 75 years old • Diagnosis of asthma for ≥ 1 year prior to visit 1 • Use of a medium- or high-dose LABA-ICS for ≥ 3 months and stable doses for ≥ 1 month prior to visit 1 • Symptomatic at screening despite treatment; patients with an ACQ-7 score ≥ 1.5 at visits 101 and 102 • Documented history of ≥ 1 asthma exacerbation requiring care from a physician, ED visit, or hospitalization in last 12 months prior to visit 1, and required oral corticosteroid • Pre-bronchodilator FEV_1 of < 80% of predicted normal value • Increase in FEV_1 of ≥ 12% and 200 mL within 15 to 30 min after administration of 400 mcg salbutamol plus 360 mcg albuterol at visit 101	• Adults aged ≥ 18 years old • Diagnosis of asthma for ≥ 6 months prior to visit 1, with current asthma severity step ≥ 4 • Use of an ICS-LABA for ≥ 3 months and at stable medium or high doses for ≥ 1 month prior to visit 1 • Symptomatic at screening despite treatment; patients with an ACQ-7 score ≥ 1.5 at visit 101 and 201 • Documented history of ≥ 1 asthma exacerbation requiring care from a physician, ED visit, or hospitalization in last 12 months prior to visit 1, and required systemic CS for at least 3 days • Pre-bronchodilator FEV_1 of < 85% of predicted normal value at visits 101 and 201 • Increase in FEV_1 of ≥ 12% and 200 mL within 15 to 30 min after administration of 400 mcg salbutamol plus 360 mcg albuterol at visit 101
	Exclusion criteria	• History of smoking within 6 months of visit 1 or for ≥ 10 pack-years[c] • Had an asthma attack/exacerbation requiring systemic steroids, hospitalization, or ED visit within 6 weeks of visit 1 • Required intubation for severe asthma attack or exacerbation • Patients with other clinical or chronic conditions, respiratory tract infections • Receiving the following without a washout period: LAMA, SAMA, fixed combinations of beta2 agonists and ICS, fixed combinations of a SABA and short-acting anticholinergic, SABA, or parenteral or intramuscular CS • Use of LAMA within 3 months prior to visit 1 • History of MI and other CV disease • Medicines in Table 9-4 and Table 9-5 • Unable to use inhalers used in the trial • History of substance abuse • Known history of nonadherence to medication or unable to complete electronic diary or questionnaires • Patients who did not maintain regular day/night, waking/sleeping cycles • Pregnant or nursing women	• History of smoking for ≥ 20 pack-years[c] • Diagnosis of chronic obstructive pulmonary disease • Had an asthma attack/exacerbation requiring systemic steroids, hospitalization, or ED visit within 6 weeks of visit 1, or between visit 1 and 201 • Required intubation for severe asthma attack or exacerbation • Patients with other clinical or chronic conditions, respiratory tract infections • Receiving the following without a washout period: LAMA, SAMA, fixed combinations of beta2 agonists and ICS, fixed combinations of a SABA and short-acting anticholinergic, SABA, parenteral CS, intramuscular CS • Use of LAMA within 3 months prior to visit 1 • History of MI within 12 months of visit 1 and other CV disease • Medicines in Table 9-4 and Table 9-5 • Patients on maintenance immunotherapy for allergies (with conditions) • Unable to use inhalers used in the trial • History of substance abuse • Known history of nonadherence to medication or unable to complete electronic diary or questionnaires

		IRIDIUM trial	ARGON trial
			• Patients who did not maintain regular day/night, waking/sleeping cycles • Pregnant or nursing women
	Intervention	QVM at 150 mcg/50 mcg/80 mcg and 150 mcg/ 50 mcg/160 mcg delivered via Breezhaler inhaler	QVM at 150 mcg/50 mcg/80 mcg and 150 mcg/ 50 mcg/160 mcg delivered via Breezhaler inhaler
DRUGS	**Comparator(s)**	QMF at 150 mcg/160 mcg and 150 mcg/320 mcg delivered via Breezhaler inhaler SF 50 mcg/500 mcg via Accuhaler	SF 50 mcg/500 mcg twice daily via Accuhaler plus TIO 5 mcg once daily via Respimat
DURATION	**Phase**		
	Screening	2 weeks	up to 1 week
	Run-in	2 weeks	2 weeks
	Double-blind	52 weeks	24 weeks
	Follow-up	30 days	1 week
OUTCOMES	**Primary end point**	Change from baseline in trough FEV_1 after 26 weeks of treatment	Change from baseline at week 24 for the AQLQ total score
	Secondary and exploratory end points	**Secondary:** ACQ-7 score after 26 weeks of treatment **Exploratory:** • Additional comparisons based on primary and secondary variables • Spirometry: trough FEV_1 at day 2 and 365, pre-dose trough FEV_1, post-dose trough FEV_1, pre- and post-dose FVC and FEF_{25-75} • ACQ-7 score at weeks 4, 12, and 52 • PEF: morning and evening values, mean over 26 weeks and 52 weeks; also summarized by 4-week intervals • Rescue medication: number of puffs per 12 hours, mean daily number of puffs over 26 weeks and 52 weeks, percent rescue medication–free days • Asthma symptoms: mean symptom score for SOB, wheeze, cough, chest tightness, hinder daily activities; daily symptom score; days, mornings, nights without symptoms • Asthma exacerbations: time to first exacerbation, time to first hospitalization, annual rate of exacerbations (and excluding patients requiring a CS after an exacerbation), duration of exacerbation in days, % of patients with ≥ 1 exacerbation, time to permanent study drug discontinuation due to exacerbation, total amounts (doses) of oral CS for exacerbations • AQLQ: mean score per domain, overall quality-of-life score, proportion of patients with 0.5 improvement from baseline	**Secondary:** • change from baseline in AQLQ domains (symptoms, emotions, exposure to environmental stimuli, activity limitation) • AQLQ total score, proportion of patients with ≥ 0.5 change from baseline • ACQ-7 mean score, change from baseline, proportion achieving MID • Spirometry: trough FEV_1 change from baseline, FVC, FEF_{25-75} **Exploratory:** • Rescue mediation: mean daily number of puffs over 24 weeks, % rescue medication–free days • PEF: average over 24 weeks, mean morning/evening PEF by 8-week intervals • Asthma symptoms: % days without daytime symptoms, % nights without awakenings, mean total daily symptom scores, % mornings without symptoms on rising • Asthma exacerbations: time to first exacerbation, time to first hospitalization, annual rate of exacerbations (and excluding patients requiring CS after exacerbation), duration of exacerbation in days, % of patients with ≥ 1 exacerbation, time to permanent study drug discontinuation due to exacerbation, total amounts (does) of oral CS for exacerbations • SGRQ scores • Treatment failure: proportion of patients • ACQ-5 score and proportion of responders

		IRIDIUM trial	ARGON trial
Notes	**Publications**	Kerstjens et al. (2020)[26]	Gessner et al. (2020)[27]

ACQ-5 = 5-item Asthma Control Questionnaire; ACQ-7 = 7-item Asthma Control Questionnaire; AE = adverse event; AQLQ = Asthma Quality of Life Questionnaire; CS = corticosteroid; DB = double-blind; ED = emergency department; FEV_1 = forced expiratory volume in 1 second; FEF_{25-75} = forced expiratory flow between 25% and 75% of the forced vital capacity; FVC = forced vital capacity; ICS = inhaled corticosteroid; LABA = long-acting beta2 agonist; MI = myocardial infarction; MID = minimally important difference; NI = noninferiority; SABA = short-acting beta2 agonist; SAMA = short-acting muscarinic antagonist; SF = salmeterol-fluticasone; SGRQ = St. George's Respiratory Questionnaire; TIO = tiotropium.

Note: Three additional reports were included.[26-28]

Source: Clinical Study Reports for IRIDIUM[5] and ARGON.[6]

Description of Studies

Two studies, IRIDIUM and ARGON, met the inclusion criteria for this review.

IRIDIUM Study

The IRIDIUM study was a multi-centre, randomized, double-blind, double-dummy, parallel-group study with a 52-week treatment period, conducted between December 2015 and October 2018. Patients were randomized using an interactive response technology (IRT) to 1 of 5 treatment groups at a ratio of 1:1:1:1:1 to QVM 150 mcg/50 mcg/160 mcg once daily, QVM 150 mcg/50 mcg/80 mcg once daily, QMF 150 mcg/320 mcg once daily, QMF 150 mcg/160 mcg once daily, or SF 50 mcg/500 mcg twice daily. All treatments except SF were delivered via the Breezhaler device; SF was delivered via an Accuhaler (Diskus). Randomization was stratified by region; 3,092 patients were randomized. Of the 415 sites in 41 countries, 12 were in Canada. The sponsor reported that treatment assignment was concealed from patients and investigator staff.

The primary and key secondary objectives of the IRIDIUM study were to demonstrate superiority in terms of FEV_1 after 26 weeks of treatment and the ACQ-7 score after 26 weeks of treatment, respectively, of either QVM 150 mcg/50 mcg/160 mcg to QMF 150 mcg/320 mcg or QVM 150 mcg/50 mcg/80 mcg to QMF 150 mcg/160 mcg, all delivered by the Breezhaler device, in patients with asthma. As shown in Figure 2, a 2-week screening period followed by a 2-week run-in period preceded the double-blind treatment period. There was also a 30-day follow-up period. The reported purpose of the screening period was to obtain consent, review and adjust medications, ensure washout of prior asthma medication as per protocol, and provide patients with salbutamol-albuterol (rescue medication) for use throughout the study as necessary. Patients were also issued an electronic diary (e-diary) and PEF meter to record asthma symptoms and rescue medication use; PEF recording started in the run-in period. The run-in period was used to assess eligibility and collect baseline values in both studies, and provide all patients whose spirometry assessments met the inclusion criteria (FEV_1 percent of predicted normal values, American Thoracic Society/European Respiratory Society criteria, and reversibility) with an open-label "medium"-dose ICS + LABA (SF 50 mcg/250 mcg twice daily) for use throughout the run-in period. Open-label ICS + LABA was discontinued at randomization. The follow-up visit involved a final telephone visit following the last treatment date.

All patients received training in the correct use of the inhaler devices used to administer study medications. The patient's use of the inhalation devices was assessed by the investigator at clinic visits.

ARGON Study

The ARGON study was a phase IIIb, multi-centre, randomized, partially blinded, parallel-group, noninferiority, open-label active-controlled study with a 24-week treatment period, conducted between February 2018 and July 2019. Patients were randomized using an IRT provider on day 1 of the treatment period at a 1:1:1 ratio to 1 of the 3 treatment arms: QVM 150 mcg/50 mcg/160 mcg once daily; QVM 150 mcg/50 mcg/80 mcg once daily; or SF 50 mcg/500 mcg twice daily and TIO 5 mcg once daily (SF + TIO). Both QVM dosage strengths were administered via Breezhaler, SF was delivered via Accuhaler, and TIO was delivered via Respimat. Patients and investigators had full knowledge of treatment allocation and SF + TIO was open-label. For the 2 QVM treatment arms, patients, investigators, persons performing assessments, and analysts were blinded to the dose of QVM. Randomization was stratified by previous ICS dose of ICS-LABA therapy (medium- or high-dose) and region. A total of 1,425 patients were randomized in the ARGON study. None of the study sites of the ARGON trial were in Canada.

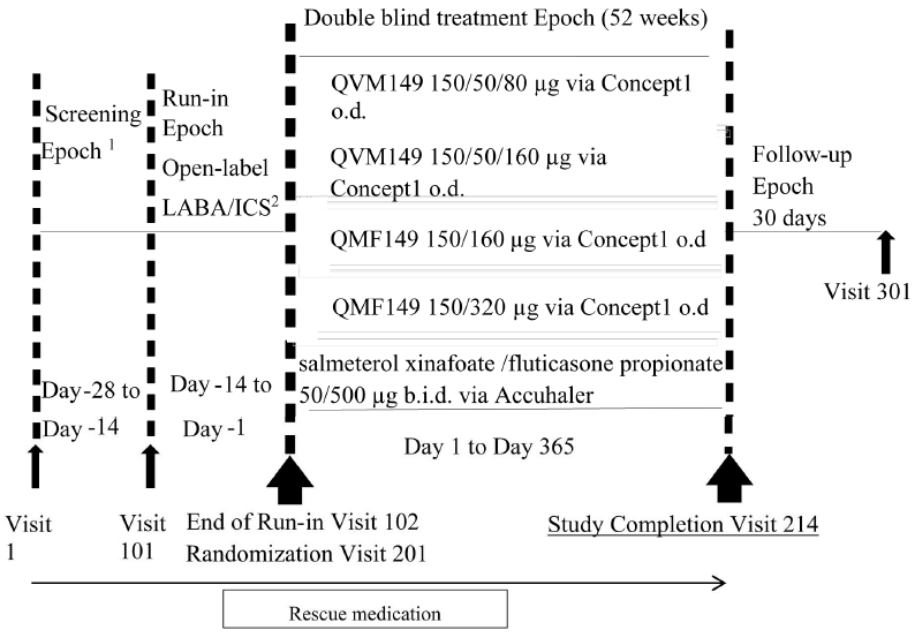
The primary objective was to demonstrate noninferiority of QVM 150 mcg/50 mcg/160 mcg or QVM 150 mcg/50 mcg/80 mcg to SF + TIO in terms of the AQLQ after 24 weeks of treatment. Briefly, the secondary objectives evaluated QVM 150 mcg/50 mcg/160 mcg and 150 mcg/50 mcg/80 mcg compared to SF + TIO in terms of trough FEV_1, AQLQ and ACQ-7 scores, and lung function.

As shown in Figure 3, the ARGON study consisted of a screening period of up to 1 week, a 2-week run-in period, a 24-week treatment period, and a 1-week follow-up period.

The purpose of the screening period was to obtain consent, review and adjust medications as needed, and provide rescue medication to patients who met the eligibility criteria, which were to be used as needed throughout the study. At the start of the run-in period, patients who met the inclusion and exclusion criteria were subjected to additional screening assessments, which included a reversibility test, an electrocardiogram, and laboratory assessments. Patients were then supplied with open-label SF 50 mcg/250 mcg twice daily or 50 mcg/500 mcg twice daily depending on their ICS background medication dose. The open-label ICS was stopped at the randomization visit. In addition, patients were trained to record asthma symptoms, rescue medication use, and PEF with an e-diary.

Of note, the 150 mcg/50 mcg/80 mcg dosage strength of QVM is not aligned with the Health Canada–approved product monograph for QVM and therefore will not be reported in the context of either study throughout the following sections of this review.

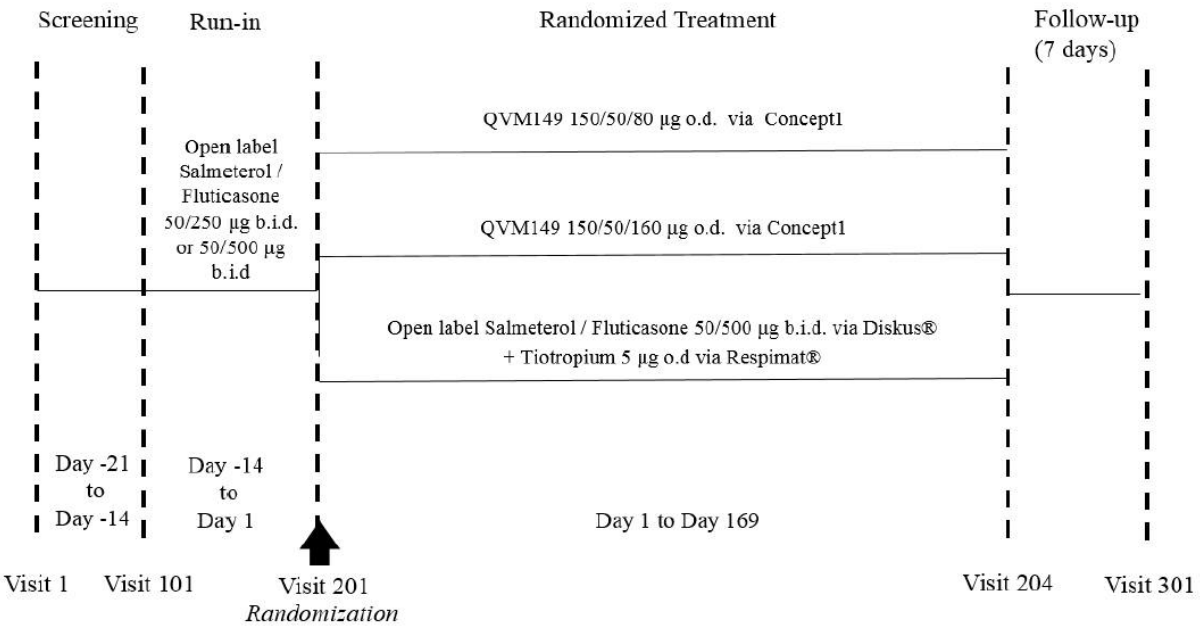
Figure 2: IRIDIUM Study Design



b.i.d. = twice daily; ICS = inhaled corticosteroid; LABA = long-acting beta2 agonist; o.d. = once daily; QMF = indacaterol-mometasone furoate; QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate.

Source: IRIDIUM Clinical Study Report.[5]

Figure 3: ARGON Study Design (24-Week Treatment Period)



b.i.d. = twice daily; o.d. = once daily; QMF = indacaterol-mometasone furoate; QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate.

Source: ARGON Clinical Study Report.[6]

Populations

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria used for the IRIDIUM and ARGON studies are summarized in Table 6.

The patients included in the 2 studies were adults (≥ 18 years old) who had a diagnosis of asthma for at least 1 year (IRIDIUM study) or 6 months (ARGON study) prior to screening. Patients in both studies had to have prior use of a medium- or high-dose LABA-ICS for at least 3 months and stable doses for at least 1 month prior to screening, be symptomatic at screening despite treatment (patients with an ACQ-7 score ≥ 1.5 at the start of the run-in period and at randomization), and have a documented history of at least 1 asthma exacerbation requiring care from a physician, ED visit, or hospitalization in the last 12 months prior to screening, and required oral corticosteroids. Lastly, patients needed to have a pre-bronchodilator FEV_1 of less than 80% (IRIDIUM study) or less than 85% (ARGON study) of predicted normal value, and an increase in FEV_1 of 12% or greater and 200 mL within 15 to 30 minutes after administration of 400 mcg salbutamol plus 360 mcg albuterol at the start of the run-in period.

Patients were excluded from the IRIDIUM and ARGON studies if they had a history of smoking, an asthma attack or exacerbation within 6 weeks of the screening visit, required intubation for a severe asthma exacerbation, or had other clinical or chronic conditions or respiratory tract infections. Patients in both studies were also excluded if they had used a LAMA within 3 months of screening or had received any of the following without a washout period: a LAMA, SAMA, fixed combinations of beta2 agonists and an ICS, fixed combinations of SABA and a short-acting anticholinergic, SABA, or parenteral or intramuscular corticosteroids.

Baseline Characteristics

A summary of baseline characteristics for randomized patients in the IRIDIUM and ARGON studies are available in Table 7 and Table 8, respectively.

In the IRIDIUM study, patients were a mean age of 52.0 (SD = 12.8) to 52.9 (SD = 12.2) years old, and the majority were female (61.5% to 67.5%) and White (73.3% to 75.7%). The duration of asthma among patients was a mean of 16.8 (SD = 14.7) to 19.2 (SD = 15.6) years and almost all reported experiencing at least 1 asthma exacerbation that required treatment in the 12 months prior to study start, with the majority reporting 1 event (range = 80.3% to 83.2%). At baseline, patients reported a mean ACQ-7 score of 2.5 (SD = 0.6) to 2.6 (SD = 0.6) indicating poorly controlled asthma. Between 60.7% and 64.4% of patients had prior treatment experience with a medium-dose ICS-LABA and 35.3% to 38.7% with a high-dose ICS-LABA. Lastly, FEV_1 reversibility was reported as a percentage increase and increase in litres at the start of the run-in period. The mean increase ranged from 26.8% (SD = 21.3) to 28.4% (SD = 21.9) across treatment groups, and the mean (SD) increase in litres ranged from [redacted].

In the ARGON study, patients were a mean age of 52.7 (SD = 13.3) to 53.1 (SD = 13.1) years old, and the majority were female (range = 60.7% to 64.5%) and White (range = 82.1% to 82.4%). The duration of asthma among patients was a mean of 20.2 (SD = 14.7) to 22.1 (SD = 16.3) years and all patients reported experiencing at least 1 asthma exacerbation that required treatment in the 12 months prior to study start, with the majority (range = 78.8% to 80.5%) reporting only 1 event. At baseline, patients reported a mean

ACQ-7 score of 2.6 (SD = 0.5), indicating poorly controlled asthma. Between 98.1% and 98.5% of patients reported prior use of an ICS-LABA, [redacted] to [redacted] used an inhaled SABA, and [redacted] to [redacted] used oral corticosteroids for asthma. Lastly, the mean FEV_1 reversibility was between 28.3% (SD = 17.9) and 28.5% (SD = 17.6), and most patients ([redacted] to [redacted]) showed an FEV_1 reversibility of at least 12% of predicted FEV_1.

Overall, the treatment groups were well balanced in the IRIDIUM study. In the ARGON study, the proportion of patients who reported prior use of an inhaled SABA was 73.9% in the QVM treatment group compared to 66.7% in the SF + TIO treatment group. All other characteristics were well balanced between treatment groups. Between the 2 studies, the IRIDIUM study had a greater proportion of Asian patients (range = 21.2% to 22.5% across treatment groups) compared to the ARGON study (6.9% to 7.1% across treatment groups).

Table 7: Summary of Baseline Characteristics (IRIDIUM Trial, Randomized Set)

Characteristic		QVM 150 mcg/50 mcg/160 mcg N = 619	QMF 150 mcg/320 mcg N = 618	SF 50 mcg/500 mcg N = 618
Age (years)	Mean (SD)	52.1 (12.9)	52.0 (12.8)	52.9 (12.2)
	< 18, n (%)	[redacted]	[redacted]	[redacted]
	18 to 64, n (%)	[redacted]	[redacted]	[redacted]
	≥ 65, n (%)	[redacted]	[redacted]	[redacted]
Gender, n (%)	Male	238 (38.4)	238 (38.5)	201 (32.5)
	Female	381 (61.6)	380 (61.5)	417 (67.5)
Race, n (%)	White	456 (73.7)	453 (73.3)	468 (75.7)
	Black	4 (0.6)	3 (0.5)	1 (0.2)
	Asian	139 (22.5)	133 (21.5)	131 (21.2)
	Native American	7 (1.1)	8 (1.3)	5 (0.8)
	Unknown	0	0	0
	Other	13 (2.1)	21 (3.4)	13 (2.1)
BMI (kg/m^2)		NR	NR	NR
Disease characteristics				
Duration of asthma (years)	Mean (SD)	19.2 (15.6)	16.8 (14.7)	18.6 (15.8)
	Median (range)	[redacted]	[redacted]	[redacted]
Number of asthma exacerbations in 12 months prior to study start that required treatment, n (%)	0	0	1 (0.2)	0
	1	515 (83.2)	501 (81.1)	496 (80.3)
	2	78 (12.6)	98 (15.9)	94 (15.2)
	3	18 (2.9)	11 (1.8)	16 (2.6)
	≥ 4	8 (1.3)	7 (1.1)	12 (1.9)
Smoking status, n (%)	Never smoker	505 (81.6)	501 (81.1)	492 (79.6)
	Former smoker	114 (18.4)	117 (18.9)	126 (20.4)
Baseline ACQ-7 score	Mean (SD)	2.5 (0.6)	2.6 (0.6)	2.5 (0.6)
	Median (range)	[redacted]	[redacted]	[redacted]
	< 1.5, n (%)	[redacted]	[redacted]	[redacted]
	1.5 to < 2.0, n (%)	[redacted]	[redacted]	[redacted]
	2.0 to < 2.5, n (%)	[redacted]	[redacted]	[redacted]

Characteristic		QVM 150 mcg/50 mcg/160 mcg N = 619	QMF 150 mcg/320 mcg N = 618	SF 50 mcg/500 mcg N = 618
	≥ 2.5, n (%)	[redacted]	[redacted]	[redacted]
	Missing, n (%)	[redacted]	[redacted]	[redacted]
Prior asthma treatment, n (%)	ICS-LABA medium-dose	389 (62.8)	398 (64.4)	375 (60.7)
	ICS-LABA high-dose	225 (36.3)	218 (35.3)	239 (38.7)
	ICS-LABA low-dose or no ICS-LABA	2 (0.3)	2 (0.3)	2 (0.3)
	Missing	3 (0.5)	0	2 (0.3)
Spirometry				
FEV_1 (L) pre-bronchodilator at start of run-in period	n	617	615	617
	Mean (SD)	1.62 (0.59)	1.60 (0.58)	1.59 (0.58)
	Median (range)	[redacted]	[redacted]	[redacted]
FEV_1 pre-bronchodilator (% predicted FEV_1) at start of run-in period	n	617	615	617
	Mean (SD)	55.1 (13.5)	54.4 (13.5)	55.4 (13.4)
	Median (range)	[redacted]	[redacted]	[redacted]
	< 40%, n (%)	[redacted]	[redacted]	[redacted]
	40% to < 60%, n (%)	[redacted]	[redacted]	[redacted]
	60% to < 80%, n (%)	[redacted]	[redacted]	[redacted]
	≥ 80 %, n (%)	[redacted]	[redacted]	[redacted]
	Missing, n (%)	[redacted]	[redacted]	[redacted]
FEV_1 reversibility (% increase) at start of run-in period	n	617	615	617
	Mean (SD)	26.8 (21.3)	28.1 (19.7)	28.4 (21.9)
	Median (range)	[redacted]	[redacted]	[redacted]
FEV_1 reversibility (increase in L) at start of run-in period	n	617	615	617
	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]	[redacted]
FEV_1 pre-bronchodilator (% predicted FEV_1) at end of run-in period/randomization	n	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]	[redacted]
	< 40%, n (%)	[redacted]	[redacted]	[redacted]
	40% to < 60%, n (%)	[redacted]	[redacted]	[redacted]
	60% to < 80%, n (%)	[redacted]	[redacted]	[redacted]
	≥ 80 %, n (%)	[redacted]	[redacted]	[redacted]
	Missing, n (%)	[redacted]	[redacted]	[redacted]

ACQ-7 = 7-item Asthma Control Questionnaire; BMI = body mass index; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; LABA = long-acting beta2 agonist; QMF = indacaterol-mometasone furoate; QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate; SD = standard deviation; SF = salmeterol-fluticasone propionate.

Note: The results for QVM 150 mcg/50 mcg/80 mcg are not displayed.

