CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

INDACATEROL/MOMETASONE FUROATE (ATECTURA BREEZHALER)

(Novartis Pharmaceuticals Canada Inc.)

Indication: Asthma maintenance (adults, children 12 or older)

Service Line:	CADTH Common Drug Review
Version:	Final (with redactions)
Publication Date:	January 2021
Report Length:	115 Pages

CADTH

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

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

CADTH

Table of Contents

Abbreviations 6
Executive Summary 8
Introduction 8
Stakeholder Engagement 9
Clinical Evidence 10
Conclusions 18
Introduction 19
Disease Background 19
Standards of Therapy 20
Drug 21
Stakeholder Engagement 24
Patient Group Input 24
Clinician Input 26
Clinical Evidence 30
Systematic Review (Pivotal and Protocol Selected Studies) 30
Findings from the Literature 32
Results 52
Indirect Evidence 77
Other Relevant Evidence 78
Discussion 86
Summary of Available Evidence 86
Interpretation of Results 87
Conclusions 92
Appendix 1: Literature Search Strategy 93
Appendix 2: Excluded Studies 96
Appendix 3: Detailed Outcome Data 97
Appendix 4: Description and Appraisal of Outcome Measures 98
Appendix 5: Breezhaler Inhaler Device and Patient Preferences 108
References 111

Tables

Table 1: Submitted for Review 8
Table 2: Summary of Key Results from Pivotal and Protocol Selected Studies 13
Table 3: Summary of Asthma Management — GINA Steps 19
Table 4: Key Characteristics of ICS Monotherapies and in Combination with LABAs 22
Table 5: Inclusion Criteria for the Systematic Review 30
Table 6: Details of Included Studies 33
Table 7: Summary of Baseline Characteristics in QUARTZ Study — Randomized Set 39
Table 8: Summary of Baseline Characteristics in PALLADIUM Study — Randomized Set 41
Table 9: Study Treatments in PALLADIUM Study 44
Table 10: Summary of Outcomes of Interest Identified in the CADTH Review Protocol 46
Table 11: Patient Disposition — All Randomized 53
Table 12: Exposure to Study Treatments — Safety Analysis Set 54
Table 13: Use of Concomitant Asthma Medications — Safety Analysis Set 54
Table 14: Acute Asthma Exacerbations 56
Table 15: Pulmonary Function — FEV_1, FVC, Morning and Evening PEF in the QUARTZ Study 57
Table 16: Pulmonary Function — FEV_1, FVC, Morning and Evening PEF in the PALLADIUM Study 58
Table 17: Health-Related Quality of Life in the QUARTZ Study 60
Table 18: Health-Related Quality of Life in the PALLADIUM Study 62
Table 19: Asthma Control — ACQ-7 and Rescue Medication Use in the QUARTZ Study 64
Table 20: Asthma Control — ACQ-7 and Rescue Medication Use in the PALLADIUM Study 66
Table 21: Night-Time Awakenings in the QUARTZ Study 68
Table 22: Night-Time Awakenings in the PALLADIUM Study 68
Table 23: Work Time Missed Due to Asthma Problems 69
Table 24: Health Care Utilization — Outpatient Visits 70
Table 25: Summary of Harms — Safety Analysis Set 72
Table 26: Summary of the Number of Studies Testing Each Triple and Dual Therapy 77
Table 27: Summary of Baseline Characteristics — Safety Population 79
Table 28: Patient Disposition — FAS 81
Table 29: Extent of Exposure to Study Drug — Safety Population 82
Table 30: Patients with Asthma Exacerbations — FAS 82
Table 31: Change From Baseline in Pre-Dose FEV_1 — FAS 83

Table 32: Asthma Control — FAS 83
Table 33: Summary of Harms That Occurred After 26 Weeks — Safety Population 84
Table 34: Excluded Studies 96
Table 35: Outcome Measures Included in Each Study 98
Table 36: Summary of Outcome Measures and Their Measurement Properties 98
Table 37: Patient Asthma Control e-Diary 106

Figures

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies 32
Figure 2: QUARTZ Study Design 37
Figure 3: PALLADIUM Study Design 37
Figure 4: [redacted] 60
Figure 5: [redacted] 67
Figure 6: [redacted] 78

Abbreviations

ACQ	Asthma Control Questionnaire
ACQ-7	Asthma Control Questionnaire (seven items)
AE	adverse event
AQLQ	Asthma Quality of Life Questionnaire
AQLQ-S+12	Asthma Quality of Life Questionnaire for 12 years and older
CI	confidence interval
COPD	chronic obstructive pulmonary disease
EMA	European Medicines Agency
EQ 5D	EuroQol 5-Dimensions
EQ-5D-5L	EuroQol 5-Dimensions 5-Levels
EQ VAS	EuroQol Visual Analogue Scale
ED	emergency department
FAS	full analysis set
FEV_1	forced expiratory volume in one second
FVC	forced vital capacity
GINA	Global Initiative for Asthma
HRQoL	health-related quality of life
ICC	intraclass correlation coefficient
ICS	inhaled corticosteroid
ITC	indirect treatment comparison
ITT	intention to treat
LABA	long-acting beta2-agonist
LAMA	long-acting muscarinic antagonist
LS	least squares
LTRA	leukotriene receptor antagonist
MAR	missing at random
MDI	metered-dose inhaler
MF	mometasone furoate
MID	minimal important difference
MMRM	mixed-effects models for repeated measures
MPPI	minimal patient perceivable improvement

NI	noninferiority
NMA	network meta-analysis
OR	odds ratio
PEF	peak expiratory flow
PPS	per-protocol set
QMF	indacaterol/mometasone furoate
RCT	randomized controlled trial
SABA	short-acting beta2-agonist
SAE	serious adverse event
SAS	safety analysis set
SD	standard deviation
SE	standard error
S/F	salmeterol/fluticasone propionate
URTI	upper respiratory tract infection
VAS	visual analogue scale
WDAE	withdrawal due to adverse event
WPAI	Work Productivity and Activity Impairment

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/mometasone furoate (Atectura Breezhaler) Available as 150 mcg/80 mcg, 150 mcg/160 mcg, and 150 mcg/320 mcg inhalation powder (hard capsules) for oral inhalation
Indication	Once-daily maintenance treatment of asthma in adults and adolescents 12 years of age and older with reversible obstructive airways disease • Should be prescribed for patients not adequately controlled on a long-term asthma medication such as an ICS or whose disease severity clearly warrants treatment with both LABA and an ICS • Not indicated for patients whose asthma can be managed by occasional use of a rapid-onset, short-duration, inhaled beta2-agonist or for patients whose asthma can be successfully managed by an ICS along with the occasional use of a rapid-onset, short-duration, inhaled beta2-agonist • Not for the relief of acute bronchospasm
Reimbursement request	As per indication
Health Canada approval status	NOC
Health Canada review pathway	Standard
NOC date	May 6, 2020
Sponsor	Novartis Pharmaceuticals Canada Inc.

ICS = inhaled corticosteroid; LABA = long-acting beta2-agonist.

Source: Atectura 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 hyperresponsiveness to endogenous and exogenous stimuli.[2] According to the *2019 Annual Asthma Survey Report* by Asthma Canada, more than 3.8 million Canadians (approximately 10.8% of the population) are currently living with asthma.[3] Pharmacologic 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 beta2-agonists, either short-acting beta2-agonists (SABAs) or long-acting beta2-agonists (LABAs). These can be used for rapid relief of asthma symptoms but should be used concurrently with inhaled corticosteroids (ICSs). Controller therapies, predominantly ICS, are used as a maintenance therapy and aim to reduce airway inflammation, control symptoms, and reduce future exacerbations.[2] Patients may add other therapies as needed, such as long-acting muscarinic antagonists (LAMA), tailored to the needs of individual patients.

Atectura Breezhaler (indacaterol/mometasone furoate [QMF]) is a combination product composed of a LABA and an ICS. QMF is available as an inhalation powder (hard capsules) for oral inhalation with three dosing strengths:150 mcg/80 mcg, 150 mcg/160 mcg, and 150 mcg/320 mcg.[1] QMF is indicated as once-daily maintenance treatment of

asthma in adults and adolescents 12 years of age or older with reversible obstructive airways disease. Further, the product monograph states that QMF "*should be prescribed for patients not adequately controlled on a long-term asthma control medication, such as ICS or whose disease severity clearly warrants treatment with both a LABA and an ICS*."[1] QMF is specifically not indicated for patients whose asthma can be managed by occasional use of rapid-onset, short-duration, inhaled beta2-agonist, or those whose asthma can be managed by an ICS along with the occasional use of a beta2-agonist.[1] QMF is also not indicated for the relief of acute bronchospasm.[1]

The objective of this review was to perform a systematic review of the beneficial and harmful effects of QMF (150 mcg/80 mcg, 150 mcg/160 mcg, and 150 mcg/320 mcg) administered by oral inhalation for once-daily maintenance treatment of asthma in adults and adolescents 12 years of age and older with reversible obstructive airways disease.

Stakeholder Engagement

The information in this section is a summary of input provided by the patient groups that responded to CADTH's call for patient input and from a clinical expert 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 that was intended for use in this review as well as in the CADTH review of indacaterol/glycopyrronium bromide/MF. The Lung Health Foundation gathered information for their submission through telephone interviews with three patients living with asthma. The interviews were completed in May 2020. In 2020, Asthma Canada gathered information for its submission through interviews (N = 24) and an online survey (N = 200). The information was gathered 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 felt 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. Lastly, two-thirds of respondents to Asthma Canada's survey indicated that they felt stigmatized due to their asthma at one 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's survey reported that 45% of respondents wanted easier management of severe asthma through novel medications, and 29% indicated patients want a reduction in fear and anxiety in managing their asthma. When patients are deciding

to try a new medication, the Lung Health Foundation identified that 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 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 clinical expert felt that the majority of patients with uncontrolled asthma can regain control with these treatments focusing upon medication adherence, self-management techniques, and inhaler education, and that approximately 5% of patients who are poorly controlled despite this will remain so and will require additional pharmacologic treatment.

The clinical expert stated that the use of a low-dose ICS/LABA is well established as the treatment of choice of patients with regular asthma symptoms. They felt that QMF in increasing mometasone doses could be used for patients with Global Initiative for Asthma (GINA) step 3 to step 5. Despite this, the clinical expert felt that QMF did not offer a paradigm shift in asthma management, although the approved range of ICS dosing via the three formulations is unique to QMF. The clinical expert stated that the negative aspect of this agent is the delivery device, Breezhaler, which requires a capsule to be inserted each day rather than being a multi-dose device. The clinical 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 (MDI), some from a multi-dose dry powder inhaler. The clinical expert felt that patients at GINA step 3 would be best suited for treatment with QMF and that those least suitable for treatment with QMF would be patients with mild disease who are better suited for daily monotherapy with ICS or as-needed treatment with ICS/formoterol, as well as patients who are unable or unwilling to use the delivery device or tolerate 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 seven-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 since, for adults, it is a lifelong disease. Treatment can be escalated or de-escalated based upon symptoms and lung function measurements.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

Two pivotal multi-centre, double-blind, randomized controlled trials (RCTs) met the inclusion criteria for the CADTH systematic review, QUARTZ (N = 802) and PALLADIUM (N = 2,216). The trials evaluated the efficacy and safety of QMF (150 mcg/80 mcg, 150 mcg/160 mcg, and 150 mcg/320 mcg) in adolescents (≥ 12 years of age) and adults with asthma over 12 weeks and 52 weeks of therapy in the QUARTZ and PALLADIUM studies, respectively. Patients included in the two 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 one second (FEV_1) of the predicted normal of 60% or more and less than 90% (QUARTZ) or 50% or more and less than 85% (PALLADIUM), and demonstrate bronchodilator reversibility. Patients also had at least one month's use of a low-dose ICS prior to screening in QUARTZ and at least three months' use of a medium-dose or high-dose ICS or low-dose ICS/LABA combination in PALLADIUM. The two trials were designed to test the superiority of QMF delivered via Breezhaler to mometasone furoate (MF) delivered via Twisthaler at a low-dose, medium-dose, and high-dose strength. More specifically, QUARTZ evaluated QMF 150 mcg/80 mcg once daily versus MF 200 mcg once daily; in PALLADIUM, QMF 150 mcg/160 mcg once daily was evaluated against MF 400 mcg once daily, and QMF 150 mcg/320 mcg versus MF 800 mcg (administered as 400 mcg twice daily). PALLADIUM also included salmeterol/fluticasone propionate (S/F) 50 mcg/500 mcg administered twice daily via Accuhaler as an active comparator for noninferiority (NI) testing of the primary end point. The two trials used a double-dummy and triple-dummy design to maintain blinding.

The primary and key secondary outcome in both trials was the change from baseline in trough FEV_1 and the change from baseline in ACQ-7, respectively. Primary and key secondary outcomes were measured at week 12 in QUARTZ and week 26 in PALLADIUM. Outcomes related to asthma exacerbations, rescue medication use, and health-related quality of life (HRQoL) were included as other secondary outcomes, as well as other measures of pulmonary function, night-time symptoms (night-time awakenings), and health care utilization. The Work Productivity and Activity Impairment (WPAI) questionnaire (percentage of work time missed due to asthma problems) was also included in PALLADIUM. Outcomes related to dyspnea, patient adherence to treatment regimen, and exercise tolerance were not included in either study.

Efficacy Results

Key efficacy results are summarized in Table 2. In the QUARTZ study, 5.1% and 15.0% of patients experienced an asthma exacerbation and 0.8% and 2.8% experienced a severe asthma exacerbation in the QMF 150 mcg/80 mcg and MF 200 mcg treatment groups, respectively. In the PALLADIUM study, between [redacted] and [redacted] of patients experienced an asthma exacerbation and [redacted] to [redacted] experienced a severe exacerbation. A numerically greater proportion of patients in the MF treatment groups experienced exacerbations (all severities, [redacted] for MF 400 mcg and [redacted] for MF 800 mcg) and severe exacerbations ([redacted] for MF 400 mcg and [redacted] for MF 800 mcg) than patients in the QMF treatment groups (all severities, [redacted] for QMF 150 mcg/160 mcg and [redacted] for QMF 150 mcg/320 mcg; severe < 10% in both groups).

Less than [redacted] of patients in any treatment group experienced an exacerbation requiring hospitalization or permanent discontinuation of the study drug. In both QUARTZ and PALLADIUM, the annualized rate of asthma exacerbations (all) was consistently lower in the QMF treatment groups compared to the corresponding MF treatment groups ([redacted]). The rate of all exacerbations was similar between the high-dose QMF treatment group (0.49; 95% confidence interval [CI], 0.41 to 0.60) and S/F treatment group (0.52; 95% CI, 0.43 to 0.63). The rate of severe asthma exacerbations was not reported in QUARTZ. The annualized rate of severe exacerbations was greater in the medium-dose MF treatment group compared to the medium-dose QMF treatment group, and similar across the high-dose QMF, MF, and S/F treatment groups.

The primary outcome in QUARTZ and PALLADIUM was change from baseline in trough FEV_1, which demonstrated an improvement with QMF that was statistically significant, with treatment group differences corresponding to the low-dose, medium-dose, and high-dose QMF versus MF comparisons of 0.18 L (95% CI, 0.15 to 0.22; P value < 0.001), 0.21 L (95% CI, 0.17 to 0.26; P value < 0.001), and 0.13 L (95% CI, 0.09 to 0.18; P value < 0.001) compared to MF. The treatment group difference was maintained at week 52 for the medium-dose and high-dose strengths in PALLADIUM, and the other measures of lung function, forced vital capacity (FVC) (L), and mean morning and evening peak expiratory flow (PEF) (L/minute) were aligned with the primary analysis when measured at the end of treatment in both studies (data shown in Table 15 and Table 16). The clinical significance of these differences is uncertain because of the lack of data for the between-group minimal important difference (MID) for FEV_1 in asthma when an active comparator is studied.

The comparison of QMF 150 mcg/320 mcg to S/F 50 mcg/500 mcg was analyzed for NI in terms of the primary outcome using an NI margin of 0.090 L to determine the difference based on the 95% CI. The least squares (LS) mean (standard error [SE]) change from baseline in trough FEV_1 was 0.04 L (95% CI, –0.01 to 0.08; P = 0.101), which met the pre-specified criteria for NI. Analyses other than the QMF versus MF comparisons at week 12 and week 26 must be considered with risk for type I error.

The Asthma Quality of Life Questionnaire (AQLQ) — specifically, the AQLQ for 12 years and older (AQLQ-S+12) — was included as a measure of HRQoL in both studies; however, none of the measures of HRQoL was controlled for multiplicity. The treatment group difference in QUARTZ was 0.15 units (95% CI, 0.06 to 0.23; P < 0.001) and in PALLADIUM, QMF 150 mcg/160 mcg versus MF 400 mcg corresponded to a treatment group difference of 0.19 units (95% CI, 0.08 to 0.30; P < 0.001). No difference was observed between the high-dose treatment group comparisons (QMF versus MF 800 mcg = 0.08 units [95% CI, –0.03 to 0.19; P = 0.154] and QMF 150 mcg/320 mcg versus S/F 50/500 mcg = 0.04 units [95% CI, –0.07 to 0.15; P = 0.455]).

The key secondary outcome in QUARTZ and PALLADIUM was ACQ-7. The treatment group differences corresponding to the low-dose, medium-dose, and high-dose QMF versus MF comparisons were –0.22 units (95% CI, –0.29 to –0.14; P < 0.001), –0.25 units (95% CI, –0.33 to –0.16; P value < 0.001), and –0.17 units (95% CI, –0.26 to –0.09; P value < 0.001). PALLADIUM was powered to detect a difference in ACQ-7 based on a pooled analysis of QMF treatment groups (150 mcg/160 mcg and 150 mcg/320 mcg) versus MF treatment groups (MF 400 mcg and MF 800 mcg), which was aligned with the analyses of the individual treatment groups with a treatment difference for QMF versus MF of –0.21 units (95% CI, –0.27 to –0.15; P < 0.001) in favour of QMF (not shown in Table 2). No difference was observed between QMF 150 mcg/320 mcg and S/F 50 mcg/500 mcg (treatment group difference of
–0.05 [95% CI, –0.14 to 0.03; P = 0.214]).

The following outcomes were also reported in the two studies unless otherwise noted, although they were not included in the statistical testing procedure and may only be considered exploratory: 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), nocturnal awakening, WPAI (work time missed due to asthma, PALLADIUM study only), and health care utilization (asthma- and asthma exacerbation-related outpatient visits by visit type and asthma-related hospitalizations).

Harms Results

Adverse events (AEs) were reported by 32.3% to 38.3% of patients in the QUARTZ study and 64.6% to 72.2% of patients in the PALLADIUM study. Reported serious adverse events (SAEs) were infrequent in QUARTZ (≤ 1.8% in both treatment groups) and ranged from 5.0% to 8.0% among treatment groups in PALLADIUM (all treatment groups were approximately 5.0% except MF 400 mcg at 8.0%). Few patients stopped treatment and initiated withdrawal due to AEs (WDAE) in both QUARTZ ([redacted]) and PALLADIUM ([redacted]). The most common reason for a SAE or WDAE in both studies was asthma, which occurred in less than 2% of patients in each treatment group. One death was reported between the two included studies; it occurred in an adolescent patient in the MF 400 mcg treatment group of PALLADIUM. The cause of death was determined by an independent adjudication committee to be due to asthma exacerbation.

Infections (systemic and local) were [redacted] reported notable harm ([redacted] to [redacted] of patients in QUARTZ and 49.2% to 76.8% of patients in PALLADIUM), followed by local systemic effects (these ranged from 5.0% to 11.0% across studies) and cardiac or vascular disorders, which occurred in less than [redacted] of patients in QUARTZ, but ranged from 4.6% to 8.3% in PALLADIUM. Local steroid effects, which included cough, oral thrush, nosebleeds, oropharyngeal pain and discomfort, dysphonia, and larynx irritation, occurred in 2.6% to 6.0% of patients across treatment groups in both studies. All other notable harms were reported in 1.1% or less of patients in any treatment group. The incidence of specific AEs was infrequent and did not suggest any imbalances between treatment groups.

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

	QUARTZ study		PALLADIUM study				
	QMF 150 mcg/ 80 mcg N = 395	MF 200 mcg N = 399	QMF 150 mcg/ 160 mcg N = 437	MF 400 mcg N = 443	QMF 150 mcg/ 320 mcg N = 443	MF 800 mcg N = 440	S/F 50 mcg/ 500 mcg N = 444
Proportion of patients with asthma exacerbations, by exacerbation category, n (%) — FAS							
All (mild, moderate, severe)	20 (5.1)	60 (15.0)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe	3 (0.8)	11 (2.8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Requiring hospitalization	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Causing permanent discontinuation of study drug	[redacted]	[redacted]	0	7 (1.6)	1 (0.2)	4 (0.9)	2 (0.5)
Rate of asthma exacerbations, all (mild, moderate, severe)[a] — FAS							
n (%)	394 (99.7)	397 (99.5)	437 (100)	443 (100)	443 (100)	440 (100)	444 (100)
Annualized rate (95% CI)	0.20 [redacted]	0.67 [redacted]	0.48 (0.40 to 0.59)	1.05 (0.89 to 1.24)	0.49 (0.41 to 0.60)	0.74 (0.62 to 0.88)	0.52 (0.43 to 0.63)
Rate ratio (95% CI)	0.30 (0.18 to 0.50)		0.46 (0.36 to 0.59) (QMF vs. MF)		0.67 (0.52 to 0.87) (QMF vs. MF) 0.95 (0.72 to 1.23) (QMF vs. S/F)		
P value[b]	[redacted]		< 0.001 (QMF vs. MF)		0.002 (QMF vs. MF) 0.681 (QMF vs. S/F)		

	QUARTZ study		PALLADIUM study				
	QMF 150 mcg/ 80 mcg N = 395	MF 200 mcg N = 399	QMF 150 mcg/ 160 mcg N = 437	MF 400 mcg N = 443	QMF 150 mcg/ 320 mcg N = 443	MF 800 mcg N = 440	S/F 50 mcg/ 500 mcg N = 444
Rate of asthma exacerbations, severe[a] — FAS							
n (%)	NR	NR	437 (100)	443 (100)	443 (100)	440 (100)	444 (100)
Annualized rate (95% CI)	NR	NR	0.13 (0.10 to 0.18)	0.29 (0.23 to 0.38)	0.13 (0.09 to 0.17)	0.18 (0.13 to 0.23)	0.14 (0.10 to 0.19)
Rate ratio (95% CI)	NR	NR	0.46 (0.31 to 0.67) (QMF vs. MF)		0.71 (0.47 to 1.08) (QMF vs. MF) 0.89 (0.58 to 1.37) (QMF vs. S/F)		
P value[b]	NR	NR	< 0.001 (QMF vs. MF)		0.108 (QMF vs. MF) 0.597 (QMF vs. S/F)		
Trough FEV_1 (L) at week 12 (QUARTZ study) or week 26 (PALLADIUM study)[c] — FAS							
N contributing to the analysis	394	395	389	376	395	372	391
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]		[redacted]		
End of treatment (week 12), LS mean (SE)	2.562 (0.0134)	2.379 (0.0134)	2.39 (0.02)	2.18 (0.02)	2.38 (0.02)	2.25 (0.02)	2.35 (0.02)
Change from baseline, LS mean (SE)	0.234 (0.0134)	0.051 (0.0134)	0.29 [redacted]	0.08 [redacted]	0.28 [redacted]	0.15 [redacted]	0.25 [redacted]
Treatment group difference vs. control, LS mean (95% CI)	0.18 (0.148 to 0.217)		0.21 (0.17 to 0.26) (QMF vs. MF)		0.13 (0.09 to 0.18) (QMF vs. MF) NI using a margin of 0.090 L: 0.04 (–0.01 to 0.08) (QMF vs. S/F)[b]		
P value	< 0.001		< 0.001 (QMF vs. MF)		< 0.001 (QMF vs. MF) NI: 0.101 (QMF vs. S/F)[b]		
AQLQ-S+12 overall score at week 12 (QUARTZ study) or week 52 (PALLADIUM study)[d] — FAS							
N contributing to the analysis	381	379	397	378	384	389	405
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment time point (specify), LS mean (SE)	5.78 (0.05)	5.63 (0.05)	5.83 (0.04)	5.64 (0.04)	5.78 (0.04)	5.71 (0.04)	5.74 (0.04)
Change from baseline, LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment group difference vs. control (95% CI)	0.15 (0.06 to 0.23)		0.19 (0.08 to 0.30) (QMF vs. MF)		0.08 (–0.03 to 0.19) (QMF vs. MF) 0.04 (–0.07 to 0.15) (QMF vs. S/F)		
P value[b]	< 0.001		< 0.001 (QMF vs. MF)		0.154 (QMF vs. MF) 0.455 (QMF vs. S/F)		

	QUARTZ study		PALLADIUM study				
	QMF 150 mcg/ 80 mcg N = 395	MF 200 mcg N = 399	QMF 150 mcg/ 160 mcg N = 437	MF 400 mcg N = 443	QMF 150 mcg/ 320 mcg N = 443	MF 800 mcg N = 440	S/F 50 mcg/ 500 mcg N = 444
ACQ-7, change from baseline at week 12 (QUARTZ study) or week 26 (PALLADIUM study)[e] — FAS							
N contributing to the analysis	387	384	407	393	407	405	410
Baseline, mean (SD)	NR	NR	2.30 (NR)				
End of treatment time point (week 12), LS mean (SE)	1.32 (0.04)	1.54 (0.04)	1.26 (0.04)	1.51 (0.04)	1.27 (0.04)	1.44 (0.04)	1.32 (0.04)
Change from baseline, LS mean (SE)	–0.95 (0.04)	–0.73 (0.04)	–1.04 (0.04)	–0.79 (0.04)	–1.03 (0.04)	–0.86 (0.04)	–0.98 (0.04)
Treatment group difference vs. control (95% CI)	–0.22 (–0.29 to –0.14)		–0.25 (–0.33 to –0.16) (QMF vs. MF)		–0.17 (–0.26 to –0.09) (QMF vs. MF) –0.05 (–0.14 to 0.03) (QMF vs. S/F)		
P value	< 0.001		< 0.001 (QMF vs. MF)		< 0.001 (QMF vs. MF) 0.214 (QMF vs. S/F)[b]		
Harms, n (%) (safety analysis set)							
AEs	128 (32.3)	153 (38.3)	292 (66.8)	320 (72.2)	286 (64.6)	308 (70.0)	290 (65.3)
SAEs	5 (1.3)	7 (1.8)	20 (4.6)	31 (7.0)	21 (4.7)	21 (4.7)	21 (4.7)
WDAEs (from study treatment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deaths	0	0	0	1 (0.2)	0	0	0
Notable harms, n (%)							
Infections (systemic and local)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac and vascular disorders	[redacted]	[redacted]	34 (7.8)	29 (6.5)	28 (6.3)	25 (5.7)	19 (4.3)
Blood glucose increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypoglycemia	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anticholinergic effects[f]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bone markers (blood alkaline phosphatase, increased or abnormal)	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HPA axis suppression[g]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	QUARTZ study		PALLADIUM study				
	QMF 150 mcg/ 80 mcg N = 395	MF 200 mcg N = 399	QMF 150 mcg/ 160 mcg N = 437	MF 400 mcg N = 443	QMF 150 mcg/ 320 mcg N = 443	MF 800 mcg N = 440	S/F 50 mcg/ 500 mcg N = 444
Systemic steroid effects[h]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Local steroid effects[i]	14 (3.7)	10 (2.6)	21 (4.8)	27 (6.0)	20 (4.5)	20 (4.5)	18 (4.1)
Growth rates	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ACQ-7 = Asthma Control Questionnaire (seven items); AE = adverse event; ANCOVA = analysis of covariance; AQLQ = Asthma Quality of Life Questionnaire; AQLQ-S+12 = Asthma Quality of Life Questionnaire for 12 years and older; CI = confidence interval; FAS = full analysis set; FEV_1 = forced expiratory volume in one second; HPA = hypothalamic-pituitary-adrenal; LS = least squares; MF = mometasone furoate; MMRM = mixed-effects models for repeated measures; NI = noninferiority; NR = not reported; QMF = indacaterol/mometasone furoate; SABA = short-acting beta2-agonist; SAE = serious adverse event; SE = standard error; S/F = salmeterol/fluticasone propionate; 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 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] 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). Estimates from the MMRM models consider the full-time course data and not only those at the respective visit, which may include fewer patients than were reported at baseline.

[d] The QUARTZ study features ANCOVA with the following covariates: Baseline AQLQ, FEV_1 prior to inhalation, and FEV_1 within 15 to 30 minutes post inhalation of salbutamol/albuterol (components of SABA reversibility). The PALLADIUM study features MMRM with the following covariates: baseline AQLQ, 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).

[e] MMRM with the following covariates: Baseline 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).

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

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

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

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

Source: Clinical Study Reports for the QUARTZ[5] and PALLADIUM[6] studies.

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 for type I error. This includes outcomes related to asthma exacerbations and HRQoL, 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 two trials is not considered a sufficient measure of efficacy when used alone for a new controller treatment for asthma.[7] The choice of ACQ-7, a measure of asthma control, as a key secondary outcome helps with this issue; however, it is based on a change over 12 weeks to 26 weeks of treatment, which may be too short to comprehensively assess asthma control in patients with asthma; 52 weeks is preferred. PALLADIUM was the only study that included a fixed-dose combination ICS/LABA as an active comparator; however, this comparison was not controlled for multiplicity, the study was not powered for the analysis, and sensitivity analyses were not conducted. Therefore, the comparison of high-dose QMF to S/F 50 mcg/500 mcg is associated with significant uncertainty and should only be considered exploratory.

The two trials were limited in their generalizability to clinical practice in Canada. First, none of the sites in either of the trials for QMF were located in Canada. Although the inclusion

and exclusion criteria of the trials were generally consistent with other asthma clinical trials, patients enrolled in QUARTZ and PALLADIUM 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 and a baseline ACQ-7 score of at least 1.5 (poorly controlled asthma) 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 combination product. The 12-week duration of the QUARTZ study was sufficient to demonstrate a difference in terms of the change in FEV_1 but may not have been long enough to comprehensively assess the ability of QMF to control asthma as a maintenance treatment. The duration of PALLADIUM included a 52-week treatment period, which was a sufficient period of analysis and consistent with the European Medicines Agency (EMA) guidelines.[7] However, it should be noted that asthma is a chronic disease that requires lifelong treatment and information regarding the efficacy and safety beyond one year was lacking. Lastly, the clinical expert consulted on this review noted that the FEV_1, in isolation, 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 QMF in clinical practice.

Indirect Comparisons

The sponsor submitted an indirect treatment comparison (ITC) report that conducted a feasibility analysis to assess the viability of doing a network meta-analysis (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 extensive heterogeneity in the literature — specifically, study populations, study duration, and varying definitions of exacerbation.

Other Relevant Evidence

Description of Studies

Study 1305 (N = 51) was a multi-centre, open-label, single-arm, 52-week treatment study designed to assess the safety and tolerability of once-daily QMF administered at 150 mcg/320 mcg in Japanese patients with inadequately controlled asthma. Patients were at least 18 years old and had previously used medium-dose or high-dose ICS plus at least one controller medication (e.g., LABA, a leukotriene receptor antagonist (LTRA), theophylline, or an anti-allergic medication) for asthma.

The mean (standard deviation [SD]) age of patients was 51.9 years (12.5) and 100% were Asian. At baseline, 72.5% of patients had not had an asthma exacerbation in the previous year, [redacted] of patients had never smoked, and the mean (SD) baseline ACQ-7 score was 1.98 (0.54). Most patients (88.2%) reported prior use of a medium-dose or high-dose ICS/LABA combination and [redacted] had prior use of a medium-dose ICS. Further, the mean (SD) reversibility at baseline was [redacted] as a percentage increase or [redacted] L [redacted] as an increase in L.

