Common Drug Review

Fixed-Dose Combination Review Report

September 2015

Drug	aclidinium/formoterol (Duaklir Genuair) fixed-dose combination (FDC)
Indication	Indicated as a long-term maintenance bronchodilator treatment for airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.
Listing request	For the long-term, twice-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, if the following clinical criteria are met: • Moderate to severe COPD • Inadequate response to a long-acting bronchodilator (i.e., a long-acting muscarinic antagonist [LAMA] or a long-acting beta-2 agonist [LABA]).
Dosage form(s)	inhalation powder, 400/12 mcg
NOC date	April 2, 2015
Manufacturer	AstraZeneca Canada Inc.

Note: The CADTH Common Drug Review (CDR) team has made changes to improve the quality and clarity of the content of the information provided in the Fixed-Dose Combination template. In line with CDR's transparency initiative these changes have been tracked.

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ABBREVIATIONS

AE	adverse event
AUC	area under the curve
CDR	CADTH Common Drug Review
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CrI	credible interval
ECG	electrocardiogram
EXACT	EXAcerbations of Chronic Obstructive Pulmonary Disease Tool
FDC	fixed-dose combination
FEV_1	forced expiratory volume in one second
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HRU	health care resource utilization
HRQoL	health-related quality of life
ICS	inhaled corticosteroid
LABA	long-acting beta2-agonist
LAMA	long-acting muscarinic antagonist
LS (mean)	least-squares (mean)
mITT	modified intention-to-treat (population)
MMRM	mixed model for repeated measures
NDS	New Drug Submission
PP	per-protocol (population)
PRO	patient-reported outcome
RCT	randomized controlled trial
RR	rate ratio
SABA	short-acting beta2-agonist
SAE	serious adverse event
SGRQ	St. George's Respiratory Questionnaire
TDI	Transition Dyspnea Index
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Chronic obstructive pulmonary disease (COPD) is a respiratory disorder characterized by progressive, partially reversible airway obstruction and lung hyperinflation, systemic manifestations, and increasing frequency and severity of exacerbations. Pathological changes in the lung vary among individuals, but usually involve a combination of airway inflammation (chronic bronchitis) and parenchymal destruction (emphysema). The nature of symptomatic impairment may vary from patient to patient; however, cough, excess sputum production, and dyspnea are the typical symptoms of COPD.[1] Statistics Canada has reported that between 2009 and 2011, 4% of Canadians aged 35 to 79 years self-reported being diagnosed with COPD.[2] The goals of COPD management are to prevent disease progression, reduce the frequency and severity of exacerbations, alleviate symptoms, improve exercise tolerance and daily activity, treat exacerbations and complications, improve health status, and reduce mortality.[3,4] Bronchodilator therapy with short- (SABAs) or long-acting inhaled beta2-agonists (LABAs) or short- (SAMAs) or long-acting muscarinic antagonists (LAMAs), as well as the fixed-dose combination (FDC) of a LABA and LAMA are mainstays of COPD therapy in addition to LABAs and inhaled corticosteroids (LABA + ICS). Currently, there are three LABA/LAMA FDCs marketed in Canada for the treatment of COPD. They are indacaterol/glycopyrronium (Ultibro Breezhaler), umeclidinium/vilanterol (Anoro Ellipta), and now aclidinium/formoterol (Duaklir Genuair).

Aclidinium/formoterol FDC (Duaklir Genuair) is indicated as a long-term maintenance bronchodilator treatment for airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema.[5] The Health Canada-approved recommended dose is aclidinium 400 mcg/formoterol 12 mcg inhaled orally twice daily. The manufacturer has requested listing of aclidinium/formoterol FDC for the long-term, twice-daily maintenance bronchodilator treatment of airflow obstruction in patients with moderate to severe COPD with inadequate response to a LABA or a LAMA monotherapy, with the same listing clinical criteria as other LABA/LAMA FDCs.

The objective of this review was to evaluate the beneficial and harmful effects of aclidinium/formoterol FDC (400 mcg/12 mcg) for the maintenance treatment of patients with COPD, including chronic bronchitis and emphysema.