Source: IRIDIUM Clinical Study Report.[5]

Table 8: Summary of Baseline Characteristics (ARGON Trial, Randomized Set)

Characteristic		QVM 150 mcg/50 mcg/160 mcg N = 476	SF 50 mcg/500 mcg + TIO 5 mcg N = 476
Age, years	Mean (SD)	52.7 (13.3)	53.1 (13.1)
	18 to 39, n (%)	85 (17.9)	73 (15.3)
	40 to 64, n (%)	290 (60.9)	308 (64.7)
	> 64, n (%)	101 (21.2)	95 (20.0)
Gender, n (%)	Male	187 (39.3)	169 (35.5)
	Female	289 (60.7)	307 (64.5)
Race, n (%)	White	392 (82.4)	391 (82.1)
	Black or African-American	5 (1.1)	3 (0.6)
	Asian	34 (7.1)	33 (6.9)
	American Indian or Alaska Native	1 (0.2)	10 (2.1)
	Other	44 (9.2)	39 (8.2)
BMI (kg/m^2)	Mean (SD)	[redacted]	[redacted]
	≤ 30.0 kg/m^2, n (%)	[redacted]	[redacted]
	> 30.0 kg/m^2, n (%)	[redacted]	[redacted]
Disease characteristics			
Duration of asthma, years	Mean (SD)	22.1 (16.3)	20.2 (14.7)
	Median (range)	19.2 (0.5 to 73.4)	17 (0.6 to 73.4)
Number of asthma exacerbations in 12 months prior to study start that required treatment, n (%)	1	375 (78.8)	383 (80.5)
	2	[redacted]	[redacted]
	3	[redacted]	[redacted]
	≥ 4	[redacted]	[redacted]
Smoking history, n (%)	Never smoker	354 (74.4)	363 (76.3)
	Ex-smoker	112 (23.5)	103 (21.6)
	Current smoker	10 (2.1)	10 (2.1)
Average amount of tobacco consumed (in pack years)	Mean (SD)	6.4 (4.2)	6 (4.2)
	Median (range)	[redacted]	[redacted]
Time since smoking stopped (years)	Mean (SD)	16.1 (14.1)	15.9 (12.1)
	Median (range)	[redacted]	[redacted]
AQLQ total sore	Mean (SD)	4.7 (0.9)	4.7 (0.9)
	Median (range)	4.7 (2.2 to 6.9)	4.6 (1.6 to 6.9)
Baseline ACQ-7 score	Mean (SD)	2.6 (0.5)	2.6 (0.5)
	Median (range)	2.6 (1.3 to 4.3)	2.6 (1.6 to 4.6)
	< 1.5, n (%)	2 (0.4)	0
	1.5 to < 2.0, n (%)	42 (8.8)	32 (6.7)
	2.0 to < 2.5, n (%)	167 (35.1)	196 (41.2)
	≥ 2.5, n (%)	265 (55.7)	247 (51.9)
	missing, n (%)	0	1 (0.2)

Characteristic		QVM 150 mcg/50 mcg/160 mcg N = 476	SF 50 mcg/500 mcg + TIO 5 mcg N = 476
SGRQ total score	Mean (SD)	39.7 (16.8)	39.4 (18.0)
	Median (range)	[redacted]	[redacted]
Baseline eosinophils count, cells/µL	Mean (SD)	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]
	< 300, n (%)	[redacted]	[redacted]
	≥ 300, n (%)	[redacted]	[redacted]
	Missing, n (%)	[redacted]	[redacted]
Prior asthma treatment discontinued prior to double-blind treatment period, n (%)	ICS-LABA	[redacted]	[redacted]
	Inhaled SABA	[redacted]	[redacted]
	Oral corticosteroid	[redacted]	[redacted]
	SAMA-SABA	[redacted]	[redacted]
	Intravenous corticosteroid	[redacted]	[redacted]
	ICS	[redacted]	[redacted]
	Xanthines	[redacted]	[redacted]
	Antibiotics	[redacted]	[redacted]
ICS component background therapy, n (%)	Mid-dose ICS-LABA	230 (48.3)	241 (50.6)
	High-dose ICS-LABA	242 (50.8)	232 (48.7)
	Missing	3 (0.6)	2 (0.4)
Spirometry			
FEV_1 reversibility (%)	Mean (SD)	28.5 (17.6)	28.3 (17.9)
	Median (range)	[redacted]	[redacted]
	< 12% of predicted FEV_1, n (%)	[redacted]	[redacted]
	≥ 12% of predicted FEV_1, n (%)	[redacted]	[redacted]
	Missing	[redacted]	[redacted]
Reversibility done through bronchoprovocation	n (%)	[redacted]	[redacted]

ACQ-7 = 7-item Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; BMI = body mass index; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; LABA = long-acting beta2 agonist; QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate; SABA = short-acting beta2 agonist; SAMA = short-acting muscarinic antagonist; SD = standard deviation; SF = salmeterol-fluticasone propionate; SGRQ = St. George's Respiratory Questionnaire; TIO = tiotropium.

Note: The results for QVM 150 mcg/50 mcg/80 mcg are not displayed.

Source: ARGON Clinical Study Report.[6]

Interventions

In the IRIDIUM study, patients were assigned to 1 of 5 treatment groups: QVM 150 mcg/50 mcg/80 mcg or QVM 150 mcg/50 mcg/160 mcg delivered once daily (in the evening) via Breezhaler, QMF 150 mcg/160 mcg delivered once daily (in the evening) via Breezhaler, QMF 150 mcg/320 mcg delivered once daily (in the evening) via Breezhaler, or SF 50 mcg/500 twice daily (in the morning and in the evening) delivered via Accuhaler (a multi-dose dry-powder inhaler). The QVM and QMF were available as powder in hard capsules, and SF was a powder pre-loaded in the Accuhaler multi-dose inhaler. To enable the

double-dummy design, patients were provided with a placebo delivered by either Breezhaler (as powder in capsules) administered in the evening, or Accuhaler (as a powder) administered in the morning and the evening.

In the ARGON study, patients were randomized to 1 of 3 treatment groups: QVM 150 mcg/50 mcg/80 mcg once daily via Breezhaler, QVM 150 mcg/50 mcg/160 mcg delivered once daily via Breezhaler, or SF 50 mcg/500 mcg twice daily via Accuhaler plus TIO 5 mcg once daily via Respimat. QVM was taken in the evening, SF was taken once in the morning and once in the evening, and TIO was delivered by 2 inhalations in the evening. Morning administrations took place between 5 a.m. and 8 a.m., evening administrations between 5 p.m. and 8 p.m. The study was partially blinded as SF + TIO was open-label, but patients, investigators, staff, persons performing assessments, and data analysts were blinded to the dose strength of QVM.

Where blinding was used in the 2 studies, the sponsor reported that blinding was maintained by concealing the identity of the treatment received using identical packaging, labelling, schedule of administration, appearance, taste, and odour. Dose adjustments and interruptions were not permitted unless it was necessary for safety reasons. If blinding was broken, study medication was permanently discontinued.

In both the IRIDIUM and ARGON studies, 100 mcg of salbutamol or 90 mcg of albuterol via a metered-dose inhaler was provided to all patients as a rescue medication at the first screening visit. Patients were instructed to use the rescue medication throughout each trial as needed. Nebulized salbutamol was not allowed during either of the trials and no other rescue treatment was permitted. The IRIDIUM study also noted that the use of a spacer for rescue medication was not permitted. Patients were asked to avoid using rescue medication within 6 hours of a study visit.

Patients received full training on the correct use of the different inhaler devices used in the 2 trials at the end of the run-in period or at randomization. Correct use of the inhalers by the patient was assessed by the investigator at clinic visits. Additional training was provided as required in the ARGON study, and information about additional training was not provided in the IRIDIUM study.

Certain asthma-related medications were prohibited in the IRIDIUM and ARGON studies, including LAMAs (within 3 months prior to screening), SAMAs (within 8 hours prior to visit 101), fixed combinations of beta2-adrenergic agonists and an ICS (within 12 to 24 hours prior to visit 101), fixed combinations of a SABA and short-acting anticholinergics (within 12 hours prior to visit 101), SABAs other than the trial rescue medication during the study or within 6 hours prior to screening, parenteral corticosteroids (within 4 weeks prior to visit 101), and intramuscular depot corticosteroids (within 3 months prior to visit 101).

The following medications were prohibited in the 2 trials, with a minimum cessation period of 7 days prior to run-in unless otherwise specified: non–potassium-sparing diuretics, non-selective systemic beta-blocking agents, cardiac anti-arrhythmic medications (classes Ia and III; amiodarone has a minimum 3-month cessation period), other drugs with the potential to significantly prolong the QT interval (14 days or 5 half-lives, whichever is longer), strong inhibitors of cytochrome P4503A (e.g., ketoconazole), tricyclic antidepressants (14 days), other investigational drugs (30 days or 5 half-lives, whichever was longer), noradrenaline reuptake inhibitors, live attenuated vaccines (30 days), all antipsychotic agents and combinations of antipsychotic drugs with antidepressants (14 days), serotonin-norepinephrine reuptake inhibitors (14 days), monoamine-oxidase

inhibitors (14 days), and systemic anticholinergics. The IRIDIUM study also prohibited the use of H_1 agonists (5 days).

The following medications were permitted in the 2 trials under certain conditions noted in Figure 4 monoclonal antibody (immunoglobin E or interleukin-5 inhibitors), oral corticosteroids, leukotriene antagonists and leukotriene synthesis inhibitors, long-acting theophylline preparations, short-acting theophylline, mucolytic agents not containing bronchodilators, systemic mast-cell stabilizers, pure selective serotonin reuptake inhibitors,

Figure 4: Permitted Background Medications With Conditions (IRIDIUM and ARGON Trials)

Class of medication	Condition
Monoclonal antibody: IgE inhibitors (e.g. omalizumab), IL-5 inhibitors (e.g. mepolizumab)	Allowed if at stable dose for at least 3 months prior to Visit 1
Oral corticosteroids*	Allowed if at stable dose for at least 1 month prior to Visit 1 and throughout the study at prednisone equivalent dose of 5 mg daily to 10 mg every other day
Leukotriene Antagonist and leukotriene synthesis inhibitors	Allowed if at stable dose for at least 1 month prior to Visit 1 and throughout the study.
Long-acting theophylline (methylxanthine) preparations	If stabilized for at least 4 weeks prior to Visit 1 and throughout the trial. Not administered within 24h prior to study visit.
Short- acting theophylline (methylxanthine)	If stabilized for at least 4 weeks prior to Visit 1 and throughout the trial. Not administered within 12h prior to study visit.
Mucolytic agents not containing bronchodilators	If stabilized for at least 4 weeks prior to Visit 1 and throughout the trial.
Systemic mast cell stabilizers e.g cromoglycate, nedocromil, ketotifen	If stabilized for at least 4 weeks prior to Visit 1 and throughout the trial.
Pure Selective Serotonin Reuptake Inhibitors (they had no documented effect on any other neurotransmitters or other biological pathways. E.g. muscarinic pathway)	Treatment regimen was stable for at least one month at Visit 1.
Inactivated influenza vaccination, pneumococcal vaccination or any other inactivated vaccine	Not administered within 48 hours prior to a study visit.
Intra-nasal corticosteroids	Stable dose for at least 4 weeks prior to Visit 101 In the case of as needed, provided an established pattern of use has been documented.
Antihistamines (e.g. loratadine, cetirizine)	If stabilized for at least 4 weeks prior to Visit 1 and throughout the trial. In the case of as needed, provided an established pattern of use has been documented
Topical corticosteroids for the treatment of eczema	In recommended doses and dosage regimens
Maintenance immunotherapy for allergies	Stable dose for at least 3 months prior to Visit 101 and unchanged throughout study treatment.

Source: Clinical Study Reports for IRIDIUM[5] and ARGON.[6]

Regarding treatment discontinuation, patients who withdrew from the study drug were asked to remain in the study and complete study visits for assessment of safety and vital status, and were given standard-of-care asthma therapy. The investigator could discontinue study treatment if it was considered detrimental to a patient's well-being. In the IRIDIUM study, this was specified as being possibly due to:

- experiencing 5 or more asthma exacerbations requiring systemic corticosteroids during the treatment period
- more than a 50% decrease in FEV_1 from baseline during the run-in or treatment period
- a medical condition that required use of prohibited treatment
- nonadherence due to use of prohibited medications
- or any safety reasons for discontinuation.

In the ARGON study, background medications could be escalated or de-escalated, to reflect the clinical practice setting. Escalation of therapy included "step-up" background medication and/or add-on maintenance treatment options (e.g., oral corticosteroids, biologic therapy, theophylline, and leukotriene receptor antagonists, "among others"). Escalation of therapy was labelled as a "treatment failure." De-escalation or "step-down" of therapy began with oral corticosteroids; TIO could also be discontinued in the open-label free-combination comparator group.

Outcomes

A list of efficacy end points identified in the CADTH review protocol that were assessed in the clinical trials included in this review is provided in Table 9. These end points are summarized in the following section. A detailed discussion and critical appraisal of the outcome measures is provided in Appendix 4.

Table 9: Summary of Outcomes of Interest Identified in the CADTH Review Protocol

Outcomes of interest	Outcome measure	IRIDIUM trial	ARGON trial
Acute asthma exacerbations	Number and rate of asthma exacerbations	Other secondary	Exploratory
Change in pulmonary function	FEV_1	Primary and other secondary	Secondary
	FVC	Other secondary	Secondary
	PEF	Other secondary	Exploratory
Health-related quality of life	AQLQ	Other secondary	Primary and secondary
	EQ-5D-5L	Exploratory	NR
	SGRQ	NR	Exploratory
Asthma control	ACQ-7	Secondary and other secondary	Secondary
Use of rescue medications	Rescue medication use and rescue medication–free days	Other secondary	Exploratory
Nocturnal awakening	Patient Asthma Control e-diary, nighttime symptoms	Other secondary	Exploratory
Days of missed work or school	WPAI: Asthma	Exploratory	NR
Health care resource utilization	Resource utilization, number of hospitalizations and unplanned outpatient visits	Exploratory	Exploratory

ACQ-7 = 7-item Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; e-diary = electronic diary; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; NR = not reported; PEF = peak expiratory flow; SGRQ = St. George's Respiratory Questionnaire; WPAI = Work Productivity and Activity Impairment Questionnaire.

Source: Clinical Study Reports for ARGON[6] and IRIDIUM.[5]

Asthma Exacerbations

For this review, asthma exacerbations were reported as the annual rate of asthma exacerbations by exacerbation category (severity), and descriptively by the percentage of patients with at least 1 asthma exacerbation by exacerbation category and the percentage of patients who permanently discontinued the study drug due to asthma exacerbations. Exacerbation categories were as follows: all (mild, moderate, severe), severe, and a combination of moderate. The former 2 categories were included in this review. In addition, exacerbations requiring hospitalization were reported descriptively. Asthma exacerbations that occurred while on treatment and 1 day after the last treatment were included. If an asthma exacerbation episode was duplicated, or nested within another exacerbation episode or within 7 days of another exacerbation, then only 1 exacerbation was counted.

A severe asthma exacerbation was defined as an aggravation of asthma symptoms (such as shortness of breath, cough, wheezing, or chest tightness) that required systemic corticosteroids for at least 3 consecutive days and/or an ED visit (or local equivalent structure), hospitalization due to asthma, or death due to asthma.

A moderate asthma exacerbation was defined as the occurrence of 2 or more of the following: progressive increase in at least 1 of the symptoms of asthma, increased use of rescue medication (≥ 50% increase in SABA use and at least 8 puffs on 2 out of any 3 consecutive days compared to baseline captured, or nighttime awakenings requiring a SABA on at least 2 of any 3 consecutive nights), or deterioration of lung function lasting for at least 2 days but not warranting systemic corticosteroids for more than 2 days or hospitalization.

A mild asthma exacerbation was defined as the occurrence of 1 of the following: deterioration of at least 1 of the symptoms of asthma, increased use of rescue medication, or deterioration of lung function lasting for at least 2 days.

Measures of Pulmonary Function

The primary outcome in IRIDIUM study was the change from baseline in trough FEV_1 after 26 weeks of treatment. The FEV_1 is the maximal amount of air forcefully exhaled in 1 second. Trough FEV_1 is used as a clinical measure of lung function, where trough FEV_1 is defined as the mean of the 2 FEV_1 values measured at 23 hours 15 minutes and 23 hours 45 minutes after the evening treatment dose is taken.[5,6] There appears to be limited published evidence relating to an MID for FEV_1 among adult patients with asthma. In 1 study of 281 adult patients with mild-to-moderate asthma symptoms (baseline mean FEV_1: 2.30 L/s [SD of 0.66 L/s]), the authors calculated the minimal patient perceivable improvement (MPPI) for FEV_1 as the mean change in FEV_1 in patients rating themselves as "a little better" (n = 86) on the global rating of change in asthma.[29] Across all patients, the MPPI for FEV_1 was 230 mL or a 10.38% change from baseline. Males and females reported similar MPPI values, but older patients had a lower MPPI (170 mL) than younger ones (280 mL) for FEV_1.[29]

No evidence for validity, reliability, responsiveness to change, or MID was identified for the FVC measure, which is the amount of air that can be forcibly exhaled from the lungs after taking the deepest breath possible as measured by spirometry. According to the European Medicines Agency (EMA), evaluation of FVC can be used as a complementary end point in clinical trials.[7]

The PEF, measured in L/min and sometimes referred to as PEF rate, is defined as "the maximum flow achieved during an expiration delivered with maximal force starting from the level of maximal lung inflation."[30] In both trials, PEF was analyzed separately for morning and evening values. Baseline values were calculated based on data recorded during the run-in period. Mean values were calculated for the first 26 weeks and the whole 52-week treatment period in the IRIDIUM study, and over 24 weeks in the ARGON study.

Health-Related Qualify of Life

The primary outcome in the ARGON study was the change from baseline in the AQLQ total score after 24 weeks of treatment. In both studies, the overall AQLQ score, scores for each individual domain, and the proportion of patients who achieved an improvement of at least 0.5 (MID) in the change from baseline in AQLQ score were reported and included in this review. The AQLQ is a patient-reported, disease-specific, HRQoL measure that was developed to evaluate asthma in the clinical trial setting.[31] The AQLQ includes 32 questions grouped into 4 domains: symptoms, activity limitations, emotional function, and environmental stimuli. Each question is scored on a 7-point scale, which ranges from 1 (severe impairment) to 7 (no impairment); a higher score indicates less impairment. The overall score is calculated as the mean of all questions, and the 4 domain scores are the means of the scores for the questions in the respective domains. Patients recall their relevant experiences during the previous 2 weeks. The AQLQ has demonstrated known-groups validity, test-retest and internal consistency reliability, and responsiveness (within-group and between groups). The AQLQ showed no evidence for a floor or a ceiling effect.[32] The MID for the AQLQ has been determined to be a cut point of 0.5, with publications reporting values such as 0.67,[32] 0.52,[33] and a range of 0.42 to 0.58 for the AQLQ domains.[34-37]

The SGRQ was included as a measure of HRQoL in the ARGON study. The SGRQ is a self-administered patient-reported outcome developed to assess HRQoL over the past 4 weeks.[6] This questionnaire contains 50 items and 3 domains: symptoms (frequency and severity of respiratory symptoms), activity (how breathlessness affects patients' activities), and impacts (psychological and social disturbances attributed to airway disease). Total and domain scores are calculated with all items, weighted, and expressed as a percentage; higher scores indicate a worse state.[38] Validity[39-42] and responsiveness[40] of the SGRQ has been demonstrated; however, no evidence of reliability was identified. An MID of 4 points has been established as a clinically meaningful change to asthma patients in a number of studies.[33,41,42]

The EuroQol 5-Dimensions (EQ-5D) questionnaire is a commonly used, well-validated, generic quality-of-life instrument developed by the EuroQol Group,[43] and was included as an exploratory outcome in the IRIDIUM study but not the ARGON study. The EuroQol 5-Dimensions 5-Levels (EQ-5D-5L) tool consists of the EQ-5D descriptive system and a Visual Analogue Survey (VAS). The VAS records the respondent's self-rated health on a vertical scale on which the end points are labelled 0 ("the worst health you can imagine") and 100 ("the best health you can imagine"). The respondents are asked to mark an X on the point of the VAS that best represents their health on that day. The EQ-5D index and VAS scores can be summarized and analyzed as continuous data.[43,44] The descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, each with 5 levels: a level-1 response = no problems, level 2 = slight problems, level 3 = moderate problems, level 4 = severe problems, and level 5 = extreme problems or unable to perform, which is the worst response in the dimension. Respondents are asked to choose the level that reflects their

health state for each of the 5 dimensions. The EQ-5D-5L was reported descriptively by domain and by VAS in the IRIDIUM study. Only the VAS was reported for this review.

Asthma Control

The ACQ-7 was evaluated in both studies and reported as a change from baseline as well as the proportion of patients who achieved an improvement (i.e., a decrease from baseline) of at least 0.5 points (MID). The change from baseline in the ACQ-7 at week 26 was included as the key secondary outcome in the IRIDIUM study. The ACQ-7 is a patient-reported outcome that was developed to evaluate asthma control in patients with asthma and is 1 of the most commonly used instruments measuring asthma control.[45,46] The questionnaire comprises 7 questions, with the responses scored on a 7-point scale. Questions regarding 6 aspects of the patient's previous week's experiences are answered by the patient and include questions on activity limitation, nocturnal waking, shortness of breath, wheezing, symptoms on waking, and the use of a SABA.[45] In addition, the seventh item includes calculations performed by clinical staff with regard to pre-bronchodilator FEV_1 or PEF (percent predicted).[45,46] The ACQ-7 score is defined as the mean of the 7 questions (as all questions are equally weighted), with scores of 0 meaning the patient has asthma that is well-controlled and those of 6 meaning the patient has asthma that is extremely poorly controlled.[45-47] The ACQ is used extensively in clinical trials to measure clinically meaningful change in asthma control.[46] The ACQ MID has been well-established and accepted as 0.5 points for within-person change.[46,48] In addition, a score of 1.5 on the ACQ-7 is the most appropriate discriminator for *well-controlled* versus *not well-controlled* asthma patients.[49]

Rescue medication use was also reported in both trials, as a measure of the mean daily number of puffs of rescue medication used as well as the change from baseline in the percentage of rescue medication–free days. Both measures were recorded by the patient in the sponsor-provided e-diary.

Nocturnal Awakening

The percentage of nights without nighttime awakenings was reported in both of the included studies. This outcome was derived from the daily patient-reported e-diary data and from the following included question and associated response: "How did you sleep last night?" and "I did not wake up because of any breathing problems," respectively. No evidence regarding the validity, reliability, responsiveness, or the MID of the Patient Asthma Control e-diary was identified.

Days of Missed Work or School

The Work Productivity and Activity Impairment (WPAI) questionnaire is a self-reported instrument used to measure the impact of general health and symptom severity on work and daily activities over the previous 7 days.[50-52] The WPAI: Asthma is the asthma-specific version of the questionnaire and is composed of 9 items that assess impairment in 3 domains (work, school, and activity).[50,53,54] Scores range from 0% to 100%, with higher scores indicating greater impairment.[50,54] This outcome was evaluated as an exploratory outcome in the IRIDIUM study, and the question pertaining to the percentage of work time missed due to asthma problems was reported for this review. The construct validity of the WPAI demonstrated a strong correlation with the AQLQ,[54] and no evidence of reliability, responsiveness, or an MID was identified.

Health Care Utilization

The number of hospitalizations and number of unplanned outpatient visits by type of facility (office or home visits, ED or hospital, other) due to an asthma or asthma exacerbation–related reason were reported in the IRIDIUM and ARGON studies for the purpose of economic evaluation. They were reported descriptively in the ARGON study, and as an annual rate of events in the IRIDIUM study.

Other Outcomes

Outcomes related to dyspnea, days of missed school, patient adherence to treatment regimen, ease of use of the treatment regimen, and exercise tolerance were included in the CADTH review protocol; however, they were not reported in either of the included studies.

Statistical Analysis

Sample Size and Power Calculation

The sample size and power calculation in the IRIDIUM study estimated that 2,980 patients (596 per arm) were needed to provide approximately 97% power to detect a treatment difference of 90 mL in trough FEV_1 between QVM and QMF, assuming an SD of 380 mL, a 10% dropout rate, and a 2-sided significance level of 0.05. The sample size was also estimated to provide 82% power to detect a treatment difference of 0.15 in the ACQ-7 score between QVM and QMF, assuming an SD of 0.80 with multiplicity adjustment.

In the ARGON study, the sample size and power calculation estimated that 1,251 patients (417 per arm) were needed to provide 99% power to demonstrate noninferiority of either the medium or high dose of QVM compared to SF + TIO for AQLQ at week 24, assuming a 10% dropout rate. A 0.25-point noninferiority margin, based on one-half of the MID for the AQLQ (an improvement of 0.5 points), a treatment difference point estimation of zero, and a 0.8 SD were assumed.

Statistical Test or Model

The primary outcome for the IRIDIUM study was trough FEV_1 after 26 weeks, which was defined as the average of the 2 FEV_1 measurements taken 23 hours 15 minutes and 23 hours 45 minutes after the evening dose of treatment. The primary efficacy analysis was analyzed using an MMRM on the full-analysis set (FAS) for QVM versus QMF. The model included the following covariates: baseline FEV_1 measurement, baseline-by-visit interaction, FEV_1 prior to inhalation, and FEV_1 within 15 to 30 minutes post-inhalation of salbutamol-albuterol (components of SABA reversibility). Treatment, region, visit (days 2, 184, and 365), and treatment-by-visit interaction were included as fixed effects. The within-patient correlation was modelled using an unstructured covariance matrix. The key secondary outcome, ACQ-7 after 26 weeks of treatment, was analyzed using the same MMRM (including all scheduled visits with ACQ-7 data) as the primary analysis, but included baseline ACQ-7 score instead of baseline FEV_1.

The primary outcome in the ARGON study was change from baseline in the AQLQ total score at week 24. The primary analysis was a noninferiority analysis comparing each of the 2 dose strengths of QVM (150 mcg/50 mcg/80 mcg and 150 mcg/50 mcg/160 mcg) versus the free combination of SF + TIO in terms of change from baseline in AQLQ total score. Only the latter comparison is described for this review. The primary outcome was analyzed using an MMRM on the FAS and included the baseline AQLQ total score as a covariate.

Treatment, region, visit, background ICS-LABA (medium- or high-dose), baseline-by-visit interaction, and treatment-by-visit interaction were included as fixed effects. The within-patient correlation was modelled using the unstructured covariance matrix in the mixed model. A noninferiority margin of −0.25 points in the AQLQ score was used based on 50% of the MID for the AQLQ score, which is 0.5 points. Noninferiority of QVM was claimed if the adjusted 1-sided P value was less than 0.025.