Efficacy Results

Study 1305 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 1305; statistical testing was not conducted. Briefly, [redacted] of patients experienced an AE, with the most common reasons being due to asthma [redacted] and nasopharyngitis [redacted]. No SAEs, WDAEs, or deaths were reported. Overall, once-daily QMF therapy seemed to be well-tolerated up to 52 weeks; however, a large proportion of patients [redacted] reported AEs due to local infection.

Critical Appraisal

The main limitations of Study 1305 included the open-label and single-arm study design.

Conclusions

The QUARTZ and PALLADIUM studies demonstrated superiority of QMF compared to corresponding doses of MF for the change from baseline in trough FEV_1 after 12 weeks and 26 weeks of treatment, respectively. NI was met for the comparison of high-dose QMF to S/F 50 mcg/500 mcg on the change from baseline in trough FEV_1. In terms of asthma control based on the ACQ-7, the treatment difference between QMF and MF was in favour of QMF at all dose strengths in both trials. Outcomes related to asthma exacerbations, rescue medication use, and HRQoL were all important to clinicians and patients, and the results from the two trials were aligned with the results of the primary and key secondary analyses; however, these outcomes are subject to uncertainty due to a lack of statistical testing or control for multiplicity. Nocturnal awakening, days of missed work, and health care utilization-related outcomes were also reported.

SAEs and WDAEs were reported infrequently in all treatment groups. One death was reported overall; it occurred in a patient in the MF 400 mcg treatment group and was due to an asthma exacerbation. No new safety signals were identified in the 52-week open-label safety extension study.

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 hyperresponsiveness 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, 211,100 Canadians (9.4%) between the ages of 12 and 17 — excluding those residing in the territories — reported being diagnosed by a health professional as having asthma.[8] The estimated number of persons 12 years and over living with asthma was 2.6 million (8.3%).[8] 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.[3] Although asthma can be diagnosed at any age, it often starts in childhood. In 2015, Statistics Canada estimated that 2.4 million Canadians aged 12 and older had a diagnosis of asthma,[9] representing 12% of all Canadian children and 8% of all Canadian adults.[9]

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 or PEF with reversibility test. The severity of asthma is assessed retrospectively, following at least two to three 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 reliver therapy
Step 4	Medium-dose ICS/LABA Option: High-dose ICS, add-on tiotropium bromide, 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.

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, 10, 11] 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:

- the frequency of daytime and night-time symptoms
- the frequency of exacerbations
- the frequency of absences from work or school due to asthma
- the ability to complete normal physical activity
- the need for a fast-acting beta2-agonist
- FEV_1 or PEF
- PEF diurnal variation.[10]

Pharmacologic management of asthma typically involves a combination of reliever therapy and controller therapy, with an option to add other therapies tailored to the needs of individual patients. The reliever therapy is provided to all patients with asthma and typically includes fast-acting beta2-agonists, either short-acting or long-acting; these can be used for rapid relief of asthma symptoms, but should be used concurrently with an ICS. Controller therapies, predominantly ICS, are used as a maintenance therapy and aim to reduce airway inflammation, control symptoms, and reduce future exacerbations.[2] Determining an appropriate controller therapy is based on the individual's current asthma control. According to the guidelines published by the Canadian Thoracic Society, a stepwise approach to pharmacologic therapy is recommended to achieve and maintain asthma control.[10] This involves escalating pharmacologic treatment, as necessary, to gain control (i.e., step up) and reduce treatment (i.e., step down) to the minimum required with respect to dose and number of medications for maintenance when possible.[10]

The use of ICS 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, 10] If control is not gained or maintained, second-line agents may be added, such as a LABA or LTRA, or the ICS dose can be titrated upward.[2, 10] 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 types of ICS and ICS/LABA available in Canada.

It has been reported that much of asthma-related morbidity is associated with poor management from under-used or poor adherence to maintenance therapy.[12] As a result, non-pharmacologic therapy such as patient education serves an essential role in the management of asthma. Additional non-pharmacologic therapies include control of asthma triggers through identification and avoidance, and monitoring for changes in symptoms or lung function.[11]

Drug

QMF is a combination product composed of a LABA and an ICS. It is available as a dry powder (in hard capsules) for oral inhalation with three dosing strengths:150 mcg/80 mcg, 150 mcg/160 mcg, and 150 mcg/320 mcg of QMF.[1] QMF is indicated as once-daily maintenance treatment of asthma in adults and adolescents 12 years of age and older with reversible obstructive airways disease. Further, the product monograph states that QMF "*should be prescribed for patients not adequately controlled on a long-term asthma control medication, such as ICS or whose disease severity clearly warrants treatment with both a LABA and an ICS*."[1] QMF is specifically not indicated for patients whose asthma can be managed by occasional use of rapid-onset, short-duration, inhaled beta2-agonist, or those whose asthma can be managed by ICS along with the occasional use of a beta2-agonist.[1] It is also not indicated for the relief of acute bronchospasm.[1]

The product monograph states that patients should be given a strength of QMF containing the appropriate dose of MF for the severity of their disease. The 150 mcg/80 mcg strength is recommended for patients who require a combination of LABA and low-dose ICS. The 150 mcg/160 mcg or 150 mcg/320 mcg is recommended for patients who require a combination of a LABA and a medium-dose or high-dose ICS.[1]

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 of cyclic 3',5'-adenosine monophosphate causes relaxation of the bronchial smooth muscle. When inhaled, indacaterol acts locally in the lung as a bronchodilator and has a rapid-onset action of long duration.[1]

MF is a synthetic corticosteroid with a high affinity for glucocorticoid receptors. Although the mechanism of action is not completely understood, it is likely that the effects of MF inhibit the release of mediators of the inflammatory cascade, thus providing it with local anti-inflammatory properties.[1] Health Canada's Notice of Compliance was received on May 6, 2020.

Table 4: Key Characteristics of ICS Monotherapies and in Combination with LABAs

	Indacaterol/ mometasone furoate (Atectura Breezhaler)[1]	Budesonide/formoterol fumarate dihydrate (Symbicort)[13]	Fluticasone furoate/vilanterol (Breo Ellipta)[14]	Fluticasone/ salmeterol (Advair pMDI and Advair Diskus)[15]	Mometasone/ formoterol fumarate dihydrate (Zenhale)[16]	ICS monotherapies[17-23]
Mechanism of action	ICS: Anti-inflammatory effects LABA: Stimulation of beta2 in the lungs leads to bronchodilation					Anti-inflammatory effects
Indication[a]	Once-daily maintenance treatment of asthma in adults and adolescents 12 years of age and older with reversible obstructive airways disease	Treatment of asthma in patients 12 years of age 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 of age and older with reversible obstructive airways disease	Indicated for the prophylactic management of steroid-responsive bronchial asthma in children and adults
Route of administration	Oral inhalation					
Recommended dose	150 mcg/80 mcg, 150 mcg/160 mcg, or 150 mcg/320 mcg, once daily	100 mcg/6 mcg, or 200 mcg/6 mcg, or 400 mcg/12 mcg, twice daily	100 mcg/25 mcg, or 200 mcg/25 mcg, once daily	125 mcg/25 mcg, or 250 mcg/25 mcg, twice daily	50 mcg/5 mcg, or 100 mcg/5 mcg, or 200 mcg/5 mcg, twice daily	Dosing is variable based on steroid equivalency
Serious adverse effects of safety issues	Use with caution in patients with cardiovascular disorders. Can cause endocrine and metabolism effects on growth, hypercorticism, and adrenal suppression. Use with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines.	Can cause sore mouth, sore throat, dysphonia, oral thrush, nervousness, tremor, tachycardia, palpitations	Use with caution in patients with cardiovascular disorders. Can cause sore mouth, sore throat, dysphonia, oral thrush, nervousness, tremor, tachycardia, palpitations	Can cause sore mouth, sore throat, dysphonia, oral thrush, nervousness, tremor, tachycardia, palpitations	Contraindicated in patients with cardiac tachyarrhythmia Can cause dysphonia, oral thrush, tremor, tachycardia, palpitations	ICS therapy may be associated with thrush, dose-dependent increases in the incidence of ocular complications, reduced bone density, suppression of HPA axis– responsiveness to stress, and inhibition of growth velocity in children. ICS is contraindicated in patients with untreated systemic

	Indacaterol/ mometasone furoate (Atectura Breezhaler)[1]	Budesonide/formoterol fumarate dihydrate (Symbicort)[13]	Fluticasone furoate/vilanterol (Breo Ellipta)[14]	Fluticasone/ salmeterol (Advair pMDI and Advair Diskus)[15]	Mometasone/ formoterol fumarate dihydrate (Zenhale)[16]	ICS monotherapies[17-23]
						infections, TB infections, or ocular herpes simplex.

HPA = hypothalamic-pituitary-adrenal; ICS = inhaled corticosteroid; LABA = long-acting beta2-agonist; pMDI = pressurized metered-dose inhaler; TB = tuberculosis.

[a] Health Canada–approved indication.

Source: Product monographs.[1, 13-23]

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 indacaterol/glycopyrronium/MF and QMF. Two patient groups provided input that was intended for use in both reviews: the Lung Health Foundation (formerly called the Ontario Lung Association) and Asthma Canada.

Both patient groups are registered charities that aim to support research and to 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 three telephone interviews with patients living with asthma. These interviews were completed in May 2020. The three 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; the information was obtained to inform a 2014 report titled *Severe Asthma: The Canadian Patient Journey*.[4] Of the 24 patients who participated in interviews, 75% were between 30 and 60 years old and the majority of participants (81%) were female. The online survey had 200 respondents from across Canada. Nearly half of the respondents (47%) 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 (the survey was available April 27, 2020, to May 8, 2020). This resulted in 192 respondents. Of these, 171 (89%) were asthma patients and 21 (11%) were caregivers. The majority of the respondents were female (86%) and half of the respondents (50%) 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 also in an acute severe attack, typically called an exacerbation.

More than 70% of the respondents to Asthma Canada's online survey (associated with their 2014 report) reported that their daily activities and exercise were limited by asthma, although 89% of patients expected that asthma should not be a reason for avoiding their

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 around 40% of respondents said their asthma affected them a "*great deal*," and 30% of respondents said that asthma caused them to miss days of school or work in the previous year, with two-thirds missing five 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; of these, one-third of respondents went more than once and one-fifth of respondents needed hospitalization. Lastly, asthma can take a psychological and emotional toll on patients. Two-thirds of respondents to Asthma Canada's survey indicated that they felt stigmatized due to their asthma at one point in time.

Experience With Treatment

The Lung Health Foundation reported that phone interview respondents had had experience with budesonide/formoterol (Symbicort), albuterol (Ventolin), fluticasone propionate/salmeterol (Advair), tiotropium bromide (Spiriva), prednisone, and montelukast (Singulair). Respondents had also tried mometasone (Nasonex), cetirizine (Reactine), and other antihistamines for allergies as needed. These respondents indicated that these treatments provide some relief for their fatigue, shortness of breath, wheezing, cough, and reduced energy. Both of the patient groups reported that side effects of medications experienced by patients include 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 prompted on whether their current asthma medication affected their life in any other way, one 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 of the respondents do not carry their short-acting reliever with them (the number of respondents is not available), and more than half of respondents do not regularly take their long-term controller medication. Asthma Canada expressed that patients often believe they do not need to continue taking their medications when they are asymptomatic. Other reasons for nonadherence include lack of efficacy (continued exacerbations) and unpleasant 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 under $50,000 or are unable to work due to their asthma. 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.

There were no patients identified by the Lung Health Foundation or Asthma Canada who had experience with QMF.

Improved Outcomes

Broadly, both patient groups expressed a desire for improved HRQoL and lung function. When asked what outcomes patients would like improved in Asthma Canada's online survey, 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 that 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 and 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 want 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 mild side effects for the management of 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, such as the patient who noted, *"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 one device safely would be very beneficial to them.

When patients are deciding to try a new medication, the Lung Health Foundation identified that they most often consider three things: 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 one clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical

appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). The following input was provided by one 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 risk, including preventing airway remodelling and limiting complications of current therapy. Finally, effective therapy can reduce the risk of asthma-related death.[24]

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,[25] with an annualized rate for severe exacerbations of 0.11 per patient-year. Therefore, the clinical expert stated that treatments are needed to improve the outcomes of patients with few daily symptoms but still at risk for severe exacerbations. The expert felt that the majority of patients with uncontrolled asthma can regain control with current treatments focusing upon medication adherence, self-management techniques, and inhaler education, and that approximately 5% of patients who are poorly controlled despite this will remain so and will require additional treatment. The clinical expert shared that simplified inhaler regimens may improve adherence to ICS use and improve asthma control, but there is little good-quality evidence to support this contention.[26] In addition, the expert stated that these patients may benefit from add-on therapies to the standard ICS/LABA inhalers. Again, there is some weak evidence[26] that reducing the numbers of different inhalers may improve adherence to therapy and thus improve clinical outcomes.

Place in Therapy

The clinical expert reported that the recommended therapy for mild asthma, as described by GINA,[2] has significantly changed in the last two years. Where previously patients would have relied upon an as-needed SABA reliever to treat mild asthma, GINA now recommends starting to use a low-dose ICS whenever a beta2-agonist reliever is used (GINA step 1). With increasingly persistent symptoms (GINA step 2), treatment includes either a daily low-dose ICS or an as-needed low-dose ICS/formoterol.[27, 28] Pharmacologic treatment is escalated with increasingly persistent symptoms to include a daily low-dose ICS combined with a LABA (ICS/LABA) (GINA step 3) or to include daily medium-dose ICS/LABA (GINA step 4). If daily high-dose ICS/LABA (GINA step 5) does not gain control, then additional pharmacologic treatments could include low-dose oral corticosteroids, inhaled tiotropium bromide, and/or biologic agents targeting specific pathways of the inflammatory cascade (e.g., anti-immunoglobulin E or anti-interleukin-5 monoclonal antibodies). Other pharmacologic agents that can be used as add-on therapy include a LTRA, theophylline, and long-term macrolide therapy; the latter treatment, however, does not have Health Canada approval.

The clinical expert stated that the use of a low-dose ICS/LABA is well established as the treatment of choice of patients with regular asthma symptoms. They felt that QMF in increasing mometasone doses could be used for patients with GINA step 3 to step 5. The clinical expert reported that this approach is not unique and there are currently many inhalers in Canada that meet this need; however, other than fluticasone furoate/vilanterol (Breo Ellipta), there are not any other once-daily ICS/LABA formulations and there are none with the range of ICS dosing approved for the three formulations of QMF. Therefore, the

clinical expert felt that these inhalers could be used as first-line therapy for most patients with moderate to severe asthma. The clinical expert also stated that QMF does not offer a paradigm shift in asthma management, but it might offer increased convenience of use. According to the clinical expert, the delivery device requires the patient to insert a capsule before using it, as it is not a multi-dose device. 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 to the steps to load the capsule and inhale a dose. There is no clear evidence on how much this might negatively affect adherence. The expert also noted that, when choosing among the available inhaled treatments, the delivery device should be personalized based on patient preference and capability. Some patients might benefit from an MDI, some from a multi-dose dry powder. In addition, three recent studies cited by the clinical expert have examined the use of budesonide/formoterol in mild asthma and GINA now recommends this as an option for GINA step 1 therapy.[25, 27, 29] The clinical expert recommended that if escalation of therapy is considered in that setting, then continuing with the same inhaler in a higher dose would be a reasonable choice rather than teaching a patient how to use a new inhaler.

Patient Population

When asked which patients would be best suited for treatment with the drug under review, the clinical expert responded that these inhalers are essentially targeted to all patients with asthma other than those with infrequent symptoms (GINA step 1 and step 2). Patients with infrequent symptoms are best treated with a daily ICS or as-needed ICS/formoterol.

The standard approaches to the diagnosis and management of asthma as outlined in the Canadian Thoracic Society guidelines[10] and the recent GINA recommendations[2] are sufficient for identifying patients who would be best suited for treatment with QMF, according to the clinical expert. The clinical expert noted that patient history, physical examination, measurements of reversibility of airway obstruction and measurement of airways hyperreactivity, if needed, are the mainstays of diagnosis. Response to treatment and achieving asthma control then guides the specific combination of therapies provided to individuals. The clinical expert felt that patients who would be least suitable for treatment with QMF were patients with a mild form of the disease who are better suited for daily monotherapy with ICS or as-needed treatment with ICS/formoterol. The expert also felt that patients who are unable or unwilling to use the delivery device or those unwilling or unable to tolerate ICS should be offered alternative treatments.

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 the 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 gaining asthma control. This can be quantified with validated tools such as the Asthma Control Questionnaire (ACQ). Often asthma control is 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 gaining 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, as per feedback from the clinical expert. The expert noted that some patients test home PEF twice daily 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 since, for adults, it is a lifelong disease. Treatment can be escalated or de-escalated based upon symptoms and lung function measurements.

Prescribing Conditions

The clinical expert felt 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. This might include patients at GINA step 5. The clinical expert also relayed that QMF delivered via Breezhaler is administered at home.

Clinical Evidence

The clinical evidence included in the review of QMF is presented in three 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 that were 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 was identified in the literature that met the selection criteria specified in the review. 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

The objective was to perform a systematic review of the beneficial and harmful effects of QMF (150 mcg/80 mcg, 150 mcg/160 mcg, and 150 mcg/320 mcg) administered by oral inhalation for once-daily maintenance treatment of asthma in adults and adolescents 12 years of age and older with reversible obstructive airways disease. QMF should be prescribed for patients not adequately controlled on a long-term asthma control medication, such as ICS, or whose disease severity clearly warrants treatment with both a LABA and an ICS.

Methods

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

Table 5: Inclusion Criteria for the Systematic Review

Patient population	Adults and adolescents 12 years of age and older with asthma (reversible obstructive airways disease) not adequately controlled on a long-term asthma control medication, such as ICS, or whose disease severity clearly warrants treatment with both a LABA and an ICS
Intervention	Indacaterol/mometasone furoate (150 mcg/80 mcg, 150 mcg/160 mcg, and 150 mcg/320 mcg) for oral inhalation, administered once daily Delivered via the Atectura Breezhaler inhalation device
Comparators	ICS alone ICS + LABA
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/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), growth rates (12 years to < 18 years age group), cardiovascular events, HPA axis suppression, bone markers, blood sugar levels
Study design	Published and unpublished phase III and phase IV RCTs

AE = adverse event; ED = emergency department; FEV_1 = forced expiratory volume in one second; HPA = hypothalamic-pituitary-adrenal; ICS = inhaled corticosteroid; LABA = long-acting beta2- agonist; 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 was performed by an information specialist using a peer-reviewed search strategy.

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.[30]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, and PubMed. The search strategy comprised both controlled vocabulary, such as the U.S. National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were indacaterol MF. Two clinical trial registries were searched: the U.S. National Library of Medicine'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 the 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:[31] 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 one 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

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

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

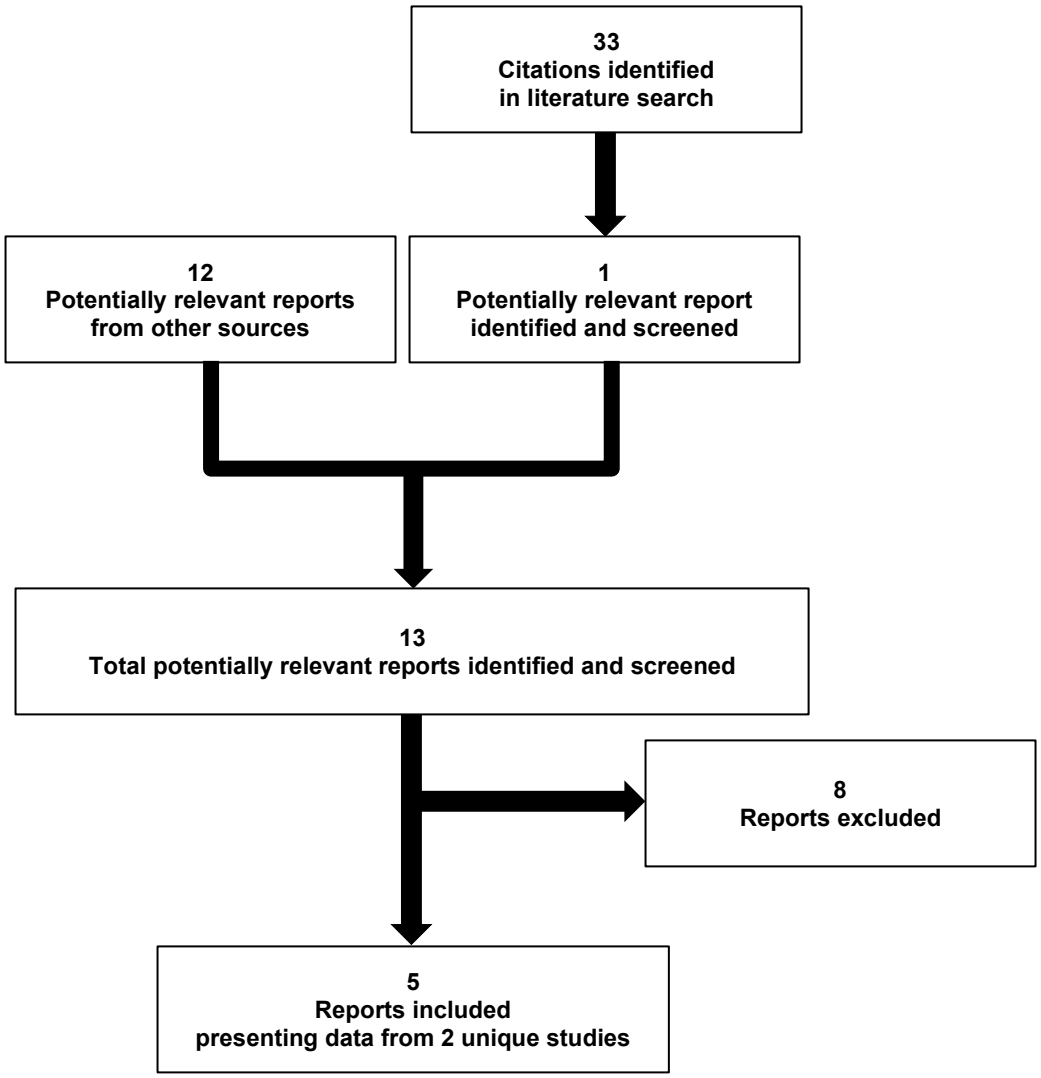


Table 6: Details of Included Studies

		QUARTZ study	PALLADIUM study
DESIGNS AND POPULATIONS	**Study design**	DB RCT, double-dummy, parallel-group, active-controlled	DB, triple-dummy, parallel-group, active-controlled
	Locations	126 sites in 22 countries, including in East Asia, Europe, South America, India, South Africa, and Sweden	316 sites in 24 countries, including in the US, China, Japan, Europe, Asia, Central America, and Africa
	Randomized (N)	802	2,216
	Inclusion criteria	• Adolescents aged ≥ 12 to < 18 years and adults aged ≥ 18 and ≤ 75 years • Diagnosis of asthma for ≥ 3 months prior to screening • Prior use of low-dose ICS with or without another controller therapy at a stable dose for ≥ 1 month prior to screening • Adults and adolescents taking low-dose ICS (without LABA) must be inadequately controlled[a] • Adolescents taking low-dose ICS/LABA with ACQ-7 score ≥ 1 and < 1.5 at visit 101 and inadequately controlled[a] at visit 102 • Pre-bronchodilator FEV_1 ≥ 60% and < 90% of predicted normal value[b] after withholding bronchodilators at visit 101 and visit 102 • Demonstrated increase in FEV_1 ≥ 12% and ≥ 200 mL within 15 to 30 minutes after administration of 400 mcg salbutamol/360 mcg albuterol at visit 101	• Adolescents aged ≥ 12 to < 18 years and adults aged ≥ 18 and ≤ 75 years • Diagnosis of asthma for ≥ 1 year prior to screening • Prior use of medium-dose or high-dose ICS or low-dose ICS/LABA combination for asthma for ≥ 3 months and at a stable dose for ≥ 1 month prior to screening • Symptomatic at screening despite treatment, and an ACQ-7 score ≥ 1.5 at visit 101 and visit 102 and qualified for treatment with medium- dose or high-dose ICS/LABA • Pre-bronchodilator FEV_1 ≥ 50% and < 85% of predicted normal value[b] after withholding bronchodilators at visit 101 and visit 102 • Demonstrated increase in FEV_1 ≥ 12% and 200 mL within 15 to 30 minutes after administration of 400 mcg salbutamol/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 or exacerbation requiring systemic steroids, hospitalization (> 24 hours), or ED visit (≤ 24 hours) within 6 weeks of visit 1 for adults and in the last 6 months for adolescents • Required intubation for severe asthma attack or exacerbation • Patients with chronic conditions affecting the upper respiratory tract that could interfere with the study • Patients with type I diabetes or uncontrolled type II diabetes • Patients with a history of chronic lung diseases other than asthma, such as COPD, sarcoidosis, interstitial lung disease, cystic fibrosis, clinically significant bronchiectasis, and active TB • History of MI in previous 12 months • Patients with unstable ischemic heart disease, NYHA Class III or Class IV left ventricular failure arrhythmia, uncontrolled hypertension, cerebrovascular disease, psychiatric disease, neurodegenerative diseases, or other	• History of smoking within 6 months of visit 1 or for ≥ 10 pack years[c] • Had an asthma attack or exacerbation requiring systemic steroids, hospitalization (> 24 hours), or ED visit (≤ 24 hours) within 6 weeks of visit 1 for adults and in the last 6 months for adolescents • Required intubation for severe asthma attack or exacerbation • Patients with chronic conditions affecting the upper respiratory tract that could interfere with the study • Patients with type I diabetes or uncontrolled type II diabetes • Patients with a history of chronic lung diseases other than asthma, such as COPD, sarcoidosis, interstitial lung disease, cystic fibrosis, clinically significant bronchiectasis, and active TB • History of MI in previous 12 months • Patients with unstable ischemic heart disease, NYHA Class III or Class IV left ventricular failure arrhythmia, uncontrolled hypertension, cerebrovascular disease, psychiatric disease, neurodegenerative diseases, or other

		QUARTZ study	PALLADIUM study
		neurological disease, uncontrolled hypothyroidism, hyperthyroidism, and other autoimmune diseases, hypokalemia, hyperadrenergic state, or ophthalmologic disorder • History of malignancy of an organ system within the last 5 years • Receiving the following without a washout period: SAMA, ICS, LABA, SABA, parenteral or OCS, intramuscular depot CS, monoclonal antibodies, xanthines, systemic mast cell stabilizers, or fixed combinations of beta2-agonists and ICS, SABA and short-acting anticholinergic, or LTRA and leukotriene synthesis inhibitors • Use of LAMA within 3 months prior to visit 1 • Patients on maintenance immunotherapy for allergies for < 3 months prior to run-in period or that was used for more than 3 months prior to run-in period but was expected to change during the study	neurological disease, uncontrolled hypothyroidism, hyperthyroidism, and other autoimmune diseases, hypokalemia, hyperadrenergic state, or ophthalmologic disorder • History of malignancy of an organ system within the last 5 years • Receiving the following without a washout period: LAMA, SAMA, ICS, LABA, SABA, parenteral or OCS, intramuscular depot CS, monoclonal antibodies, xanthines, systemic mast cell stabilizers, or fixed combinations of beta2-agonists and ICS, SABA and short-acting anticholinergic, or LTRA and leukotriene synthesis inhibitors • Patients on maintenance immunotherapy for allergies for < 3 months prior to run-in period or that was used for more than 3 months prior to run-in period but was expected to change during the study
Drugs	**Intervention**	QMF 150 mcg/80 mcg once daily via Breezhaler	QMF 150 mcg/160 mcg once daily via Breezhaler QMF 150 mcg/320 mcg once daily via Breezhaler
	Comparator(s)	MF 200 mcg once daily delivered via Twisthaler	MF 400 mcg once daily via Twisthaler MF 400 mcg twice daily via Twisthaler Salmeterol xinafoate/fluticasone propionate 50 mcg/500 mcg twice daily via Accuhaler
Duration	**Phase**		
	Screening	2 weeks	Up to 2 weeks
	Run-in	3 weeks	2 weeks
	Double-blind	12 weeks	52 weeks
	Follow-up	30 days	30 days
Outcomes	**Primary end point**	Trough FEV_1 after 12 weeks of treatment	Trough FEV_1 after 26 weeks of treatment
	Secondary and exploratory end points	**Secondary** ACQ-7 after 12 weeks of treatment **Other secondary** *Lung function* • Trough FEV_1 at day 2 of treatment period • Pre-dose FEV_1 • FVC and FEF between 25% and 75% of FVC over 12 weeks • Morning and evening PEF over 4 weeks and 12 weeks of treatment *Symptoms and asthma control* • % of patients with 0.5 units improvement from baseline in ACQ-7 score at week 12	**Secondary** ACQ-7 after 26 weeks of treatment **Other secondary** *Lung function* • Spirometry data by visit (trough FEV_1, pre-dose FEV_1, FVC, and FEF_{25-75}) *Symptoms and asthma control* • ACQ-7 at week 4, week 12, and week 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

		QUARTZ study	PALLADIUM study
		• % of asthma symptom-free days, % of nights without awakenings, and % of mornings without symptoms on awakening over 12 weeks of treatment • Asthma control by ACQ-7 at week 4 • Rescue usage over 12 weeks of treatment • % of rescue medication-free days over 12 weeks of treatment • QoL by AQLQ over 12 weeks of treatment *Exacerbations* • Time to first asthma exacerbation • Annual rate of asthma exacerbations *Safety and tolerability outcomes*	weeks and 52 weeks, and % of 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 AE, time to first hospitalization, annual rate of AEs (and excluding patients requiring CS after an AE), duration of AE in days, % of patients with ≥ 1 AE, time to permanent study drug discontinuation due to an AE, total amounts (doses) of OCS for AEs *Health-related quality of life* • AQLQ: Mean score per domain, overall QoL score, proportion of patients with 0.5 improvement from baseline *Safety and tolerability outcomes*
NOTES	**Publications**	Kornmann et al. (2020)[32]	van Zyl-Smit et al. (2020)[33]

ACQ-7 = Asthma Control Questionnaire (seven items); AE = adverse event; AQLQ = Asthma Quality of Life Questionnaire; COPD = chronic obstructive pulmonary disease; CS = corticosteroid; DB = double-blind; ED = emergency department; FEF = mean forced expiratory flow; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; ICS = inhaled corticosteroid; LABA = long-acting beta2-agonist; LAMA = long-acting muscarinic antagonist; LTRA = leukotriene receptor antagonist; MF = mometasone furoate; MI = myocardial infarction; NYHA = New York Heart Association; OCS = oral corticosteroid; PEF = peak expiratory flow; QMF = indacaterol/mometasone furoate; QoL = quality of life; RCT = randomized controlled trial; SABA = short-acting beta2-agonist; SAMA = short-acting muscarinic antagonist; SOB = shortness of breath; TB = tuberculosis.

Note: Three additional reports were included.[32-34] Visit 1 = screening, visit 101 = start of run-in period, visit 102 = end of run-in period, and visit 201 = randomization visit.

[a] Inadequate control defined by an ACQ-7 score of 1.5 or more at visit 101 and visit 102, or "symptomatic despite treatment."

[b] Normal value for the patient according to American Thoracic Society and European Respiratory Society criteria.

[c] One pack = 20 cigarettes, 10 pack years = one pack per day × 10 years, or half-pack per day × 20 years.

Source: Clinical Study Reports for the QUARTZ[5] and PALLADIUM[6] studies.