Results and Interpretation

Included Studies

Five studies[6-10] (two pivotal studies [LAC 30[6] and LAC 31[7]] and three supportive studies [LAC 39,[9] LAC 36,[8] and LAC 32[10]]) were included in the review. The two pivotal studies, LAC 30 and LAC 31, compared aclidinium/formoterol FDC with three other treatments: aclidinium monotherapy, formoterol monotherapy, and placebo. LAC 39 was a non-inferiority study that compared aclidinium/formoterol FDC with salmeterol/fluticasone, a LABA + ICS FDC inhaler. LAC 36 was a 28-week extension study of LAC 31 for patients from the US and Canada (in about 63% of the total patients who completed LAC 31 at week 24). Finally, LAC 32 was an active-comparison study (aclidinium/formoterol FDC compared with formoterol monotherapy). All were multinational, double-blind, randomized controlled studies. The included studies evaluated the efficacy and safety of aclidinium/formoterol FDC and the comparators (LAC 30, LAC 31, and LAC 39) at week 24 and longer-term safety (LAC 36 and LAC 32) at week 52. The co-primary outcomes in LAC 30 and LAC 31 were the change from baseline to week 24 in trough forced expiratory volume in once second (FEV_1) versus formoterol, and one hour post-dose FEV_1 versus

aclidinium, respectively. In LAC 39, the primary outcome was change from baseline to week 24 in peak FEV_1 versus salmeterol/fluticasone. The primary outcome was not specified in either LAC 32 or LAC 36.

The key limitations of the studies included the relative short duration (24 weeks) in the two pivotal studies and in LAC 39, which was likely of insufficient duration to assess clinical outcomes such as mortality. In addition, none of the studies were designed to evaluate the treatment effects on COPD exacerbations. A majority of patients (63% to 79%) did not experience an acute COPD exacerbation in the year prior to enrolling into the studies. The clinical expert involved in this review indicated that COPD is associated with both short- and long-term consequences on overall health. Therefore, assessing the impact of aclidinium/formoterol FDC on the rate of acute COPD exacerbations is an important clinical issue. Furthermore, there was a substantial proportion of discontinuations (ranging as high as 20% to 30%) in LAC 36 at week 24, and an extra 16% of discontinuations occurred during a 28-week extension period (at week 52)The discontinuation rate at one year was 33%, reported in LAC 32. Although there was no clear discontinuation differential between groups within studies (except that those on placebo discontinued more frequently), there is a concern regarding the validity of the findings once frequencies of discontinuations are this high. The manufacturer provided limited information describing the derivation and clinical relevance for the non-inferiority margin used in LAC 39. Finally, there were no head-to-head comparison studies of aclidinium/formoterol FDC with other LABA/LAMA combinations. As a result, there is no direct comparative evidence to guide the clinical choice amongst the three available LAMA/LABA FDCs in the long-term maintenance treatment of patients with moderate to severe COPD. A manufacturer-conducted mixed treatment comparison (MTC) suggested that aclidinium/formoterol FDC appears similar in terms of certain efficacy outcomes and withdrawals due to an adverse event (WDAEs) compared with indacaterol/glycopyrronium FDC and umeclidinium/vilanterol FDC. However, the potential limitations of the MTC means there is a high degree of uncertainty in the findings and conclusions derived from the MTC and that these results should be interpreted with caution.

Efficacy

Pulmonary Function (FEV_1)

At week 24, the change from baseline in FEV_1 at one hour post-dose was statistically and clinically significantly greater for aclidinium/formoterol FDC than for aclidinium (between-group difference, least-squares mean [LS mean] change 0.125 L and 95% confidence interval [CI], 0.090 to 0.160 in LAC 30 and between-group difference, LS mean change 0.108 L and 95% CI, 0.073 to 0.144 in LAC 31). Likewise, aclidinium/formoterol FDC was statistically significantly superior in improving FEV_1 from baseline to week 24 at one hour post-dose versus formoterol (between-group difference, LS mean change 0.139 L and 95% CI, 0.104 to 0.174 in LAC 30 and; between-group difference, LS mean change 0.0825 L and 95% CI, 0.047 to 0.118 in LAC 31).[10] The between-group difference between aclidinium/formoterol FDC and formoterol was likely clinically significant in LAC 30 (i.e., > 0.100 L), but there is uncertainty as to the clinical significance of the difference found in LAC 31.