In both studies, other continuous outcomes (e.g., change from baseline in AQLQ, ACQ-7, and FVC) were also analyzed using the same MMRM as the primary analysis, replacing baseline FEV_1 with the appropriate corresponding baseline measure, unless otherwise specified (as follows). The proportion of patients who achieved an improvement of at least 0.5 in the ACQ-7 or AQLQ was analyzed using a logistic regression model with the same terms as above without random effects. In addition to similar MMRM analyses as the primary analysis, change from baseline in PEF, rescue medication use, and asthma symptoms based on e-diary entries, and the SGRQ (ARGON study) were analyzed using an analysis of covariance model containing treatment and region as fixed effects and centre nested within region as a random effect, and corresponding baseline values as covariates. The rate of asthma exacerbations was analyzed using a generalized linear model assuming a negative binomial distribution. Treatment and history of asthma exacerbation in the 12 months prior to screening were included as fixed effects, and the same covariates as the primary analysis were used. Log exposure in years was included as an offset variable in the model.

The family-wise type I error rate at the 2-sided 5% significance level was controlled using a sequential testing procedure based on the generalized Simes test as described in Maurer et al.[55] in the IRIDIUM and ARGON studies.

In the IRIDIUM study, the family for the overall type I error rate control contains 4 hypotheses: 2 hypotheses for the primary end point of trough FEV_1 (H_1 and H_2 for comparing QVM 150 mcg/50 mcg/80 mcg versus QMF 150 mcg/160 mcg and QVM 150 mcg/50 mcg/160 mcg versus QMF 150 mcg/320 mcg, respectively) and 2 hypotheses for the key secondary end point of ACQ-7 (H_3 and H_4 for the same treatment comparisons as H_1 and H_2, respectively). The hypotheses of interest to this review are H_2 and H_4, which correspond to the analysis of the primary end point and key secondary end point, respectively, for QVM 150 mcg/50 mcg/160 mcg versus QMF 150 mcg/320 mcg.

A closed successively weighted Bonferroni test was used to adjust for multiplicity. If the null H_2 was rejected at the initial significance level of 0.025, then H_4 was tested at a 0.025 significance level. If the null hypothesis could not be rejected, testing stopped and efficacy could not be claimed for either of the doses or end points. Multiplicity adjustments were made following the testing procedure described here:

- Step 1: Retain the 4 null hypotheses if $P \leq 0.05$ and the observed difference indicates QMF outperformed QVM for any of the 4 hypotheses, stop here; otherwise go to step 2.
- Step 2: Reject the 4 null hypotheses if $P < 0.05$ for all hypothesis tests (H_1 through H_4), stop here; otherwise go to step 3.
- Step 3: If neither step 1 or step 2 applies, use the closed successive Bonferroni test with initial weights of 0.5 for H_1 (2-sided alpha = 0.025) and 0.5 to H_2. If H_1 is rejected, then H_3 can be tested at a significance level of 0.025; similarly, if H_2 is rejected at the initial significance level of 0.025, then H_4 can be tested at the same level. If neither H_1 or H_2 can be rejected, testing stops.

In the ARGON study, 2 hypotheses for the primary end point were included comparing QVM 150 mcg/50 mcg/160 mcg to SF + TIO and QVM 150 mcg/50 mcg/80 mcg to SF + TIO for noninferiority. Only the former comparison is of interest to this review. Multiplicity adjustments were made following the testing procedure described here:

- Step 1: Retain the null hypotheses if any 1-sided P value ≥ 0.975, stop here; otherwise go to step 2.
- Step 2: Reject the null hypotheses if the 1-sided P value < 0.025 for both H_1 and H_2, stop here; otherwise go to step 3.
- Step 3: If neither step 1 or step 2 applies, use the Bonferroni test and reject each hypothesis if the corresponding 1-sided P value < 0.0125.

Other than the analyses included in the statistical hierarchies described above, all other analyses will be performed at the nominal 2-sided significance level of 0.05 without multiplicity adjustment.

Lastly, all efficacy analyses were conducted in the FAS, which followed the intention-to-treat principle in both studies.

Handling of Missing Data

In the IRIDIUM study, the following measures were used to handle missing data for FEV_1 where applicable:

- If any of the measures contributing to trough FEV_1 were collected: within 3 months of a corticosteroid injection, 7 days of systemic corticosteroid use (except for patients who were on stable systemic corticosteroid as background therapy), 6 hours of rescue medication, or measurements were outside the post-evening dose time window for the treatment regimen, then the individual FEV_1 value was set to missing.
- If 1 of the 2 FEV_1 measurements was missing, the remaining non-missing value was used for trough FEV_1. If the patient withdrew from the study, they were regarded as missing.
- Patients who reported an FEV_1 > 7 L were regarded as implausible and the spirometry measurements were excluded.

For FEV_1, the sponsor reported that the MMRM model was based on data missing at random and therefore data were not imputed.

In the IRIDIUM study, values for ACQ-7 and AQLQ were imputed using a multiple imputation method under the missing-at-random assumption. Data were not imputed for other outcomes.

In the ARGON study, the MMRM model was based on the missing-at-random assumption for the missing values and assessed the treatment effects without explicit imputation. No imputation will be used for missing questions or missing total AQLQ scores for primary analysis. No formal imputations for missing values were used for primary or secondary outcomes; analyses were performed on observed data only.

Subgroup Analyses

In the IRIDIUM study, exploratory subgroup analyses of the primary efficacy outcome (trough FEV_1 at week 26) were conducted based on the following subgroups: race, sex, history of asthma exacerbation in the 12 months prior to screening, therapies used prior to the run-in period, pre-bronchodilator FEV_1 in percent of predicted FEV_1 range at visit 101,

and baseline ACQ-7 score. Subgroup analyses for prior therapies used by patients before the run-in period (medium- and high-dose LABA-ICS) were also performed for the ACQ-7 and AQLQ end points at week 26.

In the ARGON study, exploratory subgroup analyses of the AQLQ total score at week 24 were conducted using the same method as the primary analysis, to explore the treatment effect by: sex, region, age, history of asthma exacerbation in the 12 months prior to screening, and prior therapies used by patients for at least 1 month prior to screening. Subgroup analyses by prior therapies were also conducted for FEV_1 at week 24.

Sensitivity Analyses

In the IRIDIUM study, the primary analysis was also performed using the per-protocol set (PPS) and the same MMRM as a supportive analysis. A "tipping-point" analysis was performed for the primary end point to evaluate the impact of a deviation from the missing-at-random assumption of missing data.

In the ARGON study, 5 main sensitivity analyses were conducted using the same MMRM for the primary end point. This included an analysis of on-and-off treatment data values at week 24, with imputation of missing data using the last observation carried forward (LOCF) approach (only if less than 20% of observations were missing), using the PPS, excluding data for patients with treatment failures (data following treatment failure was considered missing), and considering all patients in the QVM treatment groups and only patients in the active comparator group who did not step down (only if greater then 5% patients in the comparator group stepped down).

Analysis Populations

In both studies, a randomized set including all patients who were randomized was used for patient disposition, demographics, and baseline characteristics. The FAS was the primary population used for efficacy outcomes, which included all patients who were randomized and received at least 1 dose of study medication, following the intention-to-treat principle. Patients were analyzed according to the treatment assigned at randomization for the FAS and randomized set. The PPS included patients in the FAS who did not have any major protocol deviations and was used for sensitivity analyses of the primary end point. The safety set included patients who received at least 1 dose of study medication and was used for all assessments of safety. Patients in the PPS and safety set were analyzed according to the treatment received. In the safety set, patients who switched treatment during the study were counted and analyzed only once according to their treatment.

Results

Patient Disposition

Patient disposition in the IRIDIUM and ARGON studies is provided in Table 10. A total of 3,092 (63.7%) and 1,426 (74.4%) were randomized in the IRIDIUM and ARGON studies, respectively. In the IRIDIUM study, 3, 5, and 4 patients randomized to QVM 150 mcg/50 mcg/160, QMF 150 mcg/320 mcg, and SF, respectively, were not treated. This was mostly due to randomization of ineligible patients. One patient randomized to SF + TIO in the ARGON study was not treated due to the same reason. Study discontinuation was similar across treatment groups in the IRIDIUM study, ranging from 5.8% to 6.6%. The most common reason for study discontinuation was patient or guardian decision (4.2% to 5.5%).

Study discontinuation was not reported for the ARGON study. The majority of patients in both studies completed treatment (≥ 89% in all treatment groups). Patient or guardian decision was the most common reason for discontinuation from study treatment in both studies (4.9% to 5.5% in the IRIDIUM study and 1.3% to 2.3% in the ARGON study).

Table 10: Patient Disposition (IRIDIUM and ARGON Trials)

	IRIDIUM trial			ARGON trial	
	QVM 150 mcg/ 50 mcg/ 160 mcg	QMF 150 mcg/ 320 mcg	SF 50 mcg/ 500 mcg	QVM 150 mcg/ 50 mcg/ 160 mcg	SF 50 mcg/ 500 mcg + TIO 5 mcg
Screened, n	4,851			1,917	
Randomized, n (%)[a]	619 (12.8)	618 (12.7)	618 (12.7)	476 (24.8)	476 (24.8)
Completed study, n (%)	580 (93.7)	577 (93.4)	582 (94.2)	NR	NR
Discontinued from study, n (%)	39 (6.3)	41 (6.6)	36 (5.8)	NR	NR
Patient or guardian decision	34 (5.5)	26 (4.2)	27 (4.4)	NR	NR
Protocol deviation	2 (0.3)	4 (0.6)	4 (0.6)	NR	NR
Death	1 (0.2)	4 (0.6)	0	NR	NR
Lost to follow-up	1 (0.2)	2 (0.3)	1 (0.2)	NR	NR
Physician decision	1 (0.2)	5 (0.8)	4 (0.6)	NR	NR
Completed treatment, n (%)	557 (90.0)	552 (89.3)	552 (89.3)	490 (96.6)	448 (94.1)
Discontinued from study treatment,[b] n (%)	59 (9.5)	61 (9.9)	62 (10.0)	16 (3.4)	27 (5.7)
Adverse events	12 (1.9)	17 (2.8)	21 (3.4)	3 (0.6)	3 (0.6)
Lost to follow-up	1 (0.2)	2 (0.3)	1 (0.2)	1 (0.2)	1 (0.2)
Patient or guardian decision	32 (5.2)	30 (4.9)	34 (5.5)	6 (1.3)	11 (2.3)
Technical problems	1 (0.2)	1 (0.2)	0	1 (0.2)	5 (1.1)
Physician decision	11 (1.8)	8 (1.3)	5 (0.8)	3 (0.6)	7 (1.5)
Pregnancy	1 (0.2)	0	1 (0.2)	2 (0.4)	0
Death	1 (0.2)	3 (0.5)	0	–	–
FAS, n	615	611	612	476	475
PP, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Safety, n	616	613	618	476	475

FAS = full-analysis set; NR = not reported; PP = per protocol; QMF = indacaterol-mometasone furoate; QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate; SF = salmeterol-fluticasone propionate; TIO = tiotropium.

[a] Percent of patients screened.

[b] ARGON, "from planned study treatment."

Note: The results for QVM 150 mcg/50 mcg/80 mcg and QMF 150 mcg/160 mcg in the IRIDIUM study and the results for QVM 150 mcg/50 mcg/80 mcg for the ARGON study are not displayed.

Source: Clinical Study Reports for IRIDIUM[5] and ARGON.[6]

Exposure to Study Treatments

A summary of exposure to study treatments in the IRIDIUM and ARGON trials is available in Table 11. The mean (SD) duration of exposure to study treatments in the IRIDIUM trial ranged from [redacted]. The mean (SD) duration of exposure to study treatments in the ARGON trial was between [redacted] and [redacted] days.

Treatment exposure was similar between treatment groups in both studies. The sponsor reported that [redacted] and [redacted] of patients were adherence with study medication as per protocol in the IRIDIUM and ARGON trials, respectively.

Table 11: Exposure to Study Treatments (Safety Set)

	IRIDIUM trial			ARGON trial	
	QVM 150 mcg/50 mcg/ 160 mcg N = 616	QMF 150 mcg/ 320 mcg N = 613	SF 50 mcg/500 mcg N = 618	QVM 150 mcg/50 mcg/ 160 mcg N = 476	SF 50 mcg/ 500 mcg + TIO 5 mcg N = 475
Exposure (days)					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

QMF = indacaterol-mometasone furoate; QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate; SD = standard deviation; SF = salmeterol-fluticasone propionate; TIO = tiotropium.

Source: Clinical Study Reports for IRIDIUM[5] and ARGON.[6]

Concomitant asthma medication use was reported in both studies, which included both treatments continued and started after the first dose of study treatment. Concomitant asthma medications were used by [redacted] to [redacted] of patients in the IRIDIUM study and [redacted] to [redacted] in the ARGON study.

In the IRIDIUM study, this included the use of corticosteroids (any, [redacted] to [redacted]), leukotriene modifiers (oral, [redacted] to [redacted]) and antibiotics (any, [redacted] to [redacted]); "other" medications, ICS-LABA combinations, SABAs, xanthines, and antihistamines were used in [redacted] to [redacted] of patients; and anti–immunoglobin E, SAMA-SABA combinations, short-acting anticholinergics, LABA-LAMA combinations (SF only), long-acting anticholinergics, LABAs, mast-cell stabilizers (QMF 150 mcg/320 mcg only), vaccines (SF 50 mcg/500 mcg only) were used by no more than 2.8% of patients in any treatment group.

In the ARGON study, this included the use of the following medications in the QMF and SF + TIO groups, respectively: corticosteroids ([redacted] and [redacted], mostly oral), leukotriene modifiers ([redacted] and [redacted]), SABAs ([redacted] and [redacted]), and antibiotics ([redacted] and [redacted]). In addition, ICS-LABA combinations, "other" medications, antihistamines, and xanthines, were used by ≤ [redacted] in any treatment group and SAMA-SABA combinations, anti–immunoglobin E, long-acting anticholinergics, short-acting anticholinergics, and LABA-LAMA combinations were used in < [redacted]) of patients in any treatment group.

Table 12: Use of Concomitant Asthma Medications (Safety Set)

Asthma medications	IRIDIUM trial			ARGON trial	
	QVM 150 mcg/ 50 mcg/160 mcg N = 616	QMF 150 mcg/ 320 mcg N = 613	SF 50 mcg/ 500 mcg N = 618	QVM 150 mcg/ 50 mcg/160 mcg N = 476	SF 50 mcg/ 500 mcg + TIO 5 mcg N = 475
Any asthma medication	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Corticosteroids	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intravenous	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Asthma medications	IRIDIUM trial			ARGON trial	
	QVM 150 mcg/ 50 mcg/160 mcg N = 616	QMF 150 mcg/ 320 mcg N = 613	SF 50 mcg/ 500 mcg N = 618	QVM 150 mcg/ 50 mcg/160 mcg N = 476	SF 50 mcg/ 500 mcg + TIO 5 mcg N = 475
Respiratory (inhaled)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leukotriene modifier, oral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antibiotics, all	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICS-LABA, inhaled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SABA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inhaled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nebulized	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Xanthine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intravenous	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antihistamines, oral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-IgE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAMA-SABA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long-acting anticholinergic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICS = inhaled corticosteroid; IgE = immunoglobulin E; LABA = long-acting beta2 agonist; QMF = indacaterol-mometasone furoate; QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate; SABA = short-acting beta2 agonist; SAMA = short-acting muscarinic antagonist; SF = salmeterol-fluticasone propionate; TIO = tiotropium.

Note: In the IRIDIUM study, LABA-LAMA, LABA, mast-cell stabilizers, and vaccine medications were used by less than 1% of patients in any treatment group. In the ARGON study, LABA, and LABA-LAMA were used by less than 1% of patients in any treatment group.

Source: Clinical Study Reports for IRIDIUM[5] and ARGON.[6]

Efficacy

Only those efficacy outcomes identified in the review protocol are reported below. See Appendix 3 for detailed efficacy data.

Acute Asthma Exacerbations

The results related to asthma exacerbations are provided in Table 13. Results corresponding to the number of patients experiencing asthma exacerbations were reported descriptively in both trials. Statistical testing was conducted for outcomes related to rates of asthma exacerbations in the IRIDIUM and ARGON studies; however, they were not included in the statistical testing hierarchy and are therefore presented descriptively.

During the 52-week treatment period of the IRIDIUM study, between 40.2% and 50.5% of patients experienced an asthma exacerbation and 21.8% to 23.2% experienced a severe exacerbation. A numerically greater proportion of patients in the SF treatment group experienced exacerbations (all severities, 50.5%) and severe exacerbations (29.7%) compared with patients in the QVM (40.2% overall, 21.8% severe) and QMF (41.9% overall, 23.2% severe) treatment groups. The number of patients with an asthma exacerbation requiring hospitalization or permanent discontinuation of the study drug was no more than [redacted] and no more than [redacted], respectively, in all treatment groups for the IRIDIUM study. During the 26-week treatment period in the ARGON study, [redacted] to [redacted]

of patients experienced an asthma exacerbation; [redacted] to [redacted] were severe, and fewer than [redacted] required hospitalization in both treatment groups. There were no discrepancies in the number of exacerbations between treatment groups in the ARGON study. Asthma exacerbations that caused permanent discontinuation of study drug was not reported.

In the IRIDIUM study, the annualized rate of asthma exacerbations (all severities) was 0.74 (95% CI, 0.64 to 0.85) for the QVM treatment group, 0.93 (95% CI, 0.82 to 1.06) for the QMF treatment group, and 1.23 (95% CI, 1.08 to 1.39) for the SF treatment group, corresponding to a rate ratio for all exacerbations of 0.79 (95% CI, 0.66 to 0.96; P = 0.016) for QVM compared to QMF and 0.60 (95% CI, 0.50 to 0.72; P < 0.001) for QVM compared to SF. The annualized rate of severe exacerbations was 0.26 (95% CI, 0.22 to 0.31) for the QVM treatment group, 0.33 (95% CI, 0.28 to 0.39) for the QMF treatment group, and 0.45 (95% CI, 0.39 to 0.53) for the SF treatment group, corresponding to a rate ratio of 0.78 (95% CI, 0.61 to 1.00; P = 0.050) and 0.58 (95% CI, 0.45 to 0.73; P < 0.001) for QVM compared to QMF and SF, respectively.

In the ARGON study, the annualized rate of asthma exacerbations (all severities) was 0.70 (95% CI, [redacted] to [redacted]) for the QVM treatment group and 0.86 (95% CI, [redacted] to [redacted]) for the SF + TIO treatment group, corresponding to a rate ratio of 0.81 (95% CI, 0.62 to 1.06; P = 0.123) for QVM compared to SF + TIO. The annualized rate of severe exacerbations was 0.36 (95% CI, [redacted] to [redacted]) for the QVM treatment group and 0.32 (95% CI, [redacted] to [redacted]) the SF + TIO treatment group, corresponding to a rate ratio of 1.14 (95% CI, 0.79 to 1.64; P = 0.494) for QVM compared to SF + TIO.

Table 13: Acute Asthma Exacerbations During Treatment Phase (IRIDIUM and ARGON Trials)

	IRIDIUM trial			ARGON trial	
	QVM 150 mcg/50 mcg/ 160 mcg N = 619	QMF 150 mcg/ 320 mcg N = 618	SF 50 mcg/ 500 mcg N = 618	QVM 150 mcg/ 50 mcg/160 mcg N = 476	SF 50 mcg/ 500 mcg + TIO 5 mcg N = 476
Number of patients with asthma exacerbations, by exacerbation category – FAS					
All (mild, moderate, severe)	247 (40.2)	256 (41.9)	309 (50.5)	[redacted]	[redacted]
Severe	134 (21.8)	142 (23.2)	182 (29.7)	[redacted]	[redacted]
Requiring hospitalization	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Causing permanent discontinuation of study drug	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rate of asthma exacerbations, all (mild, moderate, severe)[a] – FAS					
Number of patients contributing to the analysis	615	611	612	[redacted]	[redacted]
Annualized rate (95% CI)	0.74 (0.64 to 0.85)	0.93 (0.82 to 1.06)	1.23 (1.08 to 1.39)	0.70 ([redacted] to [redacted])	0.86 ([redacted] to [redacted])
Rate ratio (95% CI)	0.79 (0.66 to 0.96) vs. QMF 150 mcg/320 mcg 0.60 (0.50 to 0.72) vs. SF 50 mcg/500 mcg			0.81 (0.62 to 1.06) vs. SF + TIO	
P value[b]	0.016 vs. QMF 150 mcg /320 mcg < 0.001 vs. SF 50 mcg/500 mcg			0.123 vs. SF + TIO	
Rate of asthma exacerbations, severe[a] – FAS					
Number of patients contributing to the analysis	615	611	612	[redacted]	[redacted]

	IRIDIUM trial			ARGON trial	
	QVM 150 mcg/50 mcg/ 160 mcg N = 619	QMF 150 mcg/ 320 mcg N = 618	SF 50 mcg/ 500 mcg N = 618	QVM 150 mcg/ 50 mcg/160 mcg N = 476	SF 50 mcg/ 500 mcg + TIO 5 mcg N = 476
Annualized rate (95% CI)	0.26 (0.22 to 0.31)	0.33 (0.28 to 0.39)	0.45 (0.39 to 0.53)	0.36 ([redacted] to [redacted])	0.32 ([redacted] to [redacted])
Rate ratio (95% CI)	0.78 (0.61 to 1.00) vs. QMF 150 mcg/320 mcg 0.58 (0.45 to 0.73) vs. SF 50 mcg/500 mcg			1.14 (0.79 to 1.64) vs. SF + TIO	
P value[b]	0.050 vs. QMF 150 mcg/320 mcg < 0.001 vs. SF 50 mcg/500 mcg			0.494 vs. SF + TIO	

CI = confidence interval; FAS = full-analysis set; NR = not reported; QMF = indacaterol-mometasone furoate; QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate; SABA = short-acting beta2 agonist; SF = salmeterol-fluticasone propionate; TIO = tiotropium; vs. = versus.

[a] Generalized linear model assuming a negative binomial distribution with the following covariates: FEV_1 prior to inhalation and FEV_1 15 to 30 minutes post-inhalation of salbutamol-albuterol (components of SABA reversibility).

[b] P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

Source: Clinical Study Reports for IRIDIUM[5] and ARGON.[6]

Change in Pulmonary Function

The primary outcome in the IRIDIUM study, trough FEV_1 after 26 weeks of treatment, is presented in Table 14 along with change from baseline in trough FVC at week 52, and mean morning and evening PEF (L/min) during weeks 1 to 52. The treatment group difference in terms of the primary outcome was 0.07 L (95% CI, 0.03 to 0.10; P value < 0.001) for QVM compared to QMF, and 0.12 L (95% CI, 0.09 to 0.15; P value < 0.001) for QVM compared to SF. The LS mean and 95% CI for change from baseline in trough FEV_1 from baseline to week 52 is also presented in Figure 5, demonstrating a similar treatment effect at 52 weeks. A sensitivity analysis using the PPS as well as a tipping-point analysis to evaluate the impact of a deviation from the missing-at-random assumption proved to be supportive of the analysis of the primary outcome. The reported treatment effect in each of the other measures of pulmonary function was similar to that of the primary outcome, based on a change from baseline in the QVM group that was numerically greater than both the 2 comparator groups at week 52 (Table 14); however, none of these outcomes were controlled for multiplicity and should only be considered descriptively.

Subgroup analyses by prior asthma therapy (medium-dose ICS-LABA and high-dose ICS-LABA) and baseline ACQ-7 (asthma control, baseline score of [redacted] to [redacted], [redacted] to [redacted], and [redacted]) were conducted on the primary outcome (trough FEV_1 at week 26) and are provided in Figure 7. Subgroup analyses were not included in the statistical hierarchy. Briefly, a differential treatment effect by prior asthma therapy or baseline ACQ-7 was not observed, based on the LS mean difference for comparisons between QVM both the QMF and SF active comparators.

Table 14: Measures of Pulmonary Function – FEV_1, FVC, and PEF (IRIDIUM Trial)

	QVM 150 mcg/50 mcg/160 mcg N = 619	QMF 150 mcg/320 mcg N = 618	SF 50 mcg/500 mcg N = 618
Trough FEV_1 (L) at week 26[a] – FAS			
Number of patients contributing to the analysis	541	527	506
Baseline, mean (SD)	1.72 (NR)	1.75 (NR)	1.73 (NR)
End-of-treatment time point (week 26), LS mean (SE)	2.05 (0.01)	1.98 (0.01)	1.93 (0.01)
Change from baseline, LS mean (SE)	0.32 (0.01)	0.26 (0.01)	0.20 (0.01)
Treatment-group difference vs. control, LS mean (95% CI)	0.07 (0.03 to 0.10) vs. QMF 150 mcg/320 mcg 0.12 (0.09 to 0.15) vs. SF 50 mcg/500 mcg		
P value	< 0.001 vs. QMF 150 mcg/320 mcg < 0.001 vs. SF 50 mcg/50 mcg		
Trough FVC (L) at week 52, change from baseline[a] – FAS			
Number of patients contributing to the analysis	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
End-of-treatment time point (week 52), mean (SE)	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SE)	[redacted]	[redacted]	[redacted]
Treatment-group difference vs. control, LS mean (95% CI)	0.07 (0.02 to 0.12) vs. QMF 150 mcg/320 mcg 0.14 (0.09 to 0.18) vs. SF 50 mcg/500 mcg		
P value[b]	0.003 vs. QMF 150 mcg/320 mcg < 0.001 vs. SF 50 mcg/500 mcg		
Mean morning PEF (L/min) during weeks 1 to 52, change from baseline[c] – FAS			
Number of patients contributing to the analysis	596	581	586
Baseline, mean (SD)	284.0 (NR)	288.1 (NR)	283.1 (NR)
End-of-treatment time point (week 52), mean (SE)	NR	NR	NR
Change from baseline, LS mean (SE)	47.5 (2.03)	28.8 (2.05)	12.7 (2.05)
Treatment-group difference vs. control, LS mean (95% CI)	18.7 (13.4 to 24.1) vs. QMF 150 mcg/320 mcg 34.8 (29.5 to 40.1) vs. SF 50 mcg/500 mcg		
P value[b]	< 0.001 vs. QMF 150 mcg/320 mcg < 0.001 vs. SF 50 mcg/500 mcg		
Mean evening PEF (L/min) during weeks 1 to 52, change from baseline[c] – FAS			
Number of patients contributing to the analysis	593	578	578
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
End-of-treatment time point (week 52), mean (SE)	NR	NR	NR
Change from baseline, LS mean (SE)	38.7 (1.97)	21.2 (1.99)	9.2 (1.99)
Treatment-group difference vs. control, LS mean (95% CI)	17.5 (12.3 to 22.8) vs. QMF 150 mcg/320 mcg 29.5 (24.2 to 34.7) vs. SF 50 mcg/500 mcg		
P value[b]	< 0.001 vs. QMF 150 mcg/320 mcg < 0.001 vs. SF 50 mcg/500 mcg		

CI = confidence interval; FAS = full-analysis set; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; LS = least squares; MMRM = mixed model repeated measures; NR = not reported; PEF = peak expiratory flow; QMF = indacaterol-mometasone furoate; QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate; SABA = short-acting beta2 agonist; SD = standard deviation; SE = standard error; SF = salmeterol-fluticasone propionate; vs. = versus.