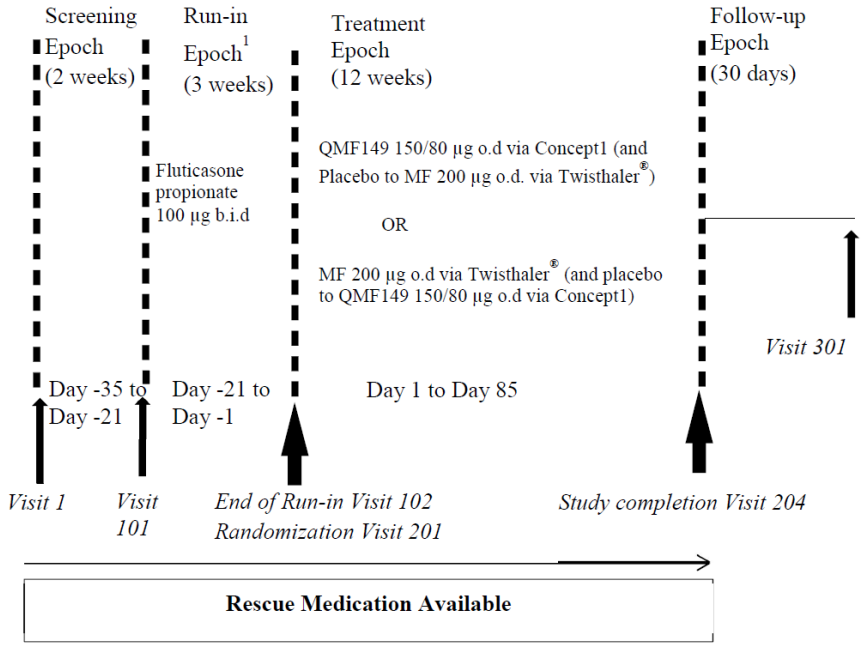
Description of Studies

Two phase III pivotal studies submitted by the sponsor, the QUARTZ and PALLADIUM studies, were included in this review. Both were double-blind, parallel-group, double-dummy (QUARTZ) or triple-dummy (PALLADIUM) RCTs. The duration of the treatment period was 12 weeks in QUARTZ and 52 weeks in PALLADIUM. None of the study sites for QUARTZ and PALLADIUM were in Canada; both studies included sites in Europe and PALLADIUM included sites in the US (Table 6). In QUARTZ, 802 patients were randomized at a 1:1 ratio to QMF 150 mcg/80 mcg once daily or MF 200 mcg once daily. In PALLADIUM, 2,216 patients were randomized at a ratio of 1:1:1:1:1 to one of five treatment groups: QMF 150 mcg/160 mcg once daily, QMF 150 mcg/320 mcg once daily, MF 400 mcg once daily, MF 800 mcg once daily, or S/F 50 mcg/500 mcg twice daily. Interactive Response Technology was used to randomize patients and randomization numbers were automated to conceal treatment assignment from patients and investigator staff in both studies. Randomization was stratified by age (≥ 12 to < 18 years or ≥ 18) and by region in both studies.

The primary objectives were to demonstrate the superiority of QMF delivered via Breezhaler in the evening to MF delivered via Twisthaler in terms of trough FEV_1 after 12 weeks of treatment in QUARTZ and 26 weeks of treatment in PALLADIUM, respectively. The key secondary objectives in QUARTZ and PALLADIUM were to demonstrate superiority based on the same comparisons in terms of ACQ-7 after 12 weeks and 26 weeks, respectively.

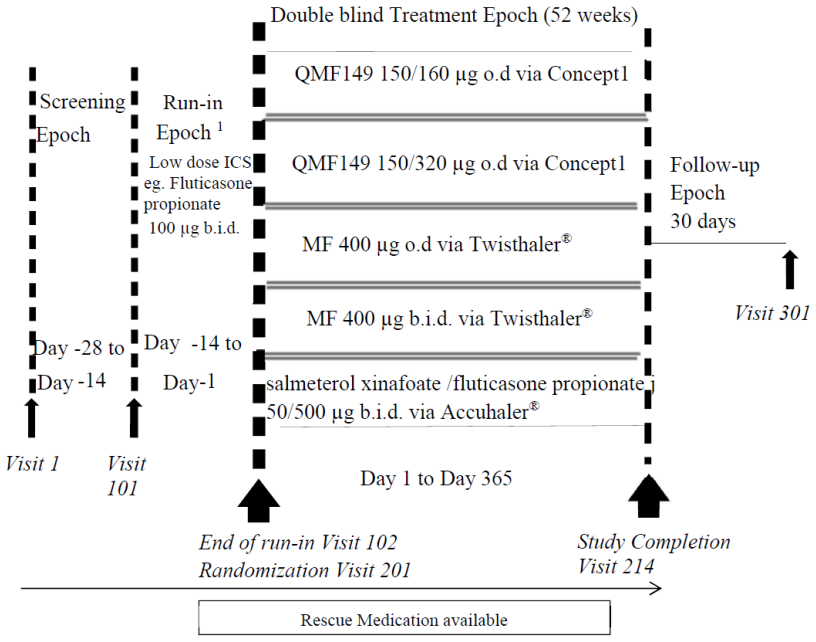
The QUARTZ study involved a screening period of up to two weeks, a three-week run-in period, a 12-week treatment period, and a 30-day follow-up period (Figure 2). In the QUARTZ study, the screening period was used to obtain consent, review and adjust medications as needed, ensure washout of prior asthma medication, and provide patients with salbutamol/albuterol for use as rescue medication throughout the study. At the start of the run-in period, patients were provided with open-label fluticasone propionate 100 mcg twice daily delivered via Accuhaler that was used throughout the run-in period and was stopped at randomization. If not available, fluticasone propionate 125 mcg twice daily via an MDI (or alternative equivalent strength) was used. The run-in period was also used to assess the eligibility of patients and collect baseline values. The PALLADIUM study only differed from the QUARTZ study by having a two-week run-in period and 52-week treatment period (Figure 3); the details of the screening and run-in period were the same.

Figure 2: QUARTZ Study Design



MF = mometasone furoate; o.d. = once daily; QMF149 = indacaterol/mometasone furoate .
Source: QUARTZ Clinical Study Report.[5]

Figure 3: PALLADIUM Study Design



b.i.d. = twice daily; ICS = inhaled corticosteroid; MF = mometasone furoate; o.d. = once daily; QMF149 = indacaterol/mometasone furoate .
Source: PALLADIUM Clinical Study Report.[6]

Populations

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria used for the QUARTZ and PALLADIUM studies are summarized in Table 6.

Both QUARTZ and PALLADIUM included adolescents (12 to 17 years old) and adults (18 to 75 years old) with a diagnosis of asthma prior to screening. Patients had at least one month's use of a low-dose ICS prior to screening in QUARTZ and at least three months' use of a medium-dose or high-dose ICS or a low-dose ICS/LABA combination in PALLADIUM. In QUARTZ, adolescents taking a low-dose ICS (without LABA) and adults had to be inadequately controlled based on an ACQ-7 score of 1.5 or more. Adolescent patients taking a low-dose ICS/LABA were only included if they were adequately controlled at the start of the run-in period (if they had an ACQ-7 score ≥ 1 and < 1.5) and inadequately controlled at randomization. In PALLADIUM, patients were required to be inadequately controlled (with an ACQ-7 score of ≥ 1.5) despite treatment. Lastly, patients with a pre-bronchodilator FEV_1 of 60% or more and less than 90% in QUARTZ and 50% or more and less than 85% in PALLADIUM had to demonstrate an increase in FEV_1 of 12% or more and 200 mL or more following use of 400 mcg salbutamol/360 mcg albuterol.

Patients were excluded from QUARTZ and PALLADIUM if they had a history of smoking, had an asthma exacerbation within six weeks of the screening visit (or six months for adolescents), 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 received any of the following without a washout period: short-acting muscarinic antagonist, ICS, LABA, SABA, parenteral or oral corticosteroid, intramuscular depot corticosteroid, monoclonal antibodies, xanthines, systemic mast cell stabilizers, or fixed combinations of beta2-agonists and ICS, SABA and short-acting anticholinergic, or LTRA and leukotriene synthesis inhibitors, as well as LAMA in PALLADIUM. In QUARTZ, patients were excluded if they had used LAMA within three months of screening.

Baseline Characteristics

A summary of the baseline characteristics for the QUARTZ and PALLADIUM studies are available in Table 7 and Table 8, respectively.

In the QUARTZ study, patients were a mean (SD) age of 45.1 years (16.3) to 46.1 years (16.3) with more than [redacted] in both groups were 18 to 64 years old; 59.7% to 62.1% were female, 65.6% to 65.8% were white, and the duration of asthma among patients was a mean (SD) of 13.6 years (12.5) to 14.4 years (13.2). Most patients (79.0% to 81.4%) reported zero asthma exacerbations requiring treatment in the 12 months prior to the start of the study, and 17.6% to 18.3% reported one exacerbation. At baseline, patients reported a mean (SD) ACQ-7 score of 2.2 (0.4) to 2.3 (0.4) indicating poorly controlled asthma. Almost all patients had prior treatment experience with a low-dose ICS/LABA (54.5% to 57.4%) or low-dose ICS alone (41.3% to 44.5%). Lastly, FEV_1 reversibility was reported as a percentage increase and increase in L at the start of the run-in period. The mean (SD) percentage of FEV_1 reversibility ranged from 20.6 (11.7) to 20.7 (11.9) across treatment groups, and the mean (SD) FEV_1 as an increase in L ranged from [redacted] to [redacted]

In the PALLADIUM study, patients were a mean (SD) age of 47.1 years (14.6) to 48.9 years (14.6), with [redacted] in both groups being 18 to 64 years old, more than half being female (57.4% to 61.3%) and white (68.4% to 71.9%), and the duration of asthma among patients being a mean (SD) of 14.3 years (12.5) to 15.1 years (13.0) . Between 67.5% to 70.7% of patients reported zero asthma exacerbations requiring treatment in the 12 months prior to the start of the study, 23.2% to 25.6% reported one exacerbation, and 5.8% to 8.3% reported more than one exacerbation. At baseline, patients reported a mean (SD) ACQ-7 score of 2.3 (0.5) in all treatment groups, indicating poorly controlled asthma. In terms of prior treatment for asthma, the majority of patients were previously using a low-dose ICS/LABA (67.6% to 71.0%) followed by a medium-dose ICS (16.9% to 21.6%) and high-dose ICS (5.5% to 7.7%). Lastly, the mean (SD) percentage of FEV_1 reversibility was between 22.6 (12.9) and 23.0 (12.8) and the mean (SD) FEV_1 as an increase in L was between 0.44 (0.27) and 0.46 (0.29).

There was a difference in the proportion of patients with a baseline ACQ-7 score of 2.5 or more in the QUARTZ study, with [redacted] in the QMF group versus [redacted] in the MF group. There was also a difference in the proportion of patients with FEV_1 pre-bronchodilator as a percentage of the predicted FEV_1 from 60% to 70%, with [redacted] in the QMF treatment group and [redacted] in the MF treatment group, as well as in the 70% to 90% range, with [redacted] in the QMF treatment group and [redacted] in the MF treatment group. Otherwise, the treatment groups in QUARTZ were well balanced by their baseline characteristics. There were no major differences between treatment groups in the PALLADIUM study.

Notable differences between treatment groups include a higher proportion of patients who reported at least one asthma exacerbation in the 12 months prior to study start in PALLADIUM (19.6% in QUARTZ versus 30.6% in PALLADIUM) and mean (SD) FEV_1 pre-bronchodilator as a percentage of predicted FEV_1 at randomization, which was 75.1 (7.76) in QUARTZ and 67.3 (8.64) in PALLADIUM. In addition, the prior use of a low-dose ICS (42.9% in QUARTZ versus 0.7% in PALLADIUM), ICS other than low dose (0.1% in QUARTZ versus 26.8% in PALLADIUM), and low-dose ICS/LABA combination (56.0% in QUARTZ versus 68.8% in PALLADIUM) differed between the two studies.

Table 7: Summary of Baseline Characteristics in QUARTZ Study — Randomized Set

Characteristic		QUARTZ study	
		QMF 150 mcg/80 mcg N = 398	MF 200 mcg N = 404
Age (years)	Mean (SD)	46.1 (16.3)	45.1 (16.3)
	12 to 17, n (%)	[redacted]	[redacted]
	18 to 64, n (%)	[redacted]	[redacted]
	≥ 65, n (%)	[redacted]	[redacted]
Gender, n (%)	Male	151 (37.9)	163 (40.3)
	Female	247 (62.1)	241 (59.7)
Race, n (%)	White	262 (65.8)	265 (65.6)
	Black	1 (0.3)	5 (1.2)
	Asian	98 (24.6)	101 (25.0)
	Other	37 (9.3)	33 (8.2)
BMI	Mean (SD), kg/m^2	26.3 (5.8)	26.7 (6.0)

Characteristic		QUARTZ study	
		QMF 150 mcg/80 mcg N = 398	MF 200 mcg N = 404
	≤ 30.0 kg/m^2, n (%)	[redacted]	[redacted]
	> 30.0 kg/m^2, n (%)	[redacted]	[redacted]
Disease characteristics			
Duration of asthma (years)	Mean (SD)	14.4 (13.2)	13.6 (12.5)
	Median (range)	[redacted]	[redacted]
Number of asthma exacerbations in 12 months prior to study start that required treatment, n (%)	0	324 (81.4)	319 (79.0)
	1	70 (17.6)	74 (18.3)
	> 1	3 (0.8)	10 (2.5)
	Missing	1 (0.3)	1 (0.2)
Smoking status, n (%)	Never smoked	[redacted]	[redacted]
	Former smoker	[redacted]	[redacted]
Baseline ACQ-7 score	Mean (SD)	2.2 (0.4)	2.3 (0.4)
	Median (range)	[redacted]	[redacted]
	< 1.5, n (%)	[redacted]	[redacted]
	1.5 to < 2, n (%)	[redacted]	[redacted]
	2 to < 2.5, n (%)	[redacted]	[redacted]
	≥ 2.5, n (%)	[redacted]	[redacted]
	Missing, n (%)	[redacted]	[redacted]
Prior asthma treatment, n (%)	ICS low dose	177 (44.5)	167 (41.3)
	ICS other than low dose	1 (0.3)	0
	ICS/LABA low dose	217 (54.5)	232 (57.4)
	ICS/LABA other than low dose	3 (0.8)	0
	Missing	0	5 (1.2)
Spirometry			
FEV_1 (L) pre-bronchodilator at the start of the run-in period	n	396	399
	Mean (SD)	2.24 (0.64)	2.22 (0.58)
	Median (range)	[redacted]	[redacted]
FEV_1 pre-bronchodilator (% of predicted FEV_1) at the start of the run-in period	n	396	399
	Mean (SD)	73.3 (7.6)	72.2 (7.6)
	Median (range)	[redacted]	[redacted]
	60% to < 70%, n (%)	[redacted]	[redacted]
	70% to < 90%, n (%)	[redacted]	[redacted]
	≥ 90%, n (%)	[redacted]	[redacted]
	Missing, n (%)	[redacted]	[redacted]
FEV_1 reversibility (% increase) at the start of the run-in period	n	396	398
	Mean (SD)	20.6 (11.7)	20.7 (11.9)
	Median (range)	[redacted]	[redacted]
	n	396	398
	Mean (SD)	[redacted]	[redacted]

Characteristic		QUARTZ study	
		QMF 150 mcg/80 mcg N = 398	MF 200 mcg N = 404
FEV_1 reversibility (increase in L) at the start of the run-in period	Median (range)	[redacted]	[redacted]
FEV_1 pre-bronchodilator (% of predicted FEV_1) at the end of the run-in period or randomization	n	396	399
	Mean (SD)	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]
	60% to < 70%, n (%)	[redacted]	[redacted]
	70% to < 90%, n (%)	[redacted]	[redacted]
	≥ 90%, n (%)	[redacted]	[redacted]
	Missing, n (%)	[redacted]	[redacted]

ACQ-7 = Asthma Control Questionnaire (seven items); BMI = body mass index; FEV_1 = forced expiratory volume in one second; ICS = inhaled corticosteroid; LABA = long-acting beta2-agonist; MF = mometasone furoate; QMF = indacaterol/mometasone furoate; SD = standard deviation.

Source: QUARTZ Clinical Study Report.[5]

Table 8: Summary of Baseline Characteristics in PALLADIUM Study — Randomized Set

Characteristic		PALLADIUM study				
		QMF 150 mcg/ 160 mcg N = 439	MF 400 mcg N = 444	QMF 150 mcg/ 320 mcg N = 445	MF 800 mcg N = 442	S/F 50 mcg/ 500 mcg N = 446
Age (years)	Mean (SD)	47.4 (14.8)	48.7 (15.0)	47.1 (14.6)	47.5 (15.0)	48.9 (14.6)
	12 to 17, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	18 to 64, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≥ 65, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender, n (%)	Male	186 (42.4)	172 (38.7)	183 (41.1)	192 (43.4)	190 (42.6)
	Female	253 (57.6)	272 (61.3)	262 (58.9)	250 (56.6)	256 (57.4)
Race, n (%)	White	311 (70.8)	312 (70.3)	313 (70.3)	318 (71.9)	305 (68.4)
	Black	2 (0.5)	8 (1.8)	5 (1.1)	4 (0.9)	4 (0.9)
	Asian	98 (22.3)	98 (22.1)	97 (21.8)	98 (22.2)	102 (22.9)
	Native American	14 (3.2)	18 (4.1)	13 (2.9)	11 (2.5)	12 (2.7)
	Other	14 (3.2)	8 (1.8)	17 (3.8)	11 (2.5)	23 (5.2)
Disease characteristics						
Duration of asthma (years)	Mean (SD)	14.4 (12.7)	15.1 (13.0)	14.5 (12.6)	14.7 (13.0)	14.3 (12.5)
	Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of asthma exacerbations in 12 months prior to study start that required treatment, n (%)	0	310 (70.6)	314 (70.7)	305 (68.5)	309 (69.9)	301 (67.5)
	1	103 (23.5)	103 (23.2)	114 (25.6)	106 (24.0)	108 (24.2)
	> 1	26 (5.9)	27 (6.1)	26 (5.8)	27 (6.1)	37 (8.3)

Characteristic		PALLADIUM study				
		QMF 150 mcg/ 160 mcg N = 439	MF 400 mcg N = 444	QMF 150 mcg/ 320 mcg N = 445	MF 800 mcg N = 442	S/F 50 mcg/ 500 mcg N = 446
Smoking status, n (%)	Never smoked	355 (80.9)	364 (82.0)	362 (81.3)	367 (83.0)	364 (81.6)
	Former smoker	84 (19.1)	80 (18.0)	83 (18.7)	75 (17.0)	82 (18.4)
Baseline ACQ-7 score	Mean (SD)	2.3 (0.5)	2.3 (0.5)	2.3 (0.5)	2.3 (0.5)	2.3 (0.5)
	Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	< 1.5, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1.5 to < 2, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2 to < 2.5, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≥ 2.5, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Missing, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior asthma treatment, n (%)	ICS low dose	7 (1.6)	3 (0.7)	1 [redacted]	1 [redacted]	4 (0.9)
	ICS medium dose	95 (21.6)	84 (18.9)	75 (16.9)	96 (21.7)	92 (20.6)
	ICS high dose	24 (5.5)	33 (7.4)	32 (7.2)	34 (7.7)	31 (7.0)
	ICS/LABA low dose	299 (68.1)	308 (69.4)	316 (71.0)	299 (67.6)	302 (67.7)
	ICS/LABA other than low dose	10 (2.3)	14 (3.2)	18 (4.0)	8 (1.8)	15 (3.4)
	Missing	4 (0.9)	2 (0.5)	3 (0.7)	4 (0.9)	2 [redacted]
Spirometry						
FEV_1 (L) pre-bronchodilator at start of run-in period	n	439	444	445	442	446
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FEV_1 pre-bronchodilator (% of predicted FEV_1) at start of run-in period	n	439	444	445	442	446
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	< 50%, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	50 to < 60%, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	60 to < 85%, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≥ 85 %, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FEV_1 reversibility (% increase) at start of run-in period	n	439	443	445	442	446
	Mean (SD)	22.7 (13.7)	23.0 (12.8)	22.8 (13.6)	22.9 (12.4)	22.6 (12.9)
	Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FEV_1 reversibility (increase in L) at	n	439	443	445	442	446
	Mean (SD)	0.46 (0.29)	0.44 (0.25)	0.46 (0.28)	0.46 (0.27)	0.44 (0.27)

Characteristic		PALLADIUM study				
		QMF 150 mcg/ 160 mcg N = 439	MF 400 mcg N = 444	QMF 150 mcg/ 320 mcg N = 445	MF 800 mcg N = 442	S/F 50 mcg/ 500 mcg N = 446
start of run-in period	Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FEV_1 pre-bronchodilator (% of predicted FEV_1) at end of run-in period or randomization	n	439	443	445	441	445
	Mean (SD)	67.3 (8.3)	67.4 (8.6)	67.3 (8.6)	67.6 (8.7)	66.8 (9.0)
	Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	50% to < 60%, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	60% to < 85%, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≥ 85%, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Missing, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ACQ-7 = Asthma Control Questionnaire (seven items); FEV_1 = forced expiratory volume in one second; ICS = inhaled corticosteroid; LABA = long-acting beta2-agonist; MF = mometasone furoate; QMF = indacaterol/mometasone furoate; SD = standard deviation; S/F = salmeterol/fluticasone propionate.

Source: PALLADIUM Clinical Study Report.[6]

Interventions

The low-dose strength of QMF (150 mcg/80 mcg once daily) was included in the QUARTZ study and the medium-dose and high-dose strengths (150 mcg/160 mcg once daily and 150 mcg/320 mcg once daily, respectively) were included in the PALLADIUM study. Both studies used MF as an active comparator (200 mcg once daily in QUARTZ, and 400 mcg and 800 mcg once daily in PALLADIUM). PALLADIUM also included S/F 50 mcg/500 mcg once daily as an active comparator.

In the QUARTZ study, patients were assigned to one of two treatment groups: QMF 150 mcg/80 mcg as powder in hard capsules once daily delivered via Breezhaler or MF 200 mcg as powder once daily delivered via a Twisthaler. Double-dummy controls were used to deliver placebo as a powder via the Twisthaler for the QMF 150 mcg/80 mcg treatment group or placebo as powder in capsules via Breezhaler for the MF 200 mcg treatment group. All treatments were to be used in the evening (between 5 p.m. and 8 p.m.).

In the PALLADIUM study, patients were assigned to one of five treatment groups (outlined in Table 9): QMF 150 mcg/160 mcg as powder in hard capsules delivered once daily (in the evening) via a Breezhaler, QMF 150 mcg/320 mcg as powder in hard capsules delivered once daily (in the evening) via a Breezhaler, MF 400 mcg as powder delivered once daily (in the evening) via a Twisthaler, MF 800 mcg as powder delivered twice daily (as two doses of MF 400 mcg, one in the morning and one in the evening) or S/F 50 mcg/500 mcg as powder delivered twice daily (in the morning and in the evening) via an Accuhaler. Placebo was provided to enable the triple-dummy design of the study as powder via the Twisthaler (in the morning and in the evening or in the morning only), as powder in capsules via a Breezhaler (in the evening), and as powder via an Accuhaler (in the morning and in the evening).

Table 9: Study Treatments in PALLADIUM Study

Treatment group	Administered in the morning	Administered in the evening
QMF 150 mcg/160 mcg once daily	• Placebo via Twisthaler • Placebo via Accuhaler	• QMF 150 mcg/160 mcg via Breezhaler • Placebo via Twisthaler • Placebo via Accuhaler
QMF 150 mcg/320 mcg once daily	• Placebo via Twisthaler • Placebo via Accuhaler	• QMF 150 mcg/320 mcg via Breezhaler • Placebo via Twisthaler • Placebo via Accuhaler
MF 400 mcg once daily	• Placebo via Twisthaler • Placebo via Accuhaler	• MF 400 mcg via Twisthaler • Placebo via Breezhaler • Placebo via Accuhaler
MF 800 mcg (administered as MF 400 mcg twice daily)	• MF 400 mcg via Twisthaler • Placebo via Accuhaler	• MF 400 mcg via Twisthaler • Placebo via Breezhaler • Placebo via Accuhaler
S/F 50 mcg/500 mcg twice daily	• S/F 50 mcg/500 mcg via Accuhaler • Placebo via Twisthaler	• S/F 50 mcg/500 mcg via Accuhaler • Placebo via Breezhaler • Placebo via Twisthaler

MF = mometasone furoate; QMF = indacaterol/mometasone furoate; S/F = salmeterol/fluticasone propionate.

Source: PALLADIUM Clinical Study Report.[6]

The sponsor reported that blinding was maintained in both studies 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 QUARTZ and PALLADIUM, a SABA (100 mcg salbutamol or 90 mcg albuterol via MDI) was provided to patients during screening and was used throughout the study as rescue medication. Nebulized salbutamol/albuterol was not permitted, nor was any other rescue treatment or use of a spacer. Patients were asked to avoid using rescue medication within six hours of a study visit.

Patients received training on how to use the e-diary and peak flow metre during the run-in period in QUARTZ and at screening in PALLADIUM. They also received full training on the correct use of the different inhaler devices used in the two trials at the end of the run-in period. Correct use of the inhalers by the patient was assessed by the investigator at clinic visits and additional device training was provided if needed.

Certain asthma-related medications were prohibited in QUARTZ and PALLADIUM. These included:

- short-acting muscarinic antagonist (discontinued within eight hours prior to start of run-in period)
- fixed combinations of beta2-adrenergic agonists and ICS (discontinued 48 hours prior to the start of the run-in period and discontinued following the run-in period)
- ICS (other than run-in treatments, must be discontinued by the start of the run-in period)
- fixed combination of SABA and short-acting anticholinergic (discontinued within eight hours prior to the start of the run-in period)

- LTRA and leukotriene synthesis inhibitors (discontinued seven days prior to the start of the run-in period)
- LABA (twice daily discontinued 48 hours prior to the start of the run-in period, once daily discontinued 14 days prior to the start of the run-in period)
- SABA other than the trial rescue medication during the study (discontinued at screening)
- parenteral or oral corticosteroids (discontinued within four weeks prior to the start of the run-in period)
- intramuscular depot corticosteroids (discontinued within three months prior to the start of the run-in period)
- monoclonal antibodies (immunoglobulin E inhibitors, or interleukin-5 inhibitors) (must be discontinued four months prior to the start of the run-in period)
- xanthines (discontinued seven days prior to the start of the run-in period)
- systemic mast cell stabilizers (both must be discontinued seven days prior to the start of the run-in period).

The following medications were prohibited in the two trials, with a minimum cessation period of seven days prior to run-in unless otherwise specified: non-potassium sparing diuretics, nonselective systemic beta-adrenergic blocking agents, cardiac antiarrhythmic medications (Class Ia and Class III; amiodarone has a minimum three-month cessation period), other drugs with the potential to significantly prolong the QT interval (14 days or five half-lives, whichever is longer), strong inhibitors of cytochrome P4503A (e.g., ketoconazole), tricyclic antidepressants (14 days), other investigational drugs (30 days or five half-lives, whichever was longer), noradrenaline reuptake inhibitors, and live attenuated vaccine (30 days).

In both QUARTZ and PALLADIUM, the following medications were permitted under certain conditions:

- mucolytic agents not containing bronchodilators if stabilized for four weeks or more prior to screening and throughout the trial
- pure selective serotonin reuptake inhibitors treatment regimen that was stable for one month or more at screening
- inactivated influenza vaccination, pneumococcal vaccination, or any other inactivated vaccine administered 48 hours or more prior to a study visit
- intranasal corticosteroids if dose was stable for four weeks or more prior to the start of the run-in period or if needed, when an established pattern of use was documented
- antihistamines if stabilized for four weeks or more prior to screening and throughout the trial or if needed, when an established pattern of use was documented
- topical corticosteroids for treatment of eczema at recommended dosage regimens
- maintenance immunotherapy for allergies if dose was stable for three months or more prior to the start of the run-in period and unchanged throughout study treatment.

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 may discontinue study treatment if it is seen to be detrimental to a patient's well-being. In the QUARTZ study, this may be due to experiencing one severe asthma exacerbation requiring systemic

corticosteroid or hospitalization during the treatment period or if a patient experienced paradoxical bronchospasm. In the PALLADIUM study, patients were subject to being discontinued from treatment if they experienced five or more asthma exacerbations during the treatment period that required systemic corticosteroid, or for adolescents who experienced one asthma exacerbation requiring hospitalization. In both studies, treatment was discontinued if a decrease of more than 50% in FEV_1 from baseline during the run-in or treatment period occurred, if a medical condition required use of a prohibited treatment or nonadherence due to the use of prohibited medications, or if there were any other safety reasons for discontinuation.

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 10. A detailed discussion and critical appraisal of the outcome measures is provided in Appendix 4.

Table 10: Summary of Outcomes of Interest Identified in the CADTH Review Protocol

Outcomes of interest	Outcome measure	QUARTZ study	PALLADIUM study
Acute asthma exacerbations	Asthma exacerbations, number of and rate of	Other secondary	Other secondary
Change in pulmonary function	FEV_1	Primary or other secondary	Primary or other secondary
	FVC	Other secondary	Other secondary
	PEF	Other secondary	Other secondary
HRQoL	AQLQ	Other secondary	Other secondary
	EQ-5D-5L	NR	Exploratory
Asthma control	ACQ-7	Secondary or other secondary	Secondary or other secondary
Use of rescue medications	Rescue medication use and rescue medication-free days	Other secondary	Other secondary
Nocturnal awakening	Patient Asthma Control e-Diary, night-time symptoms	Other secondary	Other secondary
Days of missed work or school	WPAI: Asthma	NR	Exploratory
Health care resource utilization	Resource utilization, number of hospitalizations, and unplanned outpatient visits	Exploratory	Exploratory

ACQ-7 = Asthma Control Questionnaire (seven items); AQLQ = Asthma Quality of Life Questionnaire; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; HRQoL = health-related quality of life; NR = not reported; PEF = peak expiratory flow; WPAI = Work Productivity and Activity Impairment.

Source: Clinical Study Reports for the QUARTZ[5] and PALLADIUM[6] studies.

Asthma Exacerbations

For this review, asthma exacerbations were reported as the annual rate of asthma exacerbation and by exacerbation category (severity), and descriptively by the percentage of patients with at least one asthma exacerbation by the exacerbation category and the percentage of patients who permanently discontinued the study drug due to asthma exacerbation. Exacerbation categories were as follows: all (mild, moderate, severe), severe, and a combination of moderate. The former two categories were included in this review. In addition, exacerbations requiring hospitalization were reported descriptively.

Asthma exacerbations that occurred while on treatment and one day after the last treatment were included. If an asthma exacerbation episode was duplicated or nested within another exacerbation episode or within seven days of another exacerbation, then only one 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 requires systemic corticosteroids for at least three consecutive days and/or a need for 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 two or more of the following: a progressive increase in at least one of the symptoms of asthma, increased use of rescue medication (≥ 50% increase in SABA use and greater than eight puffs on two out of any three consecutive days compared to baseline captured, or night-time awakenings requiring SABA on at least two of any three consecutive nights), or deterioration of lung function lasting for at least two days but not warranting systemic corticosteroids for more than two days or hospitalization.

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

Measures of Pulmonary Function

The primary outcome in the QUARTZ and PALLADIUM studies was the change from baseline in trough FEV_1 after 12 weeks and 26 weeks of treatment, respectively. FEV_1 is the maximal amount of air forcefully exhaled in one second. Trough FEV_1 is used as a clinical measure of lung function, where trough FEV_1 is defined as the mean of the two 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 a MID for FEV_1 among adult patients with asthma. In one 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 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.[35] 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 for FEV_1 (170 mL) than younger ones (280 mL).[35]

FVC and PEF were also reported in the two studies and included as other secondary outcomes. FVC is the amount of air that can be forcibly exhaled from the lungs after taking the deepest breath possible as measured by spirometry. No evidence for validity, reliability, responsiveness to change, or MID was identified for the FVC measure. According to the EMA, the evaluation of FVC can be used as a complementary end point in clinical trials.[7] PEF L/minute (sometimes referred to as PEF rate) is defined as "*the maximum flow achieved during an expiration delivered with maximal force starting from the level of maximal lung inflation*."[36] In the 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 for the change from baseline were calculated at various time points in the two trials.