The increases from baseline to week 24 in trough FEV_1 were statistically significantly greater for aclidinium/formoterol FDC than for formoterol (between-group difference, LS mean change 0.085 L and 95% CI, 0.051 to 0.119 in LAC 30 and ; between-group difference, LS mean change 0.0448 L and 95% CI, 0.011 to 0.079 in LAC 31). However, whether the between-group difference of change from baseline is clinically meaningful is uncertain. For the comparison with aclidinium monotherapy, there was no statistically or clinically significant difference between groups for trough FEV_1 at week 24 in either pivotal study (between-group difference, LS mean change 0.026 L and 95% CI, –0.007 to 0.060 in LAC 30

and between-group difference, LS mean change 0.028 L and 95% CI, –0.006 to 0.063 in LAC 31). It is worth noting that, in terms of trough FEV_1, no statistically significant difference was identified between aclidinium/formoterol FDC and aclidinium in studies LAC 30[6,11] and LAC 36.[11]

In both pivotal studies, aclidinium/formoterol FDC was statistically and clinically significantly superior to placebo in improving one hour post-dose FEV_1 and trough FEV_1. These effects of aclidinium/formoterol FDC observed in LAC 31 appeared to be similar until week 52 of the extension study, LAC 36.

In LAC 39, aclidinium/formoterol FDC was non-inferior to salmeterol/fluticasone FDC for the change from baseline in peak FEV_1 at week 24 (between-group difference, LS mean change 0.101 L; 95% CI, 0.070 to 0.131). Non-inferiority was based on the lower bound of the two-sided 95% CI being above the non-inferiority margin of –0.055 L. In addition, aclidinium/formoterol FDC was statistically and clinically significantly superior to salmeterol/fluticasone FDC for peak FEV_1 at week 24 based on the modified intention-to-treat (mITT) population ($P < 0.0001$). However, in terms of trough FEV_1, which is more commonly accepted as the primary outcome in studies on COPD according to clinical expert involved in this review, aclidinium/formoterol FDC was not statistically significantly superior compared with salmeterol/fluticasone at week 24, with an adjusted LS mean difference of –0.014 L (95% CI, –0.043 to 0.016).

In LAC 32, aclidinium/formoterol statistically significantly improved trough FEV_1 from baseline to week 52 versus formoterol monotherapy (between-group difference, LS mean change 0.082 L; 95% CI, 0.010 to 0.15).

Dyspnea (Transition Dyspnea Index) and Health-Related Quality of Life (St. George's Respiratory Questionnaire)

In all included studies, dyspnea was assessed with the Transition Dyspnea Index (TDI). The findings from the included pivotal studies showed that treatment with aclidinium/formoterol FDC resulted in statistically significant improvements in dyspnea as measured with TDI scores, and more responders achieved the minimal clinically important difference (MCID) of ≥ 1 unit improvement at week 24 compared with placebo. However, there were no statistically significant differences between aclidinium/formoterol FDC and aclidinium or formoterol monotherapy. Likewise, no statistically significant difference in TDI was reported between aclidinium/formoterol FDC and salmeterol/fluticasone at week 24 in LAC 39.

Health-related quality of life (HRQoL) was assessed with the St. George's Respiratory Questionnaire (SGRQ). In terms of health outcomes measured with the SGRQ total score, a statistically and clinically significant difference between aclidinium/formoterol FDC and placebo was observed only in LAC 31 (between-group difference, LS mean change –4.35; 95% CI, –6.64 to –2.24), but not in LAC 30 (between-group difference, LS mean change –0.65 L; 95% CI, –3.08 to 1.78). In addition, no statistically significant difference in SGRQ was reported between aclidinium/formoterol FDC and aclidinium or formoterol monotherapy at 24 weeks in both pivotal studies. This may, in part, be due to a lack of power to detect a difference between aclidinium/formoterol FDC and its individual components for changes from baseline in TDI or SGRQ in the two pivotal studies. No statistically significant difference between the treatment groups was reported between aclidinium/formoterol FDC and salmeterol/fluticasone in terms of change in SGRQ at week 24 (between-group difference, LS mean change [redacted]

COPD Exacerbation and Mortality

None of the included studies were adequately designed to assess mortality and COPD exacerbations. The overall rate of death was < 0.5 % in all studies, except LAC 32, in which it was about 1% at one year. No deaths were reported in placebo groups, except one death reported in LAC 36. None of the deaths were considered to be related to aclidinium/formoterol FDC.

In the pivotal studies, LAC 30 and LAC 31, there were no statistically significant differences between aclidinium/formoterol FDC and aclidinium, formoterol, or placebo at week 24. However, when the rates from both studies were pooled, there were statistically significantly fewer moderate to severe COPD exacerbations with aclidinium/formoterol FDC versus placebo at week 24 (rate ratio 0.71; 95% CI, 0.51 to 0.98). There were no statistically significant differences between aclidinium/formoterol FDC and its comparators in LAC 39 and LAC 32.