[a] MMRM with the following covariates: baseline FEV_1 measurement, baseline-by-visit interaction, FEV_1 prior to inhalation, and FEV_1 within 15 to 30 minutes post-inhalation of salbutamol-albuterol (components of SABA reversibility).

[b] P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

[c] Analysis of covariance with the following covariates: baseline morning/evening PEF, FEV_1 prior to inhalation, and FEV_1 within 15 to 30 minutes post-inhalation of salbutamol-albuterol (components of SABA reversibility).

Source: IRIDIUM Clinical Study Report.[5]

Figure 5: [redacted]

Figure 5 contained confidential information and was removed at the request of the sponsor.

[redacted]

Source: IRIDIUM Clinical Study Report.[5]

In the ARGON study, trough FEV_1 was included as a secondary outcome and measures of FVC and PEF (morning and evening) were exploratory outcomes. None of these outcomes were controlled for multiplicity. The results for each of these measures of pulmonary function at week 24 are summarized in Table 15. A treatment-group difference of 0.10 (95% CI, 0.05 to 0.15; P < 0.001) was reported for the change from baseline in trough FEV_1 at week 24. The treatment-group difference in FVC (L) at week 24 was 0.10 (95% CI, 0.05 to 0.15; P value < 0.001) for QVM versus SF + TIO. Based on the same comparison, the treatment difference in terms of mean morning and evening PEF (L/min) at week 24 was [redacted] (95% CI, [redacted] to [redacted]; P [redacted]) and [redacted] (95% CI, [redacted] to [redacted]; P [redacted]), respectively.

Subgroup analyses on trough FEV_1 at week 24, based on prior asthma therapy (medium-dose ICS-LABA or high-dose ICS-LABA) were performed (Table 36). At the end of treatment (24 weeks), the LS mean difference (95% CI) between patients who were previously on a medium-dose ICS-LABA in the QVM treatment group compared to SF + TIO was [redacted] L (95% CI, [redacted] to [redacted], P [redacted]). The same comparison was made in a subgroup of patients who were previously on a high-dose ICS-LABA, which resulted in a treatment difference of [redacted] L (95% CI, [redacted] to [redacted]; P [redacted]).

Table 15: Measures of Pulmonary Function – FEV_1, FVC, and PEF (ARGON Trial)

	QVM 150 mcg/50 mcg/160 mcg N = 476	SF 50 mcg/500 mcg + TIO 5 mcg N = 476
Trough FEV_1 (L) at week 24[a] – FAS		
Number of patients contributing to the analysis	385	372
Baseline, mean (SD)	[redacted]	
Change from baseline, LS mean (SE)	0.33 (0.02)	0.24 (0.02)
Treatment-group difference vs. control, LS mean (95% CI)	0.10 (0.05 to 0.15)	
P value[b]	< 0.001	
FVC (L) at week 24, change from baseline[a] – FAS		
Number of patients contributing to the analysis	385	372
Baseline, mean (SD)	2.94 (NR)	
Change from baseline, mean (SE)	0.28 (0.02)	0.19 (0.02)
Treatment-group difference vs. control, LS mean (95% CI)	0.10 (0.05 to 0.15)	
P value[b]	< 0.001	
Mean morning PEF (L/min) at week 24[c] – FAS		
Number of patients contributing to the analysis	476	475
Baseline, mean (SD)	[redacted]	
Change from baseline, LS mean (SE)	[redacted]	[redacted]

	QVM 150 mcg/50 mcg/160 mcg N = 476	SF 50 mcg/500 mcg + TIO 5 mcg N = 476
Treatment-group difference vs. control, LS mean (95% CI)	[redacted]	
P value[b]	< 0.001	
Mean evening PEF (L/min) at week 24[c] – FAS		
Number of patients contributing to the analysis	476	475
Baseline, mean (SD)	[redacted]	
Change from baseline, LS mean (SE)	[redacted]	[redacted]
Treatment-group difference vs. control, LS mean (95% CI)	[redacted]	
P value[b]	< 0.001	

CI = confidence interval; FAS = full-analysis set; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; LS = least squares; MMRM = mixed model repeated measures; NR = not reported; PEF = peak expiratory flow; QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate; SE = standard error; SF = salmeterol-fluticasone propionate; TIO = tiotropium; vs. versus.

[a] MMRM with baseline values (FEV_1 or FVC) as a covariate.

[b] P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

[c] Analysis of covariance with corresponding baseline PEF value as a covariate.

Source: ARGON Clinical Study Report.[6]

Health-Related Quality of Life

In the IRIDIUM study, the change from baseline for the AQLQ and EQ-5D-5L were used to assess HRQoL as secondary and exploratory outcomes, respectively. The results are provided in Table 16. Measures of HRQoL in the IRIDIUM study were not controlled for multiplicity. The AQLQ total score was similar across treatment groups at baseline, with a raw mean ranging from 4.67 to 4.71 (SD not reported). At week 52, the change from baseline was also similar across treatment groups, which corresponded to a treatment difference of 0.02 (95% CI, −0.08 to 0.12; P = 0.690) between QVM and QMF, and 0.06 (95% CI, −0.04 to 0.16; P = 0.232) between QVM and SF. Results reported for each of the domains of the AQLQ (symptoms, emotions, environmental stimuli, and activity limitation) were consistent with the total score. The results of the EQ-5D-5L were summarized descriptively. Based on the VAS, the mean (SD) change from baseline ranged from [redacted] to [redacted] at week 26 and [redacted] to [redacted] at week 52. The number of patients in each level of the EQ-5D-5L was also reported by domain (data not shown in Table 16); at week 52, [redacted] of patients reported either no problem or a slight problem for all domains and across treatment groups.

Table 16: Health-Related Quality of Life – AQLQ and EQ-5D-5L (IRIDIUM Trial)

	QVM 150 mcg/ 50 mcg/160 mcg N = 619	QMF 150 mcg/ 320 mcg N = 618	SF 50 mcg/500 mcg N = 618
AQLQ total score at week 52, change from baseline[a] – FAS			
Number of patients contributing to the analysis	552	547	546
Baseline, mean (SD)	4.67 (NR)	4.71 (NR)	4.71 (NR)
End-of-treatment time point (week 52), LS mean (SE)	[redacted]	[redacted]	[redacted]
Change from baseline, LS mean (SE)	0.87 (0.04)	0.85 (0.04)	0.81 (0.04)
Treatment-group difference vs. control, LS mean (95% CI)	0.02 (−0.08 to 0.12) vs. QMF 150 mcg/320 mcg 0.06 (−0.04 to 0.16) vs. SF		
P value[b]	0.690 vs. QMF 150 mcg/320 mcg 0.232 vs. SF		
AQLQ symptoms domain at week 52, change from baseline[a] – FAS			
Number of patients contributing to the analysis	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
End-of-treatment time point (week 52), LS mean (SE)	[redacted]	[redacted]	[redacted]
Change from baseline, LS mean (SE)	[redacted]	[redacted]	[redacted]
Treatment-group difference vs. control, LS mean (95% CI)	[redacted]		
P value[b]	[redacted]		
AQLQ emotions domain at week 52, change from baseline[a] – FAS			
Number of patients contributing to the analysis	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
End-of-treatment time point (week 52), LS mean (SE)	[redacted]	[redacted]	[redacted]
Change from baseline, LS mean (SE)	[redacted]	[redacted]	[redacted]
Treatment-group difference vs. control, LS mean (95% CI)	[redacted]		
P value[b]	[redacted]		
AQLQ environmental stimuli at week 52, change from baseline[a] – FAS			
Number of patients contributing to the analysis	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
End-of-treatment time point (Week 52), mean (SE)	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SE)	[redacted]	[redacted]	[redacted]
Treatment-group difference vs. control, LS mean (95% CI)	[redacted]		
P value[b]	[redacted]		
AQLQ activity limitation at week 52, change from baseline[a] – FAS			
Number of patients contributing to the analysis	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
End-of-treatment time point (week 52), LS mean (SE)	[redacted]	[redacted]	[redacted]

	QVM 150 mcg/ 50 mcg/160 mcg N = 619	QMF 150 mcg/ 320 mcg N = 618	SF 50 mcg/500 mcg N = 618
Change from baseline, LS mean (SE)	[redacted]	[redacted]	[redacted]
Treatment-group difference vs. control, LS mean (95% CI)	[redacted]		
P value[b]	[redacted]		
EQ-5D-5L VAS at week 26 – FAS			
n	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
End-of-treatment time point (Week 26), mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]
EQ-5D-5L VAS at week 52 – FAS			
n	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
End-of-treatment time point (week 52), mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]

AQLQ = Asthma Quality of Life Questionnaire; CI = confidence interval; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; FAS = full-analysis set; LS = least squares; NR = not reported; QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate; SABA = short-acting beta2 agonist; SD = standard deviation; SE = standard error; SF = salmeterol-fluticasone propionate; SGRQ = St. George's Respiratory Questionnaire; VAS = Visual Analogue Scale; vs. versus.

[a] Mixed model repeated measures with the following covariates: baseline AQLQ measurement, baseline-by-visit interaction, forced expiratory volume in 1 second (FEV_1) prior to inhalation and FEV_1 within 15 to 30 minutes post-inhalation of salbutamol-albuterol (components of SABA reversibility).

[b] P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

Source: IRIDIUM Clinical Study Report.[5]

The primary outcome in the ARGON study was the change from baseline in standardized AQLQ at week 24, which was used to assess noninferiority of QVM to the free combination of SF + TIO using a noninferiority margin of 0.25 points. The LS mean change from baseline in standardized AQLQ total score at week 24 was 0.83 (SE = 0.07) for patients in the QVM treatment group, and 0.75 (SE = 0.07) for patients in the SF + TIO treatment group, which corresponded to a treatment-group difference of 0.07 (1-sided 97.5% CI, −0.03 to infinity; P < 0.001) following the confirmatory testing procedure. The lower bound of the 97.5% CI was greater than −0.25, therefore noninferiority of QVM compared to SF + TIO was claimed. In addition, the primary outcome was analyzed in the PPS, which demonstrated results consistent with those of the primary analysis in the FAS based on a treatment-group difference of −0.07 (1-sided 97.5% CI, −0.032 to infinity). The sensitivity analysis conducted in the FAS using the LOCF approach was also consistent with the primary analysis.

The domains of the AQLQ and the SGRQ were included as additional assessments of HRQoL in the ARGON study and the results for both outcomes are presented in Table 17. None of these outcomes were controlled for multiplicity. The change from baseline in each of the domains of the AQLQ were similar to that of the total score. The mean (SE) change from baseline for the SGRQ was −13.29 [redacted] for the QVM treatment group and −11.30 [redacted] for SF + TIO, corresponding to a treatment-group difference of −2.00 (95% CI, −3.90 to −0.09; P = 0.040).

In the ARGON study, subgroup analyses on the primary end point, based on prior asthma therapy (medium-dose ICS-LABA or high-dose ICS-LABA) were performed (Table 36). At

the end of treatment (24 weeks), the LS mean difference between patients who were previously on a medium-dose ICS-LABA in the QVM treatment group compared to SF + TIO was [redacted] (95% CI, [redacted] to [redacted], P = [redacted]). The same comparison was made in a subgroup of patients who were previously on a high-dose ICS-LABA, which resulted in no treatment difference ([redacted], 95% CI, [redacted] to [redacted]; P [redacted]). Lastly, a sensitivity analysis of the primary end point was conducted in the PPS. The results of this analysis were consistent with the primary analysis.

Table 17: Health-Related Quality of Life – AQLQ and SGRQ (ARGON Trial)

	QVM 150 mcg/50 mcg/160 mcg N = 476	SF 50 mcg/500 mcg + TIO 5 mcg N = 475
AQLQ total score at week 24, change from baseline[a] – FAS		
Number of patients contributing to the analysis	453	435
Baseline, mean (SD)	4.67 (NR)	
Change from baseline, LS mean (SE)	0.83 (0.07)	0.75 (0.07)
Treatment difference versus SF + TIO, LS mean (97.5% CI 1-sided)[b]	0.07 (−0.03 to infinity), P < 0.001	
Treatment-group difference vs. control, LS mean (95% CI)	0.07 (−0.03 to 0.17)	
P value	0.152	
AQLQ symptoms domain at week 24, change from baseline[a] – FAS		
Number of patients contributing to the analysis	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	
Change from baseline, LS mean (SE)	[redacted]	[redacted]
Treatment-group difference vs. control, LS mean (95% CI)	[redacted]	
P value[c]	[redacted]	
AQLQ emotions domain at week 24, change from baseline[a] – FAS		
Number of patients contributing to the analysis	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	
Change from baseline, LS mean (SE)	[redacted]	[redacted]
Treatment-group difference vs. control, LS mean (95% CI)	[redacted]	
P value[c]	[redacted]	
AQLQ environmental stimuli at week 24, change from baseline[a] – FAS		
Number of patients contributing to the analysis	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	
Change from baseline, LS mean (SE)	[redacted]	[redacted]
Treatment-group difference vs. control, LS mean (95% CI)	[redacted]	
P value[c]	[redacted]	
AQLQ activity limitation at week 24, change from baseline[a] – FAS		
Number of patients contributing to the analysis	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	
Change from baseline, LS mean (SE)	[redacted]	[redacted]
Treatment-group difference vs. control, LS mean (95% CI)	[redacted]	
P value[c]	[redacted]	

	QVM 150 mcg/50 mcg/160 mcg N = 476	SF 50 mcg/500 mcg + TIO 5 mcg N = 475
SGRQ at week 24, change from baseline[d] – FAS		
Number of patients contributing to the analysis	476	475
Change from baseline, LS mean (SE)	−13.29 [redacted]	−11.30 [redacted]
Treatment-group difference vs. control, LS mean (95% CI)	−2.00 (−3.90 to −0.09)	
P value[c]	0.040	

AQLQ = Asthma Quality of Life Questionnaire; CI = confidence interval; FAS = full-analysis set; LS = least squares; MMRM = mixed model repeated measures; NR = not reported; QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate; SD = standard deviation; SE = standard error; SF = salmeterol-fluticasone propionate; SGRQ = St. George's Respiratory Questionnaire; TIO = tiotropium; vs. versus.

[a] MMRM with corresponding baseline AQLQ score as the covariate.

[b] Noninferiority analysis.

[c] P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

[d] Analysis of covariance with baseline SGRQ score as the covariate.

Source: ARGON Clinical Study Report.[6]

Asthma Control

The change from baseline in ACQ-7 score at week 26 was the key secondary outcome in the IRIDIUM study. The comparison between QVM and QMF was the only analysis included in the statistical testing hierarchy. The results for this outcome, and those for change from baseline in ACQ-7 at week 52, the proportion of patients who improved by at least 0.5 units at week 26 and week 52, the mean daily use of rescue medication over the 52-week treatment period, and the percentage of rescue medication–free days are provided in Table 18.

There was no difference in treatment between QVM and QMF (0.01; 95% CI, −0.07 to 0.09; P = 0.729). The reported treatment-group difference for QVM compared to SF was −0.09 (95% CI – 0.17 to – 0.01; P = 0.034). Similar results were observed at week 52. At week 26, the change from baseline in the ACQ-7 score ranged from a LS mean of −0.89 (SE = 0.03) to −0.99 (SE = 0.03) across treatment groups. Among the 3 treatment groups, 67.4% to 74.2% of patients achieved an improvement of at least 0.5 in the ACQ-7 score at week 26, and 72.8% to 78.8% did the same at week 52. There was no difference between QVM and the 2 comparators, with the exception of QVM and SF at week 52 based on an odds ratio of 1.41 (95% CI, 1.06 to 1.86; P = 0.017); however, this was outside of the statistical testing hierarchy.

At baseline, patients used approximately 2 puffs of rescue medication per day (mean number of puffs ranged from 1.84 to 2.07). The change from baseline in the number of puffs of rescue medication used over the 52-week treatment period was similar across treatment groups, based on an LS mean of −0.76 (SE = 0.06) to −0.88 (SE = 0.06). In addition, patients reported 38.5% to 42.7% days free of rescue medication use at baseline. The change from baseline in this outcome at week 52 ranged from an LS mean of 21.8% (SE = 1.36) to 25.0% (SE = 1.36), a difference that was not statistically significant.

A subgroup analysis by prior asthma therapy (medium-dose ICS-LABA and high-dose ICS-LABA) was also conducted on the key secondary outcome (ACQ-7 scores at week 26). Briefly, a differential treatment effect based on the LS mean difference was not observed for comparisons between QVM and both of the active comparators, with the exception of SF in patients previously on a medium-dose ICS-LABA based on an LS mean treatment

difference of [redacted] (95% CI, [redacted] to [redacted]; P [redacted]); however, subgroup analyses were not controlled for multiplicity.

Table 18: Asthma Control – ACQ-7, Rescue Medication Use (IRIDIUM Trial)

	QVM 150 mcg/50 mcg/160 mcg N = 619	QMF 150 mcg/320 mcg N = 618	SF 50 mcg/500 mcg N = 618
ACQ-7, change from baseline at week 26[a] – FAS			
Number of patients contributing to the analysis	566	562	562
Baseline, mean (SD)	2.52 (NR)		
End-of-treatment time point (week 26), LS mean (SE)	[redacted]	[redacted]	[redacted]
Change from baseline, LS mean (SE)	−0.98 [redacted]	–0.99 [redacted]	–0.89 [redacted]
Treatment-group difference vs. control, LS mean (95% CI)	0.01 (−0.07 to 0.09) vs. QMF 150 mcg/320 mcg −0.09 (−0.17 to −0.01) vs. SF[b]		
P value	0.729 vs. QMF 150 mcg/320 mcg 0.034 vs. SF[b]		
ACQ-7, change from baseline at week 52[a] – FAS			
Number of patients contributing to the analysis	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]		
End-of-treatment time point (week 52), LS mean (SE)	[redacted]	[redacted]	[redacted]
Change from baseline, LS mean (SE)	[redacted]	[redacted]	[redacted]
Treatment-group difference vs. control, LS mean (95% CI)	[redacted]		
P value[b]	[redacted]		
ACQ-7 score, proportion of patients with improvement of ≥ 0.5 units at week 26[c] – FAS			
n (%)	403 (71.2)	417 (74.2)	379 (67.4)
Odds ratio (95% CI)	0.92 (0.70 to 1.20) vs. QMF 150 mcg/320 mcg 1.21 (0.93 to 1.57) vs. SF		
P value[b]	0.535 vs. QMF 150 mcg/320 mcg 0.151 vs. SF		
ACQ-7 score, proportion of patients with improvement of ≥ 0.5 units at week 52[c] – FAS			
n (%)	435 (78.8)	426 (77.9)	398 (72.8)
Odds ratio (95% CI)	1.10 (0.837 to 1.47) vs. QMF 150 mcg/320 mcg 1.41 (1.06 to 1.86) vs. SF		
P value[b]	0.510 vs. QMF 150 mcg/320 mcg 0.017 vs. SF		
Mean daily number of puffs of rescue medication during weeks 1 to 52[d] – FAS			
Number of patients contributing to the analysis	607	596	597
Baseline, mean (SD)	1.89 (NR)	2.07 (NR)	1.84 (NR)
End-of-treatment time point (specify), mean (SE)	NR	NR	NR
Change from baseline, LS mean (SE)	−0.88 (0.06)	−0.83 (0.06)	−0.76 (0.06)
Treatment-group difference vs. control, LS mean (95% CI)	−0.04 (−0.19 to 0.10) vs. QMF 150 mcg/320 mcg −0.12 (−0.27 to 0.03) vs. SF		

	QVM 150 mcg/50 mcg/160 mcg N = 619	QMF 150 mcg/320 mcg N = 618	SF 50 mcg/500 mcg N = 618
P value[b]	0.563 vs. QMF 150 mcg/320 mcg 0.117 vs. SF		
Percentage of rescue medication–free days during weeks 1 to 52[d] – FAS			
Number of patients contributing to the analysis	583	576	578
Baseline, mean (SD)	39.5 (NR)	38.5 (NR)	42.7 (NR)
End-of-treatment time point (specify), mean (SE)	NR	NR	NR
Change from baseline, LS mean (SE)	25.0 (1.36)	24.9 (1.36)	21.8 (1.36)
Treatment-group difference vs. control, LS mean (95% CI)	0.1 (−3.4 to 3.6) vs. QMF 150 mcg/320 mcg 3.2 (−0.3 to 6.6) vs. SF		
P value[b]	0.963 vs. QMF 150 mcg/320 mcg 0.075 vs. SF		

ACQ-7 = 7-item Asthma Control Questionnaire; CI = confidence interval; FAS = full-analysis set; FEV_1 = forced expiratory volume in 1 second; LS = least squares; NR = not reported; QMF = indacaterol-mometasone furoate; QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate; SABA = short-acting beta2 agonist; SD = standard deviation; SE = standard error; SF = salmeterol-fluticasone propionate; vs. = versus.

[a] Mixed model repeated measures with the following covariates: baseline ACQ-7 score, baseline-by-visit interaction, FEV_1 prior to inhalation and FEV_1 within 15 to 30 minutes post-inhalation of salbutamol-albuterol (components of SABA reversibility).

[b] P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

[c] Logistic regression model with the following covariates: baseline ACQ-7 measurement, baseline-by-visit interaction, FEV_1 prior to inhalation and FEV_1 within 15 to 30 minutes post-inhalation of salbutamol-albuterol (components of SABA reversibility).

[d] Analysis of covariance with the following covariates: corresponding baseline value, FEV_1 prior to inhalation and FEV_1 within 15 to 30 minutes post-inhalation of salbutamol-albuterol (components of SABA reversibility).

Source: IRIDIUM Clinical Study Report.[5]

The same outcomes of asthma control were reported in the ARGON study, measured at week 24 (Table 19). None of the outcomes were included in the statistical testing hierarchy. At week 24, 85.2% and 83.9% of patients in the QVM and SF + TIO treatment groups, respectively, had an improvement of at least 0.5 on the ACQ-7. The change from baseline in the ACQ-7 was a LS mean of −1.17 (SE = 0.05) in the QVM treatment group and −1.05 (SE = 0.05) in the SF + TIO treatment group, corresponding to a treatment-group difference of −0.12 (95% CI, −0.22 to −0.03, P = 0.004). At baseline, patients used a mean number of [redacted] to [redacted] puffs per day. The change from baseline in the number of puffs of rescue medication used over the 24-week treatment period was a LS mean of [redacted] in the QVM treatment group and [redacted] in the SF + TIO treatment group. In addition, patients reported [redacted] days free of rescue medication use at baseline in both treatment groups, which increased to [redacted] in both treatment groups at week 24.

The ARGON study also used the 5-item Asthma Control Questionnaire score in an exploratory analysis of the proportion of patients who achieved a decrease of at least 0.5 units (the MCID) and at least 0.75 units. The results of both analyses were consistent with the results for the ACQ-7 (data not shown).

Table 19: Asthma Control – ACQ-7, Rescue Medication Use (ARGON Trial)

	QVM 150 mcg/50 mcg/160 mcg N = 476	SF 50 mcg/500 mcg + TIO 5 mcg N = 476
ACQ-7, change from baseline at week 24[a] – FAS		
Number of patients contributing to the analysis	452	436
Baseline, mean (SD)	2.61 (NR)	
End-of-treatment time point (week 24), LS mean (SE)		
Change from baseline, LS mean (SE)	−1.17 (0.05)	−1.05 (0.05)
Treatment-group difference vs. SF + TIO, LS mean (95% CI)	−0.12 (−0.22 to –0.03)	
P value[b]	0.004	
ACQ-7 score, proportion of patients with improvement of ≥ 0.5 units over 24 weeks[c] – FAS		
n (%)	387 (85.2)	375 (83.9)
Odds ratio vs. SF + TIO (95% CI)	1.11 (0.85 to 1.46)	
P value[b]	0.227	
Mean daily number of puffs of rescue medication over 24 weeks[d] – FAS		
Number of patients contributing to the analysis	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]
End-of-treatment time point (week 24), mean (SD)	[redacted]	[redacted]
Change from baseline, LS mean (SE)	[redacted]	[redacted]
Treatment-group difference vs. SF + TIO, LS mean (95% CI)	[redacted]	
P value[b]	[redacted]	
Percentage of rescue medication–free days over 24 weeks[d] – FAS		
Number of patients contributing to the analysis	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]
End-of-treatment time point (week 24), mean (SD)	[redacted]	[redacted]
Change from baseline, LS mean (SE)	[redacted]	[redacted]
Treatment-group difference vs. SF + TIO, LS mean (95% CI)	[redacted]	
P value[b]	[redacted]	

ACQ-7 = 7-item Asthma Control Questionnaire; CI = confidence interval; FAS = full-analysis set; LS = least squares; NR = not reported; QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate; SD = standard deviation; SE = standard error; SF = salmeterol-fluticasone propionate; TIO = tiotropium; vs. = versus.

[a] Mixed model repeated measures with corresponding baseline ACQ-7 score as the covariate.

[b] P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

[c] Logistic regression model via the generalized estimating equations with baseline ACQ-7 as the covariate.

[d] Analysis of covariance with appropriate baseline values (rescue medication use or percentage of rescue medication–free days) as the covariate.

Source: ARGON Clinical Study Report.[6]

Dyspnea

Dyspnea was a particular symptom of asthma that was important to patients and included in the systematic review protocol; however, dyspnea was not evaluated as an efficacy outcome in either of the included studies for this review.

Nocturnal Awakening

During the 52-week treatment period in the IRIDIUM study, patients reported an LS mean change of 16.9% (SE = 1.12) to 18.4% (SE = 1.13) in the percentage of nights without

nighttime awakenings (Table 20). The results for the percentage of nights without nighttime awakenings was similar during the 24-week treatment period in the ARGON study, where the LS mean (SE) change from baseline was [redacted] ([redacted]) in the QVM treatment group and [redacted] ([redacted]) in the SF + TIO treatment group (Table 21).

Table 20: Asthma Symptoms – Nighttime Awakenings (IRIDIUM Trial)

	QVM 150 mcg/50 mcg/160 mcg N = 619	QMF 150 mcg/320 mcg N = 618	SF 50 mcg/500 mcg N = 618
% nights without nighttime awakenings during weeks 1 to 52, change from baseline[a] – FAS			
Number of patients contributing to the analysis	599	582	586
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline, LS mean (SE)	18.0 (1.11)	18.4 (1.13)	16.9 (1.12)
Treatment-group difference vs. control, LS mean (95% CI)	−0.4 (−3.3 to 2.6) vs. QMF 150 mcg/320 mcg 1.1 (−1.9 to 4.0) vs. SF		
P value[b]	0.809 vs. QMF 150 mcg/320 mcg 0.467 vs. SF		

CI = confidence interval; FAS = full-analysis set; FEV_1 = forced expiratory volume in 1 second; LS = least squares; QMF = indacaterol-mometasone furoate; QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate; SABA = short-acting beta2 agonist; SE = standard error; SF = salmeterol-fluticasone propionate; vs. = versus.