HRQoL

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 units (MID) in the change from baseline in AQLQ 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.[37] The AQLQ includes 32 questions grouped into four domains: symptoms, activity limitations, emotional function, and environmental stimuli. Each question is scored on a seven-point scale that 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 four domain scores are the means of the scores for the questions in the respective domains. Patients recall their relevant experiences during the previous two weeks. 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 ceiling effect.[38] The MID for the AQLQ has been determined to be a cut point of 0.5, with publications reporting values such as 0.67,[38] 0.52,[39] and a range of 0.42 to 0.58 for the AQLQ domains.[40-43]

The EuroQol 5-Dimensions (EQ-5D) is a commonly used, well-validated generic quality-of-life instrument developed by the EuroQol Group,[44] and was included as an exploratory outcome in PALLADIUM. The EuroQol 5-Dimensions 5-Levels (EQ-5D-5L) instrument consists of the EQ-5D descriptive system and the EuroQol Visual Analogue Scale (EQ VAS). The EQ VAS records the respondent's self-rated health on a vertical visual analogue scale (VAS) where 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 EQ VAS scores can be summarized and analyzed as continuous data.[44, 45] The descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each of these dimensions has five levels: a level 1 response represents "no problems," a level 2 response represents "slight problems," a level 3 response represents "moderate problems," a level 4 response represents "severe problems," and a level 5 response represents "extreme problems" or "unable to perform," which is the worst response in the dimension. Respondents are asked to choose the level that reflects their health state for each of the five dimensions. The EQ-5D-5L was reported descriptively by domain and by the VAS in PALLADIUM. Only the VAS was reported for this review.

Asthma Control

The ACQ (specifically the seven-item version of the ACQ) was evaluated in both studies and reported as a change from baseline and 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 12 and week 26 was included as the key secondary outcome in both the QUARTZ and PALLADIUM trials. The ACQ-7 is a patient-reported outcome that was developed to evaluate asthma control in patients with asthma and is one of the most commonly used instruments measuring asthma control.[46, 47] The questionnaire comprises seven questions, the responses of which are scored on a seven-point scale. Questions regarding six 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.[46] In addition, the seventh item includes calculations performed by clinical staff with regard to pre-bronchodilator FEV_1

or PEF (percentage predicted).[46, 47] The ACQ score is defined as the mean of the seven questions (as all questions are equally weighted), with scores at 0 meaning the patient has asthma that is well controlled and scores at 6 meaning the patient has asthma that is extremely poorly controlled.[46-48] The ACQ is used extensively in clinical trials to measure clinically meaningful change in asthma control.[47] The ACQ MID has been well established and accepted as 0.5 points for within-person change.[47, 49] In addition, a score of 1.5 on the ACQ is the most appropriate discriminator for "well-controlled" and "not well-controlled" asthma patients.[50]

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 Patient Asthma Control e-Diary. One study reported a MID of 8.4% to 15.6% for rescue-free days.[51]

Nocturnal Awakening

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

Days of Missed Work or School

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 seven days.[52-54] The WPAI: Asthma is the asthma-specific version of the questionnaire and is composed of nine items that assess impairment in three domains: work, school, and activity.[52, 55, 56] Scores range from 0% to 100%, where a higher score indicates greater impairment.[52, 56] This outcome was evaluated as an exploratory outcome in the PALLADIUM 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,[56] 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 QUARTZ and PALLADIUM studies for the purpose of economic evaluation. Asthma-related hospitalizations were also reported for both studies.

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 QUARTZ study estimated that [redacted] patients ([redacted] per group) were needed to provide approximately [redacted] power to detect a treatment

difference of [redacted] mL in trough FEV_1 between QMF 150 mcg/80 mcg and MF 200 mcg, assuming a SD of [redacted] mL, a [redacted] dropout rate, and a two-sided significance level of 0.05. The sample size was also estimated to provide [redacted] power to detect a treatment difference of [redacted] in the ACQ-7 score between QMF 150 mcg/80 mcg and MF 200 mcg, assuming a SD of [redacted] with multiplicity adjustment.

In the PALLADIUM study, the sample size and power calculation estimated that [redacted] patients ([redacted] per arm) was expected to provide [redacted] power to detect a treatment difference of 100 mL between QMF and MF at the corresponding doses (QMF 150 mcg/160 mcg [a medium dose] and MF 400 mcg, and QMF 150 mcg/320 mcg [a high dose] and MF 800 mcg), assuming a SD of 380 mL and a dropout rate of 10%. The sample size was also estimated to provide [redacted] power to detect a treatment difference of 0.15 between QMF and MF (doses pooled), assuming a SD of 0.80 with multiplicity adjustment. Of note, the comparison of QMF 150 mcg/320 mcg versus S/F 50 mcg/500 mcg twice daily in PALLADIUM was not included in the sample size and power calculation.

Statistical Test or Model

In both studies, the primary efficacy analysis of trough FEV_1 (at week 12 in the QUARTZ study and week 26 in the PALLADIUM study) for QMF versus MF was defined as the average of the two FEV_1 measurements taken 23 hours 15 minutes and 23 hours 45 minutes after the evening dose of treatment. Trough FEV_1 was analyzed using a mixed-effects model for repeated measures (MMRM) on the FAS, which 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 or albuterol (components of SABA reversibility). Treatment, age, region, visit, and treatment-by-visit interaction were included as fixed effects and centre-nested within region as a random effect. An unstructured covariance matrix was used to model within-patient correlations. The treatment difference, SE, two-sided 95% CI, and two-sided P value at a significance level of 0.05 were reported.

The key secondary outcome, ACQ-7 after 12 weeks of treatment (QUARTZ) or 26 weeks of treatment (PALLADIUM), was analyzed using the same MMRM as the primary analysis, but the covariates included baseline ACQ-7 score instead of baseline FEV_1. In PALLADIUM, QMF 150 mcg/320 mcg versus S/F 50 mcg/500 mcg twice daily was analyzed in the same manner as the key secondary outcome; however, an analysis of NI was conducted on the primary outcome and if NI was shown, then an analysis of superiority was considered. An NI margin of 0.090 L was used and a 95% CI was used to interpret the treatment difference. If the lower bound was larger than –0.090 L, then the comparison was deemed noninferior; if the lower bound was greater than zero, then QMF 150 mcg/320 mcg was considered superior to S/F 50 mcg/500 mcg twice daily in terms of FEV_1 at week 26.

In both studies, other continuous outcomes (e.g., change from baseline in mean number of puffs of rescue medication) 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 points in the ACQ was analyzed using a logistic regression model with the same terms as previously mentioned without random effects. Rescue medication use, asthma symptoms based on the e-diary, and AQLQ-S+12 were analyzed using an analysis of covariance model containing treatment, age, and region as fixed effects and centre-nested within region as a random effect. Covariates were the same as the primary analysis, with baseline FEV_1 replaced by baseline medication use or baseline

AQLQ score. The rate of asthma exacerbations was analyzed using a generalized linear model assuming a negative binomial distribution. Treatment, age, and history of asthma exacerbation in the 12 months prior to screening were included as fixed effects and the same covariates as in the primary analysis were used. Log exposure in years was included as an offset variable in the model.

The hierarchical testing procedure was used in QUARTZ, where the key secondary end point was only tested if the primary end point was significant at the two-sided 0.05 level.

A sequential testing procedure was used to control the type I error rate in PALLADIUM. More specifically, three hypotheses, including two hypotheses for the primary end point, were included in the family for type I error rate control in PALLADIUM. The two primary hypotheses correspond to the following two comparisons: QMF 150 mcg/160 mcg versus MF 400 mcg and QMF 150 mcg/320 mcg versus MF 800 mcg. The third hypothesis for the key secondary end point compared overall QMF versus MF, where the dose strengths for QMF and MF were pooled. The following steps were taken for the testing procedure:

- Step 1: Retain both hypothesis 1 and hypothesis 2 if p_i is 0.05 or less **and** the observed treatment difference for the corresponding p_i is in the wrong direction (i.e., MF is performing better than QMF) for **any** i = 1, 2, stop here; otherwise, go to step 2.
- Step 2: Reject hypothesis 1 and hypothesis 2 if p_i is less than 0.05 for **both** i = 1, 2, and go to step 3; otherwise, go to step 4.
- Step 3: Reject hypothesis 3 if p_3 less than 0.05 and stop.
- Step 4: If neither step 1 nor step 2 applies, perform the Bonferroni test to hypothesis 1 and hypothesis 2. Thus, reject hypothesis 1 if p_1 is less than 0.025 or reject hypothesis 2 if p_2 is less than 0.025 and stop.

Analyses other than the ones described here were performed at the nominal two-sided 0.05 level (two-sided) without multiplicity adjustment.

Handling of Missing Data

In both studies, 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 three months of a corticosteroid injection, seven days of systemic corticosteroid use (except for patients who were on stable systemic corticosteroid as background therapy), or six hours of rescue medication, or if measurements were outside the post-evening dose time window for the treatment regimen, then the individual FEV_1 value was set to missing.
- If one of the two 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 of more than 7L 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 (MAR) and therefore data were not imputed.

For the ACQ-7 score, an interpolation method was used for missing data for individual items. For post-baseline visits for this outcome, missing data were imputed for individual items of the ACQ-7. The ACQ-7 score was set to missing if more than one individual item

was missing. For the outcome related to the proportion of patients who achieved an improvement of at least 0.5 points in the ACQ analyzed using the logistic regression model, this outcome used multiple imputations under the MAR assumption to handle missing data.

Subgroup Analyses

In both studies, exploratory subgroup analyses of the primary efficacy outcome (trough FEV_1) were conducted based on the following subgroups: age, race, gender, history of asthma exacerbation in the 12 months prior to screening, therapies used prior to the run-in period (QUARTZ: a low-dose ICS with LABA versus a low-dose ICS without LABA; PALLADIUM: a medium-dose ICS, high-dose ICS, and low-dose ICS/LABA), FEV_1 response according to percentage predicted for FEV_1 range at baseline, and baseline ACQ-7. In PALLADIUM, subgroup analyses for patients' prior therapies before the run-in period (medium-dose and high-dose ICS/LABA) were also performed for end points ACQ-7 and AQLQ at week 26. In QUARTZ, subgroup analyses for AEs of special interest were carried out for patients between the ages of 12 and 17.

Sensitivity Analyses

In both studies, 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 MAR assumption of missing data.

Analysis Populations

In both studies, the randomized set included all patients who were randomized and was used for patient disposition, demographics, and baseline characteristics. The full analysis set (FAS) was the primary population used for efficacy outcomes, and it included all patients who were randomized and received at least one 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 analysis set (SAS) included patients who received at least one dose of study medication; the SAS was used for all assessments of safety. Patients in the PPS and SAS were analyzed according to the treatment received. In the SAS, patients who switched treatment during the study were counted and analyzed only once according to their treatment.

Results

Patient Disposition

The patient disposition in the QUARTZ and PALLADIUM studies is provided in Table 11. A total of 802 patients (58.9%) and 2,216 patients (57.0%) were randomized in QUARTZ and PALLADIUM, respectively. Discontinuation from the double-blind treatment phase was infrequent in both of the studies. In QUARTZ, four patients (1.0%) discontinued from the double-blind treatment phase in the QMF treatment group and 21 patients (5.2%) discontinued in the MF treatment group. In PALLADIUM, between 5.9% and 9.2% of patients in all treatment groups discontinued from the double-blind treatment phase; the MF 400 mcg treatment group had the highest proportion of discontinuations (9.2%). The most common reason for discontinuation was patient or guardian decision in both QUARTZ (0% to 1.0%) and PALLADIUM (3.9% to 6.8%). Reasons for discontinuation were similar

between treatment groups in both studies, with the exception of AEs, which accounted for discontinuation from treatment phase in one patient in the QMF treatment group and eight patients in the MF treatment group. All other reasons for discontinuation were reported in 1% or less of patients in any treatment group.

Table 11: Patient Disposition — All Randomized

	QUARTZ study		PALLADIUM study				
	QMF 150 mcg/ 80 mcg	MF 200 mcg	QMF 150 mcg/ 160 mcg	MF 400 mcg	QMF 150 mcg/ 320 mcg	MF 800 mcg	S/F 50 mcg/ 500 mcg
Screened, N	1,362		3,890				
Randomized, N (%)	398	404	439	444	445	442	446
Discontinued from treatment phase, N (%)	4 (1.0)	21 (5.2)	26 (5.9)	41 (9.2)	35 (7.9)	30 (6.8)	30 (6.7)
Reason for discontinuation, N (%)							
Adverse events	1 (0.3)	8 (2.0)	0	0	0	0	2 (0.4)
Death	0	0	0	1 (0.2)	0	0	0
Lost to follow-up	0	1 (0.2)	3 (0.7)	2 (0.5)	4 (0.9)	4 (0.9)	2 (0.4)
Nonadherence with treatment	0	1 (0.2)	1 (0.2)	0	0	1 (0.2)	1 (0.2)
Patient or guardian decision	0	4 (1.0)	17 (3.9)	30 (6.8)	29 (6.5)	18 (4.1)	20 (4.5)
Physician decision	0	2 (0.5)	1 (0.2)	1 (0.2)	0	4 (0.9)	1 (0.2)
Pregnancy	0	0	0	1 (0.2)	0	0	1 (0.2)
Protocol deviation	3 (0.8)	4 (1.0)	3 (0.7)	4 (0.9)	1 (0.2)	3 (0.7)	2 (0.4)
Technical problems	0	1 (0.2)	1 (0.2)	2 (0.5)	1 (0.2)	0	1 (0.2)
ITT, N	395	399	437	443	443	440	444
PP, N	[redacted]	[redacted]	383	390	374	380	378
Safety, N	396	399	437	443	443	440	444

ITT = intention to treat; MF = mometasone furoate; PP = per-protocol; QMF = indacaterol/mometasone furoate; S/F = salmeterol/fluticasone propionate.

Source: Clinical Study Reports for the QUARTZ[5] and PALLADIUM[6] studies.

Exposure to Study Treatments

A summary of exposure to study treatments in the QUARTZ and PALLADIUM studies is available in Table 12. The mean (SD) duration of exposure to study treatments in QUARTZ was [redacted] to [redacted] days. The mean (SD) duration of exposure to study treatments in PALLADIUM ranged from 332.2 days (91.7) to 347.1 days (70.4). The mean (SD) number of days exposed to treatment was similar across treatment groups in each of the two studies. Based on the number of days where the study drug was administered "as per protocol," the sponsor reported that more than [redacted] of patients showed adherence with study medication as per protocol in QUARTZ and PALLADIUM.

Table 12: Exposure to Study Treatments — Safety Analysis Set

	QUARTZ study		PALLADIUM study				
	QMF 150 mcg/ 80 mcg N = 396	MF 200 mcg N = 399	QMF 150 mcg/ 160 mcg N = 437	MF 400 mcg N = 443	QMF 150 mcg/ 320 mcg N = 443	MF 800 mcg N = 440	S/F 50 mcg/ 500 mcg N = 444
Exposure (days)							
n	396	399	437	443	443	440	444
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

MF = mometasone furoate; PP = per-protocol; QMF = indacaterol/mometasone furoate; SD = standard deviation; S/F = salmeterol/fluticasone propionate.

Source: Clinical Study Reports for the QUARTZ[5] and PALLADIUM studies.[6]

All concomitant asthma medication use administered after enrolling in the two studies was reported. Concomitant asthma medications, in total, were used by [redacted] to [redacted] of patients in QUARTZ and [redacted] to [redacted] in PALLADIUM (Table 13). In QUARTZ, patients in the QMF and MF treatment groups reported the use of corticosteroids (all, [redacted] versus [redacted], and oral, [redacted] versus [redacted] respectively), oral antihistamines ([redacted] versus [redacted]) and oral antibiotics ([redacted] versus [redacted]); other medications such as leukotriene modifiers, SABA, xanthine, and ICS/LABA were used in less than [redacted] of patients in either treatment group. In PALLADIUM, between [redacted] and [redacted] of patients used corticosteroids (mostly oral), with use by a greater proportion of patients in the MF treatment groups ([redacted] to [redacted]) and S/F ([redacted]) than in the QMF treatment groups ([redacted] to [redacted]). In addition, [redacted] to [redacted] of patients reported concomitant use of antibiotics, [redacted] to [redacted] used ICS/LABA, [redacted] to [redacted] used SABA, [redacted] to [redacted] used antihistamines, [redacted] to [redacted] used xanthines, and [redacted] or less in any treatment group used leukotriene modifiers, LABAs, short-acting anticholinergic treatments, and SAMA/SABA.

Table 13: Use of Concomitant Asthma Medications — Safety Analysis Set

Asthma medications	QUARTZ study		PALLADIUM study				
	QMF 150 mcg/ 80 mcg N = 396	MF 200 mcg N = 399	QMF 150 mcg/ 160 mcg N = 437	MF 400 mcg N = 443	QMF 150 mcg/ 320 mcg N = 443	MF 800 mcg N = 440	S/F 50 mcg/ 500 mcg N = 444
Any asthma medication	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Corticosteroids	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nasal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intravenous	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inhaled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antibiotics, oral[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICS/LABA, inhaled[a, b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SABA, inhaled[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Asthma medications	QUARTZ study		PALLADIUM study				
	QMF 150 mcg/ 80 mcg N = 396	MF 200 mcg N = 399	QMF 150 mcg/ 160 mcg N = 437	MF 400 mcg N = 443	QMF 150 mcg/ 320 mcg N = 443	MF 800 mcg N = 440	S/F 50 mcg/ 500 mcg N = 444
Xanthine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antihistamines, oral[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICS = inhaled corticosteroid; LABA = long-acting beta2-agonist; QMF = indacaterol/mometasone furoate; SABA = short-acting beta2-agonist; SAMA = short-acting muscarinic antagonist; SD = standard deviation; S/F = salmeterol/fluticasone propionate.

Note: In the PALLADIUM study, the following was used by 2% or less of patients in any treatment group (data not shown): intramuscular, nebulized, and rectal corticosteroids; intravenous and antibiotics; nebulized, intravenous, nasal, and oral SABA; other antihistamines; intravenous and intramuscular xanthines; leukotriene modifiers; LABA; short-acting anticholinergic; and SAMA/SABA. In the QUARTZ study, intravenous xanthine and leukotriene modifier use was reported by less than 1% of patients in any treatment group (data not shown).

[a] All reported use of this asthma medication in the QUARTZ study used the route of administration noted.

[b] All reported use of this asthma medication in the PALLADIUM study used the route of administration noted.

Source: Clinical Study Reports for the QUARTZ[5] and PALLADIUM[6] studies.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported as follows.

Acute Asthma Exacerbations

The results related to asthma exacerbations are provided in Table 14. Results corresponding to the number of patients experiencing asthma exacerbations were reported descriptively in both trials. Statistical testing was conducted for outcomes related to asthma exacerbations in the QUARTZ and PALLADIUM studies; however, they were not included in the statistical testing hierarchy and are therefore presented descriptively.

During QUARTZ's 12-week treatment period, 5.1% and 15.0% of patients experienced an asthma exacerbation and 0.8% and 2.8% of patients experienced a severe asthma exacerbation in the QMF 150 mcg/80 mcg and MF 200 mcg treatment groups, respectively. Only one patient in both treatment groups required hospitalization and four patients (all in the MF 200 mcg treatment group) had an exacerbation causing permanent discontinuation of the study drug.

During PALLADIUM's 52-week treatment period, between [redacted] and [redacted] of patients across the five treatment groups experienced an asthma exacerbation and [redacted] to [redacted] experienced a severe exacerbation. A numerically greater proportion of patients in the MF treatment groups experienced exacerbations (all severities, [redacted] for MF 400 mcg and [redacted] for MF 800 mcg) and severe exacerbations ([redacted] for MF 400 mcg and [redacted] for MF 800 mcg) than patients in the QMF treatment groups (all severities, [redacted] for QMF 150 mcg/160 mcg and [redacted] for QMF 150 mcg/320 mcg; severe [redacted] in both groups). The number of patients with an asthma exacerbation requiring hospitalization or permanent discontinuation of the study drug was [redacted] and [redacted], respectively, in all treatment groups for PALLADIUM with MF 400 mcg being the treatment group with the greatest proportion of patients for each outcome.

In both QUARTZ and PALLADIUM, the annualized rate of asthma exacerbations (all) was consistently lower in the QMF treatment groups compared to the corresponding MF treatment groups ([redacted]). The rate of all exacerbations was similar between the high-

dose QMF and S/F treatment groups. The rate of severe asthma exacerbations was not reported in QUARTZ. The annualized rate of severe exacerbations was greater in the medium-dose MF treatment group compared to the medium-dose QMF treatment group, and similar across the high-dose QMF, MF, and S/F treatment groups in PALLADIUM.

Table 14: Acute Asthma Exacerbations

	QUARTZ study		PALLADIUM study				
	QMF 150 mcg/ 80 mcg N = 395	MF 200 mcg N = 399	QMF 150 mcg/ 160 mcg N = 437	MF 400 mcg N = 443	QMF 150 mcg/ 320 mcg N = 443	MF 800 mcg N = 440	S/F 50 mcg/ 500 mcg N = 444
Proportion of patients with asthma exacerbations, by exacerbation category, n (%) — FAS							
All (mild, moderate, severe)	20 (5.1)	60 (15.0)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe	3 (0.8)	11 (2.8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Requiring hospitalization	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Causing permanent discontinuation of study drug	[redacted]	[redacted]	0	7 (1.6)	1 (0.2)	4 (0.9)	2 (0.5)
Rate of asthma exacerbations, all (mild, moderate, severe)[a] — FAS							
n (%)	394 (99.7)	397 (99.5)	437 (100)	443 (100)	443 (100)	440 (100)	444 (100)
Annualized rate (95% CI)	0.20 [redacted]	0.67 [redacted]	0.48 (0.40 to 0.59)	1.05 (0.89 to 1.24)	0.49 (0.41 to 0.60)	0.74 (0.62 to 0.88)	0.52 (0.43 to 0.63)
Rate ratio (95% CI)	0.30 (0.18 to 0.50)		0.46 (0.36 to 0.59) (QMF vs. MF)		0.67 (0.52 to 0.87) (QMF vs. MF) 0.95 (0.72 to 1.23) (QMF vs. S/F)		
P value[b]	[redacted]		< 0.001 (QMF vs. MF)		0.002 (QMF vs. MF) 0.681 (QMF vs. S/F)		
Rate of asthma exacerbations, severe[a] — FAS							
n (%)	NR	NR	437 (100)	443 (100)	443 (100)	440 (100)	444 (100)
Annualized rate (95% CI)	NR	NR	0.13 (0.10 to 0.18)	0.29 (0.23 to 0.38)	0.13 (0.09 to 0.17)	0.18 (0.13 to 0.23)	0.14 (0.10 to 0.19)
Rate ratio (95% CI)	NR	NR	0.46 (0.31 to 0.67) (QMF vs. MF)		0.71 (0.47 to 1.08) (QMF vs. MF) 0.89 (0.58 to 1.37) (QMF vs. S/F)		
P value[b]	NR	NR	< 0.001 (QMF vs. MF)		0.108 (QMF vs. MF) 0.597 (QMF vs. S/F)		

CI = confidence interval; FAS = full analysis set; FEV_1 = forced expiratory volume in one second; MF = mometasone furoate; NR = not reported; QMF = indacaterol/mometasone furoate; SABA = short-acting beta2-agonist; S/F = salmeterol/fluticasone propionate; vs. = versus.

[a] Generalized linear model assuming a negative binomial distribution with the following covariates: 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: Clinical Study Reports for the QUARTZ[5] and PALLADIUM[6] studies.

Change in Pulmonary Function

The primary outcome in the QUARTZ and PALLADIUM studies was change from baseline in trough FEV_1 after 12 weeks and 26 weeks of treatment, respectively. The results have been presented in Table 15 for QUARTZ and Table 16 for PALLADIUM, along with change from baseline in trough FVC at the end of the treatment period, and mean morning and evening PEF (L/minute) during the treatment period.

In QUARTZ, the treatment group difference between QMF 150 mcg/80 mcg and MF 200 mcg in change from baseline of trough FEV_1 after 12 weeks was 0.18 L (95% CI, 0.15 to 0.22; P value < 0.001) in favour of QMF. Similar results were reported in PALLADIUM after 26 weeks. The treatment group difference between QMF 150 mcg/160 mcg and MF 400 mcg in change from baseline of trough FEV_1 after 26 weeks was 0.21 L (95% CI, 0.17 to 0.26; P value < 0.001) and the difference between QMF 150 mcg/320 mcg and MF 800 mcg in change from baseline of trough FEV_1 after 26 weeks was 0.13 L (95% CI, 0.09 to 0.18; P value < 0.001), both in favour of QMF. The LS mean (95% CI) for change from baseline in trough FEV_1 from baseline to week 52 demonstrated a similar treatment effect in all treatment groups at 52 weeks. In both studies, a sensitivity analysis using the PPS as well as a tipping point analysis to evaluate the impact of a deviation from the MAR assumption were conducted and supportive of the analysis of the primary outcome.

The comparison of QMF 150 mcg/320 mcg to S/F 50 mcg/500 mcg was analyzed for NI in terms of the primary outcome. An NI margin of 0.090 L was used to determine the difference based on the 95% CI. This analysis was not included in the statistical testing hierarchy. The LS mean (SE) change from baseline in trough FEV_1 was 0.04 L (95% CI, –0.01 to 0.08; P = 0.101), demonstrating NI.

The reported treatment effect in each of the other measures of pulmonary function, trough FVC (L), mean morning PEF (L/minute), and mean evening PEF (L/minute) was similar to that of the primary outcome in both studies, based on a change from baseline in the QMF 150 mcg/80 mcg, QMF 150 mcg/160 mcg, and QMF 150 mcg/320 mcg treatment groups that was numerically greater than the corresponding MF 200 treatment groups at the end of the treatment periods (Table 15 and Table 16). However, none of these outcomes was controlled for multiplicity and should only be considered descriptively. In addition, there was no difference (0.04; 95% CI, –0.01 to 0.09) between the QMF 150 mcg/320 mcg and S/F 50 mcg/500 mcg treatment groups in trough FVC (L) at week 52, similar to the results at week 26. At week 52, the treatment group difference between QMF 150 mcg/320 mcg and S/F 50 mcg/500 mcg in terms of mean morning PEF was 13.8 L/minute (95% CI, 7.7 to 19.8; P < 0.001) and mean evening PEF was 9.1 L/minute (95% CI, 3.3 to 14.9; P = 0.002).

Table 15: Pulmonary Function — FEV_1, FVC, Morning and Evening PEF in the QUARTZ Study

	QUARTZ study	
	QMF 150 mcg/80 mcg N = 395	MF 200 mcg N = 399
Trough FEV_1 (L) at week 12[a] — FAS		
Number of patients contributing to the analysis	394	395
Baseline, mean (SD)	[redacted]	[redacted]
End of treatment (week 12), LS mean (SE)	2.562 (0.0134)	2.379 (0.0134)
Change from baseline, LS mean (SE)	0.234 (0.0134)	0.051 (0.0134)
Treatment group difference vs. control, LS mean (95% CI)	0.182 (0.148 to 0.217)	
P value	< 0.001	
Trough FVC (L) at week 12[a] — FAS		
Number of patients contributing to the analysis	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]
End of treatment (week 12), LS mean (SE)	[redacted]	[redacted]
Change from baseline, LS mean (SE)	[redacted]	[redacted]

	QUARTZ study	
	QMF 150 mcg/80 mcg N = 395	MF 200 mcg N = 399
Treatment group difference vs. control, LS mean (95% CI)	[redacted]	
P value[b]	[redacted]	
Morning PEF (L/minute) from week 1 to week 12[c] — FAS		
Number of patients contributing to the analysis	382	382
Baseline, mean (SD)	[redacted]	[redacted]
End of treatment (week 12), LS mean (SE)	[redacted]	[redacted]
Change from baseline, LS mean (SE)	31.0 (2.0)	3.8 (2.0)
Treatment group difference vs. control, LS mean (95% CI)	27.2 (22.1 to 32.4)	
P value[b]	< 0.001	
Evening PEF (L/minute) from week 1 to week 12[c] — FAS		
Number of patients contributing to the analysis	386	386
Baseline, mean (SD)	[redacted]	[redacted]
End of treatment (week 12), LS mean (SE)	[redacted]	[redacted]
Change from baseline, LS mean (SE)	26.8 (1.8)	0.7 (1.8)
Treatment group difference vs. control, LS mean (95% CI)	26.1 (21.0 to 31.2)	
P value[b]	< 0.001	

ANCOVA = analysis of covariance; CI = confidence interval; FAS = full analysis set; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; LS = least squares; MF = mometasone furoate; MMRM = mixed-effects models for repeated measures; PEF = peak expiratory flow; SABA = short-acting beta2-agonist; SD = standard deviation; SE = standard error; QMF = indacaterol/mometasone furoate; 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). Estimates from the MMRM models consider the full-time course data and not only those at the respective visit, which may include fewer patients than were reported at baseline.

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

[c] ANCOVA with the following covariates: Baseline morning and 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: QUARTZ Clinical Study Report.[5]

Table 16: Pulmonary Function — FEV_1, FVC, Morning and Evening PEF in the PALLADIUM Study

	PALLADIUM study				
	QMF 150 mcg/ 160 mcg N = 437	MF 400 mcg N = 443	QMF 150 mcg/ 320 mcg N = 443	MF 800 mcg N = 440	S/F 50 mcg/ 500 mcg N = 444
Trough FEV_1 (L) at week 26[a] — FAS					
Number of patients contributing to the analysis	389	376	395	372	391
Baseline, mean (SD)	[redacted]				
End of treatment time point (week 26), LS mean (SE)	2.39 (0.02)	2.18 (0.02)	2.38 (0.02)	2.25 (0.02)	2.35 (0.02)
Change from baseline, LS mean (SE)	0.29 [redacted]	0.08 [redacted]	0.28 [redacted]	0.15 [redacted]	0.25 [redacted]
Treatment group difference vs. control, LS mean (95% CI)	0.21 (0.17 to 0.26) (QMF vs. MF)		0.13 (0.09 to 0.18) (QMF vs. MF) NI analysis: 0.04 (–0.01 to 0.08) (QMF vs. S/F)		
P value	< 0.001 (QMF vs. MF)		< 0.001 (QMF vs. MF)		

	PALLADIUM study				
	QMF 150 mcg/ 160 mcg N = 437	MF 400 mcg N = 443	QMF 150 mcg/ 320 mcg N = 443	MF 800 mcg N = 440	S/F 50 mcg/ 500 mcg N = 444
			0.101 (QMF vs. S/F)		
Trough FVC (L) at week 52[a] — FAS					
Number of patients contributing to the analysis	383	369	372	365	382
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment time point (week 52), LS mean (SE)	3.36 (0.02)	3.22 (0.02)	3.39 (0.02)	3.32 (0.02)	3.36 (0.02)
Change from baseline, LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment group difference vs. control, LS mean (95% CI)	0.15 (0.10 to 0.20) (QMF vs. MF)		0.08 (0.03 to 0.13) (QMF vs. MF) 0.04 (–0.01 to 0.09) (QMF vs. S/F)		
P value[b]	< 0.001 (QMF vs. MF)		0.002 (QMF vs. MF) 0.143 (QMF vs. S/F)		
Morning PEF (L/minute) from week 1 to week 52[c] — FAS					
Number of patients contributing to the analysis	420	422	415	427	424
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment time point (week 52), mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, LS mean (SE)	36.9 (2.22)	6.7 (2.22)	42.1 (2.24)	13.4 (2.21)	28.3 (2.22)
Treatment group difference vs. control, LS mean (95% CI)	30.2 (24.2 to 36.3) (QMF vs. MF)		28.7 (22.7 to 34.8) (QMF vs. MF) 13.8 (7.7 to 19.8) (QMF vs. S/F)		
P value[b]	< 0.001 (QMF vs. MF)		< 0.001 (QMF vs. MF) < 0.001 (QMF vs. S/F)		
Evening PEF (L/minute) from week 1 to week 52[c] — FAS					
Number of patients contributing to the analysis	420	418	416	424	422
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment time point (week 52), LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, LS mean (SE)	28.7 (2.13)	–0.3 (2.14)	31.2 (2.14)	7.4 (2.13)	22.1 (2.13)
Treatment group difference vs. control, LS mean (95% CI)	29.1 (23.3 to 34.8) (QMF vs. MF)		23.7 (18.0 to 29.5) (QMF vs. MF) 9.1 (3.3 to 14.9) (QMF vs. S/F)		
P value[b]	< 0.001 (QMF vs. MF)		< 0.001 (QMF vs. MF) 0.002 (QMF vs. S/F)		

ANCOVA = analysis of covariance; CI = confidence interval; FAS = full analysis set; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; LS = least squares; MF = mometasone furoate; MMRM = mixed-effects models for repeated measures; NI = noninferiority; PEF = peak expiratory flow; QMF = indacaterol/mometasone furoate; SABA = short-acting beta2-agonist; SD = standard deviation; SE = standard error; S/F = 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] ANCOVA with the following covariates: Baseline morning and 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: PALLADIUM Clinical Study Report.[6]

Figure 4: [redacted]

Figure 4 contained confidential information and was removed at the request of the sponsor.