[a] Analysis of covariance with the following covariates: baseline percent of nights without nighttime awakenings, FEV_1 prior to inhalation and FEV_1 within 15 to 30 minutes post-inhalation of salbutamol-albuterol (components of SABA reversibility).

[b] P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

Source: IRIDIUM Clinical Study Report.[5]

Table 21: Asthma Symptoms – Nighttime Awakenings (ARGON Trial)

	QVM 150 mcg/50 mcg/160 mcg N = 476	SF 50 mcg/500 mcg + TIO 5 mcg N = 476
% nights without nighttime awakenings over 24 weeks, change from baseline[a] – FAS		
Number of patients contributing to the analysis	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	
Change from baseline, LS mean (SE)	[redacted]	[redacted]
Treatment-group difference vs. SF + TIO, LS mean (95% CI)	[redacted]	
P value[b]	[redacted]	

CI = confidence interval; FAS = full-analysis set; LS = least squares; QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate; SD = standard deviation; SE = standard error; SF = salmeterol-fluticasone propionate; TIO = tiotropium; vs. = versus.

[a] Analysis of covariance with baseline percent of nights without nighttime awakenings as the covariate.

[b] P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

Source: ARGON Clinical Study Report.[6]

Days of Missed Work or School

The number of days of missed work was not evaluated in the ARGON study. The number of days of missed school was not evaluated in either study.

In the IRIDIUM study, the percent of work time missed due to asthma problems was reported as a parameter of the WPAI, which was included as an exploratory measure of resource utilization in the study. At baseline, patients reported missing between [redacted] and [redacted] of work time due to asthma-related problems. The LS mean (SE) change from baseline ranged from [redacted] to [redacted] and did not correspond to treatment-group differences between QVM and each of the comparator groups.

Table 22: Days of Missed Work (IRIDIUM Trial)

	QVM 150 mcg/50 mcg/160 mcg N = 619	QMF 150 mcg/320 mcg N = 618	SF 50 mcg/500 mcg N = 618
% work time missed due to asthma problems[a]			
Number of patients contributing to the analysis	[redacted]	[redacted]	[redacted]
Baseline, raw mean	[redacted]	[redacted]	[redacted]
Change from baseline, LS mean (SE)	[redacted]	[redacted]	[redacted]
Treatment-group difference vs. control (95% CI)	[redacted]		
P value[b]	[redacted]		

CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; LS = least squares; QMF = indacaterol-mometasone furoate; QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate; SABA = short-acting beta2 agonist; SE = standard error; SF = salmeterol-fluticasone propionate; vs. = versus.

[a] Mixed media repeated measures with the following covariates: baseline percent work time missed due to asthma problems, baseline-by-visit interaction, FEV_1 prior to inhalation and FEV_1 within 15 to 30 min post-inhalation of salbutamol-albuterol (components of SABA reversibility).

[b] P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

Source: IRIDIUM Clinical Study Report.[5]

Patient Adherence to Regimens

Outcomes related to patient adherence to treatment regimens were not included in the IRIDIUM or ARGON studies. Treatment adherence was reported as a measure of safety and is reported in the Interventions section under Findings From the Literature of this review.

Ease of Use

Outcomes related to the ease of use of treatment regimens and their corresponding inhalation device were not included in the IRIDIUM or ARGON studies.

Exercise Tolerance

Outcomes related to exercise tolerance were not included in the IRIDIUM or ARGON studies.

Health Care Resource Utilization

Data related to health care utilization from the IRIDIUM and ARGON studies are provided in Table 23 and Table 24, respectively. The annualized rate of asthma or asthma

exacerbation–related visits to any facility type was [redacted] (95% CI, [redacted] to [redacted]), [redacted] (95% CI, [redacted] to [redacted]), and [redacted] (95% CI, [redacted] to [redacted]) in the QVM, QMF, and SF treatment groups, respectively. Patients in the QVM treatment group were less likely to visit a health care facility due to an asthma-related event compared to those in the SF treatment group, based on a rate ratio of [redacted] (95% CI, [redacted] to [redacted]; P [redacted]). The rate of hospitalizations during study treatment was not analyzed in the IRIDIUM study because less than [redacted] of patients experienced at least 1 event.

In the ARGON study, [redacted] of patients experienced an unplanned asthma-related outpatient visit to any facility type during study treatment and unplanned outpatient visits by facility type were similar between groups. Two patients in the QVM treatment group and 1 patient in the SF + TIO treatment group experienced an asthma-related hospitalization during study treatment.

Table 23: Health Care Utilization – Rate of Asthma-Related Outpatient Visits During Study Treatment (IRIDIUM Trial)

	QVM 150 mcg/50 mcg/160 mcg N = 619	QMF 150 mcg/320 mcg N = 618	SF 50 mcg/500 mcg N = 618
Asthma or asthma exacerbation–related outpatient visits to any facility type – FAS			
Number of patients contributing to the analysis	[redacted]	[redacted]	[redacted]
Annualized rate (95% CI)	[redacted]	[redacted]	[redacted]
Rate ratio (95% CI)		[redacted]	
P value[b]		[redacted]	

CI = confidence interval; FAS = full-analysis set; FEV_1 = forced expiratory volume in 1 second; QMF = indacaterol-mometasone furoate; QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate; SABA = short-acting beta2 agonist; SF = salmeterol-fluticasone propionate.

[a] Generalized linear model assuming a negative binomial distribution with the following covariates: FEV_1 prior to inhalation and FEV_1 15 to 30 minutes post-inhalation of salbutamol-albuterol (components of SABA reversibility).

[b] P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

Source: IRIDIUM Clinical Study Report.[5]

Table 24: Health Care Utilization – Outpatient Visits (ARGON Trial)

	QVM 150 mcg/50 mcg/160 mcg N = 476	SF 50 mcg/500 mcg + TIO 5 mcg N = 475
Number of patients with unplanned outpatient visits by facility type, n (%) – FAS		
Any facility type	[redacted]	[redacted]
Office or home visit	[redacted]	[redacted]
Emergency room or hospital	[redacted]	[redacted]
Other	[redacted]	[redacted]
Number of patients with asthma-related hospitalizations during study treatment – FAS		
n (%)	[redacted]	[redacted]

FAS = full-analysis set; QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate; SF = salmeterol-fluticasone propionate; TIO = tiotropium.

Source: ARGON Clinical Study Report.[6]

Harms

Only those harms identified in the review protocol are reported below. See Table 25 for detailed harms data.

Adverse Events

The proportion of patients reporting at least 1 AE ranged from 51.6% to 78.8% across treatment groups in both the ARGON and IRIDIUM studies. The most common reason for AEs in both studies was asthma (40.1% to 50.0% in the IRIDIUM study and 24.2% to 26.5% in the ARGON study). Other common reasons for AEs included nasopharyngitis (7.1% to 13.4% in both studies), bronchitis (4.0% to 8.9% in both studies), upper respiratory tract infection (URTI) (1.9% to 2.1% in the ARGON study and 5.4% to 8.5% in the IRIDIUM study), and viral URTI (2.1% to 2.3% in the ARGON study and 3.4% to 7.6% in the IRIDIUM study). There were no major discrepancies in AEs between treatment groups in the 2 studies.

Serious Adverse Events

The proportion of patients that reported an SAE ranged from 2.3% to 2.5% in the ARGON study and 7.0% to 9.3% in the IRIDIUM study. The most commonly reported SAE was asthma, reported by 1.5% to 2.0% of patients in the IRIDIUM study. All other SAEs (cholelithiasis, lower respiratory tract infection, pneumonia, and pulmonary embolism) were reported in no more than 1.1% of patients in any treatment group across the 2 studies.

Withdrawals Due to Adverse Events

Less than 4% of patients in any treatment group between the 2 studies stopped treatment due to an AE. The proportion of patients who withdrew due to an AE ranged from 2.1% to 3.4% in the IRIDIUM study and was ≤ 0.6% in the 2 treatment groups in the ARGON study. The most common reason for a WDAE was asthma (0.5% to 1.7% across treatments) in the IRIDIUM study.

Mortality

Six deaths were reported during the IRIDIUM study and 1 death was reported in the ARGON study. In the IRIDIUM study, 2 deaths occurred in the QVM treatment group due to cardiovascular events (“other cardiovascular”), and 4 deaths occurred in the QMF treatment group due to cancer (n =1), cardiovascular events (n = 2, both sudden death), and accidental reasons (n = 1); no deaths were reported in the SF treatment group. In the ARGON study, the single death in the SF + TIO treatment group was due to a cardiovascular event (hemorrhagic stroke).

Notable Harms

Infections (systemic and local), steroid effects (topical, systemic), cardiovascular events, anticholinergic effects, hypothalamic-pituitary-adrenal axis suppression, bone markers, and blood sugar levels were included as notable harms in the CADTH systematic review protocol. Infections were reported by [redacted] to [redacted] of patients in the IRIDIUM study and [redacted] to [redacted] of patients in the ARGON study, with the [redacted] reasons being due to nasopharyngitis, bronchitis, URTI, pharyngitis, and viral URTI, similar to what was reported for overall AEs. Cardiac and vascular disorders were reported in [redacted] to [redacted] of patients in the IRIDIUM study and [redacted] to [redacted] of patients in the ARGON study, and local systemic effects, including cough, oral thrush, nosebleeds, oropharyngeal pain and discomfort,

dysphonia, and larynx irritation, were reported in [redacted] to [redacted] of patients and [redacted] to [redacted] of patients in the IRIDIUM and ARGON studies, respectively. All other notable harms were reported in [redacted] of patients in any treatment group across both studies.

Table 25: Summary of Harms (Safety Set)

	IRIDIUM trial			ARGON trial	
	QVM 150 mcg/ 50 mcg/ 160 mcg N = 616	QMF 150 mcg/ 320 mcg N = 613	SF 50 mcg/ 500 mcg N = 618	QVM 150 mcg/ 50 mcg/ 160 mcg N = 476	SF 50 mcg/ 500 mcg + TIO 5 mcg N = 476
Patients with ≥ 1 AE					
n (%)	458 (74.4)	454 (74.1)	487 (78.8)	249 (52.3)	245 (51.6)
Most common events,[a] n (%)					
Asthma	247 (40.1)	256 (41.8)	309 (50.0)	115 (24.2)	126 (26.5)
Nasopharyngitis	64 (10.4)	73 (11.9)	83 (13.4)	34 (7.1)	43 (9.1)
Bronchitis	49 (8.0)	46 (7.5)	55 (8.9)	22 (4.6)	19 (4.0)
URTI	33 (5.4)	52 (8.5)	52 (8.4)	10 (2.1)	9 (1.9)
Cough	24 (3.9)	11 (1.8)	15 (2.4)	7 (1.5)	9 (1.9)
Dysphonia	24 (3.9)	10 (1.6)	12 (1.9)	8 (1.7)	7 (1.5)
Headache	23 (3.7)	24 (3.9)	25 (4.0)	15 (3.2)	9 (1.9)
Pharyngitis	22 (3.6)	21 (3.34)	20 (3.2)	17 (3.6)	10 (2.1)
Viral URTI	21 (3.4)	38 (6.2)	47 (7.6)	11 (2.3)	10 (2.1)
Influenza	19 (3.1)	23 (3.8)	25 (4.0)	1 (0.2)	0
Rhinitis allergic	19 (3.1)	9 (1.5)	20 (3.2)	3 (0.6)	6 (1.3)
Respiratory tract viral infection	18 (2.9)	11 (1.8)	22 (3.6)	9 (1.9)	6 (1.3)
Bacterial URTI	17 (2.8)	27 (4.4)	29 (4.7)	9 (1.9)	9 (1.9)
Hypertension	16 (2.6)	14 (2.3)	23 (3.7)	5 (1.1)	5 (1.1)
LRTI	14 (2.3)	14 (2.3)	24 (3.9)	6 (1.3)	7 (1.5)
Sinusitis	14 (2.3)	9 (1.5)	14 (2.3)	8 (1.7)	9 (1.9)
Patients with ≥ 1 SAE					
n (%)	46 (8.2)	52 (9.3)	39 (7.0)	18 (3.8)	19 (4.0)
Most common events,[b] n (%)					
Asthma	9 (1.6)	12 (2.1)	9 (1.6)	2 (0.4)	2 (0.4)
Cholelithiasis	3 (0.5)	0	1 (0.2)	[redacted]	[redacted]
Lower respiratory tract infection	1 (0.2)	3 (0.5)	2 (0.3)	–	–
Pneumonia	3 (0.5)	1 (0.2)	5 (0.9)	5 (1.1)	0
Pulmonary embolism	1 (0.2)	3 (0.5)	0	–	–
Patients who stopped treatment due to AEs					
n (%)	13 (2.1)	18 (2.9)	21 (3.4)	2 (0.4)	3 (0.6)
Most common events,[c] n (%)					
Asthma	3 (0.5)	6 (1.0)	10 (1.7)	–	–

	IRIDIUM trial			ARGON trial	
	QVM 150 mcg/ 50 mcg/ 160 mcg N = 616	QMF 150 mcg/ 320 mcg N = 613	SF 50 mcg/ 500 mcg N = 618	QVM 150 mcg/ 50 mcg/ 160 mcg N = 476	SF 50 mcg/ 500 mcg + TIO 5 mcg N = 476
Deaths					
n (%)	2 (0.3)	4 (0.6)	0	0	1 (0.2)
Causes of death, n (%)					
Cancer	0	1 (0.2)	0	0	0
Cardiovascular events	2 (0.3)	2 (0.3)	0	0	1 (0.2)
Accidental	0	1 (0.2)	0	0	0
Notable harms					
AEs of interest, n (%)					
Infections (systemic and local)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac and vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood glucose increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood glucose decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypoglycemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anticholinergic effects[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bone markers (blood alkaline phosphatase increased)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HPA axis suppression[e]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Systemic steroid effects[f]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Local systemic effects[g]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

– = not recorded; AE = adverse event; HPA = hypothalamic-pituitary-adrenal; LRTI = lower respiratory tract infection; QMF = indacaterol-mometasone furoate; QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate; SAE = serious adverse event; SF = salmeterol-fluticasone; TIO = tiotropium; URTI = upper respiratory tract infection.

[a] Frequency of at least 3% of patients affected in any treatment group.

[b] Frequency of at least 3 patients in any treatment group.

[c] Frequency of at least 2 patients in any treatment group.

[d] Includes dry mouth, constipation, urinary retention, bowel obstruction, dilated pupils, blurred vision, increased heart rate, and decreased sweating.

[e] Includes secondary glucocorticoid insufficiency and adrenal hypercorticism (Cushing's, hyperglycemia, and glycosuria).

[f] Includes glaucoma, loss of vision, cataract, osteoporosis, increased appetite, insomnia, adrenal insufficiency.

[g] Includes cough, oral thrush, nosebleeds, oropharyngeal pain and discomfort, dysphonia, and larynx irritation.

Source: Clinical Study Reports for IRIDIUM[5] and ARGON.[6]

Critical Appraisal

Internal Validity

Both of the studies randomized patients using an acceptable methodology, IRT. The IRIDIUM trial also employed a double-dummy technique to maintain the double-blind study design. In contrast, the ARGON study was a partially blinded study as the active comparator, SF + TIO, was open-label and patients randomized to the 2 QVM treatment groups were blinded only to the dose of QVM they were given. Patients and investigators also had full knowledge of treatment allocation. The primary end point in the ARGON study was a measure of HRQoL based on a patient-reported outcome, which is a potential limitation given the partially blinded study design.

A high proportion of patients had severely uncontrolled asthma based on a baseline ACQ-7 score or at least 2.5 in both studies, with a slight imbalance across treatment groups (IRIDIUM: [redacted] and [redacted] for QVM, QMF, and SF, respectively; ARGON: [redacted] for QVM and [redacted] for SF+ TIO). Additionally, patients were required to demonstrate bronchodilator reversibility for inclusion in both of the clinical trials, which may have resulted in a trial population more responsive to therapy. The treatment groups were otherwise well balanced by their baseline characteristics in both of the trials.

The proportion of patients who discontinued from the study was low and similar across treatment groups in IRIDIUM ([redacted]); this was not reported for the ARGON study. Discontinuation from study treatment was also infrequent, and similar across treatment groups in both studies (9.5% to 10.0% in the IRIDIUM study and 3.4% to 5.7% in the ARGON study). Concomitant asthma medications were permitted in both studies, and usage was high, occurring in [redacted] to [redacted] of patients in the IRIDIUM study and [redacted] to [redacted] in the ARGON study, possibly inflating the observed treatment effect in the 2 trials. Further, there was an imbalance in the reported use of oral corticosteroids, particularly in the IRIDIUM study ([redacted] for QVM, [redacted] for QMF, and [redacted] for SF) that could have biased the results in favour of the active comparator, SF.

The primary and key secondary outcomes in the IRIDIUM study were the change from baseline in $FEV_{1,}$ and change from baseline in ACQ-7 score at week 26. The former is an objective measure of lung function used in clinical practice. The ACQ-7 is a patient-reported tool used to assess asthma control with demonstrated validity, reliability, and responsiveness,[37,47,56] and a well-established within-patient MID of 0.5 points.[46,48] The primary outcome in the ARGON study is based on the patient-reported AQLQ, which assesses functional impairments experienced by patients with asthma. The AQLQ is also well-validated, demonstrating validity, reliability, and responsiveness,[32,57,58] with an MID of 0.5.[32-37] The IRIDIUM and ARGON studies did not explicitly impute missing data; however, the MMRM analyses used for the primary and secondary outcomes are based on the assumption of data missing at random. Both studies included planned sensitivity analyses on the primary analysis to evaluate the impact of missing data. This was done via a tipping-point analysis in the IRIDIUM study and using the LOCF approach in the ARGON study, both of which were supportive of the primary analysis in their respective studies. The impact of missing data on the remaining outcomes, which ranged from [redacted] to [redacted] in the ARGON study and [redacted] to [redacted] in the IRIDIUM study (depending on the outcome) is unclear due to a lack of sensitivity analyses on these end points. Further, the amount of missing data was greater in the active comparator groups, particularly SF, in the IRIDIUM study compared to QVM, but the impact of this issue on the results is also unclear.

A sequential testing procedure was used to control for inflated type I error due to multiple testing in both the IRIDIUM and ARGON studies. Both studies included 2 hypotheses for the primary end point and the IRIDIUM study also included 2 hypotheses for the secondary end point. No other outcomes were controlled for multiplicity and were therefore subject to inflated risk of type I error. In particular, asthma exacerbations and HRQoL (in the IRIDIUM study), outcomes of importance to clinicians and patients, were not controlled for multiplicity.

The primary and key secondary end points in the IRIDIUM study were analyzed at week 26 of the 52-week study. An interim analysis was conducted at this time by members of a pre-specified group from the sponsor's program team who were unblinded while the study was ongoing, which introduces the potential for bias, presumably in favour of QVM; however,

the primary outcome is based on an objective clinical measure and therefore less of a concern. The sponsor reported that the study continued under the management of a separate blinded team that replaced the pre-specified unblinded team.

The primary end point in the ARGON study was a test of noninferiority, using a noninferiority margin of −0.25 points on the AQLQ. The noninferiority margin was selected based on a clinically meaningful difference on the AQLQ, or one-half of the MID (0.5 points) for the AQLQ, which was considered reasonable by the clinical expert consulted for this review. No additional information about the selection of the noninferiority margin was provided.

Pre-specified exploratory subgroup analyses were conducted in the IRIDIUM and ARGON studies. Only patient randomization in the ARGON study was stratified by 1 of the subgroups analyzed (prior therapies used by patients; i.e., medium- and high-dose LABA-ICS), and neither study adjusted subgroup analyses for multiplicity. Interaction P values were reported for the subgroup analysis of the primary outcome in the IRIDIUM study only. Overall, the limitations of the subgroup analyses preclude concrete conclusions from being drawn.

External Validity

Based on the baseline characteristics, the ARGON and IRIDIUM studies appear to have included a cohort of patients for whom QVM 150 mcg/160 mcg is indicated; that is, patients who are not adequately controlled with a maintenance combination of a LABA and a medium or high dose of an ICS and who experienced 1 or more asthma exacerbations in the previous 12 months. According to the clinical expert consulted for this review, a high proportion of patients had severely uncontrolled asthma based on a baseline ACQ-7 score equal to or greater than 2.5 in both studies and the proportion of patients with a history of smoking was also higher than is typically seen in Canadian clinical practice. The clinical expert consulted by CADTH on this review also noted that the inclusion and exclusion criteria of the ARGON and IRIDIUM studies would capture less than half of patients in their clinical practice, although this is similar to other RCTs for asthma-related therapies. One exception was that patients were required to demonstrate bronchodilator reversibility for inclusion in both of the clinical trials, which, in the opinion of the expert, was atypical of the target population of patients and may represent an enriched population. This is also reflected by the high proportion of screening failures ([redacted] to [redacted]) in both studies, although specific reasons for screening failure were not reported. Additionally, a baseline ACQ-7 score of at least 1.5 points was used as an indication of inadequately controlled asthma, which was used as an inclusion criterion in both trials; however, this may not be followed exactly by clinicians in clinical practice, where the use of ACQ-7 is not a standard of practice, according to the clinical expert consulted for this review. This typical enrichment trial design would have made the treatment effect appear more optimal than what could be seen in the “real world,” where the patient population is less selective. Moreover, a total of 12 out of 451 sites for the IRIDIUM study were in Canada; the ARGON study did not include any Canadian sites. Therefore, the study results reflect a mean group-treatment effect based on a diverse patient population from various countries across different regions, which also made it difficult to extrapolate the results to a Canadian clinical setting.

The 2 trials included a range of efficacy outcomes that were important to patients and clinicians, such as outcomes related to asthma exacerbations, pulmonary function, HRQoL, and asthma control. While FEV_1 is a clinically relevant measure of pulmonary function, the clinical expert consulted for this review noted that it is generally not useful for making

decisions regarding the selection of treatments for asthma. Further, the ACQ-7, which was included as the key secondary outcome in the IRIDIUM study and used for inclusion criteria in both studies, is typically not used by family physicians, who would also be expected to be prescribing QVM in clinical practice. Outcomes related to dyspnea, days of missed school, exercise tolerance, patient adherence to regimens, and ease of use were not included in either of the trials for QVM. The lack of information regarding the latter 2 outcomes is a limitation of the QVM trials, as the Breezhaler device may be a barrier for use, according to the clinical expert. It is worth highlighting that correct and efficient use of the Breezhaler device would be more likely among patients in a clinical trial setting than among patients who received the device from their family physicians and use them at home. Studies and patient input show that adherence is 1 of the most critical determinants in treatment effect in a real-world setting, which could largely compromise the generalizability of the findings.

All of the treatment regimens used within the 2 trials, QVM 150 mcg/160 mcg, SF 50 mcg/500 mcg, and SF 50 mcg/500 mcg + TIO 5 mcg, were aligned with their use (or anticipated use) in Canadian clinical practice. The IRIDIUM and ARGON studies also included QVM 150 mcg/80 mcg as a treatment arm; however, this was subsequently not approved for use by Health Canada and was therefore not reported throughout this review. As previously described, concomitant medication use of asthma medications was common in both studies, but this is aligned with clinical practice according to the clinical expert consulted for this review.

Asthma is a chronic disease with seasonal patterns, and therefore clinical trials for controller therapies should be at least 6 months, and ideally at least 12 months, in duration. The treatment phases in the ARGON and IRIDIUM studies were 24 and 52 weeks in duration, respectively.[7] Therefore, both trials were of sufficient length to evaluate the primary and key secondary outcomes related to pulmonary function and HRQoL, according to the clinical expert consulted for this review. The 24-week duration of the ARGON study is likely insufficient for evaluating the effects of QVM on asthma exacerbations.

Indirect Evidence

The sponsor submitted an ITC report that involved a feasibility analysis for the purposes of assessing the viability of conducting an NMA for ITCs between Enerzair, Atectura, and other dual and triple asthma therapies for the treatment of patients with uncontrolled asthma. The sponsor concluded that it was not feasible due to the extensive heterogeneity in the literature, specifically study populations, study duration, and varying definitions of exacerbation.

The submitted feasibility assessment leveraged a robust systematic literature review of published asthma studies in adults and adolescents (12 years and older) between 1998 and 2019. The search aimed to locate drugs of interest with any comparisons to fixed or loose dual or triple therapies for asthma treatment and included sponsor-sponsored studies. The search identified 45 publications that meet the predefined inclusion criteria. The located studies represented a broad network of studies (Table 26 and Figure 6) across a number of treatment arms. When assessed for the comparability of the studies and inclusion into a larger network, the sponsor concluded that the studies were too heterogenous to allow for a meaningful analysis.

Previously published NMAs have reached similar conclusions regarding the heterogeneity of baseline characteristics, length of studies, and definitions of exacerbations found in the literature. This may be due in large part to the wide range in years of publication for a

clinical indication that has seen a large number of new agents and shifts in treatment patterns over the past decade. In addition, the patient population, requirements for trial length, and delivery devices have added greater variance over time to the evidence base.

Recent NMAs and systematic reviews have cited evident differences in baseline lung function and asthma severity that may explain potential inconsistencies in the evidence base.[59-61] Based on previously conducted systematic reviews with similar search strategies it can be assumed that studies that would meet inclusion were highly heterogeneous in terms of inclusion criteria and patient characteristics. It is important to note that techniques such as meta-regression are available to account for differences in study characteristics, but these methods often require a larger evidence base. However, the greatest limitation in the evidence base is the variation in definitions of exacerbation across studies. Extensive work has been completed to develop standard definitions but this forward-looking initiative makes it difficult to compare to previous studies that established many current first-line treatments.[62,63]

The conclusion of the sponsor feasibility assessment that no analysis was feasible due clinical heterogeneity in patient characteristic and outcome definitions is in line with recently published NMAs that cited similar challenges.

Table 26: Summary of the Number of Studies Testing Each Triple and Dual Therapy

Therapy type	Number of studies (N = 51)				
	Treatment	Low	Medium	High	Total
Fixed triple	QVM	[redacted]	[redacted]	[redacted]	[redacted]
	BDP-FOR-GLY	[redacted]	[redacted]	[redacted]	[redacted]
Loose triple	BDP-FOR + TIO	[redacted]	[redacted]	[redacted]	[redacted]
	ICS-LAB + TIO	[redacted]	[redacted]	[redacted]	[redacted]
	FP-SAL+TIO	[redacted]	[redacted]	[redacted]	[redacted]
Fixed dual	QMF	[redacted]	[redacted]	[redacted]	[redacted]
	BDP-FOR	[redacted]	[redacted]	[redacted]	[redacted]
	BUD-FOR	[redacted]	[redacted]	[redacted]	[redacted]
	FF-VI	[redacted]	[redacted]	[redacted]	[redacted]
	FP-FOR	[redacted]	[redacted]	[redacted]	[redacted]
	FP-SAL	[redacted]	[redacted]	[redacted]	[redacted]
	MF-FOR	[redacted]	[redacted]	[redacted]	[redacted]

BDP = beclomethasone dipropionate; BUD = budesonide; FF = fluticasone furoate; FOR = formoterol; FP = fluticasone propionate; GLY = glycopyrronium; ICS = inhaled corticosteroid; LABA = long-acting beta2 agonist; QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate; SAL = salmeterol; TIO = tiotropium; VI = vilanterol.

Source: Adopted from sponsor-submitted indirect treatment comparison.[64]

Figure 6: [redacted]

Figure 6 contained confidential information and was removed at the request of the sponsor.

[redacted]

Source: Adapted from sponsor-submitted indirect treatment comparison.[64]

Other Relevant Evidence

This section includes 1 sponsor-conducted study that was considered to address important gaps in the evidence included in the systematic review.

Long-Term Safety Study: Study 1304

Methods

Study 1304 is a multi-centre, open-label, single-arm, 52-week treatment study designed to assess the safety and tolerability of once-daily QVM administered at 150 mcg/50 mcg/160 mcg in Japanese patients with inadequately controlled asthma.

Study 1304 began with an initial 4-week screening period to assess study eligibility of patients, and to record their baseline values. At the beginning of the screening period, patients were prescribed 100 mcg of salbutamol as rescue medication to be used in the event of an asthma exacerbation. The treatment period lasted 52 weeks, followed by a telephone safety follow-up 30 days later.

Populations

Inclusion and Exclusion Criteria

The study population enrolled 94 Japanese patients, aged 18 years or older, from 25 sites in Japan, who had previously used a medium- or high-dose ICS-LABA for at least 3 months, and these medications had been used at a stable dose for at least 1 month prior to the study.

A key difference between Study 1304 and the pivotal trials is the inclusion of participants in the pivotal trials of patients with a documented history of 1 or more asthma exacerbations requiring medical care in the past year. Unique to the ARGON study, patients were required to have an asthma diagnosis for 6 months prior to study initiation with a GINA step greater than or equal to 4, while in Study 1304 patients had a diagnosis of persistent asthma for 1 year prior to study initiation based on the GINA 2016 guidelines.

Baseline Characteristics

The baseline demographics and disease characteristics of patients included in Study 1304 are summarized in Table 27. Patients in Study 1304 were a mean age of 50.3 years old (similar to the pivotal trials), 53.2% were males ([redacted] more males than in the pivotal trials), and 100% were Asian. Overall, patients had been diagnosed with asthma for a mean of [redacted] years, which was 2 to 5 years longer than in the pivotal trials. Approximately [redacted] of patients had not had an asthma exacerbation in the previous year while in the pivotal trials all the patients had at least 1 exacerbation. [redacted] of patients in Study 1304 had never smoked. Mean baseline ACQ-7 score in Study 1304 was [redacted] which was approximately [redacted] points lower than the pivotal trials.

Baseline spirometry in Study 1304 were generally higher than those of patients enrolled in the IRIDIUM study.

Table 27: Summary of Baseline Characteristics (Safety Population)

Characteristic		QVM 150 mcg/50 mcg/160 mcg N = 94
Age (years)	Mean (SD)	50.3 (12.46)
	18 to 39, n (%)	15 (16.0)
	40 to 64, n (%)	68 (72.3)
	≥ 65, n (%)	11 (11.7)
Sex	Male, n (%)	50 (53.2)
Race	Asian	94 (100)
Duration of asthma (years)	Mean (SD)	[redacted]
	Median (range)	[redacted]
	< 1 year, n (%)	[redacted]
	1 to 5, n (%)	[redacted]
	> 5 to 10, n (%)	[redacted]
	> 10 to 15, n (%)	[redacted]
	> 15 to 20, n (%)	[redacted]
	> 20, n (%)	[redacted]
Number of asthma exacerbations in 12 months prior to study start that required treatment, n (%)	0	[redacted]
	1	[redacted]
	2	[redacted]
	3	[redacted]
	≥ 4	[redacted]
Smoking status, n (%)	Never smoker	[redacted]
	Former smoker	[redacted]
Baseline ACQ-7 score	Mean (SD)	[redacted]
	Median (range)	[redacted]
	< 1.5, n (%)	[redacted]
	1.5 to < 2.2, n (%)	[redacted]
	2.2 to < 2.5, n (%)	[redacted]
	≥ 2.5, n (%)	[redacted]
Prior asthma treatment	ICS low-dose	[redacted]
	ICS medium-dose	[redacted]
	ICS high-dose	[redacted]
	ICS-LABA low-dose	[redacted]
	ICS-LABA other than low-dose	[redacted]
FEV_1 pre-bronchodilator at baseline	n	[redacted]
	Mean (SD)	[redacted]
	Median (range)	[redacted]
FEV_1 pre-bronchodilator (% predicted FEV_1) at baseline	n	[redacted]
	Mean (SD)	[redacted]
	Median (range)	[redacted]
	< 40%, n (%)	[redacted]

Characteristic		QVM 150 mcg/50 mcg/160 mcg N = 94
	40% to < 60%, n (%)	[redacted]
	60% to ≤ 85%, n (%)	[redacted]
	> 85 %, n (%)	[redacted]
FEV_1 reversibility (% increase) at baseline	n	[redacted]
	Mean (SD)	[redacted]
	Median (range)	[redacted]
FEV_1 reversibility (increase in L) at baseline	n	[redacted]
	Mean (SD)	[redacted]
	Median (range)	[redacted]

ACQ-7 = 7-item Asthma Control Questionnaire; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; LABA = long-acting beta2 agonist; QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate; SD = standard deviation.

Source: Study 1304 Clinical Study Report[65].

Interventions

Patients took once-daily QVM administered at a dose of 150 mcg/50 mcg/160 mcg via Breezhaler at the same time of the evening. Use of rescue medication in the form of 100 mcg of salbutamol delivered via a pressurized metered-dose inhaler was permitted on an as-needed basis determined by the patient based on their symptoms. Training on use of the pressurized metered-dose inhaler for administration of salbutamol was provided on visit 1. Training on use of the Breezhaler device was completed on visit 99 within the screening phase; training kits were provided. If patients were unable to use the Breezhaler device correctly at this visit they were not eligible to enter the treatment phase. At each clinic visit thereafter investigators checked to ensure patients were using the Breezhaler device correctly.

Outcomes

The incidence and severity of treatment-emergent AEs was the primary outcome of Study 1304.

Secondary efficacy outcomes of interest to CADTH as important for inclusion in this review were efficacy in terms of lung function (assessed by pre-dose FEV_1), asthma control (ACQ-7), and the proportion of patients with an asthma exacerbation.

Statistical Analysis

Only descriptive statistics were reported for the safety and efficacy outcomes. The safety analysis set was used to summarize the safety outcomes, which included patients who received at least 1 dose of study medication. The FAS was used to summarize the efficacy outcomes, which also included patients who received at least 1 dose of study medication. An event was classified as a treatment-emergent AE if it occurred 7 days after the last administration of the study drug, and as an SAE if it occurred up to 30 days after the last administration of the study drug.

Baseline was defined as the last measurement before the first dose of the study drug, unless otherwise specified. No imputation was made for post-baseline missing data. In assessments in which 2 baseline values were recorded (pre-dose FEV_1), if 1 value was missing, then the other non-missing value was used as the baseline value. If both values

were missing, the baseline value was set to missing. For a missing ACQ-7 value, an ACQ-7 score obtained from the second screening visit, or any unscheduled screening visits, could be used as a baseline value.

Patient Disposition

The patient disposition for Study 1304 is summarized in Table 28. Of the 161 patients screened, 94 entered the treatment phase and 8 were discontinued from the study, 7 due to a patient or guardian decision.

Table 28: Patient Disposition (FAS)

	QVM 150 mcg/50 mcg/160 mcg
Screened, n	161
Randomized, n	94
Discontinued from study, n (%)	8 (8.5)
Reason for discontinuation, n (%)	
Patient or guardian decision	7 (7.4)
Physician decision	1 (1.1)
ITT, n	94
PP, n	NR
Safety, n	94

ITT = intention-to-treat; PP = per-protocol; QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate.

Source: Study 1304 Clinical Study Report.[65]

Exposure to Study Treatments

Patients were exposed to study treatment for a mean of [redacted] days, with [redacted] of patients exposed for between [redacted] and [redacted] days (Table 29). Patients in Study 1304 had a duration of exposure similar to those in the pivotal trials.

Table 29: Extent of Exposure to Study Drug (Safety Population)

	QVM 150 mcg/50 mcg/160 mcg N = 94
Exposure (days)	
Mean (SD)	[redacted]
Median (range)	[redacted]
Exposure categories, n (%)	
1 to 29 days	[redacted]
30 to 86 days	[redacted]
87 to 183 days	[redacted]
184 to 254 days	[redacted]
255 to 365 days	[redacted]
> 365 days	[redacted]

QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate; SD = standard deviation.

Source: Study 1304 Clinical Study Report.[65]

Efficacy

Acute Asthma Exacerbations

The proportion of patients with an acute asthma exacerbation and the corresponding severity level are described in Table 30. During the 52-week study, [redacted] and [redacted] of patients had a severe or moderate asthma exacerbation, respectively.

Table 30: Patients With Asthma Exacerbations (FAS)

	QVM 150 mcg/50 mcg/160 mcg N = 94
Proportion of patients with asthma exacerbations, by exacerbation category, n (%), FAS	
Moderate or severe	[redacted]
Severe	[redacted]
Moderate	[redacted]
Requiring hospitalization	[redacted]
Causing permanent discontinuation of study drug	[redacted]

QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate; FAS = full-analysis set.

Source: Study 1304 Clinical Study Report.[65]

Pre-Dose FEV_1

Overall, patients had a mean increase from baseline in pre-dose FEV_1 of [redacted], and [redacted] L at 12, 26, and 52 weeks, respectively (Table 31).

Table 31: Change From Baseline in Pre-Dose FEV_1 (FAS)

Pre-dose FEV_1[a]	Baseline	Post	Change
Baseline			
n	[redacted]		
Mean (SD)	[redacted]		
Week 12			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Week 26			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Week 52			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]

FAS = full-analysis set; FEV_1 = forced expiratory volume in 1 second; SD = standard deviation.

[a] Pre-dose FEV_1 is the average of the FEV_1 values taken 45 minutes and 15 minutes prior to administration of the first dose of study drug.

Source: Study 1304 Clinical Study Report.[65]

Asthma Control

Asthma control, in terms of ACQ-7 score, is described in Table 32. Patients exhibited an LS mean decrease from baseline of [redacted], [redacted], and [redacted], at 12, 26, and 52 weeks, respectively. At 26 and 52 weeks, there were [redacted] and [redacted] of patients with a decrease of 0.5 points or more in their ACQ-7 score.

Table 32: Asthma Control (FAS)

	Baseline	Week 12	Week 26	Week 52
ACQ-7, change from baseline				
Number of patients contributing to the analysis	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment, LS mean (SE)		[redacted]	[redacted]	[redacted]
Change from baseline, LS mean (SE)		[redacted]	[redacted]	[redacted]
ACQ-7, proportion of patients				
Proportion of patients with decrease of ≥ 0.5 units, n/m[a] (%)			[redacted]	[redacted]

ACQ-7 = 7-item Asthma Control Questionnaire; FAS = full-analysis set; LS = least squares; SD = standard deviation; SE = standard error.

[a] *m* is defined as the number of patients with data at the respective visit.

Source: Study 1304 Clinical Study Report.[65]

Harms

Adverse events of varying severity, WDAEs, and deaths are described in Table 33. During the 52-week study, 48.3% of patients experienced an AE at week 26 or later. Study 1304 saw 13.5% of patients report asthma as an AE, and 12.4% experienced nasopharyngitis.

Overall, there were 10 SAEs, and 2 patients withdrew from Study 1304 due to an AE. One patient in Study 1304 died due to an esophageal rupture. Regarding the harms identified as important in the review protocol, 22 patients experienced a local infection, and 2 patients experienced a local steroid effect.

Table 33: Summary of Harms (Safety Population)

	QVM 150 mcg/50 mcg/160 mcg N = 89
Patients with ≥ 1 AE[a]	
n (%)	43 (48.3)
Most common events,[b] n (%)	
Nasopharyngitis	11 (12.4)
Bronchitis	3 (3.4)
Pharyngitis	3 (3.4)
Headache	2 (2.2)
Asthma	12 (13.5)
Dysphonia	2 (2.2)
Patients with at least 1 SAE	
n (%)	6 (6.4)
Anal fistula	1 (1.1)

	QVM 150 mcg/50 mcg/160 mcg N = 89
Appendicitis	1 (1.1)
Cataract	1 (1.1)
Disseminated intravascular coagulation	1 (1.1)
Hypotension	1 (1.1)
Inguinal hernia	1 (1.1)
Lower respiratory tract infection	1 (1.1)
Esophageal rupture	1 (1.1)
Respiratory failure	1 (1.1)
Uterine leiomyosarcoma	1 (1.1)
Patients who stopped treatment due to an AE	
n (%)	2 (2.1)
Disseminated intravascular coagulation	1 (1.1)
Dysphonia	1 (1.1)
Hypotension	1 (1.1)
Lower respiratory tract infection	1 (1.1)
Esophageal rupture	1 (1.1)
Respiratory failure	1 (1.1)
Deaths	
n (%)	1 (1.1)
Esophageal rupture	1[c] (1.1)
Notable harms[a]	
n (%)	
Systemic infection	4 (4.5)
Local infection	22 (24.7)
Cardiac and vascular disorders	2 (2.2)
Blood glucose increased	NR
Anticholinergic effects	0
Local steroid effects	2 (2.2)
Systemic steroid effects	0
HPA axis suppression	0

AE = adverse events; HPA = hypothalamic-pituitary-adrenal; NR = not reported; QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate; SAE = serious adverse event.

Note: If a patient reported more than 1 AE with the same preferred term, the AE was counted only once.

[a] The AEs that had onset at 26 weeks or later were reported.

[b] At least 2 patients in the treatment group.

[c] Discontinued from study due to physician decision and died 92 days later.

Source: Study 1304 Clinical Study Report.[65]

Critical Appraisal

Internal Validity

The main limitations of Study 1304 include the open-label and single-arm design. The absence of a comparator limits the certainty of conclusions on efficacy and safety of QVM 150 mcg/50 mcg/320 mcg. Related to the open-label study design, investigators and patients were aware of the study drug administered, which may have biased the reporting of subjective outcomes such as safety.

External Validity

The generalizability of the results to the Canadian clinical practice context is uncertain because Study 1304 was conducted solely in Japan.

Summary

Results of Study 1304 are difficult to interpret because of the open-label, noncomparative design, lack of statistical testing, and because the study was conducted in Japan only.

Discussion

Summary of Available Evidence

Two RCTs conducted by the sponsor met the inclusion criteria for the systematic review, IRIDIUM (N = 3,092) and ARGON (N = 1,425). The IRIDIUM study was a phase III, multi-centre, randomized, double-blind, double-dummy, parallel-group study with a 52-week treatment period. The ARGON study was a phase IIIb, multi-centre, randomized, partially blinded, parallel-group, noninferiority, open-label, active-controlled study with a 24-week treatment period. The 2 trials evaluated the efficacy and safety of QVM 150 mcg/50 mcg/160 mcg via Breezhaler in adults with asthma. Patients included in the 2 trials were required to have a diagnosis of asthma that was inadequately controlled (an ACQ-7 score ≥ 1.5 at baseline), a pre-bronchodilator FEV_1 of at least 60% and less than 80% (IRIDIUM study) or less than 85% (ARGON study) of the predicted normal, and demonstrate bronchodilator reversibility. Patients also had at least 3 months of experience using a medium- or high-dose LABA-ICS at a stable dose for at least 1 month prior to screening.

The IRIDIUM study was designed to test the superiority of QVM 150 mcg/50 mcg/160 mcg once daily to QMF 150 mcg/320 mcg once daily in terms of the primary and key secondary end points, which were the change from baseline in trough FEV_1 and the ACQ-7 score, respectively, after 26 weeks of treatment. It also included SF 50 mcg/500 mcg administered twice daily via Accuhaler, although this comparison was not included in the statistical testing procedure. The ARGON study was designed to demonstrate noninferiority of QVM 150 mcg/50 mcg/160 mcg via Breezhaler to SF 50 mcg/500 mcg (via Diskus) + TIO 5 mcg (via Respimat) in terms of the AQLQ after 24 weeks of treatment. Outcomes related to asthma exacerbations, rescue medication use, and HRQoL were included as other secondary outcomes, as well as other measures of pulmonary function, nighttime symptoms (nighttime awakenings), and health care utilization. The WPAI (percent of work time missed due to asthma problems) was also included in the IRIDIUM study. Outcomes related to dyspnea, patient adherence to treatment regimen, and exercise tolerance were not included in either study.

A 52-week, open-label, single-arm, safety study, Study 1304, was also summarized for this review.

No ITCs were provided by the sponsor with the submission to CADTH. The sponsor's feasibility analysis for ITCs between QVM and other dual and triple asthma therapies for the treatment of patient with uncontrolled asthma concluded that ITCs were not feasible. A supplemental search of the literature did not identify published ITCs comparing QVM with other available treatments for asthma.

A key limitation of both studies is that they were not designed to evaluate the efficacy of QVM on asthma exacerbations, which is a patient important outcome and a key driver of health resource use in patients with asthma. The IRIDIUM study was designed to assess asthma control using the validated ACQ-7 as a key secondary outcome. An HRQoL measurement according to the change from baseline in the AQLQ was the primary outcome in the ARGON study. However, the partially blinded design of the study is a limitation considering the AQLQ is a patient-reported outcome, and may be susceptible to reporting bias related to knowledge of study treatment assignment. The 24-week duration of treatment in the ARGON study was also a limitation as it may not have provided a sufficient amount of time to assess the efficacy of a life-long treatment for asthma. Both studies are

limited by the generalizability of the results due to the select patient population enrolled (64% to 74% of screened patients were randomized, patients with severely uncontrolled asthma, and reversibility post-bronchodilator), which may not be representative of patients with asthma in Canadian clinical practice.

Interpretation of Results

Efficacy

A reduction in asthma exacerbations is an outcome important to patients, of key clinical relevance to treating physicians, and 1 of 2 outcomes recommended by the EMA for demonstrating efficacy of a new asthma controller medication in clinical trials.[7] Outcomes related to asthma exacerbations were reported in both the IRIDIUM and ARGON studies as other secondary outcomes. The IRIDIUM study confirms that adding a LAMA to an ICS-LABA therapy in patients who have poorly controlled severe asthma (GINA Steps 4 to 5) reduces the rate of asthma exacerbations. The proportion of patients with asthma exacerbations were reported descriptively and, based on numerical differences, patients treated with QVM experienced fewer exacerbations overall, and fewer severe exacerbations, than patients in the SF 50 mcg/500 mcg treatment group in the IRIDIUM study. Exacerbation rates were numerically similar between treatment groups in the ARGON study and QVM versus QMF in the IRIDIUM study. In addition, [redacted] of patients in any treatment group across the 2 trials experienced an exacerbation requiring hospitalization or, in the IRIDIUM study, causing permanent discontinuation of study drug. The annualized rate of all asthma exacerbations and severe exacerbations was also reported in both studies. The annualized rate of all exacerbations was lower in all of the QVM treatment groups versus comparators. The results for severe exacerbations did not follow the same trend. In the IRIDIUM study, treatment with QVM was associated with the lowest annualized rate of severe exacerbations, with a rate ratio of 0.78 (95% CI 0.61 to 1.00; P = 0.050) compared to QMF. The rate of severe exacerbations in patients treated with QVM was nearly half that of those treated with SF (rate ratio of 0.58; 95% CI, 0.45 to 0.73; P < 0.001). In the ARGON study, the annualized rate of severe exacerbations was numerically similar in the QMF and SF + TIO treatment groups (0.36; 95% CI, [redacted] to [redacted] and 0.32; 95% CI, [redacted] to [redacted], respectively). An MID has not been identified for the reduction in asthma exacerbations. While it can be argued that the impact of an exacerbation on HRQoL and the capacity to be life-threatening make any reduction in exacerbations clinically relevant,[66] the context of the analysis should be considered. Based on the available evidence, QVM appears to offer a benefit compared to ICS-LABA combinations, and is no worse than SF 50 mcg/500 mcg + TIO 5 mcg in terms of exacerbations; however, no firm conclusion could be drawn due to limitations in the study design. Further, the results in the ARGON study are based on 24 weeks of therapy, which may be of insufficient duration to properly assess the efficacy of a treatment for a disease that requires life-long treatment and has seasonal effects.

Various measures of pulmonary function were reported in the 2 trials and the change from baseline in trough FEV_1 and FVC at the end of the treatment period, and mean morning and evening PEF (L/min) during the treatment period were reported for this review. The primary outcome in the IRIDIUM study was the change from baseline in trough FEV_1 after 26 weeks of treatment, and superiority of QVM compared to QMF 150 mcg/320 mcg was demonstrated. The change from baseline was also numerically greater than that of the SF comparator group (treatment-group difference of 0.12 L; 95% CI, 0.09 to 0.15) in the IRIDIUM study and the SF + TIO treatment group at week 24 in the ARGON study

(treatment-group difference of 0.10 L; 95% CI, 0.05 to 0.15), although neither of these analyses were included in the statistical testing procedure. The minimal improvement from baseline in FEV_1 perceivable by a patient has been reported to be 230 mL.[29] The difference that constitutes a clinically meaningful difference between treatment groups, particularly when an active comparator is used, has been much debated, and remains uncertain because of limited published evidence relating to a between-group MID for FEV_1 among patients with asthma. The observed treatment effect decreased slightly at week 52 for all treatment groups in the IRIDIUM study, with the exception of QVM 150 mcg/50 mcg/160 mcg, for which the treatment effect was maintained. The treatment effect was similar in terms of FVC and mean morning and evening PEF at the end of treatment in both studies, or at week 52 in the IRIDIUM study and week 24 in the ARGON study. An MID was not available for FVC, but the within-group LS mean change from baseline in PEF, morning and evening, was clinically meaningful based on an MID of 25 L/min[67,68] for all QVM treatment groups as well as the QMF treatment group in the IRIDIUM study. According to the GINA guidelines, FEV_1 can be used as a predictor of risk of exacerbations and to determine if a new controller therapy is working; however, it does not correlate strongly with asthma symptoms in adults or children and between-visit variability limits its use for treatment adjustments in clinical practice.[2] The guidelines also state that an improvement in FEV_1 can be observed within days with regular ICS treatment and reaches a plateau around 2 months,[2] which makes the 24-week ARGON trial a sufficient duration for this particular outcome. The limitations associated with FEV_1 were relayed by the clinical expert consulted for this review as well. Overall, QVM demonstrated efficacy in terms of lung function; however, the applicability of the results to long-term use of a controller therapy is limited.

Health-related quality of life was identified as an outcome that is important to patients and was evaluated in both of the trials using the AQLQ, as well as the EQ-5D-5L VAS in the IRIDIUM study and SGRQ in the ARGON study; however, the total AQLQ score in the ARGON study was the only outcome controlled for multiplicity between the 2 trials. The primary outcome in the ARGON study was the change from baseline in AQLQ at week 24, which demonstrated the noninferiority of QVM to the free combination of SF + TIO using a noninferiority margin of 0.25 points (treatment-group difference of 0.07; 1-sided 97.5% CI, −0.03 to infinity; $P < 0.001$). While the selection of a partially blinded study design when the primary outcome is a patient-reported outcome can lead to bias, the study was appropriately powered for this analysis, sensitivity analysis using the PPS was in agreement with the results of the primary analysis, and the comparator was an active treatment for asthma, thereby potentially reducing expectations associated with use of a new treatment. The results of the domain scores were consistent with the overall score in the ARGON study as well, and the change from baseline in the SGRQ scores at week 24 was consistent with the results for the AQLQ between QVM and SF + TIO. At the end of treatment (week 24 or week 52), and based on the MID for the AQLQ (0.5 points), a clinically meaningful change in AQLQ overall score was reported for all treatment groups in the 2 trials. The EQ-5D-5L VAS results were reported descriptively in the IRIDIUM study and aligned with the results of the AQLQ. In summary, the analyses of HRQoL demonstrated the noninferiority of QVM compared to SF + TIO in the ARGON study, and the results of the IRIDIUM study indicate no difference in terms of HRQoL by QVM compared to QMF or SF; however, no conclusions can be drawn regarding between-group comparisons for HRQoL in the IRIDIUM study due to a lack of statistical testing (EQ-5D-5L VAS) or the absence of a control for multiplicity (AQLQ).

Asthma control, measured by the change from baseline in the ACQ-7 at week 26, was the key secondary outcome in the IRIDIUM study. The ACQ-7 is a multidimensional, patient-

reported (to clinic staff) questionnaire that is 1 of the most commonly used instruments for measuring asthma control in clinical trials and specialist clinical practice settings.[45,46] The treatment difference between QVM and QMF for the change from baseline in the ACQ-7 at week 26 was 0.01 points (95% CI, – 0.07 to 0.09; P = 0.729) and therefore did not demonstrate the superiority of QVM to QMF in terms of asthma control. The comparison of QVM to SF 50 mcg/500 mcg corresponded to a greater treatment difference (−0.09 points; 95% CI, −0.17 to −0.01; P = 0.034) although it was not included in the statistical testing procedure and was associated with an inflated risk for type I error. The proportion of patients with a clinically meaningful improvement in the ACQ-7, based on the MID of 0.5 points[46,48] was high across treatment groups (72.8% to 78.8%), and in favour of QVM based on the comparison to SF (between-groups difference of 1.21; 95% CI, 0.93 to 1.57; P = 0.017). In the ARGON study, the change from baseline in the ACQ-7 score (at week 24) between-groups difference for QVM versus SF + TIO favoured QVM (−0.12 points; 95% CI −0.22 to −0.03; P = 0.004); however, the difference was not considered clinically significant. The proportion of patients in the ARGON study with a difference in the ACQ-7 score of at least 0.5 points was similar between treatment groups (83.9% to 85.2%; P = 0.227). Asthma control was also assessed in the studies based on the use of rescue medication. No statistically significant differences were observed between groups based on use of rescue medication in both studies. With regards to within-group differences, the LS mean (SE) change from baseline for all treatment groups at the end of the corresponding treatment periods was clinically meaningful in terms of the ACQ-7.[46,48] The percentage of rescue medication–free days also improved among all treatment groups at the end of treatment, which corresponded to a clinically meaningful difference based on an MID of 8.4% to 15.6%.[69]

Nocturnal awakening, days of missed school or work, and health care resource utilization were outcomes included in the CADTH systematic review protocol that were also reported in the QMF clinical trials. The results for these outcome measures in the trials provide limited information regarding the effects of QMF partly because they were included as exploratory outcomes or evaluated as secondary outcomes outside of the statistical procedure for controlling for inflated type I error.