[redacted]

Source: PALLADIUM Clinical Study Report.[6]

Health-Related Quality of Life

The AQLQ, including the total score and individual domain scores, was used to assess HRQoL in both of the included studies, as well as the EQ-5D-5L in PALLADIUM. None of the analyses were included in the statistical testing procedure. The results are provided in Table 17 and Table 18.

Based on a higher score for the AQLQ, patients in all treatment groups across the two studies experienced an improvement in HRQoL. In QUARTZ, the change from baseline in AQLQ-S+12 was numerically greater in the QMF 150 mcg/80 mcg group than the MF 200 mcg group for the total score and all domain scores, with treatment group differences ranging from [redacted] units to [redacted] units. The proportion of patients who achieved an improvement of 0.5 units or more in the AQLQ-S+12 total score at week 12 was also numerically greater in the QMF 150 mcg/80 mcg group [redacted] compared with the MF group (50.8%) (odds ratio [OR] = [redacted]; 95% CI, [redacted] to [redacted] P [redacted]). In PALLADIUM, there appeared to be benefit in terms of HRQoL for patients in the QMF 150 mcg/160 mcg group compared to the MF 400 mcg group based on a numerically greater change from baseline in AQLQ-S+12, for the total score and all domain scores. In addition, the proportion of patients who achieved an improvement of 0.5 units or more in the AQLQ-S+12 total score at week 52 was higher in the QMF group [redacted] compared with the MF group [redacted] (OR = [redacted]; 95% CI, [redacted] to [redacted]; P [redacted]) as well. There was no difference in quality of life between the QMF 150 mcg/320 mcg and the MF 800 mcg and S/F 50 mcg/500 mcg treatment groups based on the AQLQ-S+12. Regarding the EQ VAS at week 52, the mean (SD) change from baseline was as follows: [redacted] for QMF 150 mcg/160 mcg and [redacted] for MF 400 mcg; [redacted] for QMF 150 mcg/320 mcg, [redacted] for MF 800 mcg, and [redacted] for S/F 50/500 mcg.

Table 17: Health-Related Quality of Life in the QUARTZ Study

	QUARTZ study	
	QMF 150 mcg/80 mcg N = 395	MF 200 mcg N = 399
AQLQ-S+12 overall score at week 12[a] — FAS		
Number of patients contributing to the analysis	381	379
Baseline, mean (SD)	[redacted]	[redacted]
End of treatment time point (specify), LS mean (SE)	5.78 (0.05)	5.63 (0.05)
Change from baseline, LS mean (SE)	[redacted]	[redacted]
Treatment group difference vs. control, LS mean (95% CI)	0.15 (0.06 to 0.23)	
P value[b]	< 0.001	
AQLQ-S+12 symptoms domain score at week 12[a] — FAS		
Number of patients contributing to the analysis	381	379

	QUARTZ study	
	QMF 150 mcg/80 mcg N = 395	MF 200 mcg N = 399
Baseline, mean (SD)	[redacted]	[redacted]
End of treatment time point (week 12), LS mean (SE)	[redacted]	[redacted]
Change from baseline, LS mean (SE)	[redacted]	[redacted]
Treatment group difference vs. control, LS mean (95% CI)	[redacted]	
P value[b]	[redacted]	
AQLQ-S+12 activity limitation domain score at week 12[a] — FAS		
Number of patients contributing to the analysis	381	379
Baseline, mean (SD)	[redacted]	[redacted]
End of treatment time point (week 12), LS mean (SE)	[redacted]	[redacted]
Change from baseline, LS mean (SE)	[redacted]	[redacted]
Treatment group difference vs. control, LS mean (95% CI)	[redacted]	
P value[b]	[redacted]	
AQLQ-S+12 emotional function domain score at week 12[a] — FAS		
Number of patients contributing to the analysis	381	379
Baseline, mean (SD)	[redacted]	[redacted]
End of treatment time point (week 12), LS mean (SE)	[redacted]	[redacted]
Change from baseline, LS mean (SE)	[redacted]	[redacted]
Treatment group difference vs. control, LS mean (95% CI)	[redacted]	
P value[b]	[redacted]	
AQLQ-S+12 environmental stimuli domain score at week 12[a] — FAS		
Number of patients contributing to the analysis	381	379
Baseline, mean (SD)	[redacted]	[redacted]
End of treatment time point (week 12), LS mean (SE)	[redacted]	[redacted]
Change from baseline, LS mean (SE)	[redacted]	[redacted]
Treatment group difference vs. control, LS mean (95% CI)	[redacted]	
P value[b]	[redacted]	
Proportion of patients with improvement of ≥ 0.5 units in AQLQ-S+12 overall score at week 12[c] — FAS		
n (%)	[redacted]	[redacted]
Adjusted proportion	[redacted]	[redacted]
OR (95% CI)	[redacted]	
P value[b]	[redacted]	

ANCOVA = analysis of covariance; AQLQ = Asthma Quality of Life Questionnaire; AQLQ-S+12 = Asthma Quality of Life Questionnaire for 12 years and older; CI = confidence interval; FAS = full analysis set; FEV_1 = forced expiratory volume in one second; LS = least squares; ITT = intention to treat; MF = mometasone furoate; OR = odds ratio; QMF = indacaterol/mometasone furoate; SABA = short-acting beta2-agonist; SD = standard deviation; SE = standard error; vs. = versus.

[a] ANCOVA with the following covariates: Baseline AQLQ, 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 via generalized estimating equation with the following covariates: Baseline AQLQ, FEV_1 prior to inhalation, and FEV_1 within 15 to 30 minutes post inhalation of salbutamol/albuterol (components of SABA reversibility).

Source: QUARTZ Clinical Study Report.[5]

Table 18: Health-Related Quality of Life in the PALLADIUM Study

	PALLADIUM study				
	QMF 150 mcg/ 160 mcg N = 437	MF 400 mcg N = 443	QMF 150 mcg/ 320 mcg N = 443	MF 800 mcg N = 440	S/F 50 mcg/ 500 mcg N = 444
AQLQ-S+12 overall score at week 52[a] — FAS					
Number of patients contributing to the analysis	397	378	384	389	405
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment time point (week 52), LS mean (SE)	5.83 (0.04)	5.64 (0.04)	5.78 (0.04)	5.71 (0.04)	5.74 (0.04)
Change from baseline, LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment group difference vs. control, LS mean (95% CI)	0.19 (0.08 to 0.30) (QMF vs. MF)		0.08 (–0.03 to 0.19) (QMF vs. MF) 0.04 (–0.07 to 0.15) (QMF vs. S/F)		
P value[b]	< 0.001 (QMF vs. MF)		0.154 (QMF vs. MF) 0.455 (QMF vs. S/F)		
AQLQ-S+12 symptoms domain score at week 52[a] — FAS					
Number of patients contributing to the analysis	397	378	384	389	405
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment time point (week 52), LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment group difference vs. control, LS mean (95% CI)	[redacted]		[redacted]		
P value[b]	[redacted]		[redacted]		
AQLQ-S+12 activity limitation domain score at week 52[a] — FAS					
Number of patients contributing to the analysis	397	378	384	389	405
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment time point (week 52), LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment group difference vs. control, LS mean (95% CI)	[redacted]		[redacted]		
P value[b]	[redacted]		[redacted]		
AQLQ-S+12 emotional function domain score at week 52[a] — FAS					
Number of patients contributing to the analysis	397	378	384	389	405
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment time point (week 52), LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	PALLADIUM study				
	QMF 150 mcg/ 160 mcg N = 437	MF 400 mcg N = 443	QMF 150 mcg/ 320 mcg N = 443	MF 800 mcg N = 440	S/F 50 mcg/ 500 mcg N = 444
Change from baseline, LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment group difference vs. control, LS mean (95% CI)	[redacted]		[redacted]		
P value[b]	[redacted]		[redacted]		
AQLQ-S+12 environmental stimuli domain score at week 52[a] — FAS					
Number of patients contributing to the analysis	397	378	384	389	405
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment time point (week 52), LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment group difference vs. control, LS mean (95% CI)	[redacted]		[redacted]		
P value[b]	[redacted]		[redacted]		
Proportion of patients with ≥ 0.5 unit improvement in AQLQ-S+12 overall score at week 52[c] — FAS					
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OR (95% CI)	[redacted]		[redacted]		
P value[b]	[redacted]		[redacted]		
EQ VAS at week 52 — FAS					
n	397	378	384	389	405
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment time point (week 52), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AQLQ = Asthma Quality of Life Questionnaire; AQLQ-S+12 = Asthma Quality of Life Questionnaire for 12 years and older; CI = confidence interval; EQ VAS = EuroQol Visual Analogue Scale; FAS = full analysis set; FEV_1 = forced expiratory volume in one second; LS = least squares; ITT = intention to treat; MF = mometasone furoate; MMRM = mixed-effects models for repeated measures; OR = odds ratio; QMF = indacaterol/mometasone furoate; SABA = short-acting beta2-agonist; SD = standard deviation; SE = standard error; S/F = salmeterol/fluticasone propionate; vs. = versus.

[a] MMRM with the following covariates: Baseline AQLQ, 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 via generalized estimating equation with the following covariates: Baseline AQLQ, 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).

Source: PALLADIUM Clinical Study Report.[6]

Asthma Control

The change from baseline in the ACQ-7 score, the proportion of patients with an improvement of 0.5 units or more in the ACQ-7 score, and rescue medication use (daily mean number of puffs used and percentage of rescue medication-free days) were reported in the QUARTZ study (Table 19) and the PALLADIUM study (Table 20) and summarized as measures of asthma control for this review.

The change from baseline in ACQ-7 at week 12 was the key secondary outcome used in QUARTZ. The ACQ-7 score decreased at week 12 in both the QMF 150 mcg/80 mcg and MF 200 mcg treatment groups, corresponding to an improvement in asthma control, with a LS mean treatment difference of –0.22 units (95% CI, –0.29 to –0.14; P < 0.001) in favour of QMF. Further, 74.7% and 64.9% in the QMF and MF treatment groups, respectively, reported an improvement of 0.5 units or more for the ACQ-7 (OR = 1.69; 95% CI, 1.23 to 2.33; P = 0.001). The change from baseline in ACQ-7 was the key secondary outcome used in PALLADIUM as well, measured at week 26; however, the analysis was conducted in a pooled QMF treatment group (150 mcg/160 mcg and 150 mcg/320 mcg) and pooled MF treatment group (MF 400 mcg and MF 800 mcg). An improvement in asthma control was reported for both treatment groups in PALLADIUM as well, with a LS mean treatment difference for QMF versus MF that was –0.21 units (95% CI, –0.27 to –0.15; P < 0.001) in favour of QMF (pooled). The treatment difference for QMF 150 mcg/160 mcg versus MF 400 mcg and QMF 150 mcg/320 mcg versus MF 800 mcg was –0.25 units (95% CI, –0.33 to –0.16; P < 0.001) and –0.17 (95% CI, –0.26 to –0.09; P < 0.001), respectively. In addition, absolute difference in the proportion of patients with an improvement of 0.5 units or more for the ACQ-7 was [redacted] (OR = 2.24; 95% CI, 1.58 to 3.17; P < 0.001) for the medium-dose treatment comparison, and [redacted] and [redacted] for the QMF 150 mcg/320 mcg versus MF 800 mcg (OR = 1.34; 95% CI, 0.96 to 1.87; P = 0.088) and S/F 50 mcg/500 mcg (OR = 1.05; 95% CI, 0.75 to 1.49; P < 0.771) treatment groups, respectively.

Analyses of rescue medication use showed a greater reduction in the mean daily number of puffs of rescue medication over the treatment phase, and a greater change (increase) in the percentage of rescue medication-free days during the treatment between all dose strengths of QMF and the corresponding doses of MF across the two studies. The LS mean (SE) change from baseline in the daily mean number of puffs of rescue medication was [redacted] puffs [redacted] for high-dose QMF and [redacted] puffs [redacted] for S/F 50 mcg/500 mcg. For the same comparison, the treatment group difference for the percentage of rescue medication-free days during the treatment phase was 4.3% (95% CI, 0.3 to 8.3; P = 0.034).

Table 19: Asthma Control — ACQ-7 and Rescue Medication Use in the QUARTZ Study

	QUARTZ study	
	QMF 150 mcg/80 mcg N = 395	MF 200 mcg N = 399
ACQ-7, change from baseline at week 12[a]		
Number of patients contributing to the analysis	387	384
Baseline, mean (SD)	NR	NR
End of treatment time point (week 12), LS mean (SE)	1.32 (0.04)	1.54 (0.04)
Change from baseline, LS mean (SE)	–0.95 (0.04)	–0.73 (0.04)

	QUARTZ study	
	QMF 150 mcg/80 mcg N = 395	MF 200 mcg N = 399
Treatment group difference vs. control, LS mean (95% CI)	–0.22 (–0.29 to –0.14)	
P value	< 0.001	
ACQ-7 score, proportion of patients with improvement of ≥ 0.5 units at week 12[b]		
n (%)	280 (74.7)	240 (64.9)
OR (95% CI)	1.69 (1.23 to 2.33)	
P value[c]	[redacted]	
Mean daily number of puffs of rescue medication from week 1 to week 12[d]		
Number of patients contributing to the analysis	393	392
Baseline, mean (SD)	[redacted]	[redacted]
End of treatment time point (week 12), mean (SE)		
Change from baseline, LS mean (SE)	–0.65 (0.05)	–0.40 (0.05)
Treatment group difference versus control, LS mean (95% CI)	–0.26 (–0.37 to –0.14)	
P value[c]	[redacted]	
Percentage of rescue medication-free days from week 1 to week 12[d]		
Number of patients contributing to the analysis	384	385
Baseline, mean (SD)	[redacted]	[redacted]
End of treatment time point (week 12), mean (SE)		
Change from baseline, LS mean (SE)	22.2 (1.81)	14.1 (1.80)
Treatment group difference vs. control, LS mean (95% CI)	8.1 (4.3 to 11.8)	
P value[c]	< 0.001	

ACQ-7 = Asthma Control Questionnaire (seven items); ANCOVA = analysis of covariance; CI = confidence interval; FAS = full analysis set; LS = least squares; FEV_1 = forced expiratory volume in one second; ITT = intention to treat; MF = mometasone furoate; MMRM = mixed-effects models for repeated measures; OR = odds ratio; QMF = indacaterol/mometasone furoate; SABA = short-acting beta2-agonist; SD = standard deviation; SE = standard error; vs. = versus.

[a] MMRM with the following covariates: Baseline 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).

[b] Analyzed using a logistic regression model.

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

[d] ANCOVA with the following covariates: Baseline rescue medication use, FEV_1 prior to inhalation, and FEV_1 within 15 to 30 minutes post inhalation of salbutamol/albuterol (components of SABA reversibility).

Source: QUARTZ Clinical Study Report.[5]

Table 20: Asthma Control — ACQ-7 and Rescue Medication Use in the PALLADIUM Study

	PALLADIUM study				
	QMF 150 mcg/ 160 mcg N = 437	MF 400 mcg N = 443	QMF 150 mcg/ 320 mcg N = 443	MF 800 mcg N = 440	S/F 50 mcg/ 500 mcg N = 444
ACQ-7, change from baseline at week 26[a]					
Number of patients contributing to the analysis	407	393	407	405	410
Baseline, mean (SD)	2.30 (NR)				
End of treatment time point (week 26), LS mean (SE)	1.26 (0.04)	1.51 (0.04)	1.27 (0.04)	1.44 (0.04)	1.32 (0.04)
Change from baseline, mean (SE)	–1.04 (0.04)	–0.79 (0.04)	–1.03 (0.04)	–0.86 (0.04)	–0.98 (0.04)
Treatment group difference vs. control, LS mean (95% CI)	–0.25 (–0.33 to –0.16) (QMF vs. MF)		–0.17 (–0.26 to –0.09) (QMF vs. MF) –0.05 (–0.14 to 0.03) (QMF vs. S/F)		
P value	< 0.001 (QMF vs. MF)		< 0.001 (QMF vs. MF) 0.214 (QMF vs. S/F)[b]		
ACQ-7, change from baseline at week 52[a]					
Number of patients contributing to the analysis	397	377	385	387	405
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment time point (week 52), LS mean (SE)	1.18 (0.04)	1.45 (0.04)	1.23 (0.04)	1.37 (0.04)	1.22 (0.04)
Change from baseline, mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment group difference vs. control, LS mean (95% CI)	–0.27 (–0.35 to –0.18) (QMF vs. MF)		–0.14 (–0.23 to –0.05) (QMF vs. MF) 0.01 (–0.08 to 0.10) (QMF vs. S/F)		
P value[b]	< 0.001 (QMF vs. MF)		0.002 (QMF vs. MF) 0.824 (QMF vs. S/F)		
ACQ-7 score, proportion of patients with improvement of ≥ 0.5 units at week 52[c]					
n (%)	326 (82.1)	261 (69.2)	299 (77.7)	285 (73.6)	313 (77.3)
OR (95% CI)	2.24 (1.58 to 3.17) (QMF vs. MF)		1.34 (0.96 to 1.87) (QMF vs. MF) 1.05 (0.75 to 1.49) (QMF vs. S/F)		
P value[b]	< 0.001 (QMF vs. MF)		0.088 (QMF vs. MF) 0.771 (QMF vs. S/F)		
Mean daily number of puffs of rescue medication from week 1 to week 52[d]					
Number of patients contributing to the analysis	428	428	426	433	432
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment time point (week 52), mean (SE)					
Change from baseline, LS mean (SE)	–0.80 (0.06)	–0.56 (0.06)	–1.00 (0.06)	–0.72 (0.06)	–0.91 (0.06)
Treatment group difference vs. control, LS mean (95% CI)	–0.23 (–0.39 to –0.07) (QMF vs. MF)		–0.28 (–0.44 to –0.12) (QMF vs. MF) –0.09 (–0.25 to 0.06) (QMF vs. S/F)		
P value[b]	0.004 (QMF vs. MF)		< 0.001 (QMF vs. MF) 0.245 (QMF vs. S/F)		
Percentage of rescue medication-free days from week 1 to week 52[d]					
Number of patients contributing to the analysis	416	414	408	420	416

	PALLADIUM study				
	QMF 150 mcg/ 160 mcg N = 437	MF 400 mcg N = 443	QMF 150 mcg/ 320 mcg N = 443	MF 800 mcg N = 440	S/F 50 mcg/ 500 mcg N = 444
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment time point (week 52), mean (SE)					
Change from baseline, mean (SE)	29.4 (1.54)	20.8 (1.54)	33.1 (1.55)	23.5 (1.54)	28.8 (1.54)
Treatment group difference vs. control, LS mean (95% CI)	8.6 (4.7 to 12.6) (QMF vs. MF)		9.6 (5.7 to 13.6) (QMF vs. MF) 4.3 (0.3 to 8.3) (QMF vs. S/F)		
P value[b]	< 0.001 (QMF vs. MF)		< 0.001 (QMF vs. MF) 0.034 (QMF vs. S/F)		

ACQ-7 = Asthma Control Questionnaire (seven items); ANCOVA = analysis of covariance; CI = confidence interval; FAS = full analysis set; FEV_1 = forced expiratory volume in one second; LS = least squares; ITT = intention to treat; MF = mometasone furoate; MMRM = mixed-effects models for repeated measures; NR = not reported; OR = odds ratio; QMF = indacaterol/mometasone furoate; SABA = short-acting beta2-agonist; SD = standard deviation; SE = standard error; S/F = salmeterol/fluticasone propionate; vs. = versus.

[a] MMRM with the following covariates: Baseline 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).

[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 generalized estimating equation with the following covariates: Baseline 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] ANCOVA with the following covariates: Baseline rescue medication use, FEV_1 prior to inhalation, and FEV_1 within 15 to 30 minutes post inhalation of salbutamol/albuterol (components of SABA reversibility).

Source: PALLADIUM Clinical Study Report.[6]

Figure 5: [redacted]

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

[redacted]

Source: PALLADIUM 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

In both studies, patients were asked to record asthma symptoms based on an e-diary that included data regarding the percentage of nights with no night-time awakenings. The results for QUARTZ and PALLADIUM are presented in Table 21 and Table 22, respectively. This was a secondary outcome in both studies that was not included in the statistical testing hierarchy. In QUARTZ, patients in the QMF 150 mcg/80 mcg treatment group reported a numerically greater increase in the percentage of nights without awakenings compared to the MF 200 mcg treatment groups (13.4% versus 8.7%, respectively) over the 12-week treatment period, corresponding to a treatment group difference of 4.8% (95% CI, 1.8 to 7.7; P = [redacted]). The percentage of nights without night-time awakenings increased in all treatment groups in PALLADIUM by a LS mean (SE) that ranged from 12.5% (1.27) to 17.0% (1.28). The reported treatment group difference for QMF 150 mcg/160 mcg versus

MF 400 mcg was 3.9% (95% CI, 0.5 to 7.3; P = 0.024). For QMF 150 mcg/320 mcg versus MF 800 mcg and versus S/F, the treatment group difference was 2.8% (95% CI, –0.6 to 6.2; P = 0.104) and 0.9% (95% CI, –2.5 to 4.3; P = 0.588), respectively. There was no difference between the high-dose QMF compared to MF 800 mcg and S/F 50 mcg/500 mcg treatment groups.

Table 21: Night-Time Awakenings in the QUARTZ Study

	QUARTZ study	
	QMF 150 mcg/80 mcg N = 395	MF 200 mcg N = 399
% nights without night-time awakenings from week 1 to week 12, change from baseline[a] — FAS		
Number of patients contributing to the analysis	384	384
Baseline, mean (SD)	[redacted]	[redacted]
End of treatment time point (specify), mean (SE)	[redacted]	[redacted]
Change from baseline, LS mean (SE)	13.4 (1.37)	8.7 (1.36)
Treatment group difference vs. control, LS mean (95% CI)	4.8 (1.8 to 7.7)	
P value[b]	[redacted]	

ANCOVA = analysis of covariance; CI = confidence interval; FAS = full analysis set; FEV_1 = forced expiratory volume in one second; LS = least squares; MF = mometasone furoate; NR = not reported; QMF = indacaterol/mometasone furoate; SABA = short-acting beta2-agonist; SD = standard deviation; SE = standard error; vs. = versus.

[a] ANCOVA with the following covariates: Baseline percentage of nights without night-time awakening, 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: QUARTZ Clinical Study Report.[5]

Table 22: Night-Time Awakenings in the PALLADIUM Study

	PALLADIUM study				
	QMF 150 mcg/ 160 mcg N = 437	MF 400 mcg N = 443	QMF 150 mcg/ 320 mcg N = 443	MF 800 mcg N = 440	S/F 50 mcg/ 500 mcg N = 444
% of nights without night-time awakenings from week 1 to week 52, change from baseline[a] — FAS					
Number of patients contributing to the analysis	420	422	415	428	424
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment time point (week 52), mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, LS mean (SE)	16.4 (1.27)	12.5 (1.27)	17.0 (1.28)	14.2 (1.27)	16.1 (1.27)
Treatment group difference vs. control, LS mean (95% CI)	3.9 (0.5 to 7.3) (QMF vs. MF)		2.8 (–0.6 to 6.2) (QMF vs. MF) 0.9 (–2.5 to 4.3) (QMF vs. S/F)		
P value[b]	0.024 (QMF vs. MF)		0.104 (QMF vs. MF) 0.588 (QMF vs. S/F)		

ANCOVA = analysis of covariance; CI = confidence interval; FAS = full analysis set; FEV_1 = forced expiratory volume in one second; LS = least squares; ITT = intention to treat; MF = mometasone furoate; QMF = indacaterol/mometasone furoate; SABA = short-acting beta2-agonist; SD = standard deviation; SE = standard error; S/F = salmeterol/fluticasone propionate; vs. = versus.

[a] ANCOVA with the following covariates: Baseline percentage of nights without night-time awakening, 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: PALLADIUM Clinical Study Report.[6]

Days of Missed Work or School

Days of missed work or school were not reported in QUARTZ. The percentage of work time missed due to asthma problems was reported as part of the WPAI in PALLADIUM. The change from baseline in the percentage of work time missed due to asthma problems at week 52 ranged from [redacted] to [redacted] across treatment groups. There was no difference between QMF and the corresponding active comparators for this outcome.

Table 23: Work Time Missed Due to Asthma Problems

	PALLADIUM study				
	QMF 150 mcg/ 160 mcg N = 437	MF 400 mcg N = 443	QMF 150 mcg/ 320 mcg N = 443	MF 800 mcg N = 440	S/F 50 mcg/ 500 mcg N = 444
% of work time missed due to asthma problems, change from baseline to week 52[a] — FAS					
Number of patients contributing to the analysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment time point (week 52), mean (SE)					
Change from baseline, LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment group difference vs. control, LS mean (95% CI)	[redacted]		[redacted]		
P value[b]	[redacted]		[redacted]		

CI = confidence interval; FAS = full analysis set; LS = least squares; MF = mometasone furoate; QMF = indacaterol/mometasone furoate; SD = standard deviation; SE = standard error; S/F = salmeterol/fluticasone propionate; vs. = versus.

[a] Specify model, covariates, analysis population, and time point for each outcome.

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

Source: PALLADIUM Clinical Study Report.[6]

Patient Adherence to Regimen

Outcomes related to patient adherence to treatment regimens were not included in QUARTZ or PALLADIUM. Treatment adherence was reported as a measure of safety and is reported in the “Interventions” section 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 QUARTZ or PALLADIUM.

Exercise Tolerance

Outcomes related to exercise tolerance were not included in QUARTZ or PALLADIUM.

Health Care Resource Utilization

A summary of asthma- and asthma exacerbation-related outpatient visits by type of facility and asthma-related hospitalizations in the two included studies are summarized in Table 24.

In QUARTZ, two patients ([redacted]) in the low-dose QMF group reported an asthma- or asthma exacerbation-related outpatient visit to any facility type (both were office or home visits). In contrast, the MF 200 mcg treatment group reported [redacted] visits to any facility type, [redacted] of which were office or home visits. One asthma-related hospitalization was reported overall in a patient in the MF 200 mcg treatment group; no asthma-related hospitalizations were reported in the QMF 150 mcg/80 mcg treatment group.

In PALLADIUM, all asthma- or asthma exacerbation-related outpatient visits ranged from [redacted] to [redacted] of patients in the QMF and S/F treatment groups, and [redacted] to [redacted] in the MF treatment groups, with the majority of visits being office or home visits. Hospital or ED visits were reported by [redacted] and [redacted] of patients in the medium-dose QMF and MF 400 mcg treatment groups, respectively, and [redacted] and [redacted] of patients in the high-dose QMF and MF 800 mcg treatment groups, respectively. Visits to the ED or hospital were reported by [redacted] of patients in the S/F 50 mcg/500 mcg treatment group. Lastly, [redacted] of patients reported an asthma-related hospitalization in any treatment group in PALLADIUM, although hospitalizations were approximately twice as frequent in MF treatment groups ([redacted] for both) compared to QMF (medium-dose [redacted], high-dose [redacted]) and S/F 50 mcg/500 mcg ([redacted]) treatment groups.

Table 24: Health Care Utilization — Outpatient Visits

	QUARTZ study[a]		PALLADIUM study[b]				
	QMF 150 mcg/ 80 mcg N = 395	MF 200 mcg N = 399	QMF 150 mcg/ 160 mcg N = 437	MF 400 mcg N = 443	QMF 150 mcg/ 320 mcg N = 443	MF 800 mcg N = 440	S/F 50 mcg/ 500 mcg N = 444
Asthma- and asthma exacerbation-related outpatient visits, n (%)							
Any facility type	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Office or home visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ED or hospital	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other facility type	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asthma-related hospitalizations, n (%)							
Any facility type	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; ED = emergency department; FAS = full analysis set; LS = least squares; MF = mometasone furoate; ITT = intention to treat; QMF = indacaterol/mometasone furoate; SD = standard deviation; SE = standard error; S/F = salmeterol/fluticasone propionate.

[a] 12-week treatment period.

[b] 52-week treatment period.

Source: Clinical Study Reports for the QUARTZ[5] and PALLADIUM[6] studies.

Harms

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

Adverse Events

The proportion of patients with at least one AE was 32.3% and 38.3% in the QMF and MF treatment groups, respectively, for QUARTZ. The most common AEs in the QMF and MF treatment groups were asthma (5.3% and 15.3%), nasopharyngitis (4.3% and 4.8%), overdose (1.3% and 2.5%), and upper respiratory tract infection (URTI) (1.0% and 2.5%),

respectively. In PALLADIUM, the proportion of patients with at least one AE ranged from 65.3% to 72.2% across treatment groups. The most common events were asthma (25.8% to 44.7%), nasopharyngitis (10.6% to 18.5%), URTI (5.0% to 9.1%), headache (4.8% to 5.9%), and bronchitis (3.8% to 5.0%). In both studies, the frequency of AEs was similar between treatment groups in general, with the exception of asthma and viral URTI, which were both more common in the MF treatment groups than in the QMF treatment groups. Nasopharyngitis was also more common in MF groups than in the QMF and S/F groups in the PALLADIUM study.

Serious Adverse Events

Reported SAEs were infrequent in QUARTZ (≤ 1.8% in both treatment groups) and ranged from 5.0% to 8.0% among treatment groups in PALLADIUM (all treatment groups were approximately 5.0% except MF 400 mcg at 8.0%). The most common reason for a SAE in both studies was asthma, which occurred in less than 2% of patients in each treatment group.

Withdrawals Due to Adverse Events

Few patients stopped treatment due to an AE in both QUARTZ ([redacted]) and PALLADIUM ([redacted]). The proportion of patients reporting a WDAE was numerically greater in PALLADIUM's MF 400 mcg and MF 800 mcg treatment groups ([redacted] and [redacted], respectively) than in its medium-dose and high-dose QMF treatment groups ([redacted] and [redacted], respectively).The most common reason for a WDAE was asthma in both studies.

Mortality

One death was reported between the two included studies; it occurred in an adolescent patient in PALLADIUM's MF 400 mcg treatment group. The cause of death was determined by an independent adjudication committee to be due to asthma exacerbation.

Notable Harms

Infections (systemic and local), steroid effects (topical, systemic), growth rates (12 to < 18 year age group), cardiovascular events, hypothalamic-pituitary-adrenal axis suppression, bone markers, and blood sugar levels were included as notable harms in the CADTH review protocol. Infections were reported by [redacted] to [redacted] of patients in QUARTZ and [redacted] to [redacted] of patients in PALLADIUM. In QUARTZ, specific causes of infection that occurred in at least [redacted] of patients in any treatment group were nasopharyngitis and URTI. In PALLADIUM, specific causes of infection that occurred in at least [redacted] of patients in any treatment group were nasopharyngitis, URTI, and bronchitis. Cardiac and vascular disorders occurred in [redacted] of both treatment groups in QUARTZ, and between 4.3% and 7.8% of treatment groups in PALLADIUM; the most common reason was due to hypertension in both studies ([redacted] patients in QUARTZ and [redacted] to [redacted] in PALLADIUM). In PALLADIUM, there was a smaller proportion of patients in the S/F treatment group with cardiac and vascular disorders compared to the QMF and MF treatment groups. Local steroid effects, which included cough, oral thrush, nosebleeds, oropharyngeal pain and discomfort, dysphonia, and larynx irritation, occurred in [redacted] to [redacted] of patients across treatment groups in both studies. All other notable harms were reported in [redacted] of patients in any treatment group.

Table 25: Summary of Harms — Safety Analysis Set

	QUARTZ study		PALLADIUM study				
	QMF 150 mcg/ 80 mcg N = 396	MF 200 mcg N = 399	QMF 150 mcg/ 160 mcg N = 437	MF 400 mcg N = 443	QMF 150 mcg/ 320 mcg N = 443	MF 800 mcg N = 440	S/F 50 mcg/ 500 mcg N = 444
Patients with ≥ 1 AE							
n (%)	128 (32.3)	153 (38.3)	292 (66.8)	320 (72.2)	286 (64.6)	308 (70.0)	290 (65.3)
Most common events,[a] n (%)							
Asthma	21 (5.3)	61 (15.3)	113 (25.8)	198 (44.7)	113 (25.5)	159 (36.1)	137 (30.9)
Nasopharyngitis	17 (4.3)	19 (4.8)	58 (13.3)	82 (18.5)	50 (11.3)	78 (17.7)	47 (10.6)
Cough	5 (1.3)	4 (1.0)	9 (2.1)	15 (3.4)	8 (1.8)	12 (2.7)	8 (1.8)
Overdose	5 (1.3)	10 (2.5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pharyngitis	5 (1.3)	2 (0.5)	11 (2.5)	12 (2.7)	10 (2.3)	12 (2.7)	14 (3.2)
Headache	4 (1.0)	9 (2.3)	21 (4.8)	24 (5.4)	26 (5.9)	24 (5.5)	22 (5.0)
Influenza	4 (1.0)	4 (1.0)	13 (3.0)	10 (2.3)	12 (2.7)	19 (4.3)	15 (3.4)
Rhinitis, allergic	4 (1.0)	0	11 (2.5)	11 (2.5)	5 (1.1)	7 (1.6)	7 (1.6)
Rhinitis	[redacted]	[redacted]	10 (2.3)	5 (1.1)	10 (2.3)	9 (2.0)	8 (1.8)
URTI	4 (1.0)	10 (2.5)	27 (6.2)	37 (8.4)	22 (5.0)	40 (9.1)	38 (8.6)
Bronchitis	1 (0.3)	6 (1.5)	22 (5.0)	21 (4.7)	20 (4.5)	22 (5.0)	17 (3.8)
Viral URTI	1 (0.3)	6 (1.5)	11 (2.5)	20 (4.5)	7 (1.6)	21 (4.8)	21 (4.7)
Hypertension	[redacted]	[redacted]	14 (3.2)	11 (2.5)	10 (2.3)	13 (3.0)	6 (1.4)
Oropharyngeal pain	[redacted]	[redacted]	6 (1.4)	9 (2.0)	11 (2.5)	8 (1.8)	8 (1.8)
Respiratory tract viral infection	[redacted]	[redacted]	16 (3.7)	12 (2.7)	10 (2.3)	14 (3.2)	13 (2.9)
Back pain	[redacted]	[redacted]	17 (3.9)	6 (1.4)	9 (2.0)	9 (2.0)	8 (1.8)
Viral infection	[redacted]	[redacted]	8 (1.8)	7 (1.6)	7 (1.6)	11 (2.5)	6 (1.4)
Gastroenteritis	[redacted]	[redacted]	9 (2.1)	6 (1.4)	4 (0.9)	4 (0.9)	8 (1.8)
Diarrhea	[redacted]	[redacted]	9 (2.1)	4 (0.9)	3 (0.7)	5 (1.1)	9 (2.0)
Patients with ≥ 1 SAE							
n (%)	5 (1.3)	7 (1.8)	20 (4.6)	31 (7.0)	21 (4.7)	21 (4.7)	21 (4.7)
Most common events,[b] n (%)							
Asthma	1 (0.3)	1 (0.3)	2	8	3	6	2
Acute myocardial infarction	—	—	0	0	2	0	1
Pneumonia	—	—	3	2	1	5	0
Peritonitis	—	—	0	0	0	1	3
Rib fracture	—	—	0	2	0	0	0
Patients who stopped treatment due to AEs							
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	QUARTZ study		PALLADIUM study				
	QMF 150 mcg/ 80 mcg N = 396	MF 200 mcg N = 399	QMF 150 mcg/ 160 mcg N = 437	MF 400 mcg N = 443	QMF 150 mcg/ 320 mcg N = 443	MF 800 mcg N = 440	S/F 50 mcg/ 500 mcg N = 444
Most common events,[b] n (%)							
Asthma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Angioedema	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dysphonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Electrocardiogram, QT prolonged	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deaths							
n (%)	0	0	0	1 (0.2)	0	0	0
Notable harms							
AEs of interest, n (%)							
Infections (systemic and local)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac and vascular disorders	[redacted]	[redacted]	34 (7.8)	29 (6.5)	28 (6.3)	25 (5.7)	19 (4.3)
Blood glucose, increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypoglycemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anticholinergic effects[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bone markers (blood alkaline phosphatase, increased or abnormal)	—	—	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HPA axis suppression[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Systemic steroid effects[e]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Local steroid effects[f]	14 (3.7)	10 (2.6)	21 (4.8)	27 (6.0)	20 (4.5)	20 (4.5)	18 (4.1)
Growth rates	-	-	-	-	-	-	-

AE = adverse event; HPA = hypothalamic-pituitary-adrenal; MF = mometasone furoate; QMF = indacaterol/mometasone furoate; SAE = serious adverse event; S/F = salmeterol/fluticasone propionate; URTI = upper respiratory tract infection.

[a] Frequency of 2% or more in any treatment group. A patient with multiple AEs is counted only once in the summary count of the AE section.

[b] Frequency of two or more patients in any treatment group. A patient with multiple SAEs is counted only once in the summary count of the SAE section. AEs that were not recorded are indicated by a "-".

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

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

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

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

Source: Clinical Study Reports for the QUARTZ[5] and PALLADIUM[6] studies.

Critical Appraisal

Internal Validity

Patients were randomized and treatment allocation was concealed from patients and investigator staff via the use of an Interactive Response Technology system in both of the included trials. QUARTZ and PALLADIUM also employed a double-dummy and triple-dummy technique, respectively, to maintain their double-blind study design.

A high proportion of patients had severely uncontrolled asthma based on a baseline ACQ-7 score of 2.0 or more in both studies. Further, patients were required to demonstrate bronchodilator reversibility for inclusion in both of the clinical trials, which may have resulted in a trial population that would be more responsive to therapy. Overall, the treatment groups were generally balanced by their baseline characteristics in both of the trials, with the exception of a difference in the proportion of patients with a baseline ACQ-7 score of 2.5 or more and pre-bronchodilator FEV_1 as 60% to 70% of the predicted FEV_1 in QUARTZ. Both were greater for the MF 200 mcg group than the QMF 150 mcg/80 mcg group at baseline, which may be suggestive of a population that has more poorly controlled asthma and biases the results in favour of QMF. Further, the fact that both treatment groups were poorly controlled at baseline means they would have been more responsive to treatment in a closely monitored trial setting. The magnitude and direction of the potential bias from this issue is difficult to determine.

Concomitant asthma medications were permitted in both studies. Reported usage after enrolment in the two studies ranged from [redacted] to [redacted] in QUARTZ and [redacted] to [redacted] in PALLADIUM, with a greater proportion of patients using concomitant asthma medications in the MF 400 mcg and MF 800 mcg treatment groups in PALLADIUM ([redacted] to [redacted] for QMF and [redacted] to [redacted] for MF). The impact of the differential use of concomitant medications in PALLADIUM is unclear; however, it has the potential to bias the between-group difference to the null.

The proportion of patients who discontinued from the study was low, ranging from 1.0% to 5.2% in the QUARTZ trial and 5.9% to 9.2% in the PALLADIUM trial; this was unlikely to have an impact on randomization. The two trials did not explicitly impute missing data. However, the MMRM analyses used for the primary and secondary outcomes are based on the assumption of data MAR. Both studies included planned sensitivity analyses on the primary analysis to evaluate the impact of missing data via a tipping point analysis, and these analyses were supportive of the primary analysis in each study. The impact of missing data on the remaining outcomes is unclear due to a lack of sensitivity analyses for these end points.

The primary and key secondary outcomes were the change from baseline in FEV_1 and change from baseline in ACQ-7 for both studies, assessed at week 26 and week 12 for PALLADIUM and QUARTZ, respectively. The former is an objective measure of lung function. While FEV_1 is a clinically relevant measure of pulmonary function, the clinical expert consulted on this review noted that it is generally not useful for making decisions regarding the selection of treatments for asthma. As per guidance from the EMA, measures of lung function are insufficient for the assessment of overall therapeutic effect for controller medications and should be included as a co-primary or key secondary end point.[7] The two trials featured a range of efficacy outcomes, which included those that were important to patients and clinicians, such as outcomes related to asthma exacerbations, HRQoL, and asthma control. The ACQ-7 is a patient-reported tool used to assess asthma control with

demonstrated validity, reliability, and responsiveness,[43, 48, 57] and a well-established within-patient MID of 0.5 points.[47, 49]

Further, the ACQ-7, which was included as the key secondary outcome in both trials and was used for inclusion criteria in both studies, is typically not used by family physicians, who would be expected to be prescribing QMF in clinical practice. Outcomes related to dyspnea, days of missed school, and exercise tolerance are not studied. Outcomes of patient importance such as HRQoL and asthma exacerbations were analyzed and showed differences in favour of QMF consistently in various comparison groups, even though statistical inference was restricted.

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

A sequential testing procedure was used to control for inflated type I error due to multiple testing in both QUARTZ and PALLADIUM. In cases where all of the hypotheses included in the family could not be retained or all could not be rejected, a closed successive Bonferroni test was employed. PALLADIUM included two hypotheses for the primary end point; a third hypothesis of the secondary end point was performed in a pooled group of patients treated with QMF versus patients treated with MF, regardless of the dose strength. No other outcomes, including an analysis of the secondary end point by the individual treatment groups, were controlled for multiplicity and were therefore subject to inflated risk of type I error. In particular, asthma exacerbations and HRQoL, outcomes of importance to clinicians and patients, were not controlled for multiplicity.

The comparison between QMF 150 mcg/320 mcg and S/F 50 mcg/500 mcg in PALLADIUM for the primary end point was a test of NI, using a NI margin of –0.090 L in FEV_1. The NI margin was based on historical evidence of drug effect of active control over placebo (derived from a meta-analysis of three trials comparing fluticasone furoate/vilanterol [Breo Ellipta] with placebo) and less than half of the MID (0.200 L to 0.230 L). No information related to the approach taken for the meta-analysis was provided. In fact, it is not clear how the three studies that were analyzed were identified and selected. There is no mention of whether a systematic review was conducted looking more broadly for data to include in the estimation of the active treatment versus placebo effect. The methods for pooling the data from the three selected studies were also not reported. As well, although the analysis was a predefined secondary one, there was no stepwise approach — namely, it was not specified that proof of concept (superiority of QMF versus MF) had to be satisfied prior to testing NI. The NI margin used was accepted by Health Canada[34] and considered reasonable by the clinical expert consulted for this review.

External Validity

Patients with a history of smoking within six months of screening or for 10 pack years or more and patients with clinical or chronic conditions other than asthma were excluded from both trials. While this is typical of RCTs for asthma, it excludes a number of patients who would be treated with QMF in clinical practice, as per the opinion of the clinical expert consulted for this review. The lack of Canadian sites and exclusion criteria limit the

generalizability of the studies to the patients seen within Canadian clinical practice. QMF is indicated for adolescents (ages 12 to 17) as well as adults; however, adolescents only accounted for a small proportion of patients enrolled in the two trials ([redacted] to [redacted] in QUARTZ and [redacted] to [redacted] of patients in PALLDIUM). Additionally, a baseline ACQ-7 measure of at least 1.5 points that was used as an indication of inadequately controlled asthma 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 on this review. This typical enrichment trial design would have made the treatment effect appear more optimal than that which could be seen in the real world, where the patient population is less selective. Moreover, none of the sites in either of the trials for QMF were located in Canada. Therefore, the study results reflected a mean group treatment effect based on diverse patient population from different regions across various countries, which also rendered it difficult to extrapolate the results to a Canadian clinical setting.

Both trials included Health Canada–approved doses of QMF (150 mcg/80 mcg, 150 mcg/160 mcg, and 150 mcg/320 mcg, once daily). A SABA (100 mcg salbutamol or 90 mcg albuterol via MDI) was provided to all patients in both trials for use throughout the study as rescue therapy. In addition, certain asthma-related concomitant medications such as corticosteroids, antihistamines, and antibiotics were permitted for use in both trials and adjusted as necessary during the run-in period. Lastly, all patients received training on how to properly use the inhalation devices used in the trials as well as additional training at assessment visits, as needed. Rescue medication and concomitant medication use and training are all aligned with typical clinical practice.

Asthma is a chronic disease with seasonal patterns; therefore, clinical trials for controller therapies should be at least six months in duration. The QUARTZ study was a short-term trial involving a 12-week treatment period, which is sufficient to demonstrate a difference in terms of the change in FEV_1, but may not be long enough to comprehensively assess the ability of QMF to control asthma as a maintenance treatment. The duration of PALLADIUM included a 52-week treatment period, which was a sufficient period of analysis and consistent with the EMA guidelines;[7] however, it should be noted that asthma is a chronic disease that requires lifelong treatment. Information regarding efficacy and safety beyond one year was lacking.

The two trials included a range of efficacy outcomes, which included those 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 on this review noted that it is generally not useful for making decisions regarding the selection of treatments for asthma. Patient adherence to regimen and ease of use were not included in either of the trials for QMF. The lack of information regarding the latter two outcomes is a limitation of the QMF trials as the Breezhaler device is expected to be a barrier for use according to the clinical expert. It is worth highlighting that the correct and efficient use of the Breezhaler device would be more favourable in a clinical trial setting than with patients who received the device from their family physicians and used them at home. Studies and patient input already showed that adherence is one of the most critical determinants in treatment effect in a real-world setting, which could largely compromise the generalizability of findings from the two included trials.

Indirect Evidence

The sponsor submitted an ITC report that conducted a feasibility analysis to assess the viability of doing a 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 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) 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 that included sponsor-included studies. The search identified 45 publications that met 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 concluded similar issues related to 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 many new agents and shifts in treatment patterns over the past decade. In addition, over time, the patient population, requirements for trial length, and delivery devices have added greater variance to the evidence base.

Recent NMAs and systematic reviews have cited evident difference in baseline lung function and asthma severity that may have explained potential inconsistencies in the evidence base.[58-60] 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 methods are available to account for differences in study characteristics, such as meta-regression techniques, but these methods often require a larger evidence base. However, the greatest limitation in the evidence base is the variation in defining "exacerbation" across studies. Extensive work has been completed to develop standard definitions but this forward-looking initiative makes it hard to compare to previous studies that established many current first-line treatments.[61, 62]

As previously described, the sponsor feasibility assessment concluded that no analysis was feasible due to clinical heterogeneity in patient characteristic and outcome definitions. The conclusion 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

	Number of studies (n = 51)				
Therapy type	**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/LABA + TIO	[redacted]	[redacted]	[redacted]	[redacted]

	Number of studies (n = 51)				
Therapy type	**Treatment**	**Low**	**Medium**	**High**	**Total**
	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 bromide; ICS = inhaled corticosteroid; LABA = long-acting beta2-agonist; QMF = indacaterol/mometasone furoate; QVM = indacaterol/glycopyrronium bromide/mometasone furoate; SAL = salmeterol; TIO = tiotropium bromide; VI = vilanterol.

Source: Adopted from the sponsor-submitted ITC feasibility analysis.[63]

Figure 6: [redacted]

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

[redacted]

Source: Adopted from the sponsor-submitted indirect treatment comparison.[63]

Other Relevant Evidence

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

Long-Term Safety Study: Study 1305

Methods

Study 1305 was a multi-centre, open-label, single-arm, 52-week treatment study designed to assess the safety and the tolerability of once-daily QMF administered at 150 mcg/320 mcg in Japanese patients with inadequately controlled asthma.

Study 1305 began with an initial four-week screening period that was used to assess the study eligibility of patients and to record their baseline values. At the beginning of the screening period, patients were prescribed 100 mcg 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 51 Japanese patients aged 18 years or older from 15 sites in Japan. The patients had previously used medium-dose or high-dose ICS plus at least one controller medication (e.g., LABA, a LTRA, theophylline, or an anti-allergic medication) for asthma.

The key inclusion and exclusion criteria of difference between Study 1305 and the pivotal trials are the inclusion of younger participants in the PALLADIUM study (aged 12 to 18). Study 1305 also included patients who had to have been on a prior controller medication for three months; the pivotal clinical trials did not specify criteria in this regard.

Baseline Characteristics

The baseline demographics and disease characteristics of patients included in Study 1305 are summarized in Table 27. Patients in Study 1305 were a mean age of 51.9 years; 45.1% of patients were male and 100% of patients were Asian. Overall, patients had been diagnosed with asthma for a mean duration of 23.0 years. A total of 70% of patients had not had an asthma exacerbation in the previous year, and [redacted] of patients had never smoked. The mean baseline ACQ-7 score in Study 1305 was 1.98. and 88.1% of patients had been treated with an ICS/LABA other than low dose.

Baseline spirometry were generally similar to those of the patients enrolled in QUARTZ, and generally higher than those of the patients enrolled in the PALLADIUM study.

Table 27: Summary of Baseline Characteristics — Safety Population

Characteristic		QMF 150 mcg/320 mcg N = 51
Age (years)	Mean (SD)	51.9 (12.5)
	18 to 39, n (%)	[redacted]
	40 to 64, n (%)	[redacted]
	≥ 65, n (%)	[redacted]
Sex	Male, n (%)	23 (45.1)
Race	Asian	51 (100)
Duration of asthma (years)	Mean (SD)	23.0 [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	37 (72.5)
	1	[redacted]
	2	[redacted]
	3	[redacted]
	≥ 4	[redacted]
Smoking status, n (%)	Never smoked	[redacted]
	Former smoker	[redacted]
Baseline ACQ-7 score	Mean (SD)	1.98 (0.54)
	Median (range)	[redacted]
	< 1.5, n (%)	[redacted]

Characteristic		QMF 150 mcg/320 mcg N = 51
	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	45 (88.2)
FEV_1 pre-bronchodilator at baseline	n	51
	Mean (SD)	2.1565 (0.5807) L
	Median (range)	[redacted]
FEV_1 pre-bronchodilator (% of predicted FEV_1) at baseline	n	51
	Mean (SD)	73.2% [redacted]
	Median (range)	[redacted]
	< 50%, n (%)	[redacted]
	50% to < 60%, n (%)	[redacted]
	60% to ≤ 85%, n (%)	[redacted]
	> 85%, n (%)	[redacted]
FEV_1 reversibility (% increase) at baseline	n	51
	Mean (SD)	[redacted]
	Median (range)	[redacted]
FEV_1 reversibility (increase in L) at baseline	n	51
	Mean (SD)	[redacted]
	Median (range)	[redacted]

ACQ-7 = Asthma Control Questionnaire (seven items); FEV_1 = forced expiratory volume in one second; ICS = inhaled corticosteroid; LABA = long-acting beta2-agonist; QMF = indacaterol/mometasone furoate; SD = standard deviation.

Source: Study 1305 Clinical Study Report.[64]

Interventions

Patients took once-daily QMF administered at a dose of 150 mcg/320 mcg delivered via Breezhaler, to be taken at the same time daily in the evening. The use of rescue medication of 100 mcg salbutamol delivered via pressurized MDI was permitted on an as-needed basis determined by the patient, based on their symptoms. Training on the use of the pressurized MDI for administration of salbutamol was provided on visit 1. Training on the use of the Breezhaler device was completed on visit 99 in 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 1305.

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), HRQoL (assessed by 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 SAS was used to summarize the safety outcomes, which included patients who received at least one dose of study medication. The FAS was used to summarize the efficacy outcomes, which also included patients who received at least one dose of study medication. An event was classified as a treatment-emergent AE if it occurred seven days after the last administration of study drug, and was classified as a SAE if it occurred up to 30 days after the last administration of the study drug.

Baseline is 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 where two baseline values were recorded (pre-dose FEV_1), if one 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 1305 has been summarized in Table 28. Of the 86 patients screened, 51 entered the treatment phase, with three patients who discontinued the study — all due to patient or guardian decision.

Table 28: Patient Disposition — FAS

	QMF 150 mcg /320 mcg N = 51
Screened, N	[redacted]
Randomized, N	51
Discontinued from study, N (%)	3 (5.9)
Reason for discontinuation, N (%)	
Patient or guardian decision	[redacted]
ITT, N	51
PP, N	NR
Safety, N	51

FAS = full analysis set; ITT = intention to treat; NR = not reported; PP = per-protocol; QMF = indacaterol/mometasone furoate.

Source: Study 1305 Clinical Study Report.[64]

Exposure to Study Treatment

Patients were exposed to study treatment for a mean of 356 days, with 72.5% of patients exposed to study treatment between 255 days and 365 days (Table 29).

Table 29: Extent of Exposure to Study Drug — Safety Population

	QMF 150 mcg/320 mcg N = 51
Exposure (days)	
Mean (SD)	[redacted]
Median (range)	[redacted]
Exposure categories, n (%)	
87 to 183 days	[redacted]
184 to 254 days	[redacted]
255 to 365 days	[redacted]
> 365 days	[redacted]

QMF = indacaterol/mometasone furoate; SD = standard deviation.

Source: Study 1305 Clinical Study Report.[64]

Efficacy

Acute Asthma Exacerbations

The proportion of patients with an acute asthma exacerbation and the corresponding severity level is described in Table 30. During the 52-week study, 11.8% and 13.7% of patients had a severe or moderate asthma exacerbation, respectively. No patients required hospitalization or discontinued the study drug permanently due to an asthma exacerbation.

Table 30: Patients with Asthma Exacerbations — FAS

	QMF 150 mcg/320 mcg N = 51
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]

FAS = full analysis set; QMF = indacaterol/mometasone furoate.

Source: Study 1305 Clinical Study Report.[64]

Pre-Dose FEV_1

Overall, patients had a mean increase from baseline in pre-dose FEV_1 of [redacted], 0.242 L, and 0.183 L at 12 weeks, 26 weeks, and 52 weeks, respectively (Table 31).

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

	Baseline	Post	Change
Baseline			
n	51		
Mean (SD)	2.1565 (0.5807)		
Week 12			
n	51	51	51
Mean (SD)	[redacted]	[redacted]	[redacted]
Week 26			
n	49	49	49
Mean (SD)	[redacted]	[redacted]	0.2417 (0.2636)
Week 52			
n	48	48	48
Mean (SD)	2.1497 (0.5480)	2.3324 (0.5301)	0.1827 (0.2663)

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

Source: Study 1305 Clinical Study Report.[64]

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], 0.689, and 0.830 at 12 weeks, 26 weeks, and 52 weeks, respectively. At 26 weeks and 52 weeks, 66% and 72.9% of patients had exhibited a decrease of 0.5 points or greater 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	51	51	50	48
Baseline, mean (SD)	1.983 (0.538)	[redacted]	[redacted]	1.991 (0.553)
End of treatment, LS mean (SE)		[redacted]	[redacted]	1.161 (0.692)
Change from baseline, LS mean (SE)		[redacted]	–0.689 (0.627)	–0.830 (0.685)
ACQ-7, proportion of patients				
Proportion of patients with decrease of ≥ 0.5 units, n/m (%)			33/50 (66.0)	35/48 (72.9)

ACQ-7 = Asthma Control Questionnaire (seven items); FAS = full analysis set; LS = least squares; m = the number of patients with data at the respective visit; SD = standard deviation; SE = standard error.

Source: Study 1305 Clinical Study Report.[64]

Harms

AEs of varying severity, WDAEs, and deaths are described in Table 33. During the latter half of the study, [redacted] of patients exhibited an AE, with [redacted] experiencing nasopharyngitis, [redacted] experiencing asthma, and two patients each experiencing bronchitis and oropharyngeal pain.

No SAEs, WDAEs, or deaths occurred after 26 weeks in the treatment phase of Study 1305. Of the harms identified as important in the review protocol, [redacted] of patients experienced a local infection and three patients experienced a local steroid effect.

Table 33: Summary of Harms That Occurred After 26 Weeks — Safety Population

	QMF 150 mcg/320 mcg N = 50
Patients with ≥ 1 AE	
n (%)	[redacted]
Most common events,[a] n (%)	
Nasopharyngitis	[redacted]
Bronchitis	[redacted]
Asthma	[redacted]
Oropharyngeal pain	[redacted]
Patients with ≥ 1 SAE	
n (%)	[redacted]
Patients who stopped treatment due to AEs	
n (%)	[redacted]
Deaths	
n (%)	[redacted]
Notable harms	
n (%)	
Systemic infection	[redacted]
Local infection	[redacted]
Cardiac and vascular disorders	—
Blood glucose, increased	[redacted]
Anticholinergic effects	—
Local steroid effects	[redacted]
Systemic steroid effects	—
HPA axis suppression	—
Growth rates	—

AE = adverse event; HPA = hypothalamic-pituitary-adrenal; QMF = indacaterol/mometasone furoate; SAE = serious adverse event.

[a] Frequency of two or more patients in the treatment group.

Source: Study 1305 Clinical Study Report.[64]

Critical Appraisal

Internal Validity

The main limitations of Study 1305 include the open-label and single-arm study design. The absence of a comparator limits the certainty of conclusions on efficacy and safety of QMF. Related to the open-label study design, investigators and patients were aware of the study drug administered, which may bias 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 1305 was conducted solely in Japan.

Summary

Results of Study 1305 are difficult to interpret because of the open-label, noncomparative design and lack of statistical testing, and because the study was conducted in Japan only.

Discussion

Summary of Available Evidence

Two pivotal, multi-centre, double-blind RCTs met the inclusion criteria for the systematic review, QUARTZ (N = 802) and PALLADIUM (N = 2,216). The trials evaluated the efficacy and safety of QMF (150 mcg/80 mcg, 150 mcg/160 mcg, and 150 mcg/320 mcg) in adolescents (≥ 12 years of age) and adults with asthma over 12 weeks and 52 weeks of therapy in QUARTZ and PALLADIUM, respectively. Patients included in the two trials were required to have a diagnosis of asthma that was inadequately controlled (ACQ-7 score ≥ 1.5 at baseline), a pre-bronchodilator FEV_1 of 60% or more and less than 90% (QUARTZ) or 50% or more and less than 85% (PALLADIUM) of the predicted normal, and demonstrate bronchodilator reversibility. Patients also had at least one month's use of a low-dose ICS prior to screening in QUARTZ and at least three months' use of a medium-dose or high-dose ICS or low-dose ICS/LABA combination in PALLADIUM. The two trials were designed to test the superiority of QMF delivered via Breezhaler against MF delivered via Twisthaler at a low-dose, medium-dose, and high-dose strength. More specifically, QUARTZ evaluated QMF 150 mcg/80 mcg once daily versus MF 200 mcg once daily; in PALLADIUM, QMF 150 mcg/160 mcg once daily was evaluated against MF 400 mcg once daily and QMF 150 mcg/320 mcg once daily was evaluated against MF 800 mcg (administered as 400 mcg twice daily). PALLADIUM also included S/F 50 mcg/500 mcg administered twice daily via Accuhaler as an active comparator for NI testing of the primary end point. The two trials used a double-dummy and triple-dummy design to maintain blinding.

The primary and key secondary outcomes in both trials were the change from baseline in trough FEV_1, a measure of lung function, and the change from baseline in ACQ-7, a patient-reported measure of asthma control. Primary and key secondary outcomes were measured at week 12 in QUARTZ and week 26 in PALLADIUM. Outcomes related to asthma exacerbations, rescue medication use, and HRQoL were included as other secondary outcomes, as well as other measures of pulmonary function, night-time symptoms (night-time awakenings), and health care utilization. The WPAI (percentage of work time missed due to asthma problems) was also included in PALLADIUM. 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 1305, was also summarized for this review.

No ITCs were provided by the sponsor with the submission to CADTH. Instead, the sponsor provided a feasibility analysis for ITCs between QMF and other dual and triple asthma therapies for the treatment of patients with uncontrolled asthma; it concluded ITCs were not feasible. A supplemental search of the literature did not identify published ITCs comparing QMF with other available treatments for asthma.

A key limitation of both studies is that they were not designed to evaluate the efficacy of QMF on asthma exacerbations, which is a patient-important outcome and a key driver of health resource use in patients with asthma. Other limitations included the short (12-week) duration of QUARTZ, having change in trough FEV_1 as the primary outcome as opposed to asthma control, and, as mentioned, asthma exacerbations. The generalizability of the trials was also limited due to the patient selection criteria, which may not capture a representative sample of patients with asthma in Canadian clinical practice. The available evidence on

comparative effectiveness is limited to a direct comparison of QMF to S/F (at the high-dose of QMF) and the ICS component of QMF and MF.

Interpretation of Results

Efficacy

A reduction in asthma exacerbations is an outcome important to patients. It is also of key clinical relevance to treating physicians and one of two 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 QUARTZ and PALLADIUM studies as other secondary outcomes. The proportion of patients with asthma exacerbations was reported descriptively and based on numerical differences. Patients treated with QMF experienced fewer exacerbations overall, and fewer severe exacerbations, than patients treated with the corresponding dose of MF. In addition, less than [redacted] of patients in any treatment group across the two trials experienced an exacerbation requiring hospitalization or permanently discontinued the study drug. The annualized rate of all asthma exacerbations was also reported in both studies, and the annualized rate of severe exacerbations was reported in PALLADIUM. The rate of all exacerbations was lower in all of the QMF treatment groups compared to the corresponding MF treatment groups. Similar results were observed for the annualized rate of severe exacerbations in the high-dose treatment groups. Regarding the medium-dose treatment groups, the rate of severe asthma exacerbations in the QMF treatment group was approximately half that of the MF treatment group (rate ratio = 0.46; 95% CI, 0.31 to 0.67; P < 0.001). A difference in exacerbations was not observed between high-dose QMF and S/F 50 mcg/500 mcg. An MID has not been identified for the reduction in asthma exacerbations; however, the impact of an exacerbation on quality of life and the capacity to be life threatening makes any reduction in exacerbations clinically relevant.[65] QMF appears to offer benefit compared to MF alone and comparable benefit to another ICS/LABA, S/F 50 mcg/500 mcg, in terms of exacerbations. However, the results are likely subject to a certain degree of uncertainty due to a lack of statistical testing or control for multiplicity for the between-group comparisons of rates of asthma exacerbations. Further, the results of the low-dose comparison (QMF 150 mcg/80 mcg versus MF 200 mcg) are based on 12 weeks of therapy, which is an insufficient duration to properly assess the efficacy of a treatment for a disease that requires lifelong treatment and has seasonal effects.

A variety of measures of pulmonary function were reported in the two pivotal 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/minute) during the treatment period, were reported for this review. The primary outcome in QUARTZ and PALLADIUM was trough FEV_1 after 12 weeks and 26 weeks of treatment, respectively, and superiority of QMF compared to corresponding doses of MF was demonstrated at all dose strengths.