Preplanned subgroup analyses were conducted in both trials. The primary and key secondary outcomes in the IRIDIUM study were analyzed by prior asthma therapy (medium-dose ICS-LABA and high-dose ICS-LABA) and baseline ACQ-7 (asthma control, baseline score of 1.5 to < 2.0, 2.0 to < 2.5, and ≥ 2.5) and the AQLQ total score and trough FEV_1 at week 24 were analyzed by prior asthma therapy in the ARGON study. None of the subgroup analyses were included in the statistical testing procedure and must be considered exploratory. The only analysis that demonstrated a between-groups difference was the LS mean change from baseline in trough FEV_1 at week 24 in the medium-dose ICS-LABA subgroup in the ARGON study, which suggested a differential treatment effect in favour of QVM (LS mean [SE] of [redacted]) compared to SF + TIO (LS mean [SE] of [redacted]).

A key component of the sponsor's added clinical value of QVM is that it provides once-daily dosing of a combination of ICS-LABA-LAMA treatments in an easy-to-use inhaler device. The sponsor accurately noted that nonadherence, multiple inhalers, and critical errors using inhaler devices contribute to uncontrolled asthma. The sponsor's submission also highlighted that "Patients prefer combination inhalers, as well as once-daily dosing. This helps reduce treatment errors and is highly associated with a patient's willingness to use a medication."[70-72] Adherence to treatment regimens and ease of use of the Breezhaler

device were not evaluated in the IRIDIUM or ARGON studies. As the efficacy of inhaled treatment is partly dependent on the correct use of the inhalers, which was noted as a common issue for patients, the absence of data in the clinical trials for QVM regarding this issue is a notable gap in the evidence. A supplemental literature search was completed by CADTH for studies that assessed asthma patient preferences for the use of the Breezhaler device relative to comparator devices, which is summarized in Appendix 5. Three studies that included patients with asthma and chronic obstructive pulmonary disease (COPD) were identified that evaluated the use of Breezhaler as well as Genuair, Handihaler, Respimat, Turbuhaler, Diskus, Atrovent, and Ellipta. Briefly, the Breezhaler device was the least preferred device by patients, as well as the device for which patients required the most instruction and attempts to prepare correctly. A sponsor-submitted observational study that evaluated handling errors of inhaler devices, including Breezhaler, in patients with COPD was also reviewed. The Breezhaler had the lowest proportion of patients making critical errors at 15.4% (95% CI, 13.0% to 17.8%) compared to greater than 21% to 47% made with Diskus, Handihaler, a pressurized metered-dose inhaler, Respimat, or Turbuhaler. In the opinion of the clinical expert for this review, the Breezhaler device is disadvantaged by the need to insert a capsule each day rather than being a multi-dose device. Although adherence for all treatment groups in both the IRIDIUM and ARGON studies was generally high, which is not unusual in tightly managed trials, there remains a need for more data about the comparative impacts of the Breezhaler on adherence to treatment in clinical practice, and consequently the treatment efficacy.

Harms

The proportion of patients reporting at least 1 AE ranged from 51.6% to 78.8% across treatment groups in both the ARGON and IRIDIUM studies. Serious AEs were infrequent in both studies, where the proportion of patients who reported an SAE ranged from 2.3% to 2.5% in the ARGON study and 7.0% to 9.3% in the IRIDIUM study. Withdrawals from treatment due to AEs was also infrequent and reported by less than 4% of patients in any treatment group between the 2 studies. Asthma was the most commonly reported AE in both studies, which occurred in between 24.2% and 50.0% of patients, as well as the most commonly reported SAE and cause of WDAEs in the IRIDIUM study. Therefore, excluding asthma as an AE, the overall frequency of AEs was considered relatively low. Six deaths were reported during the IRIDIUM study and 1 death was reported in the ARGON study. In the IRIDIUM study, 2 deaths occurred in the QVM treatment group and 4 deaths occurred in the QMF treatment group. No deaths were reported in the SF treatment group. In the ARGON study, the single death occurred in the SF + TIO treatment group. The majority of deaths were caused by cardiovascular events, and none were adjudicated as asthma-related or considered related to the study drug.

Of the notable harms for this review, infections were reported most frequently by [redacted] to [redacted] of patients in the IRIDIUM study and [redacted] to [redacted] of patients in the ARGON study, with the most common reasons being nasopharyngitis, bronchitis, URTI, pharyngitis, and viral URTI, similar to what was reported for overall AEs. Local systemic effects, including cough, oral thrush, nosebleeds, oropharyngeal pain and discomfort, dysphonia, and larynx irritation, were reported in [redacted] to [redacted] of patients and [redacted] to [redacted] of patients in the IRIDIUM and ARGON studies, respectively.

The 24-week duration of the ARGON study was insufficient to draw conclusions about the long-term safety of QVM 150 mcg/50 mcg/160 mcg, and reporting of AEs was subject to bias due to the partial blinding of the study design. Evidence beyond 52 weeks of treatment

was available through 1 long-term safety study, Study 1304, which was a multi-centre, open-label, single-arm, 52-week treatment study designed to assess the safety and the tolerability of once-daily QVM administered at 150 mcg/50 mcg/160 mcg in Japanese patients with inadequately controlled asthma. The results are limited by the study design, which is subject to bias due to the absence of blinding and lack of a comparator, as well as uncertain applicability to the Canadian context based on the patient population. Overall, none of the specific AEs were associated with an imbalance between treatment groups in either of the trials for QVM.

Conclusions

QVM 150 mcg/50 mcg/160 mcg demonstrated superiority to high-dose ICS-LABA comparators, QMF 150 mcg/320 mcg and SF 50 mcg/500 mcg, in terms of the change from baseline in trough FEV_1 after 26 weeks of treatment and other measures of lung function; however, it failed to demonstrate superiority in terms of asthma control based on ACQ-7 scores after 26 weeks. The corresponding results of the noninferiority trial, which compared QVM 150 mcg/50 mcg/160 mcg to a loose triple ICS-LABA + LAMA combination, SF 50 mcg/500 mcg + TIO 5 mcg, were aligned with the IRIDIUM study in terms of these outcomes. QVM 150 mcg/50 mcg/160 mcg was noninferior to SF 50 mcg/500 mcg + TIO 5 mcg in terms of HRQoL based on the change from baseline measurements for the AQLQ after 24 weeks of treatment. The results of the other HRQoL outcomes included in both trials were aligned with this finding that no treatment differences in HRQoL were observed. In terms of asthma-related exacerbations, QVM appears to offer a benefit compared to ICS-LABA combinations, and no difference in benefit was observed when compared with SF 50 mcg/500 mcg + TIO 5 mcg; however, the results related to exacerbations in the 2 trials are subject to uncertainty due to a lack of statistical testing or control for multiplicity. There were insufficient data to determine whether the combination of QVM delivered via the Breezhaler device provides superior adherence to treatment or decreased critical errors in drug administration compared with other ICS-LABA treatments plus LAMA comparators administered separately.

Reports of SAEs and WDAEs were infrequent in all treatment groups. Seven deaths were reported between the 2 trials, most of which were caused by cardiovascular events and none were adjudicated as asthma-related or related to the study drug. No new safety signals were identified in the 52-week, open-label, safety-extension study.

The included evidence on the comparative effectiveness and safety of QVM to other alternative combination therapies is limited to the 2 RCTs that have been described, compromising the ability to sufficiently assess the advantages and disadvantages of QVM in the broader context of currently available treatments for asthma. The evidence that is available suggests that QVM 150 mcg/50 mcg/160 mcg is another option for patients with poorly controlled severe asthma (GINA Steps 4 to 5) who require a LAMA added to ICS-LABA therapy.

Appendix 1: Literature Search Strategy

Clinical Literature Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946–) Embase (1974–) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	June 16, 2020
Alerts:	Bi-weekly search updates until project completion
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as 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
MeSH	Medical Subject Heading
exp	Explode a subject heading
.ti	Title
.ab	Abstract
.dq	Candidate term word (Embase)
.ot	Original title
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.mp	Mapped term
.rn	Registry number
.yr	Publication year
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
Line #	**Search Strategy**
1	(indacaterol or glycopyrronium bromide plus indacaterol or qab 149* or qab149* or Onbrez or Arcapta or Hirobriz or Onbrize or Oslif or QVA149* or QVA 149* or ultibro or ulunar or utibron or xoterna or 8OR09251MQ or 2JEC1ITX7R).ti,ab,kf,ot,rn,nm,hw.
2	mometasone furoate/
3	(mometasone or mometason* or asmanex or danitin or ecural or elocon or elocone or elomet or flumeta or LAS 41002 or LAS41002 or monovo or nasonex or nosorex or ovixan or propel or rimelon or sinuva or elecom or mosaspray or rinelon

MULTI-DATABASE STRATEGY	
	or Sch 32088 or Sch32088 or BRN 4340538 or BRN4340538 or 04201GDN4R or 8HR4QJ6DW8 or MTW0WEG809).ti,ab,kf,ot,rn,nm,hw.
4	2 or 3
5	1 and 4
6	(indacaterol plus mometasone furoate or Enerzair* or qmf 149* or qmf149* or qvm149* or qvm 149* or indacaterol glycopyrronium mometasone).ti,ab,kf,ot,rn,nm,hw.
7	(IND adj3 GLY adj3 MF).ti,ab,kf,ot,rn,nm,hw.
8	6 or 7
9	5 or 8
10	9 use medall
11	*indacaterol/ or *glycopyrronium bromide plus indacaterol/
12	(indacaterol or glycopyrronium bromide plus indacaterol or qab 149* or qab149* or Onbrez or Arcapta or Hirobriz or Onbrize or Oslif or qva149* or qva 149* or ultibro or ulunar or utibron or xoterna).ti,ab,kw,dq.
13	11 or 12
14	*mometasone furoate/
15	(mometasone or mometason* or asmanex or danitin or ecural or elocon or elocone or elomet or flumeta or LAS 41002 or LAS41002 or monovo or nasonex or nosorex or ovixan or propel or rimelon or sinuva or elecom or mosaspray or rinelon or Sch 32088 or Sch32088 or BRN 4340538 or BRN4340538).ti,ab,kw,dq.
16	14 or 15
17	13 and 16
18	*indacaterol plus mometasone furoate/
19	(indacaterol plus mometasone furoate or Enerzair* or qmf 149* or qmf149* or qvm149* or qvm 149* or indacaterol glycopyrronium mometasone).ti,ab,kw,dq.
20	(IND adj3 GLY adj3 MF).ti,ab,kw,dq.
21	or/18-20
22	17 or 21
23	22 use oemezd
24	23 not (conference review or conference abstract).pt.
25	10 or 24
26	remove duplicates from 25

CLINICAL TRIAL REGISTRIES		
ClinicalTrials.gov	Produced by the U.S. National Library of Medicine. Targeted search used to capture registered clinical trials. Search updated prior to the completion of stakeholder feedback period. Search terms: indacaterol mometasone furoate OR QVM149 OR QVM 149 OR Enerzair	

OTHER DATABASES		
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	

Grey Literature

Search dates:	June 11, 2020
Keywords:	Indacaterol mometasone furoate OR QVM149 OR QVM 149 OR Enerzair
Limits:	None
Updated:	Search updated prior to the completion of stakeholder feedback period

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* (https://www.cadth.ca/grey-matters) were searched:

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

Appendix 2: Excluded Studies

Table 34: Excluded Studies

Reference	Reason for exclusion
Chapman KR, van Zyl-Smit R, Kerstjens HAM, Gessner C, Hosoe M, Tanase A, Pethe A, Shu X, D'Andrea P. Indacaterol/mometasone furoate fixed-dose combination improves lung function and decreases exacerbations compared with salmeterol/fluticasone in patients with uncontrolled asthma: pooled analyses of PALLADIUM and IRIDIUM studies. ATS 2020 Abstract A3004 (Conference cancelled).	Conference abstract
Kerstjens HAM, Maspero JF, Chapman KR, van Zyl-Smit R, Kato M, Hosoe M, Tanase A, Lavecchia C, Pethe A, Shu X, D'Andrea P. Indacaterol/glycopyrronium/mometasone furoate improves lung function and reduces exacerbations versus long-acting β2-agonist/inhaled corticosteroid standard-of-care in patients with uncontrolled asthma: the phase III IRIDIUM study. ATS 2020 Abstract A3007 (Conference cancelled).	Conference abstract
Papi A, Humbert M, Kostikas K, Domingo C, Maspero JF, Hosoe M, Tanase A, Pethe A, Shu X, D'Andrea P. Medium-dose indacaterol/glycopyrronium/mometasone furoate fixed-dose combination improves lung function compared with high-dose indacaterol/mometasone furoate and salmeterol/fluticasone and reduces exacerbation rates versus high-dose salmeterol/fluticasone in moderate-to-severe asthma: the IRIDIUM study. ATS 2020 Abstract A3008 (Conference cancelled).	Conference abstract
Gessner C, Kornmann O, Maspero J, van Zyl-Smit R, Krüll M, Sojo A, Salina A, Gupta P, Conde LG. Non-inferior improvement in asthma quality of life and favorable benefit in terms of lung function and asthma control with inhaled combination of indacaterol/glycopyrronium/mometasone furoate once-daily compared with the "loose" combination of salmeterol/fluticasone twice-daily plus tiotropium in patients with uncontrolled asthma: results of the phase III ARGON study. ATS 2020 Abstract A3010 (Conference cancelled).	Conference abstract
Study NCT03108027. Assess Bronchodilator Effect QVM149 Dosed Either in the Morning or Evening Compared to Placebo in Patients With Asthma. https://clinicaltrials.gov/ct2/show/study/NCT03108027	Phase II study

Appendix 3: Detailed Outcome Data

Subgroup Analyses

Figure 7: [redacted]

Figure 7 contained confidential information and was removed at the request of the sponsor.

Figure 8: [redacted]

Figure 8 contained confidential information and was removed at the request of the sponsor.

Table 35: IRIDIUM Trial Subgroup Analyses of ACQ-7 Scores

Subgroup	Treatment group	n	Baseline mean	End-of-treatment time point (week 26)		LS mean difference versus control	
				LS mean (SE)	LS mean change from baseline (SE)	LS mean difference (95% CI)	P value
ACQ-7 score, change from baseline at week 26 by prior asthma therapy[a]							
Medium ICS-LABA dose	QVM 150 mcg/ 50 mcg/ 160 mcg	[redacted]					
	QMF 150 mcg/ 320 mcg	[redacted]					
	SF 50 mcg/ 500 mcg	[redacted]					
High ICS-LABA dose	QVM 150 mcg/ 50 mcg/ 160 mcg	[redacted]					
	QMF 150 mcg/ 320 mcg	[redacted]					
	SF 50 mcg/ 500 mcg	[redacted]					

ACQ-7 = 7-item Asthma Control Questionnaire; CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; LABA = long-acting beta2 agonist; LS = least squares; SABA = short-acting beta2 agonist; SE = standard error.

[a] Mixed model repeated measures with the following covariates: baseline ACQ-7 score, baseline-by-visit interaction, FEV_1 prior to inhalation and FEV_1 within 15 to 30 minutes post-inhalation of salbutamol-albuterol (components of SABA reversibility).

[b] P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

Source: IRIDIUM Clinical Study Report.[5]

Table 36: ARGON Trial Subgroup Analyses (AQLQ Total Score and Trough FEV_1)

Subgroup	Treatment group	n	Baseline mean	End-of-treatment time point (week 24)		LS mean difference versus control	
				LS mean (SE)	LS mean change from baseline (SE)	LS mean difference (95% CI)	P value
AQLQ total score at week 24 by prior asthma therapy[a]							
Medium ICS-LABA dose	QVM 150 mcg/ 50 mcg/ 160 mcg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SF 50 mcg/ 500 mcg + TIO 5 mcg	[redacted]	[redacted]	[redacted]	[redacted]		
High ICS-LABA dose	QVM 150 mcg/ 50 mcg/ 160 mcg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SF 50 mcg/500 + TIO 5 mcg	[redacted]	[redacted]	[redacted]	[redacted]		
Trough FEV_1 at week 24 by prior asthma therapy[a]							
Medium ICS-LABA dose	QVM 150 mcg/ 50 mcg/160	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SF 50 mcg/ 500 mcg + TIO 5 mcg	[redacted]	[redacted]	[redacted]	[redacted]		
High ICS-LABA dose	QVM 150 mcg/ 50 mcg/ 160 mcg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SF 50 mcg/ 500 mcg + TIO 5 mcg	[redacted]	[redacted]	[redacted]	[redacted]		

AQLQ = Asthma Quality of Life Questionnaire; CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; LABA = long-acting beta2 agonist; LS = least squares; SD = standard deviation; SE = standard error.

[a] Mixed model repeated measures with appropriate baseline value (ACQ-7 total score or trough FEV_1) as the covariate.

[b] P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

Source: ARGON Clinical Study Report.[6]

Appendix 4: Description and Appraisal of Outcome Measures

Aim

To describe the following outcome measures summarized in Table 37 and review their measurement properties including validity, reliability, responsiveness to change, and MID.

Table 37: Outcome Measures Included in Each Study

Outcome measure	IRIDIUM trial	ARGON trial
FEV_1	Primary and other secondary	Secondary
FVC	Secondary	Secondary
PEF	Other secondary	Exploratory
AQLQ	Other secondary	Primary and secondary
EQ-5D-5L	Exploratory	NR
SGRQ	NR	Exploratory
ACQ-7	Secondary and other secondary	Secondary
Patient asthma control e-diary	Other secondary	Exploratory
WPAI: Asthma	Exploratory	NR

ACQ-7 = 7-item Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; NR = not reported; PEF = peak expiratory flow; SGRQ = St. George's Respiratory Questionnaire; WPAI = Work Productivity and Activity Impairment Questionnaire.

Source: Clinical Study Reports for ARGON[6] and IRIDIUM.[5]

Findings

Table 38: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MID
FEV_1	FEV_1 is the volume of air that can be forcibly expired in 1 second after a full inspiration.	**Validity:** Weak-to-strong correlations between the FEV_1 and various measures of clinical status (such as patient-reported symptoms), and quality of life measures (such as the AQLQ, the EuroQol VAS, and the Juniper AQLQ) support the presence of construct validity of the FEV_1.[73-76] **Reliability:** FEV_1 values demonstrated high within-session repeatability, with 90% of 18,526 patients able to reproduce FEV_1 within 120 mL.[77] **Responsiveness:** Weak correlations of change in percent predicted FEV_1 with patient-reported symptom-free days (r = 0.26) and moderate correlations with the change in AQLQ overall score (r = 0.38)	The MPPI for FEV_1 is 230 mL or a 10.38% change from baseline.[29]

Outcome measure	Type	Conclusions about measurement properties	MID
		support the presence of responsiveness.[73]	
FVC	FVC is the amount of air that can be forcibly exhaled from the lungs after taking the deepest breath possible.	No evidence regarding the validity, reliability, and responsiveness of the FVC has been identified.	No evidence regarding the MID of the FVC has been identified.
PEF	PEF is the maximum flow achieved during an expiration delivered with maximal force starting from the level of maximal lung inflation.	There is minimal evidence supporting the construct validity of the PEF through a moderate-strength correlation with the FEV_1.[78] No evidence was identified regarding the reliability or the responsiveness of the PEF.	An MID of 25 L/min has been used in clinical trials previously.[67,68] The MPPI for PEF was 18.8 L/min or a 5.39% change from baseline. In patients with acute asthma exacerbations presenting to the ED a predicted PEF of 12% has been identified as the MID.[79]
AQLQ	AQLQ is a patient-reported assessment of functional impairments experienced by patients with asthma. It includes 32 questions grouped into 4 domains: symptoms, activity limitations, emotional function, and environmental stimuli. Each question is scored on a 7-point Likert scale, which ranges from 7 (no impairment) to 1 (severe impairment). The overall score is calculated as the mean of all questions, and the 4 domain scores are the means of the scores for the questions in the respective domains.	**Validity:** Known-groups validity was established through large Cohen d values in patients with different levels of asthma severity.[32] Moderate-to-strong Spearman rank correlations with a variety of measures of health status indicate adequate longitudinal and cross-sectional validity.[57] **Reliability:** Test-retest and internal consistency reliability was adequate with an ICC > 0.7 and Cronbach alpha > 0.7 in 2 independent publications.[32,57] **Responsiveness:** The AQLQ is responsive to within-subject,[58] between-group, and to within-group changes in asthma severity.[57] Moreover, the AQLQ is responsive to between-group changes when groups are divided on a 3-point change in the ACT (the MID of the ACT).[32]	The MID for the AQLQ has been determined to be a cut point of 0.5, with publications reporting values such as 0.67,[32] 0.52,[33] and a range of 0.42 to 0.58 for the AQLQ domains.[34-37]
EQ-5D-5L	EQ-5D-5L is a general, non–disease-specific health-related quality-of-life questionnaire.	**Validity:** Known-groups validity was present when the ACQ-5 was used to classify patients in terms of asthma severity,[80] but was not present when PEF values were used to classify patients into categories of varying asthma severity.[81] Convergent validity was established through moderate-to-strong Spearman rank correlations with the Asthma Quality of Life Utility Index.[81]	There was no MID established in a population of patients with asthma. An MID of 0.056 is in general use for the Canadian population.[82]

Outcome measure	Type	Conclusions about measurement properties	MID
		Reliability: No evidence of reliability was identified. **Responsiveness:** The EQ-5D-5L was able to effectively discriminate between patient-reported improvement or deterioration in asthma.[81]	
SGRQ	SGRQ is a self-administered, asthma-specific, health-related quality-of-life questionnaire.	**Validity:** Content validity of the SGRQ was confirmed in a qualitative interview-based study, and a number of studies correlating the SGRQ with alternative measures of health status.[39-41] Longitudinal (assessed over a period of time) and cross-sectional (assessed at a point in time) validity were deemed acceptable for the SGRQ in a number of publications.[40-42] **Reliability:** No evidence regarding the reliability of the SGRQ was identified. **Responsiveness:** The SGRQ showed a large standardized response mean (−0.9) when 49 patients with improved asthma were assessed.[40]	An MID of 4 points has been established as a clinically meaningful change to asthma patients in a number of studies.[33,41,42]
ACQ-7	ACQ-7 is a patient-reported tool to assess asthma control. It comprises the following 7 questions, of which the mean of the results is the overall score ranging from 0 for well-controlled asthma to 6 for extremely poorly controlled asthma: • Daytime symptoms • Nighttime awakening or symptoms • Activity limitation • Rescue treatment requirements (use of SABA) • Lung function (FEV_1) • Shortness of breath • Wheezing	**Validity:** Studies support the presence of longitudinal, cross-sectional, and construct validity of the ACQ-7 through correlations with a variety of measures of health status.[37,47,56] Known-groups validity was established by significantly different ($P < 0.001$) ACQ-7 scores in patient groups split by presence of and lack of nighttime awakenings and rescue medication use.[37] **Reliability:** Test-retest and internal consistency reliability was adequate with an ICC > 0.7 and Cronbach alpha > 0.7 in 3 independent publications.[37,47,56] **Responsiveness:** The ACQ-7 was able to distinguish between adults with stable and unstable asthma in 2 independent publications ($P < 0.001$).[47,56]	The ACQ-7 MID has been well-established and accepted as 0.5 points for within-person change.[46,48]
Patient asthma control e-diary	An e-diary is provided to patients to record their rescue medication use, clinical symptoms, and PEF in the morning and evening.	No evidence was identified regarding the validity, reliability, or the responsiveness of the Patient Asthma Control e-diary; however, the EMA recommends the use of patient-recorded electronic diaries in the clinical investigation of the treatment of asthma.[7]	There was no MID identified for the Patient Asthma Control e-diary.

Outcome measure	Type	Conclusions about measurement properties	MID
WPAI: Asthma	WPAI is a patient-reported questionnaire for assessing the impact of a disease on work or school as well as daily activities specific to asthma.	**Validity:** Construct validity was assessed through Spearman correlations of weak strength with FEV_1 percent predicted, strong strength with the Asthma Therapy Assessment Questionnaire, and strong strength with the AQLQ score.[54] No evidence regarding the reliability and responsiveness of the WPAI: Asthma was identified.	No MID for the WPAI: Asthma was identified.

ACQ-5 = 5-item Asthma Control Questionnaire; ACQ-7 = 7-item Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; ACT = Asthma Control Test; EMA = European Medicines Agency; e-diary = electronic diary; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; ICC = intraclass correlation coefficient; MID = minimal important difference; MPPI = minimal patient perceivable improvement; PEF = peak expiratory flow; SGRQ = St. George's Respiratory Questionnaire; SABA = short-acting beta agonist; VAS = Visual Analogue Scale; WPAI = Work Productivity and Activity Impairment Questionnaire.