NI was demonstrated (pre-specified NI margin of 0.090 L) for the comparison of high-dose QMF to S/F 50 mcg/500 mcg in PALLADIUM. The value used for the NI margin was not clearly based on typical methods used to define the margin a priori. In the sponsor's submission to Health Canada, it was noted that:

> There is no published literature on a clinically relevant NI margin for an ICS in asthma and the approach taken is to use a non-inferiority margin of 0.090 L. This figure represents one-third of the conservative estimated effect size (0.270 L). In addition the

baseline assumption was that there was no difference i.e., 0 L, in the effect of MF delivered *via* Breezhaler and Twisthaler. Standard deviation was estimated to be 0.250 L in this population.[34]

So, the NI margin was established as approximately one-third of the effect size of MF (> 0.270 L). As noted previously, the sponsor pooled data from three trials of fluticasone furoate/vilanterol (Breo Ellipta) versus placebo to estimate the treatment effect for deriving the NI margin. There are several unreported aspects of this analysis that make it difficult to assess it fully. It was not reported whether a systematic literature search was conducted or how the three trials were selected for meta-analysis. The statistical approaches to pooling data were not described, nor were assessments of heterogeneity reported. Therefore, the validity of the approach to the meta-analysis and how exactly it was used to determine the NI margin is unclear. It is accurate that there is a lack of data establishing what the NI margin should be in these types of trials. Given the lack of an established standard of care against which to standardize and the level of heterogeneity in the evidence as highlighted in the ITC feasibility analysis, the standard approach to conducting a full systematic review and meta-analysis may not have been suitable in this instance to calculate the NI margin. Another common approach is to define the NI margin as 50% of the MID. There is no formal MID defined for between-group comparisons related to the change from baseline in trough FEV_1. The MID for the within-group change is often reported as between 0.200 L and 0.230 L, and the clinical expert consulted by CADTH suggested that 0.230 L is the minimum perceivable change for patients and that in more severe asthma (lower baseline FEV_1 or a greater extent of airway hyperresponsiveness), the perception of change in FEV_1 becomes weaker. Nonetheless, agencies (both regulatory and health technology assessment agencies) will use this value to help judge the clinical significance of between-group differences in the absence of a defined MID. If such an approach was used here, then the NI margin is less than half of this MID. Therefore, the NI margin used is likely to be sufficiently conservative. Health Canada likewise accepted the NI margin.[34]

The treatment effect observed with FEV_1 was consistent in terms of FVC and mean morning and evening PEF at the end of treatment in both studies. 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 a MID of 25 L/minute[66, 67] for all QMF groups. 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 two months,[2] which makes the 12-week QUARTZ trial a sufficient duration for this particular outcome. The limited clinical relevance of FEV_1 was relayed by the clinical expert consulted for this review as well. Overall, QMF demonstrated efficacy in terms of lung function; however, the applicability of the results to long-term use of a controller therapy is limited.

HRQoL was identified as an outcome that is important to patients and was evaluated in both of the trials using the AQLQ and, in PALLADIUM, the EQ-5D-5L as well. At the end of treatment (week 12 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 two trials and more than half of the patients in every treatment group reported an improvement of 0.5 or more in the overall score. The change from baseline in the scores for each of the domains of the AQLQ was consistent with the overall score. The LS mean (SE)

change from baseline was greater in the QMF treatment groups compared to MF treatment groups for the overall score and domain scores for both the low-dose and medium-dose comparisons, whereas the treatment group differences for the high-dose comparison to MF and S/F 50 mcg/500 mcg were less than 0.10 points. The EQ-5D-5L results were reported descriptively; they were also reported categorically based on the five levels of the five dimensions and as a change from baseline in the VAS. In summary, the results suggest that the use of QMF is associated with an improved HRQoL; however, no conclusions can be drawn regarding between-group comparisons in HRQoL due to a lack of statistical testing (EQ-5D-5L) or absence of control for multiplicity (AQLQ).

Asthma control, measured by the change from baseline in the ACQ-7, was included as the key secondary outcome in both QUARTZ at week 12 and PALLADIUM at week 26. The ACQ-7 is a multi-dimensional, patient-reported (to clinic staff) questionnaire that is one of the most commonly used instruments for measuring asthma control in clinical trials and specialist clinical practice settings.[46, 47] The treatment difference (at week 12 in QUARTZ and at week 26 and week 52 in PALLADIUM) between QMF and MF for the change from baseline in the ACQ-7 was in favour of QMF at all dose strengths (P [redacted]). Moreover, the LS mean change from baseline was clinically meaningful for all treatment groups based on the MID; therefore, QMF demonstrated superiority to MF in terms of asthma control based on the ACQ-7 at week 12 in QUARTZ and week 26 in PALLADIUM. In addition, the absolute difference in proportion of patients with a clinically meaningful improvement in the ACQ-7, based on the MID of 0.5 points,[47, 49] was [redacted] and [redacted] for the low-dose, medium-dose, and high-dose comparisons of QMF versus MF, respectively. (Note, the medium dose and high dose were measured at week 52.) There was no difference in ACQ-7 outcomes between high-dose QMF and S/F 50 mcg/500 mcg. Rescue medication use is another way of assessing asthma control,[2, 10] which was reported in both of the trials. All treatment groups reported a reduction in the mean daily number of puffs of rescue medication used over the course of the treatment period, with a numerically greater change reported for the QMF treatment groups than the corresponding MF treatment groups (treatment group differences ranged from –0.23 to –0.28). The percentage of rescue medication-free days increased by a mean (SE) ranging from 14.1% (1.80) to 33.1% (1.55), which corresponded to a clinically meaningful difference based on an MID of 8.4% to 15.6%.[51] Again, the change from baseline was greater among the QMF treatment groups compared to MF. Further, the results for the other outcomes described were similar for the high-dose QMF treatment group and ICS/LABA comparator, S/F 50 mcg/500 mcg. Overall, the trials demonstrated that QMF performed better than MF alone in terms of the ACQ-7 and performed similarly to another ICS/LABA product, S/F 50 mcg/500 mcg, in patients who were previously uncontrolled on treatment with ICS alone, or a low-dose ICS/LABA (PALLADIUM).The results for the other measures of asthma control were consistent with the results of the key secondary outcome. The duration of QUARTZ is also a limitation of the assessment of QMF 150 mcg/80 mcg, for the same reasons as previously described.

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 the percentage of nights without night-time awakenings were derived from a patient-reported e-diary and were consistent with the other efficacy outcomes that have been discussed. Namely, the increase in the percentage of nights without awakenings was greater in the QMF treatment groups compared to the corresponding MF treatment groups and the high-dose QMF was similar to S/F 50 mcg/500 mcg. With regard to asthma- or asthma exacerbation-related health care utilization, descriptive results reported few patients with outpatient visits to the ED or hospital [redacted]

and [redacted] of patients in any treatment group in QUARTZ and PALLADIUM, respectively) and less than [redacted] in any treatment group were hospitalized; outpatient visits to any facility type occurred in a smaller proportion of patients in the QMF groups compared to MF groups. Work time missed due to asthma problems was derived from the WPAI, which was only included as an outcome in PALLADIUM. There was virtually no change in the percentage of work time missed due to asthma problems in any treatment group and baseline values for this outcome were low to begin with, ranging from [redacted] to [redacted].

The results that have been discussed demonstrate that QMF provides additional benefit compared to MF alone and is no worse in terms of efficacy than another commonly used ICS/LABA, S/F 50/500 mcg, at the high-dose strength. However, evidence of efficacy beyond 12 weeks of treatment was not available for QMF 150 mcg/80 mcg, which has limited generalizability to a controller therapy for asthma that would be used long-term. The available evidence for the review of QMF is also limited to comparisons to the ICS component of QMF alone, and one ICS/LABA for the high-dose QMF only. A wide variety of treatments for asthma are currently available and the lack of direct comparisons or absence of indirect comparisons to available products (as a fixed-dose combination or loose combination) is a considerable gap in the evidence, particularly for the low dose and medium dose of QMF. The clinical expert consulted for this review also noted that there are currently many inhalers in Canada that address the same need as QMF, but that fluticasone furoate/vilanterol (Breo Ellipta) is the only other once-daily ICS/LABA formulation. However, the clinical expert also shared that simplified inhaler regimens may improve adherence to ICS use and thus improve asthma control, but there is little good-quality evidence to support this contention.[26] Therefore, the lack of comparative evidence is still a considerable limitation for this review.

Lastly, QUARTZ and PALLADIUM did not include efficacy outcomes related to dyspnea, days of missed school (or work for QUARTZ), or exercise tolerance, all of which were noted as important to patients based on the patient input for this review. Further, adherence to treatment regimens and ease of use of the Breezhaler device were not evaluated in either of the two studies. As the efficacy of inhaled treatment is dependent on correctly using the inhalers, which is a common issue for patients, the absence of data in the pivotal trials regarding this issue is a notable gap in the evidence. To address this gap, CADTH completed a supplemental literature search for studies that assessed asthma patient preferences for the Breezhaler device relative to comparator devices. This has been summarized in Appendix 5. Three studies were identified that evaluated the use of the Breezhaler as well as the Genuair, Handihaler, Respimat, Turbuhaler, Diskus, Atrovent, and Breo Ellipta. Briefly, the Breezhaler device was the device least preferred by patients, and the one for which patients required the most instruction and made the most attempts to prepare correctly. In addition, a sponsor-submitted observational study was reviewed in which the Breezhaler had the greatest proportion of patients making no critical errors at 36.5% (95% CI, 33.3 to 39.7) compared to Diskus, Handihaler, pressurized MDI, Respimat, and 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. While adherence was generally high for all treatment groups in both QUARTZ and PALLADIUM, 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

Between 32.3% and 38.3% of patients in QUARTZ and 64.6% and 72.2% of patients in PALLADIUM reported at least one AE. It is unclear whether the difference in AEs is due to the lower dose strengths used in QUARTZ, the shorter treatment period, or both. Numerically, a smaller proportion of patients in the QMF treatment groups reported AEs compared to MF and, like the efficacy results, AEs in the S/F 50 mcg/500 mcg group were numerically similar to QMF 150 mcg/320 mcg. Asthma was the most commonly reported AE in both studies. It occurred in between [redacted] and [redacted] more patients in MF treatment groups relative to the corresponding QMF treatment groups. AEs due to asthma were reported by 25.5% of patients in the QMF 150 mcg/320 mcg treatment group and 30.9% of patients in the S/F 50 mcg/500 mcg treatment group.

Few SAEs were reported in the two studies (< 2% in QUARTZ and ≤ 8% in PALLADIUM, in any treatment group). The most common SAE was asthma as well, although it was only reported by two patients in QUARTZ (one per treatment group) and between two and eight patients per treatment group in PALLADIUM. WDAEs were also infrequent, occurring in [redacted] of patients in any treatment group across the two studies, and [redacted] of patients in the low-dose and medium-dose QMF treatment groups. One death was reported overall; it occurred in a patient in the MF 400 mcg treatment group and was due to an asthma exacerbation.

Infections (systemic and local), steroid effects (topical, systemic), growth rates (12 to < 18 year age group), cardiovascular events, hypothalamic-pituitary-adrenal axis suppression, bone markers, and blood sugar levels were included as notable harms in the CADTH review protocol. Infections were reported by the greatest proportion of patients, although the most commonly reported infections were due to nasopharyngitis, URTI, and bronchitis, which are typically commonly reported in clinical trials. Cardiac and vascular disorders were the second most commonly reported AEs of the notable harms, occurring in between 4.3% and 7.8% of patients in PALLADIUM and fewer than 1% of patients in QUARTZ; hypertension was the most common reason in both studies.

Overall, no major safety signals were detected with the exception of asthma-related AEs, which may suggest patients were undertreated. The duration of the QUARTZ study was insufficient to draw conclusions about the long-term safety of QMF 150 mcg/80 mcg and long-term safety studies were not identified for this dose strength. Evidence beyond 52 weeks of treatment was only available for the high-dose QMF through one long-term safety study, Study 1305. Study 1305 was an open-label, single-arm, 52-week study designed to assess the safety and tolerability of QMF 150 mcg/320 mcg in Japanese patients with inadequately controlled asthma (N = 51). Tolerability of the treatment over the 52-week period was demonstrated, although the results are limited by the study design subject to bias due to the absence of blinding and the lack of a comparator, as well as the applicability to the Canadian context based on the patient population. No evidence of ITCs that evaluated safety of QMF were identified either.

Conclusions

QUARTZ and PALLADIUM demonstrated superiority of QMF compared to corresponding doses of MF for the change from baseline in trough FEV_1 after 12 weeks and 26 weeks of treatment, respectively. NI was met for the comparison of high-dose QMF to S/F 50 mcg/500 mcg on the change from baseline in trough FEV_1. In terms of asthma control based on the ACQ-7, the treatment difference between QMF and MF was in favour of QMF at all dose strengths in both trials. Outcomes related to asthma exacerbations, rescue medication use, and HRQoL were all important to clinicians and patients and the results from the two trials were aligned with the results of the primary and key secondary analyses. However, these outcomes are subject to uncertainty due to a lack of statistical testing or control for multiplicity. Nocturnal awakening, days of missed work, and health care utilization-related outcomes were also reported.

SAEs and WDAEs were reported infrequently in all treatment groups. One death was reported overall; it occurred in a patient in the MF 400 mcg treatment group and was due to an asthma exacerbation. No new safety signals were identified in the 52-week open-label safety extension study.

Appendix 1: Literature Search Strategy

Clinical Literature Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946-present) Embase (1974-present) **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 qab 149* or qab149* or Onbrez or Arcapta or Hirobriz or Onbrize or Oslif or 8OR09251MQ or 2JEC1ITX7R).ti,ab,kf,ot,rn,nm,hw.
2	mometasone furoate/
3	(mometasone or mometason* or 94andomi or danitin or ecural or elocon or elocone or elomet or flumeta or LAS 41002 or LAS41002 or monovo or 94andomi 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 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 Atectura* or qmf 149* or qmf149*).ti,ab,kf,ot,rn,nm,hw.
7	5 or 6
8	7 use 94ando
9	*indacaterol/
10	(indacaterol or qab 149* or qab149* or Onbrez or Arcapta or Hirobriz or Onbrize or Oslif).ti,ab,kw,dq.
11	9 or 10
12	*mometasone furoate/
13	(mometasone or mometason* or 94andomi or danitin or ecural or elocon or elocone or elomet or flumeta or LAS 41002 or LAS41002 or monovo or 94andomi 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.
14	12 or 13
15	11 and 14
16	*indacaterol plus mometasone furoate/
17	(indacaterol plus mometasone furoate or Atectura* or qmf 149* or qmf149*).ti,ab,kw,dq.
18	16 or 17
19	15 or 18 .
20	19 use oemezd
21	20 not (conference review or conference abstract).pt.
22	8 or 21
23	remove duplicates from 22

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 QMF149 OR QMF 149 OR Atectura	

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 QMF149 OR QMF 149 OR Atectura
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* 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
D'Andrea P, Kornmann O, Mucsi J, Kato M, Bandelli L, Sen B. Efficacy and safety of once-daily low-dose indacaterol/mometasone via Breezhaler® in symptomatic adult and adolescent patients with inadequately controlled asthma: Phase III 96andomized QUARTZ study findings. ERS 2019 Abstract RCT3780.	Conference abstract
Van Zyl-Smit R, Krüll M, Gessner C, Gon Y, Richard A, de los Reyes A, Shu X, Pethe A, D'Andrea P. Efficacy and long-term safety of QMF149 (indacaterol acetate/mometasone furoate) versus mometasone furoate and versus salmeterol xinafoate/fluticasone propionate in patients with inadequately-controlled asthma: The PALLADIUM study. BTS 2019 Abstract P224.	Conference abstract
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
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
Kornmann O, Mucsi J, Kolosa N, et al. Efficacy and safety of inhaled once-daily low-dose indacaterol acetate/mometasone furoate in patients with inadequately controlled asthma: Phase III 96andomized QUARTZ study findings. Respir Med. 2020 01;161:105809. PubMed: PM32056721	Duplicate (submitted by sponsor and included in the clinical literature search)

Appendix 3: Detailed Outcome Data

None.

Appendix 4: Description and Appraisal of Outcome Measures

Aim

To describe the following outcome measures summarized in Table 35 and review their measurement properties, including validity, reliability, responsiveness to change, and MID.

Table 35: Outcome Measures Included in Each Study

Outcome measure	QUARTZ study	PALLADIUM study
FEV_1	Primary or other secondary	Primary or other secondary
FVC	Other secondary	Other secondary
PEF	Other secondary	Other secondary
AQLQ-S+12	Other secondary	Other secondary
EQ-5D-5L	NR	Exploratory
ACQ-7	Secondary or other secondary	Secondary or other secondary
Patient Asthma Control e-Diary	Other secondary	Other secondary
WPAI: Asthma	NR	Exploratory

ACQ-7 = Asthma Control Questionnaire (seven items); AQLQ-S+12 = Asthma Quality of Life Questionnaire for 12 years and older; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; NR = not reported; PEF = peak expiratory flow; WPAI = Work Productivity and Activity Impairment.

Source: Clinical Study Reports for the QUARTZ[5] and PALLADIUM[6] studies.

Findings

Table 36: 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 one 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 ACQ, the EQ VAS, and the Juniper AQLQ) support the presence of construct validity of the FEV_1.[69-72] **Reliability:** FEV_1 values demonstrated high within-session repeatability, with 90% of 18,526 patients able to reproduce FEV_1 within 120 mL.[73] **Responsiveness:** Weak correlations of change in % of predicted FEV_1 with patient-reported symptom-free days (r = 0.26) and moderate correlations with the change in AQLQ overall score	The MPPI for FEV_1 is 230 mL or a 10.38% change from baseline.[36]

Outcome measure	Type	Conclusions about measurement properties	MID
		(r = 0.38) support the presence of responsiveness.[69]	
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.[74] No evidence was identified regarding the reliability or the responsiveness of the PEF.	An MID of 25 L/minute has been used in clinical trials previously.[67,68] The MPPI for PEF was 18.8 L/minute or a 5.39% change from baseline. In patients with acute asthma exacerbations presenting to the ED, a % of predicted PEF of 12% has been identified as the MID.[75]
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.
AQLQ-S+12	AQLQ-S+12 is a patient-reported questionnaire for assessing problems experienced by patients with asthma in their daily lives.	**Validity:** Cross-sectional and longitudinal construct validity was evaluated in 2,433 patients and showed weak to moderate correlations with other measures of clinical status, such as % of predicted FEV_1, PEF, symptoms, night waking, and amount of rescue medication.[42] When the AQLQ-S+12 was correlated with the baseline ACQ score, and daytime and night-time symptoms, there was moderate to strong evidence of construct and known-groups validity.[43] **Reliability:** High internal consistency reliability (Cronbach's alpha 0.96 and 0.97) in a post-hoc analysis of 2 phase III clinical trials.[76] Test-retest reliability was demonstrated (ICC of 0.86 and 0.83) in a pooled analysis of 2 studies.[43] **Responsiveness:** Responsiveness was demonstrated in a pooled analysis of 2 studies when the change in AQLQ-S+12 correlated with the change in ACQ.[43]	There is no evidence regarding the MID for the AQLQ-S+12; however, given the significant overlap between the AQLQ-S+12 and the AQLQ, researchers consider a cut point of 0.5 points to be clinically meaningful.[42-44]
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,[77] but was not present when PEF values were used to classify patients into categories of	There was no MID established in a population of patients with asthma.

Outcome measure	Type	Conclusions about measurement properties	MID
		varying asthma severity.[78] Convergent validity was established through moderate to strong Spearman rank correlations with the Asthma Quality of Life Utility Index.[78] **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.[78]	There is an MID of 0.056 for general use in the Canadian population.[79]
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 • night-time awakening/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.[44,49,58] Known-groups validity was established by significantly different ($P < 0.001$) ACQ-7 scores in patient groups split by the presence of and lack of night-time awakenings and rescue medication use.[44] **Reliability:** Test-retest and internal consistency reliability was adequate with ICC > 0.7 and Cronbach's alpha > 0.7 in 3 independent publications.[44,49,58] **Responsiveness:** The ACQ-7 was able to distinguish between adults with stable and unstable asthma in 2 independent publications ($P < 0.001$).[49, 58]	The ACQ MID has been well established and accepted as 0.5 points for within-person change.[48,50]
Patient Asthma Control e-Diary	This is an electronic diary 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 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]	No MID was identified for the Patient Asthma Control e-Dairy.
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 rank correlations: the WPAI demonstrated a week correlation with FEV_1 % predicted, a strong correlation with the Asthma Therapy Assessment Questionnaire, and a strong correlation with the AQLQ score.[57]	No MID was identified for the WPAI: Asthma questionnaire.

Outcome measure	Type	Conclusions about measurement properties	MID
		No evidence regarding the reliability and responsiveness of the WPAI: Asthma questionnaire was identified.	

ACQ = Asthma Control Questionnaire; ACQ-5 = Asthma Control Questionnaire (five items); ACQ-7 = Asthma Control Questionnaire (seven items); AQLQ = Asthma Quality of Life Questionnaire; AQLQ-S+12 = Asthma Quality of Life Questionnaire for 12 years and older; EMA = European Medicines Agency; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels; EQ VAS = EuroQol Visual Analogue Scale; ED = emergency department; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; ICC = intraclass correlation coefficient; MID = minimal important difference; MPPI = minimal patient perceivable improvement; PEF = peak expiratory flow; SABA = short-acting $beta_2$-agonist; WPAI = Work Productivity and Activity Impairment.

Source: Carranza et al. (2004),[69] Voorend-van et al. (2014),[70] Ehrs and Larsson (2001),[71] Moy et al. (2001),[72] Enright and Sherrill (2004),[73] Santanello et al. (1999),[36] Ulrik and Backer (2005),[74] Drazen et al. (1996),[67] Boushey et al. (2005),[68] Karras et al. (2000),[75] Juniper et al. (2005),[42] Wyrwich et al. (2011),[43] Wyrwich et al. (2011),[44] Hernandez et al. (2016),[77] Crossman-Barnes et al. (2020),[78] McClure et al. (2017),[79] Juniper et al. (2004),[49] Juniper et al. (1999),[58] Barnes et al. (2014),[48] Jia et al. (2013),[50] and EMA guidelines (2015).[7]

Forced Expiratory Volume in One Second

FEV_1 is the maximal amount of air forcefully exhaled in one second. The measured volume can be converted to a percentage of predicted normal value, which is adjusted based on height, weight, and race. The percentage of predicted FEV_1 is one of the most commonly reported pulmonary function tests.[80] Moreover, trough FEV_1 and pre-dose FEV_1 are also used as clinical measures of lung function, where trough FEV_1 is defined as the mean of the two 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 is defined as the mean of the two FEV_1 values measured at 45 minutes and 15 minutes prior to the evening dose.[81,82] 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.[83,84] 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.[69-72] Conversely, FEV_1 values appear to correlate well with certain clinical outcomes, such as the likelihood of hospitalization in adults.[85] Furthermore, FEV_1 values demonstrated high within-session repeatability. In a study of 18,526 adult patients, of whom 11% gave a history of physician-diagnosed asthma, 90% were able to reproduce FEV_1 within 120 mL.[73] Moreover, responsiveness of the FEV_1 has been demonstrated through weak correlations of change in percentage of predicted FEV_1 with patient-reported symptom-free days ($r = 0.26$) and moderate correlations with the change in AQLQ overall score ($r = 0.38$).[69]

There appears to be limited published evidence relating to an MID for FEV_1 among adult patients with asthma. In one 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.[36] 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.[36]

Peak Expiratory Flow

PEF, sometimes referred to as PEF rate, is defined as "the maximum flow achieved during an expiration delivered with maximal force starting from the level of maximal lung inflation."[37] Electronic peak flow metres automatically store and download measurements as needed, circumventing the need for patients to manually record PEF values in diaries. PEF is usually expressed in units of L per minute and sometimes as a percentage of the predicted normal value or as a change from baseline average values.[86] 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.[87] PEF values also appear to be a valid clinical marker of airway responsiveness and asthma severity.[86] In addition, they seem to correlate well with other measures of lung function, including FEV_1 in adolescents and young adults aged 13 to 23,[74] although evidence that directly links PEF with quality of life is lacking. Some trialists have used a value of 25 L/minute as an MID for PEF values among patients with asthma.[67,68] However, no research seems to support the use of this MID. In one study of 281 adult patients with mild to moderate asthma symptoms, researchers calculated the MPPI for PEF as the mean change in PEF in patients rating themselves as "a little better" (n = 86) on the global rating of change in asthma. The MPPI for PEF was 18.8 L/minute, or a 5.39% change from baseline, with no differences in MPPI values by gender or age.[36] In another study, researchers noted a predicted PEF of about 12% to be a minimal clinically significant improvement among patients presenting to the ED with acute asthma exacerbation.[75]

Forced Vital Capacity

FVC is the amount of air that can be forcibly exhaled from the lungs after taking the deepest breath possible as measured by spirometry. 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, the use of FVC in clinical trials may be limited by evidence that evaluated 6,323 adults who had never smoked, ages 20 to 24, from 42 study centres around the world. In this study, Chinn et al. (2006) 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.[88]

Asthma Quality of Life Questionnaire for 12 Years and Older

The AQLQ-S+12 is a patient-reported, disease-specific, HRQoL measure that is a variant of the validated standardized version of the AQLQ developed by Juniper et al.[89] To accommodate the larger group of patients with asthma in whom the instrument is intended to be used (i.e., those 12 years and older versus adults only), the developers of the AQLQ altered one question about "work-related limitations" to "work-/school-related limitations."[42] As with the original questionnaire, the AQLQ-S+12 includes 32 questions grouped into four domains: symptoms, activity limitations, emotional function, and environmental stimuli. Each question is scored on a seven-point scale ranging from 7 (no impairment) to 1 (severe impairment). The overall score is derived from the mean of the 32 questions, and therefore also ranges from 1 to 7, with higher scores indicating less severe impairment. Further, the questionnaire may be reported by domain, which would include the mean of the scores for the questions corresponding to the domain of interest.[90] Patients score each item based on a recall of their experiences during the previous two weeks. It should be noted that the EMA

recommends the use of patient-reported outcomes that assess HRQoL, such as the validated AQLQ.[7]

A post-hoc analysis of data collected from two phase III studies including asthma patients aged 12 and older was used to assess the validity of the AQLQ-S+12.[76] Overall, the AQLQ-S+12 showed high internal consistency reliability at baseline based on a Cronbach's alpha of 0.96 and 0.97 for the overall score of each of the two studies, respectively.[43,76] The internal consistency reliability for the subscales also ranged from 0.84 to 0.94. [43,76] Evidence of construct validity of the AQLQ-S+12 was generated in a secondary analysis of two clinical trials that included 2,433 patients with asthma. The baseline mean FEV_1 percentage predicted (range) was 18 years and older = 75.4 (32 to 136) and 73.3 (41 to 107), and 12 to 17 years = 83.9 (47 to 125) and 77.8 (54 to 114) in trials 1 and 2, respectively.[42] The cross-sectional (baseline) and longitudinal (baseline to end of study) construct validity between AQLQ-S+12 and other measures of asthma clinical status — including FEV_1 percentage of predicted value, PEF, symptoms, night waking, and amount of rescue medication — was variable, with Pearson correlation coefficients indicating none to moderate associations. In a subsequent pooled analysis conducted by another group of researchers, however, the AQLQ-S+12 demonstrated excellent overall test-retest reliability (intraclass correlation coefficients [ICCs] of 0.86 in one study and 0.83 in the other), moderate to strong construct validity with other indices of asthma (i.e., baseline ACQ score and mean daytime and night-time symptom diary scale scores), strong known-groups validity, and excellent responsiveness.[43] No study appears to have formally estimated the MID for AQLQ-S+12, although given the significant overlap between the AQLQ-S+12 and the original AQLQ-S (AQLQ done in Sydney [S], Australia), researchers consider a cut point of 0.5 to indicate a clinically important difference, since this is the MID for the Sydney AQLQ.[42-44]

EuroQol 5-Dimensions 5-Levels Questionnaire

EQ-5D is a generic quality-of-life instrument developed by the EuroQol Group.[45] It may be applied to a wide range of health conditions and treatments.[45] 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 to this purpose, the EQ-5D is used in clinical trials to obtain utility weights for economic models.[46] The EQ-5D-5L consists of the EQ-5D descriptive system and the EQ VAS. The descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each of these five dimensions has five levels: a level 1 response represents "no problems," a level 2 response represents "slight problems," a level 3 response represents "moderate problems," a level 4 response represents "severe problems," and a level 5 response represents "extreme problems" or "unable to perform," which is the worst response in the dimension. Respondents are asked to choose the level that reflects their health state for each of the five dimensions. In total, there are 3,125 possible unique health states defined by the EQ-5D-5L, with the values of 11111 and 55555 representing the best and worst health states. The numerical values assigned to levels 1 to 5 for each dimension reflect rank order categories of function. In terms of measurement properties, these are ordinal data; they do not have interval properties and therefore should not be summed or averaged to, for example, produce an individual dimension "score." Results from the EQ-5D-5L descriptive system can be converted into a single index score using a scoring algorithm that takes the local patient and population preferences into account. Therefore, the index score is a country-specific value and a major feature of the EQ-5D instrument.[46] The range of index scores will differ according to the scoring algorithm

used; however, in all scoring algorithms of the EQ-5D-5L, a score of 0 represents the health state "dead" and 1.0 reflects "perfect health." Negative scores are also possible for those health states that society (not the individual patient) considers to be "worse than dead."

The EQ VAS records the respondent's self-rated health on a vertical VAS where 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 EQ VAS scores can be summarized and analyzed as continuous data.[45,46] Hence, the EQ-5D produces three types of data for each respondent:

- a profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11,121 or 21,143
- a population preference-weighted health index score based on the descriptive system
- a self-reported assessment of health status based on the EQ VAS.

The EQ-5D-5L has been validated in terms of feasibility, ceiling effects, discriminatory power, and convergent validity in a diverse patient population from six countries with chronic conditions (including patients with asthma or COPD).[45] MID estimates for the index score in the general Canadian population were generated by simulating the effects of single-level transitions in each dimension.[79] 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).[79] In a European cohort of 316 patients with asthma aged 12 to 40 years, construct validity was established using the known-groups method in groups with good, intermediate, and bad asthma control defined by the ACQ-5.[77] The EQ-5D-5L index score was significantly different between the groups with good control (mean [95% CI] = 0.91 [0.89 to 0.93]), intermediate control (mean [95% CI] = 0.84 [0.81 to 0.87]), and poor control (mean [95% CI] = 0.73 [0.69 to 0.78]).[77] Convergent validity was established in a prospective observational cohort study (N = 121) with asthma patients. The EQ-5D-5L displayed moderate to strong Spearman's rank correlations with the Asthma Quality of Life Utility Index. Within the same study, there was no evidence of known-groups validity identified when patients were classified in categories of asthma severity based on PEF values.[78] When the authors evaluated responsiveness by asking patients "*Compared to your asthma state when you were in hospital approximately four weeks ago, how would you rate your asthma now?*", the EQ-5D-5L displayed large standardized response means for the good and poor groups (0.95 and –1.03, respectively), and 0.75 for the very good, and 0.303 for the moderate response options.[78] No information was found on the reliability or MID of the EQ-5D-5L in an asthma population.

Asthma Control Questionnaire-7

The ACQ was developed in order to evaluate asthma control in patients with asthma and is one of the most commonly used instruments measuring asthma control.[47,48] The questionnaire has several iterations, one of which comprises seven questions, the responses of which are scored on a seven-point scale. (The questionnaire with seven items is abbreviated as ACQ-7.) Questions regarding six 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.[47] In addition, the seventh item includes calculations performed by clinical staff with regard to pre-bronchodilator FEV_1 or PEF (percentage predicted).[47,48] The ACQ score is calculated as the mean of the seven questions (as all questions are equally weighted), with

scores at 0 meaning the patient has asthma that is well controlled and those at 6 meaning the patient has asthma that is extremely poorly controlled.[47-49] The ACQ is used extensively in clinical trials to measure clinically meaningful change in asthma control.[48]

Validity

Evidence for longitudinal and cross-sectional construct validity has been observed by correlations between the ACQ and other asthma health status measures in two separate studies.[49,58] The ACQ showed variable evidence for presence of construct validity in patients with persistent asthma aged 12 years or older (r = –0.77), with a strong Pearson correlation coefficient for the AQLQ-S+12, strong correlation with shortened versions of the ACQ (r > 0.9), and weak correlation with the PEF in the morning or evening (r = –0.16 and r = –0.15, respectively).[44] In the same study, the ACQ scores were significantly different (P < 0.001) between four pre-established patient groups (those with night-time awakenings compared to those with no night-time awakenings, those with daytime use of SABAs compared to those with no daytime SABA use, those with night-time SABA use compared to those with no night-time SABA use, and those with any use of SABAs compared to those with no SABA use). The scores indicated that the ACQ is able to distinguish between clinical groups with different levels of asthma severity and, thus, the presence of known-groups validity.[44]

Reliability

The ACQ is a multi-dimensional and standardized tool[50] that has high test-retest reliability in three separate publications. In two studies published by Juniper et al. (1999 and 2004), the authors reported an ICC of 0.90 in both studies.[58, 49] Furthermore, test-retest (ICC > 0.7) and internal consistency (Cronbach's alpha > 0.7) reliability was present (ICC > 0.7) when patients aged 12 years or older with stable persistent asthma were evaluated four weeks apart in two clinical trials.[44]

Responsiveness

Responsiveness of the ACQ has been evaluated in a number of studies.[44,49,58] Overall, the ACQ was very responsive to change in studies published by Juniper et al. (2004 and 1999), as the ACQ scores were significantly different (P < 0.001*)* between adults with stable and unstable asthma .[49, 58] To evaluate the responsiveness of the ACQ in patients aged 12 years or older, the change in ACQ score from baseline to 26 weeks was presented with a Pearson correlation coefficient to the change in AQLQ-S+12 and the percentage of predicted FEV_1 in two separate clinical trials. Responders were identified with the previously established ACQ cut point of 1.0 to distinguish between "well-controlled" versus "not well-controlled" asthma.[76] Overall, the change in ACQ correlated well with the change in the AQLQ-S+12 (Pearson correlation coefficient = 0.74 to 0.78), but did not correlate with the change in percentage of predicted FEV_1 (Pearson correlation coefficient = 0.01 to 0.03).[44]

Clinical Relevance

The ACQ MID has been well established and accepted as 0.5 points for within-person change.[48,50] However, Bateman et al. questioned its use as a measure between groups or between patients, further speculating that patient-reported outcomes should be presented as a responder rate comparison or a net-treatment benefit analysis.[91] In addition, a score of 1.5 on the ACQ is the most appropriate discriminator for "well-controlled" and " not well-controlled" asthma patients.[51]

Additional Information

There is also evidence of the construct validity, test-retest reliability, and responsiveness of the ACQ in children with asthma who are aged six to 16.[92]

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 six items and the evening questions consist of 11 items, displayed in Table 37. No evidence regarding the validity, reliability, responsiveness, or the MID of the Patient Asthma Control e-Diary was identified. However, a patient record of daytime and night-time symptoms with an electronic diary is considered desirable for the clinical investigation of the treatment of asthma, according to the EMA.[7]

Table 37: 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?	Hours: Minutes
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; 3 = I awoke more than 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; 4 = very severe
Number of puffs of rescue medication during the past 12 hours	0 to 50 puff(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?	Hours: Minutes
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

Weekly morning questions	Possible answers
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 to 50 puff(s)

Work Productivity and Activity Impairment Questionnaire: Asthma

The WPAI questionnaire is a self-report instrument used to measure the impact of general health and symptom severity on work and on daily activities over the previous seven days.[53-55] 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.[93] The WPAI: Asthma is the asthma-specific version of the questionnaire. The WPAI: Asthma is composed of nine items that assess impairment in three domains: work, school, and activity.[56, 53,57] Scores range from 0% to 100%, where a higher score indicates greater impairment.[53,57]

The 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.[57] However, this version of the WPAI calculates work absenteeism without asking about work missed due to other reasons.[57] 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 percentage 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).[57]

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.[12,94,95] The efficacy of inhaled treatment is partly dependent on the correct use of inhalers, 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, especially if multiple inhalers are being used.[96,97] This issue is reflected in multiple studies that have assessed patient preferences for attributes of inhalers; studies 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.[94,98,99] Of the many types of inhalers, pressurized MDIs and dry powder inhalers are most commonly used for the treatment of asthma.[12,94,100]

The product under review is QMF administered via the Breezhaler, which is an inhalation-driven, single-dose dry powder inhaler with active ingredients dispersed in a lactose monohydrate excipient.[101]

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. The following describes the studies identified, in addition to one 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); the study assessed patients' usability and preference of the Breezhaler, Genuair, and Handihaler devices via the Handling Questionnaire, a validated questionnaire used to assess the determinants of choice and patient usability of inhaler devices in diseases of airflow limitation. Patients were divided into three groups. One group (n = 127) tested all three devices, another (n = 110) compared the Breezhaler and the Genuair, and the last group (n = 96) tested the Breezhaler and the Handihaler devices. The Handling Questionnaire was administered to all three groups. Within this study, a nurse demonstrated the functioning of the device, after which patients described their first impressions of the device. 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 three devices, approximately 50% preferred the Genuair, with only 5% saying they preferred the Breezhaler. The Breezhaler was 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 five minutes (SD = 0.4 minutes) for the

Genuair and six minutes (SD = 0.5 minutes) for the Handihaler. This included the nurse's explanation and the maneuvres the patient had to perform to prepare the device. Patient age was a contributing factor where older patients needed more attempts to perform the first proper inhalation and more time to learn how to use the device; their success rate was lower. The Breezhaler device was the least favourite of the three evaluated even when an asthma-only subgroup was analyzed.[102]

The second study is an observational study (N = 333) that evaluated patient preference of the Breezhaler, Genuair, and Respimat devices in asthma and COPD patients. It is published by the same authors of the previous study and has a very similar study design. In this study, the Handling Questionnaire informed that the Breezhaler was the least liked by patients, and was perceived by patients and nurses as the most difficult to use. Here, the Breezhaler was the device that 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). As well, 82%, 44.3%, and 37.6% of patients were unable to prepare the Breezhaler, Genuair, or Respimat, respectively, on their first attempt. The persisting trait 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.[103]

The third study was a prospective, single-centre, observational study (N = 216) that evaluated the number of instructions necessary to minimize errors in pressurized MDIs, Turbuhaler, Breezhaler, Respimat, and Ellipta in patients with asthma (n = 135) and COPD (n = 81). All the devices tested required at least three instructions to minimize the error rate to 10% or less. Of the patients who tested the Breezhaler device (n = 32; three patients had asthma and 29 patients had COPD), around 60%, 20%, and 3% made a mistake in overall handling and device inhalation after one set, two sets, and three sets of pharmacist instructions on device use, respectively. This was largely similar to all the other devices tested. This study illustrates that three sets of instructions may be necessary to teach patients about proper Breezhaler use.[104]

Additionally, an observational study (N = 2,935) that evaluated handling errors of inhaler devices in patients with COPD — including the Breezhaler — was submitted by the sponsor.[105] A total of 876 patients used the Breezhaler device, 452 used Diskus, 598 used Handihaler, 422 used a pressurized MDI, 625 used Respimat, and 420 used Turbuhaler. (Note: Patients may have used more than one 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% of patients (95% CI, 26.1 to 34.9) without an error. The worst performing device was the Handihaler at 10.7% of patients (95% CI, 8.2 to 13.5) 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 MDIs (43.8%), and Respimat (46.9%). It should be noted that the first three studies outlined earlier included both asthma and COPD patients, and the study provided by the sponsor was only on patients with COPD. No studies were identified that assessed Breezhaler device preference in asthma patients only. There are differences in baseline characteristics of asthma patients versus COPD patients. For example, asthma patients tend to be younger than COPD patients and typically have fewer comorbidities that could influence uptake of instructions and the use of an inhaler device.[102] A younger population is one that can exert more physical strength and dexterity related to their inhaler technique. In a study published by Ciciliani et al. (2019) evaluating finger

strength and its relation to patient device satisfaction, the authors found that finger strength differed between the age groups evaluated (five 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 MDIs. 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 (like the Breezhaler). Overall, patients were the least satisfied by the Breezhaler when compared to the Respimat, Aerolizer, Genuair, Diskus, Ellipta, Handihaler, Turbuhaler, and Atrovent.[106] The study on patients with COPD that was identified by the sponsor did not control for factors such as health literacy and prior device training, which may influence proper inhaler technique. Moreover, it only included patients with COPD, who were older (mean age of 65.4 years). Therefore, the generalizability of the results of this study to Canadian patients with asthma may be limited.

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

References

1. Atectura Breezhaler (indacaterol (as acetate)/mometasone furoate): 150 mcg/80 mcg, 150 mcg/160 mcg, 150 mcg/320 mcg; inhalation powder hard capsules [product monograph]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2020 May 5: https://pdf.hres.ca/dpd_pm/00055861.PDF. Accessed 2020 Oct 2.
2. Global strategy for asthma management and prevention. Fontana (WI): Global Initiative for Asthma; 2020: https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_-final-_wms.pdf. Accessed 2020 Oct 5.
3. A snapshot of asthma in Canada. 2019 annual asthma survey report. Toronto (ON): Asthma Canada; 2019: https://asthma.ca/wp-content/uploads/2019/09/A-Snapshot-of-Asthma-in-Canada-2019-Annual-Asthma-Survey-Report-1.pdf. Accessed 2020 Oct 5.
4. Severe asthma: the Canadian patient journey. Toronto (ON): Asthma Society of Canada; 2014: https://asthma.ca/wp-content/uploads/2017/06/SAstudy.pdf. Accessed 2020 Oct 5.
5. Clinical Study Report: CQVM149B2303. A multi-center, randomized, 12-week treatment, double-blind study to assess the efficacy and safety of QMF149 (150/80 µg) compared with mometasone furoate (MF) Twisthaler (200 µg) in adult and adolescent patients with asthma [**CONFIDENTIAL** internal sponsor's report]. East Hanover (NJ): Novartis 2019 Mar 5.
6. Clinical Study Report: CQVM149B2301. A multi-center, randomized, 52-week treatment, double-blind, triple-dummy, parallel-group study to assess the efficacy and safety of QMF149 compared with mometasone furoate in patients with asthma [**CONFIDENTIAL** internal sponsor's report]. East Hanover (NJ): Novartis; 2019 Sep 24.
7. Committee for Medicinal Products for Human Use. Guideline on the clinical investigation of medicinal products for the treatment of asthma. Amsterdam (NL): European Medicines Agency; 2015 Oct 22: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-asthma_en.pdf. Accessed 2020 Oct 5.
8. Statistics Canada. Table 13-10-0096-08. Asthma, by age group. 2020; https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310009608. Accessed 2020 Oct 5.
9. van der Palen J, Thomas M, Chrystyn H, et al. A randomised open-label cross-over study of inhaler errors, preference and time to achieve correct inhaler use in patients with COPD or asthma: comparison of ELLIPTA with other inhaler devices. *NPJ Prim Care Respir Med.* 2016;26:16079.
10. Lougheed MD, Lemiere C, Dell SD, et al. Canadian Thoracic Society Asthma Management Continuum--2010 consensus summary for children six years of age and over, and adults. *Can Respir J.* 2010;17(1):15-24.
11. Fanta CH. An overview of asthma management. In: Wood RA, Bochner BS, eds. *UpToDate*. Waltham (MA): UpToDate; 2020: www.uptodate.com. Accessed 2020 Oct 5.
12. Jahedi L, Downie SR, Saini B, Chan HK, Bosnic-Anticevich S. Inhaler technique in asthma: how does it relate to patients' preferences and attitudes toward their inhalers? *J Aerosol Med Pulm Drug Deliv.* 2017;30(1):42-52.
13. Symbicort Turbuhaler (budesonide/formoterol fumarate dihydrate): 100 mcg/6 mcg, 200 mcg/6 mcg, 400 mcg/12 mcg: dry powder inhalation powder [product monograph] Mississauga (ON): AstraZenca Canada Inc.; 2019 Sep 26: https://pdf.hres.ca/dpd_pm/00053454.PDF. Accessed 2020 Oct 2.
14. Breo Ellipta (fluticasone furoate/ vilanterol (as trifenatate)): 100 mcg/25 mcg, 200 mcg/25 mcg; inhalation powder [product monograph]. Mississauga (ON): GlaxoSmithKline Inc.; 2019 January 7: https://pdf.hres.ca/dpd_pm/00049111.PDF. Accessed 2020 Oct 2.
15. Advair Diskus (fluticasone propionate and salmeterol): 100 mcg/50 mcg, 250 mcg/50 mcg, 500 mcg/ 50 mcg; dry powder. Advair (fluticasone propionate and salmeterol): 125 mcg/25 mcg, 250 mcg/25 mcg; pressurised inhalation suspension. [product monograph]. Mississauga (ON): GlaxoSmithKline Inc.; 2020 June 17: https://pdf.hres.ca/dpd_pm/00056976.PDF. Accessed 2020 Oct 2.
16. Zenhale (mometasone furoate/formoterol fumarate dihydrate): 50 mcg/5 mcg, 100 mcg/5 mcg, 200 mcg/5 mcg; inhalation aerosol [product monograph]. Kirkland (QC): Merck Canada Inc.; 2018 January 30.
17. Asmanex Twisthaler (mometasone furoate dry powder inhaler): 100 mcg, 200 mcg, 400 mcg /metered inhalation [product monograph]. Kirkland (QC): Merck Canada Inc.; 2018 Jan 24: https://pdf.hres.ca/dpd_pm/00043661.PDF. Accessed 2020 Oct 2.
18. Alvesco (ciclesonide inhalation aerosol): 100 mcg and 200 mcg/ actuation (ex-valve) [product monograph]. Mississauga (ON): AstraZeneca Canada Inc.; 2017 Jan 19: https://pdf.hres.ca/dpd_pm/00037859.PDF. Accessed 2020 Oct 2.
19. Pulmicort Turbuhaler (budesonide): 100 mcg, 200 mcg, and 400 mcg / metered dose [product monograph]. Mississauga (ON): AstraZeneca Canada Inc.; 2017 Nov 8: https://pdf.hres.ca/dpd_pm/00042073.PDF. Accessed 2020 Oct 2.
20. Qvar (beclomethasone dipropionate) metered dose aerosol 50 ìg and 100 mg [product monograph]. Laval (QC): Valeant Canada LP; 2013 Sep 18: https://pdf.hres.ca/dpd_pm/00022021.PDF. Accessed 2020 Oct 2.
21. Aermony RespiClick (fluticasone propionate): 55 mcg, 113 mcg, 232 mcg inhalation powder [product monograph]. Toronto (ON): Teva Canada Limited; 2017.
22. Flovent HFA (fluticasone propionate inhalation aerosol): 50, 125, and 250 mcg/metered dose; Flovent Diskus (fluticasone propionate powder for inhalation): 100, 250, AND 500 mcg/blister [product monograph]. Mississauga (ON): GlaxoSmithKline Inc.; 2016 June 1: https://pdf.hres.ca/dpd_pm/00035198.PDF. Accessed 2020 Oct 2.

23. Arnuity Ellipta (fluticasone furoate dry powder for oral inhalation): 100 mcg and 200 mcg [product monograph]. Mississauga (ON): GlaxoSmithKline Inc.; 2017 Feb 22: https://pdf.hres.ca/dpd_pm/00038221.PDF. Accessed 2020 Oct 2.

24. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med.* 2000;343 (5):332-336.

25. Bateman ED, Reddel HK, O'Byrne PM, et al. As-needed budesonide-formoterol versus maintenance budesonide in mild asthma. *N Engl J Med.* 2018;378(20):1877-1887.

26. Normansell R, Kew K, Stovold E, Mathioudakis AG, Dennett E. Interventions to improve inhaler technique and adherence to inhaled corticosteroids in children with asthma. *Paediatr Respir Rev.* 2017;23:53-55.

27. O'Byrne PM, FitzGerald JM, Bateman ED, et al. Inhaled combined budesonide–formoterol as needed in mild asthma. *N Engl J Med.* 2018;378(20):1865-1876.

28. Beasley R, Holliday M, Reddel HK, et al. Controlled trial of budesonide–formoterol as needed for mild asthma. *N Engl J Med.* 2019;380(21):2020-2030.

29. Hardy J, Baggott C, Fingleton J, et al. Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial. *Lancet.* 2019;394(10202):919-928.

30. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 guideline statement. *J Clin Epidemiol.* 2016;75:40-46.

31. Grey matters: a practical tool for searching health-related grey literature. Ottawa (ON): CADTH; 2019: https://www.cadth.ca/grey-matters. Accessed 2020 June 4.

32. Kornmann O, Mucsi J, Kolosa N, et al. Efficacy and safety of inhaled once-daily low-dose indacaterol acetate/mometasone furoate in patients with inadequately controlled asthma: Phase III randomised QUARTZ study findings. *Respir Med.* 2020;161:105809.

33. van Zyl-Smit RN, Krüll M, Gessner C, et al. Once-daily mometasone plus indacaterol versus mometasone or twice-daily fluticasone plus salmeterol in patients with inadequately controlled asthma (PALLADIUM): a randomised, double-blind, triple-dummy, controlled phase 3 study. *Lancet Respir Med.* 2020.

34. Health Canada reviewer's report: Atectura Breezhaler (indacaterol /mometasone furoate)[**CONFIDENTIAL** internal report]. Ottawa (ON): Therapeutics Products Directorate, Health Canada; 2020.

35. Santanello NC ZJ, Seidenberg B, Reiss TF, Barber BL. What are minimal important changes for asthma measures in a clinical trial? *Eur Respir J.* 1999;14(1):23-27.

36. Quanjer PH LM, Gregg I, Miller MR, Pedersen OF. Peak expiratory flow: conclusions and recommendations of a Working Party of the European Respiratory Society. *Eur Respir J Suppl.* 1997;24:2S-8S.

37. Williams AE AL, Wiklund I, Frith L, Gul N, Juniper E. Transcultural and measurement evaluation of the asthma quality-of-life questionnaire. *Health Outcomes Res Med.* 2010;1(2):e69-79.

38. Szentes BL, Schultz K, Nowak D, Schuler M, Schwarzkopf L. How does the EQ-5D-5L perform in asthma patients compared with an asthma-specific quality of life questionnaire? *BMC Pulm Med.* 2020;20(1):168.

39. Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. *Eur Respir J.* 2002;19(3):398-404.

40. Juniper EF GG, Willan A, Griffith LE. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. *J Clin Epidemiol.* 1994;47(1):81-87.

41. Juniper EF SK, Mork AC, Stahl E. Modification of the Asthma Quality of Life Questionnaire (standardised) for patients 12 years and older. *Health Qual Life Outcomes.* 2005;3:58.

42. Wyrwich KW IA, Navaratnam P, Nolte H, Gates DF, Jr. Validation of the AQLQ12+ among adolescents and adults with persistent asthma. *Qual Life Res.* 2011;20(6):903-912.

43. Wyrwich KW KS, Navaratnam P, Nolte H, Gates DF, Jr. Validation and agreement across four versions of the asthma control questionnaire in patients with persistent asthma. *Respir Med.* 2011;105(5):698-712.

44. van Reenen M, Janssen B. EQ-5D-5L user guide: basic information on how to use the EQ-5D-5L instrument Rotterdam (NL): EuroQol Research Foundation; 2015.

45. 2014 Alberta population norms for EQ-5D-5L. Calgary (AB): Health Quality Council of Alberta; 2014: https://d10k7k7mywg42z.cloudfront.net/assets/542f01f2edb2f37083002e54/2014_EQ_5D_5L_report_FINALFINAL.pdf. Accessed 2020 Oct 5.

46. Sastre J OJ, Vega JM, Del P, V, Picado C, Lopez VA. Cut-off points for defining asthma control in three versions of the Asthma Control Questionnaire. *J Asthma.* 2009;47(8):865-870.

47. Barnes PJ CT, Dahl R, Pavord ID, Wechsler ME. The Asthma Control Questionnaire as a clinical trial endpoint: past experience and recommendations for future use. *Allergy.* 2014;69(9):1119-1140.

48. Juniper EF CA, Neville E, Chatterjee A, Svensson K, Mork AC, et al. Clinicians tend to overestimate improvements in asthma control: an unexpected observation. *Prim Care Respir J.* 2004;13(4):181-184.

49. Jia CE ZH, Lv Y, Liang R, Jiang YQ, Powell H, et al. The Asthma Control Test and Asthma Control Questionnaire for assessing asthma control: systematic review and meta-analysis. *J Allergy Clin Immunol.* 2013;131(3):695-703.

50. Halbert RJ TD, Globe DR, Lin SL. Measuring asthma control is the first step to patient management: a literature review. *J Asthma.* 2009;46:659-664.

51. Clark M, Martin S, Svedsater H, Dale P, Jacques L. Measurement properties of an asthma symptom and rescue medication use diary. *J Asthma.* 2015;52(1):88-97.

52. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics.* 1993;4(5):353-365.

53. Zhang W, Bansback N, Boonen A, Young A, Singh A, Anis AH. Validity of the work productivity and activity impairment questionnaire--general health version in patients with rheumatoid arthritis. *Arthritis Res Ther.* 2010;12(5):R177.

54. Reilly MC, Tanner A, Meltzer EO. Work, classroom and activity impairment instruments. *Clin Drug Investig.* 1996;11:278-288.

55. Eisner MD, Yegin A, Trzaskoma B. Severity of asthma score predicts clinical outcomes in patients with moderate to severe persistent asthma. *Chest.* 2012;141(1):58-65.

56. Chen H, Blanc PD, Hayden ML, et al. Assessing productivity loss and activity impairment in severe or difficult-to-treat asthma. *Value Health.* 2008;11(2):231-239.

57. Juniper EF OBP, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J.* 1999;14:902-907.

58. Tricco AC, Ashoor HM, Zarin W, et al. Comparative safety and effectiveness of inhaled corticosteroids and beta-agonists for chronic asthma: a rapid review and network meta-analysis. Toronto (ON): Ontario Drug Policy Research Network; 2015: https://odprn.ca/wp-content/uploads/2015/04/ICS-LABA-asthma-FINAL-CENSORED-rapid-review-team-25-02-15_AS-srk.pdf. Accessed 2020 Oct 5.

59. Loymans RJ, Gemperli A, Cohen J, et al. Comparative effectiveness of long term drug treatment strategies to prevent asthma exacerbations: network meta-analysis. *BMJ.* 2014;348:g3009.

60. Chipps B, Taylor B, Bayer V, et al. Relative efficacy and safety of inhaled corticosteroids in patients with asthma: systematic review and network meta-analysis. *Ann Allergy Asthma Immunol.* 2020;14:14.

61. Hill AT, Haworth CS, Aliberti S, et al. Pulmonary exacerbation in adults with bronchiectasis: a consensus definition for clinical research. *Eur Respir J.* 2017;49(6):1700051.

62. Reddel HK, Taylor DR, Bateman ED, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med.* 2009;180(1):59-99.

63. Network meta-analysis (Enerzair and Atectura vs. other asthma therapies): feasibility report. In: CDR submission: Atectura Breezhaler (indacaterol (as acetate)/mometasone furoate), 150 mcg/80 mcg, 150 mcg/160 mcg, 150 mcg/320 mcg; inhalation powder hard capsules [**CONFIDENTIA**L additional sponsor's information]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2020 Apr 30.

64. Clinical Study Report: CQVM149B1305. A multicenter, open-label, single-arm, 52-week treatment study to assess the safety of QMF149 in Japanese patients with asthma [**CONFIDENTIAL** internal sponsor's report]. Tokyo (JP): Novartis; 2019 Aug 6.

65. Bonini M, Di Paolo M, Bagnasco D, et al. Minimal clinically important difference for asthma endpoints: an expert consensus report. *Eur Respir Rev.* 2020;29(156):190137.

66. Drazen JM IE, Boushey HA, Chinchilli VM, Fahy JV, Fish JE, et al. Comparison of regularly scheduled with as-needed use of albuterol in mild asthma. *Acad Emerg Med.* 1996;335(12):841-847.

67. Boushey HA SC, King TS, Sullivan SD, Fahy JV, Lazarus SC, et al. Daily versus as-needed corticosteroids for mild persistent asthma. *N Engl J Med.* 2005;352(15):1519-1528.

68. Carranza R J, Edwards L, Lincourt W, Dorinsky P, ZuWallack RL. The relationship between health-related quality of life, lung function and daily symptoms in patients with persistent asthma. *Respir Med.* 2004;98(12):1157-1165.

69. Voorend-van BS V-VA, Landstra AM, Brackel HJ, van den Berg NJ, Caudri D, et al. Monitoring childhood asthma: web-based diaries and the asthma control test. *J Allergy Clin Immunol.* 2014;133(6):1599-1605.

70. Ehrs PO AH, Larsson K. Quality of life in primary care asthma. *Respir Med.* 2001;95(1):22-30.

71. Moy ML IE, Weiss ST, Juniper EF, Dube L, Drazen JM, et al. Clinical predictors of health-related quality of life depend on asthma severity. *Am J Respir Crit Care Med.* 2001;163(4):924-929.

72. Enright PL BK, Sherrill DL. Repeatability of spirometry in 18,000 adult patients. *Am J Respir Crit Care Med.* 2004;169(2):235-238.

73. Ulrik CS PD, Backer V. Recognition of asthma in adolescents and young adults: which objective measure is best? *J Asthma.* 2005;42(7):549-554.

74. Karras DJ SM, Terregino CA, Lopez BL, Griswold SK, Arnold GK. Clinically meaningful changes in quantitative measures of asthma severity. *Acad Emerg Med.* 2000;7(4):327-334.

75. Juniper EF, Bousquet J, Abetz L, Bateman ED, GOAL Committee. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. *Respir Med.* 2006;100(4):616-621.

76. Gimena Hernandez H, Pont À, Garin O, et al. Validity of the five-level new version of the EQ-5D in asthma patients. *J Thorac Dis.* 2016;8 (Suppl 5):AB022.

77. Crossman-Barnes CJ, Sach T, Wilson A, Barton G. The construct validity and responsiveness of the EQ-5D-5L, AQL-5D and a bespoke TTO in acute asthmatics. *Qual Life Res.* 2020;29(3):619-627.

78. McClure NS SF, Xie F, Luo N, Johnson JA. Instrument-defined estimates of the minimally important difference for EQ-5D-5L index scores. *Value Health.* 2017;20(4):644-650.

79. van Dalen C, Harding E, Parkin J, Cheng S, Pearce N, Douwes J. Suitability of forced expiratory volume in 1 second/forced vital capacity vs percentage of predicted forced expiratory volume in 1 second for the classification of asthma severity in adolescents. *Arch Pediatr Adolesc Med.* 2008;162(12):1169-1174.

80. Clinical Study Report: CQVM149B2302. A multicenter, randomized, 52-week, double-blind, parallel-group, active controlled study to compare the efficacy and safety of QVM149 with QMF149 in patients with asthma [**CONFIDENTIAL** internal sponsor's report]. East Hanover (NJ): Novartis; 2019 Sep 19.

81. Clinical Study Report: CQVM149B2306. A multicenter, partially-blinded, randomized, 24-week, parallel-group, non-inferiority, open-label active controlled study to compare the efficacy and safety of QVM149 with a free triple combination of salmeterol/fluticasone + tiotropium in patients with uncontrolled asthma [**CONFIDENTIAL** internal sponsor's report]. East Hanover (NJ): Novartis; 2020 Jan 27.

82. Yawn BP. Factors accounting for asthma variability: achieving optimal symptom control for individual patients. *Prim Care Respir J.* 2008;17(3):138-147.

83. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): guidelines for the diagnosis and management of asthma-summary report 2007. *J Allergy Clin Immunol.* 2007;120(5 Suppl):S94-138.

84. Corre KA RR. Assessing severity of adult asthma and need for hospitalization. *Ann Emerg Med.* 1985;14(1):45-52.

85. Tepper RS WR, Covar R, Irvin CG, Kercsmar CM, Kraft M, et al. Asthma outcomes: pulmonary physiology. *J Allergy Clin Ummunol.* 2012;129(3 Suppl):S65-S87.

86. Dekker FW SA, Sterk PJ, Dijkman JH. Validity of peak expiratory flow measurement in assessing reversibility of airflow obstruction. *Thorax.* 1992;47(3):162-166.

87. Chinn S, Jarvis D, Svanes C, Burney P. Sources of variation in forced expiratory volume in one second and forced vital capacity. *Eur Respir J.* 2006;27(4):767-773.

88. Juniper EF, Buist AS, Cox FM, Ferrie PJ, King DR. Validation of a standardized version of the Asthma Quality of Life Questionnaire. *Chest.* 1999;115(5):1265-1270.

89. Usmani OS, Lavorini F, Marshall J, et al. Critical inhaler errors in asthma and COPD: a systematic review of impact on health outcomes. *Respiratory Research.* 2018;19(1):10.

90. Bateman ED ED, Chirila C, Fernandez M, Fowler A, Moroni-Zentgraf P, et al. Magnitude of effect of asthma treatments on Asthma Quality of Life Questionnaire and Asthma Control Questionnaire scores: systematic review and network meta-analysis. *J Allergy Clin Immunol.* 2015;136(4):914-922.

91. Juniper EF G-JK, Ward S, Svensson K. Asthma Control Questionnaire in children: validation, measurement properties, interpretation. *Eur Respir J.* 2010;36(6):1410-1416.

92. Reilly Associates. WPAI:SHP V2.0. 2010; http://www.reillyassociates.net/WPAI_SHP.html. Accessed 2020 Oct 5.

93. Ding B, Small M, Scheffel G, Holmgren U. Maintenance inhaler preference, attribute importance, and satisfaction in prescribing physicians and patients with asthma, COPD, or asthma-COPD overlap syndrome consulting for routine care. *Int J Chron Obstruct Pulmon Dis.* 2018;13:927-936.

94. Zervas E, Samitas K, Gaga M. Assessment of satisfaction with different dry powder inhalation devices in Greek patients with COPD and asthma: the ANASA study. *Int J Chron Obstruct Pulmon Dis.* 2016;11:1845-1855.

95. Bjermer L. The importance of continuity in inhaler device choice for asthma and chronic obstructive pulmonary disease. *Respiration.* 2014;88(4):346-352.

96. Chrystyn H, Price D. Not all asthma inhalers are the same: factors to consider when prescribing an inhaler. *Prim Car Respir J.* 2009;18(4):243-249.

97. Hawken N, Torvinen S, Neine ME, et al. Patient preferences for dry powder inhaler attributes in asthma and chronic obstructive pulmonary disease in France: a discrete choice experiment. *BMC Pulm Med.* 2017;17(1):99.

98. Price D, Harrow B, Small M, Pike J, Higgins V. Establishing the relationship of inhaler satisfaction, treatment adherence, and patient outcomes: a prospective, real-world, cross-sectional survey of US adult asthma patients and physicians. *World Allergy Organ J.* 2015;8(1):26, 2015.

99. Ramadan WH, Sarkis AT. Patterns of use of dry powder inhalers versus pressurized metered-dose inhalers devices in adult patients with chronic obstructive pulmonary disease or asthma: an observational comparative study. *Chron Respir Dis.* 2017;14(3):309-320.

100. Lavorini F. Easyhaler an overview of an inhaler device for day-to-day use in patients with asthma and chronic obstructive pulmonary disease. *Drugs Context.* 2019;8:212596.

101. Dal Negro RW, Povero M. Dry-powder inhalers in patients with persistent airflow limitation: usability and preference. *Multidiscip.* 2016;11(1):31.

102. Dal Negro RW, Povero M. Acceptability and preference of three inhalation devices assessed by the Handling Questionnaire in asthma and COPD patients. *Multidiscip.* 2015;11:7.

103. Takaku Y, Kurashima K, Ohta C, et al. How many instructions are required to correct inhalation errors in patients with asthma and chronic obstructive pulmonary disease? *Respir Med.* 2017;123:110-115.

104. Molimard M, Raherison C, Lignot S, et al. Chronic obstructive pulmonary disease exacerbation and inhaler device handling: real-life assessment of 2935 patients. *Eur Respir J.* 2017;49(2):1601794.

105. Ciciliani AM, Langguth P, Wachtel H. Handling forces for the use of different inhaler devices. *Int J Pharm.* 2019;560:315-321.