Source: Carranza et al. (2004),[73] Voorend-van et al. (2014),[74] Ehrs et al. (2001),[75] Moy et al. (2001),[76] Enright et al. (2004),[77] Santanello et al. (1999),[29] Ulrik et al. (2005),[78] Drazen et al. (1996),[67] Boushey et al. (2005),[68] Karras et al. (2000),[79] Szentes et al. (2020),[32] Juniper et al. (1993),[57] Juniper et al. (1999),[58] Jones et al. (2002),[33] Juniper et al. (2005),[35] Wyrwich et al. (2011),[37] Wywrich et al. (2011),[36] Hernandez et al. (2016),[80] Crossman-Barnes et al. (2020),[81] McClure et al. (2017),[82] Nelsen et al. (2017),[39] Sanjuas et al. (2002),[40] Jones et al. (1992),[41] Jones et al. (1991),[42] Juniper et al. (2004),[47] Juniper et al. (1999),[56] Barnes et al. (2014),[46] Jia et al. (2013),[48] and EMA Guidelines.[7]

Forced Expiratory Volume in 1 Second

Forced expiratory volume in 1 second is the maximal amount of air forcefully exhaled in 1 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 1 of the most commonly reported pulmonary function tests.[83] Moreover, trough FEV_1 and pre-dose FEV_1 are also used as clinical measures of lung function, with trough FEV_1 defined as the mean of the 2 FEV_1 values measured at 23 hours 15 minutes and 23 hours 45 minutes after the evening treatment dose is taken, and pre-dose FEV_1 defined as the mean of the 2 FEV_1 values measured 45 minutes and 15 minutes prior to the evening dose.[5,6] The EMA considers pre-bronchodilator FEV_1 as the most suitable measure of asthma control as it changes with acute fluctuations in airway limitation.[7]

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 COPD. Together with measures of asthma symptoms and use of inhaled SABAs, FEV_1 is used to classify the severity of asthma.[84,85] However, the extent to which FEV_1 values are associated with quality of life is uncertain, as researchers have reported variable correlations among adults and children with asthma, ranging from no association to strong associations.[73-76] Conversely, FEV_1 values appear to correlate well with certain clinical outcomes, such as the likelihood of hospitalization.[86] Furthermore, FEV_1 values have demonstrated high within-session repeatability. In a study of 18,526 adult patients, of whom 11% had a history of physician-diagnosed asthma, 90% were able to reproduce FEV_1 within 120 mL.[77] Moreover, responsiveness of the FEV_1 has been demonstrated through weak correlations of change in percent predicted FEV_1 with patient-reported symptom-free days ($r = 0.26$) and moderate correlations with the change in AQLQ overall score ($r = 0.38$).[73]

There appears to be limited published evidence relating to a MID for FEV_1 among adult patients with asthma. In 1 study of 281 adult patients with mild-to-moderate asthma symptoms (baseline mean = FEV_1: 2.30 L/s; SD = 0.66 L/s), the authors calculated the MPPI for FEV_1 as the mean change in FEV_1 in patients rating themselves as "a little better"

(n = 86) on the global rating of change in asthma.[29] Across all patients, the MPPI for FEV_1 was 230 mL or a 10.38% change from baseline. Males and females showed similar MPPI values, but older patients had a lower MPPI (170 mL) than younger ones (280 mL) for FEV_1.[29]

Forced Vital Capacity

The amount of air that can be forcibly exhaled from the lungs after taking the deepest breath possible as measured by spirometry is known as FVC. No evidence for validity, reliability, responsiveness to change, or MID was identified for the FVC measure. According to the EMA, evaluation of FVC can be used as a complementary end point in clinical trials.[7] However, use of FVC in clinical trials may be limited by evidence drawn from an evaluation of 6,323 never-smoking adults, aged 20 to 24 at 42 study centres around the world. In this study, Chinn et al. described the variation typically seen in FVC values, and when the FVC values were adjusted for multiple factors (such as age, height, sex, country, and type of instrument) only half of the observed variation could be accounted for.[87]

Peak Expiratory Flow

Peak expiratory flow, sometimes referred to as PEF rate, is defined as "the maximum flow achieved during an expiration delivered with maximal force starting from the level of maximal lung inflation."[30] Electronic peak flow meters automatically store and download measurements as needed, circumventing the need for patients to manually record PEF values in diaries. The PEF is usually expressed in units of litres per minute (L/min) and sometimes as a percentage of the predicted normal value or as a change from baseline average values.[88] The EMA considers PEF (along with FEV_1) a valid spirometric evaluation for anti-asthmatic drugs.[7] PEF values appear to discriminate between patients with reversible and irreversible airflow obstruction.[89] PEF values also appear to be valid clinical markers of airway responsiveness and asthma severity.[88] In addition, they seem to correlate well with other measures of lung function, including FEV_1,[78] although evidence that directly links PEF with quality of life is lacking. Some trial researchers have used a value of 25 L/min as an MID for PEF values among patients with asthma.[67,68] However, no research appears to support the use of this MID. In 1 study of 281 adult patients with mild-to-moderate asthma symptoms, researchers calculated the MPPI for PEF as the mean change in PEF in patients rating themselves as "a little better" (n = 86) on the global rating of change in asthma. The MPPI for PEF was 18.8 L/min, or a 5.39% change from baseline, with no differences in MPPI values by gender or age.[29] In another study, researchers noted a predicted PEF of approximately 12% to be a minimal clinically significant improvement among patients presenting to the ED with acute asthma exacerbation.[79]

Asthma Quality of Life Questionnaire

The AQLQ is a patient-reported, disease-specific, health-related quality-of-life measure that was developed to evaluate asthma in the clinical trial setting.[31] The AQLQ includes 32 questions grouped into 4 domains: symptoms, activity limitations, emotional function, and environmental stimuli. Each question is scored on a 7-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 4 domain scores are the means of the scores for the questions in the respective domains. Patients recall their relevant experiences during the previous 2 weeks. The EMA recommends the use of patient-reported outcomes such as the validated AQLQ, in clinical trials that assess HRQoL.[7] The AQLQ showed no evidence for a floor or a ceiling effect.[32]

Validity

The AQLQ was assessed 3 months apart in a group of patients defined as having either *well-controlled asthma* or *not well-controlled asthma* to evaluate known-groups validity. The AQLQ showed the best discriminatory power when compared to the EQ-5D as evaluated through large Cohen d values, indicating that the AQLQ was able to distinguish between clinical groups with different asthma severities.[32] Cross-sectional validity, evaluated at a point in time, and longitudinal validity, evaluated over time, was evaluated in a cohort of patients with symptomatic asthma (N = 39) with Spearman rank correlations. The change in the AQLQ domains showed no correlations to strong correlations with measure of clinical status such as the percent predicted FEV_1 (r = 0.27 to 0.43), asthma control, asthma global ratings of change (r = 0.52 to r = 0.82), the Sickness Impact Profile (r = 0 to r = 0.24), and the Rand General Health Survey (r = 0.3 to r = 0.51), indicating the presence of longitudinal construct validity. With regards to cross-sectional validity, the AQLQ domains displayed a strong Spearman rank correlation coefficient with asthma control (r = 0.31 to r = 0.69), and there were no relationships with the other measures of clinical status outlined above.[57]

Reliability

Test-retest reliability was evaluated 4 weeks apart in 2 separate studies with patients whose asthma was deemed stable for 4 weeks, evaluated by the investigators. In both studies an intraclass correlation coefficient (ICC) of greater than 0.7 indicated that the AQLQ displayed test-retest reliability.[32,57]

Responsiveness

The AQLQ is responsive to within-subject changes both in patients whose asthma was stable and whose asthma changed (responsiveness indices of 1.35 for the AQLQ).[58] The AQLQ is also responsive to changes between groups with stable and with worsened asthma ($P < 0.001$), and to changes within groups ($P < 0.001$).[57] In a publication by Szentes et al.,[32] when the patients were divided into those who had a 3-point change in the asthma control test (MID of the asthma control test) and those who did not, the AQLQ was highly responsive, explaining 0.63 of the variance.

Clinical Relevance

The MID for the AQLQ has been determined to be a cut point of 0.5, with publications reporting values such as 0.67,[32] 0.52,[33] and a range of 0.42 to 0.58 for the AQLQ domains.[34,35-37]

EuroQol 5-Dimensions 5-Levels Questionnaire

The EQ-5D questionnaire is a generic quality-of-life instrument developed by the EuroQol Group.[43] It can be applied to a wide range of health conditions and treatments.[43] As a generic measure of HRQoL that can capture the net effect of treatment benefits and harms, the EQ-5D provides valuable information from a patient perspective. In addition, the EQ-5D is used in clinical trials to obtain utility weights for economic models.[44] The EQ-5D-5L consists of the EQ-5D descriptive system and a VAS. The descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, each with 5 levels: a level-1 response = no problems, level 2 = slight problems, level 3 = moderate problems, level 4 = severe problems, and level 5 = extreme problems or unable to perform, which is the worst response in the dimension. Respondents

are asked to choose the level that reflects their health state for each of the 5 dimensions. In total, 3,125 possible unique health states can be defined by the EQ-5D-5L, with 11111 and 55555 representing the best and worst health states. The numerical values assigned to levels 1 to 5 for each dimension reflect rank order categories of function. In terms of measurement properties, these are ordinal data; they do not have interval properties and therefore should not be summed or averaged to produce, for example, an individual dimension "score." Results from the EQ-5D-5L descriptive system can be converted into a single index score using a scoring algorithm that takes local patient and population preferences into account. Therefore, the index score is a country-specific value and a major feature of the EQ-5D instrument.[44] The range of index scores will differ according to the scoring algorithm used; however, in all scoring algorithms of the EQ-5D-5L, a score of 0 represents the health state "dead" and 1.0 reflects "perfect health." Negative scores are also possible for those health states that society (not the individual patient) considers to be "worse than dead."

The EQ-5D VAS records the respondent's self-rated health on a vertical scale on which the end points are labelled 0 ("the worst health you can imagine") and 100 ("the best health you can imagine"). The respondents are asked to mark an X on the point of the VAS that best represents their health on that day. The EQ-5D index and VAS scores can be summarized and analyzed as continuous data.[43,44] Hence, the EQ-5D produces 3 types of data for each respondent:

- a profile indicating the extent of problems on each of the 5 dimensions represented by a 5-digit descriptor, such as 11121 or 21143
- a population preference–weighted health index score based on the descriptive system
- a self-reported assessment of health status based on the VAS.

The EQ-5D-5L has been validated in terms of feasibility, ceiling effects, discriminatory power, and convergent validity in a diverse patient population with chronic conditions (including patients with asthma or COPD from 6 countries).[43] Estimates of the MID for the index score in the general Canadian population were generated by simulating the effects of single-level transitions in each dimension.[82] The results yielded MIDs with a summarized mean of 0.056 (SD = 0.011), and a summarized median of 0.056 (interquartile range, 0.049 to 0.063).[82] In a European cohort of 316 patients with asthma aged 12 to 40 years, construct validity was established using the known-groups method in groups with good, intermediate, and bad asthma control as defined by the 5-item Asthma Control Questionnaire.[80] The EQ-5D-5L index score was significantly different between the groups with good control (mean = 0.91; 95% CI, 0.89 to 0.93), intermediate control (mean = 0.84; 95% CI, 0.81 to 0.87), and poor control (mean = 0.73; 95% CI, 0.69 to 0.78).[80] Convergent validity was established in a prospective observational cohort study (N = 121) with asthma patients. The EQ-5D-5L displayed moderate-to-strong Spearman rank correlations with the Asthma Quality of Life Utility Index. Within the same study, no evidence of known-groups validity was identified when patients were classified in categories of asthma severity based on PEF values.[81] When the authors evaluated responsiveness by asking patients "Compared to your asthma state when you were in hospital approximately 4 weeks ago, how would you rate your asthma now?", the EQ-5D-5L displayed large standardized response means for the good and poor groups of 0.95 and −1.03, respectively, 0.75 for the very good, and 0.303 for the moderate response options.[81] No information was found on the reliability or MID of the EQ-5D-5L in an asthma population.

St. George's Respiratory Questionnaire

The SGRQ is a self-administered patient-reported outcome developed to assess HRQoL over the past 4 weeks.[9] This questionnaire contains 50 items and 3 domains: symptoms (frequency and severity of respiratory symptoms), activity (how breathlessness affects patients' activities), and impacts (psychological and social disturbances attributed to airway disease). Total and domain scores are calculated for all items, weighted, and expressed as a percentage; higher scores indicate a worse state.[38]

Sanjuas et al. evaluated the presence of floor and ceiling effects of the SGRQ, and found acceptable levels (< 15%) of both effects.[40] The SGRQ displays acceptable test-retest and internal consistency reliability, with values greater than 0.7 when the ICC, or Cronbach alpha is evaluated, respectively.[38,40]

Validity of the SGRQ has been highlighted through correlations with a variety of measures of clinical status. Content validity was confirmed in a qualitative interview-based study[39], as well as with strong correlations [Spearman's rank correlation coefficient (ρ) = −0.81] with the AQLQ,[40] and with correlations ranging from moderate to strong with the FVC (r^2 = 0.18), 6-minute walk distance (r^2 = 0.37), Modified Medical Research Council Dyspnea Scale (r^2 = 0.51), and with the Hospital Anxiety and Depression Scale (r^2 = 0.35).[41] Longitudinal validity was independently evaluated for 2-month and 1-year intervals by correlating the change in SGRQ scores with alternative measures of health status; the SGRQ displayed strong and weak correlations when the 2-month and 1-year time points were evaluated, respectively.[40-42] When cross-sectional validity was evaluated by Sanjuas et al., the SGRQ correlated strongly with the Modified Medical Research Council Dyspnea Scale (r > 0.5 for each SGRQ domain evaluated), and moderately with percent predicted FEV_1 (r > 0.3 for each SGRQ domain evaluated).[40] Lastly, in a multivariable regression model, Jones et al. successfully correlated each domain of the SGRQ with a reference measure that was clinically relevant.[41]

With respect to responsiveness, the SGRQ showed a large standardized response mean (−0.9) when 49 patients who had improved asthma were assessed.[40] Finally, an MID of 4 points has been established as a clinically meaningful change to asthma patients in a number of studies.[33,41,42]

7-Item Asthma Control Questionnaire

The ACQ-7 was developed to evaluate asthma control in patients and is 1 of the most commonly used instruments measuring asthma control.[45,46] The questionnaire is comprised of 7 questions, the responses to which are scored on a 7-point scale. Questions regarding 6 aspects of the patient's previous week's experiences are answered by the patient and include activity limitation, nocturnal waking, shortness of breath, wheezing, symptoms on waking, and the use of 2 agonista SABA.[45] The seventh item includes calculations performed by clinical staff with regard to pre-bronchodilator FEV_1 or PEF (percent predicted).[45,46] The ACQ-7 score is calculated as the mean of the 7 questions (as all questions are equally weighted), with scores of 0 meaning the patient has asthma that is well-controlled and those of 6 meaning the patient has asthma that is extremely poorly controlled.[45-47] The ACQ is used extensively in clinical trials to measure clinically meaningful change in asthma control.[46]

Validity

Evidence for longitudinal and cross-sectional construct validity has been observed by correlations between the ACQ-7 and other asthma health status measures in 2 separate studies.[47,56] The ACQ-7 showed variable evidence for the presence of construct validity; with a strong Pearson correlation coefficient for the AQLQ for patients 12 years or older (r = −0.77), strong correlation with shortened versions of the questionnaire (r > 0.9), and weak correlation with the PEF in the morning or evening (r = −0.16 and r = −0.15, respectively).[37] In the same study, the ACQ-7 scores were significantly different (P < 0.001) among 4 pre-established patient groups (those with nighttime awakenings compared to those with no nighttime awakenings; those with daytime use of SABAs compared to those with no daytime SABA use; those with nighttime SABA use compared to those with no nighttime SABA use; and those with any use of SABAs compared to those with no SABA use), indicating that the ACQ-7 is able to distinguish between clinical groups with different levels of asthma severity, and thus, the presence of known-groups validity.[37]

Reliability

The ACQ is a multidimensional and standardized tool[48] that has high test-retest reliability in 3 separate publications. In 2 studies published by Juniper et al., the authors reported an ICC of 0.90 in both studies.[56,47] Furthermore, test-retest (ICC > 0.7) and internal consistency (Cronbach alpha > 0.7) reliability was present (ICC > 0.7) when patients with stable and persistent asthma were evaluated 4 weeks apart in 2 clinical trials.[37]

Responsiveness

Responsiveness of the ACQ-7 has been evaluated in a number of studies.[37,47,56] Overall, the ACQ-7 was very responsive to change in studies published by Juniper et al. as the scores were significantly different (P < 0.001*)* between adults with stable and unstable asthma.[47,56] To further evaluate the responsiveness of the ACQ, the change in ACQ score from baseline to 26 weeks was presented with a Pearson correlation coefficient to the change in the standardized AQLQ + 12, and the percent predicted FEV_1 in 2 separate clinical trials. Responders were identified with the previously established ACQ-7 cut point of 1.0 to distinguish between *well-controlled* and *not well-controlled* asthma.[90] Overall, the change in ACQ correlated well with the change in the standardized AQLQ + 12 (Pearson correlation coefficient, 0.74 to 0.78), but did not correlate with the change in percent predicted FEV_1 (Pearson correlation coefficient, 0.01 to 0.03).[37]

Clinical Relevance

The ACQ-7 MID has been well-established and accepted as 0.5 points for within-person change.[46,48] However, Bateman et al. questioned its use as a measure between groups or between patients, speculating that patient-reported outcomes should be presented as a responder rate comparison or a net treatment benefit analysis.[91] In addition, a score of 1.5 on the ACQ-7 is the most appropriate discriminator for *well-controlled* versus *not well-controlled* asthma patients.[49]

Patient Asthma Control e-Diary

The patient asthma control e-diary is an electronic diary provided to patients to record rescue medication use, clinical symptoms, and PEF at the same time each morning and evening. The diary prompts different questions in the morning compared to the evening. The morning questions consist of 6 items, and the evening questions consist of 11 items

(Table 39). No evidence regarding the validity, reliability, responsiveness, or the MID of the Patient Asthma Control e-diary was identified; however, patient records of daytime and nighttime symptoms using an e-diary are considered desirable for the clinical investigation of the treatment of asthma, according to the EMA.[7]

Table 39: Patient Asthma Control e-diary

Weekly morning questions	Possible answers
Did you miss any doses of your Inhaler A medication in the morning in the past week?	0 = Yes 1 = No
Please indicate the number of morning doses missed.	1 to 7 dose(s)
At what time in the morning did you usually take your inhalations this week?	HH:MM
How did you sleep last night?	0 = I did not wake up because of breathing problems; 1 = I awoke once because of my breathing problems but did not use my rescue medication; 2 = I awoke once because of my breathing problems, but my rescue medication controlled my symptoms; 4 = I had difficulty sleeping because of my breathing problems even though I used my rescue medication
Did you have asthma symptoms upon awakening in the morning?	0 = None; 1 = Mild; 2 = Moderate; 3 = Severe
Number of puffs of rescue medication during the past 12 hours	0 to 50 dose(s)
Weekly evening questions	**Possible answers**
Did you miss any doses of your Inhaler A medication in the evening in the past week?	0 = Yes 1 = No
Please indicate the number of evening doses missed.	1 to 7 dose(s)
Did you miss any doses of your Inhaler B medication in the evening in the past week?	0 = Yes 1 = No
Please indicate the number of evening doses missed.	1 to 7 dose(s)
At what time in the evening did you usually take your inhalations this week?	HH:MM
Did your respiratory symptoms stop you from performing your usual daily activities?	0 = Not at all; 1 = a little; 2 = moderately; 3 = quite a lot; 4 = completely
How severe was your shortness of breath today?	0 = None; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe
How was your wheeze during the past 12 hours?	0 = None; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe
How was your cough during the past 12 hours?	0 = None; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe
Did you have chest tightness during the past 12 hours?	0 = None; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe
Number of puffs of rescue medication during the past 12 hours	0…50 puff(s)

Work Productivity and Activity Impairment Questionnaire: Asthma

The WPAI questionnaire is a self-reported instrument used to measure the impact of general health and symptom severity on work and on daily activities over the previous 7 days.[50-52] The WPAI questionnaire can be adapted for a specific disease or condition by replacing the word *problem* in the Specific Health Problem version of the WPAI with the specific disease.[92] The WPAI: Asthma is the asthma-specific version of the questionnaire. It

is composed of 9 items that assess impairment in 3 domains (work, school, and activity).[53,50,54] Scores range from 0% to 100%, with higher scores indicating greater impairment.[50,54]

Construct validity of the asthma-specific WPAI was assessed in 2,529 patients (1,397 patients were employed and 233 patients were in school and not employed) with severe or difficult-to-treat asthma.[54] However, this version of the WPAI calculates work absenteeism without asking about work missed due to other reasons.[54] Work impairment (an outcome similar to work productivity loss), school impairment (similar to class productivity loss), and activity impairment were weakly correlated with FEV_1 percent predicted (Spearman correlation coefficients of −0.11 to −0.05), moderately correlated with asthma control measured by the Asthma Therapy Assessment Questionnaire control index (Spearman correlation coefficients of 0.54, 0.37, and 0.55 for work, school, and activity impairment, respectively), and moderately correlated with the AQLQ score (Spearman correlation coefficients of −0.65, −0.52, and −0.69 for work, school, and activity impairment, respectively).[54]

Appendix 5: Breezhaler Inhaler Device and Patient Preferences

To date, the most effective treatment available for asthma is the regular use of inhaled medications, which delivers the medication directly to the lungs and allows for optimal efficacy and safety.[11,93,94] The efficacy of inhaled treatment is partly dependent on the correct use of the inhalers, which is a common issue reported by patients and clinicians. There are many products and devices available on the market for delivering a variety of drugs from different classes. However, the inhalation technique varies between products and this increases the chance of administration-related error and consequently reduces the ability to control the disease, particularly if multiple inhalers are being used.[95,96] This issue is reflected in multiple studies that have assessed patient preferences for attributes of inhalers, and that frequently cited ease of use, functionality, and instructions that are simple and easy to follow as aspects of an inhaler that are important to patients.[11,93,97,98] Of the many types of inhalers, pressurized metered-dose inhalers and dry-powder inhalers are the most commonly used for the treatment of asthma.[93,99]

The product under review is QVM administered via the Breezhaler, which is an inhalation-driven, single-dose, dry-powder inhaler with active ingredients dispersed in a lactose monohydrate excipient.[100]

A supplemental literature search was completed by CADTH for studies that assessed asthma patient preferences for and use of the Breezhaler device in an effort to evaluate Breezhaler performance in comparison to other available products in terms of device preference, ease of use, and device satisfaction. Described below are the studies that were identified, in addition to 1 observational study submitted by the sponsor that included patients with COPD.

The first is an observational study (N = 333) that included outpatients with asthma (n = 175) and COPD (n = 158; COPD) which assessed patients' usability and preference for the Breezhaler, Genuair, and Handihaler devices via the Handling Questionnaire. Patients were divided into 3 groups; 1 group (n = 127) tested all 3 devices, another (n = 110) compared the Breezhaler and the Genuair, and the last group (n = 96) tested the Breezhaler and the Handihaler devices. All 3 groups were administered the Handling Questionnaire, a validated questionnaire used to assess the determinants of choice and patient usability of inhaler devices in diseases of airflow limitation. Within this study, a nurse demonstrated the functioning of the device, after which patients described their first impressions. Then, patients prepared the actuation of the device, and the nurse recorded technical errors made. Lastly, both patients and nurses recorded their preferences and comments on device functionality. Of the patients who tested all 3 devices, approximately 50% preferred the Genuair, with only 5% saying they preferred the Breezhaler. The Breezhaler was the least preferred in terms of appearance, comfort, safety, and convenience. According to the patients and nurses, the Breezhaler was the most problematic; 50% of patients perceived that they made a mistake in preparing the Breezhaler, while 90% of nurses perceived that patients made a mistake, and 80% of patients were still unable to use the Breezhaler after the first demonstration. The mean number of patient attempts to prepare the first proper inhalation was 1.5, 2.5, and 2.6 for the Genuair, Breezhaler, and Handihaler, respectively (Genuair versus Breezhaler; $P < 0.0001$). It took a mean of 12 minutes (SD = 0.6 minutes) to teach patients how to correctly use the Breezhaler, compared to approximately 5 minutes for the Genuair (SD = 0.4 minutes), and 6 minutes for the Handihaler (SD = 0.5 minutes).

This included the nurse's explanation and the manoeuvres the patient had to perform to prepare the device. Patient age was a contributing factor, with older patients needing more attempts to perform the first proper inhalation and more time to learn how to use the device, and their success rate was lower. The Breezhaler device was the least favourite of the 3 evaluated even when an asthma-only subgroup was analyzed.

The second study is an observational study (N = 333) that evaluated patient preference for the Breezhaler, Genuair, and the Respimat devices in asthma and COPD patients. It was published by the same authors of the study described previously, and has a similar study design. In this study, the Handling Questionnaire informed that the Breezhaler was the least liked by patients and perceived by patients and nurses as the most difficult to use. The Breezhaler took the most attempts to prepare the first actuation (2.6 ± 1.1 versus 1.6 ± 0.8 for Genuair and 1.6 ± 1.0 for the Respimat; P < 0.0001 for Breezhaler versus Genuair and Breezhaler versus Respimat), and 82%, 44.3%, and 37.6% of patients were unable to prepare the Breezhaler, the Genuair, and the Respimat, respectively, on their first attempt. The persistence of the Breezhaler device as the least-favourite and most difficult-to-use device was evident even when an asthma-only subgroup of the population was analyzed.[101]

The third-study was a prospective, single-centre, observational study (N = 216), which evaluated the number of instructions necessary to minimize errors in pressurized metered-dose inhalers, Turbuhaler, Breezhaler, Respimat, and Ellipta in patients with asthma (n = 135) and COPD (n = 81). All the devices tested required at least 3 instructions to minimize the error rate to 10% or less. Of the patients who tested the Breezhaler device (n = 32; 3 patients had asthma and 29 patients had COPD) approximately 60%, 20%, and 3% made a mistake in overall handling and device inhalation after 1 set, 2 sets, and 3 sets of pharmacist instructions on device use, respectively, and this was largely similar to all the other devices tested. This study indicates that 3 sets of instructions may be necessary to teach patients proper Breezhaler use.[102]

Additionally, an observational study (N = 2,935) that evaluated handling errors of inhaler devices, including the Breezhaler, in patients with COPD was submitted by the sponsor.[103] A total of 876 patients used the Breezhaler device, 452 used Diskus, 598 used Handihaler, 422 used a pressurized metered-dose inhaler, 625 used Respimat, and 420 used Turbuhaler (patients may have used more than 1 type of inhaler). Correct use of the devices was assessed by 212 general practitioners and 50 respirologists. The Breezhaler had the greatest proportion of patients making no errors, at 36.5% (95% CI, 33.3% to 39.7%), followed by the Turbuhaler at 30.5% (95% CI, 26.1% to 34.9%). The worst-performing device was the Handihaler at 10.7% (95% CI, 8.2% to 13.5%) patients without an error. Correspondingly, the Breezhaler was associated with the fewest patients (15.4%) making critical errors in administration, followed by Diskus (21.2%), Handihaler (29.3%), Turbuhaler (32.1%), pressurized metered-dose inhalers (43.8%), and Respimat (46.9%).

The first 3 studies outlined above included both asthma and COPD patients, and the study provided by the sponsor was restricted to patients with COPD. No studies were identified that assessed Breezhaler device preference in asthma patients only. There were differences in baseline characteristics of asthma patients versus COPD patients, such as asthma patients tended to be younger than COPD patients (44 years old versus 68 years old) and typically have fewer comorbidities that could influence uptake of instructions and use of an inhaler.[104] A younger population is 1 that can exert more physical strength and dexterity related to their inhaler technique. In a study published by Cicilliani et al. evaluating finger strength and its relation to patient device satisfaction, the authors found that finger

strength differed between the age groups evaluated (5 years to 17 years, 18 years to 64 years, > 65 years), but all age groups had sufficient finger strength to operate the Breezhaler. Moreover, participants expressed dissatisfaction related to “the inhaler buttons did not move once pressed” for all the inhalers tested, except for the pressurized metered-dose inhalers. Generally, participants with arthritis reported that the hand position required to operate the Breezhaler was uncomfortable, and the elderly preferred larger devices while children preferred smaller devices (such as the Breezhaler). Overall, patients were the least satisfied by the Breezhaler when compared to the Respimat, Aerolizer, Genuair, Diskus, Ellipta, Handihaler, Turbohaler, and Atrovent.[105] The study identified by the sponsor in patients with COPD did not control for factors such as health literacy and prior device training, which may influence proper inhaler technique. Moreover, as it included only patients with COPD, who were older (mean age of 65.4 years), the generalizability of the results of this study to Canadian patients with asthma may be limited.

The studies presented above, when taken together, suggest that the Breezhaler device may be the device least preferred by patients with asthma. There are conflicting data regarding whether the device requires the most instruction and attempts to prepare correctly in order to deliver a dose with no critical errors. However, larger comparative studies in patients with asthma are required to draw concrete conclusions regarding the ease of use and patient preferences related to the Breezhaler device.

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