Harms

The primary safety data for aclidinium/formoterol FDC are provided from the two pivotal studies (LAC 30 and LAC 31), LAC 39, as well as the two long-term (52-week) supportive studies, LAC 32 and LAC 36. Across studies, the overall incidence of treatment-emergent AEs (TEAEs) between treatment groups were generally similar at both week 24[6,7,9] and week 52,[8,10] although numerically more TEAEs were reported in the aclidinium/formoterol FDC groups. The proportion of patients who died was low and similar across the treatment groups (0.3% to 0.6%), and the proportion of patients with treatment-emergent serious adverse events (SAEs) was similar for placebo (7.4%) and for aclidinium/formoterol FDC (8.1%). The reported discontinuation rates at week 24 were higher in placebo groups (17.5% to 30%) than in the active treatment groups (9% to 21%); however, the discontinuation rates at one year were as high as 33%. It is worth noting that in extension study LAC 36, an extra 16% of patients discontinued from the study during the 28-week extension period. The discontinuation rates were comparable among the active treatment arms. The most commonly reported TEAEs (incidence > 5%) in patients treated with aclidinium/formoterol FDC were exacerbations of COPD (although it was evaluated as efficacy in LAC 31), nasopharyngitis, and headache.[10,12,13]

Notable harms were considered based on the anticholinergic and beta-agonist components of aclidinium/formoterol FDC. The frequency of AEs associated with anticholinergic syndrome, including dry mouth, dizziness, urinary retention, and worsening vision, were low, with similarities across treatment groups. The frequency of dry mouth in patients treated with aclidinium/formoterol FDC was 1.8%, and ranged from 0.8% to 1.0% in the other active treatment groups (0.8% to 1.0%). Events related to cardiovascular death and non-fatal myocardial infarction were rare and similar in patients who received either of the active treatments. The incidence of pneumonia was numerically higher in the salmeterol/fluticasone group (1.9%) than in the aclidinium/formoterol FDC group (1%), as reported in LAC 39, LAC 30, and LAC 31.

Conclusion

Supported by the findings from the five included studies, aclidinium/formoterol FDC appears superior to placebo in terms of improving lung function (FEV_1) at week 24 and week 52. Aclidinium/formoterol FDC also showed statistically significantly greater improvement in terms of trough FEV_1 than formoterol at both week 24 and week 52, but not when compared to aclidinium monotherapy. None of the studies were sufficiently powered to assess comparative efficacy for clinically important outcomes such as mortality, health care resource use (HRU), and COPD exacerbations. In terms of HRQoL measured with the SGRQ, aclidinium/formoterol FDC showed a statistically significant difference (in favour of

aclidinium/formoterol FDC) compared with placebo in only one study, and did not show a statistically significant difference compared with aclidinium or formoterol monotherapy. Up to week 52, the overall safety profiles were similar between aclidinium/formoterol FDC and aclidinium or formoterol monotherapy. A key limitation of the included studies was the lack of a head-to-head comparison with another LAMA/LABA combination inhaler such as indacaterol/glycopyrronium FDC or umeclidinium/vilanterol FDC. The manufacturer's MTC suggested that aclidinium/formoterol FDC appears similar in terms of changes in FEV_1, TDI, HRQoL, and WDAEs when compared with indacaterol/glycopyrronium FDC and umeclidinium/vilanterol FDC. However, due to potential limitations (i.e., the relatively short duration and potential clinical heterogeneity of the included trials), the validity of the results of the MTC are considered to be highly uncertain.

At the submitted price of $2.47 per day, aclidinium/formoterol FDC is less expensive than other LAMA/LABA FDCs (range: $2.67 to $2.70 daily) and separately administered LAMA+LABA monotherapies (range: $3.26 to $3.85 daily). The lack of comparative studies or a well-conducted indirect comparison for aclidinium/formoterol FDC limits the relative assessment to other LAMA/LABA FDCs and introduces uncertainty regarding its comparative efficacy on patient-important outcomes.

1. PRODUCT INFORMATION

1.1 Health Canada–Approved Indications

Indication(s) to be Reviewed by the CADTH Common Drug Review
Aclidinium/formoterol fixed-dose combination is a combination of a long-acting muscarinic antagonist (LAMA) and a long-acting beta2-agonist (LABA) indicated as a long-term maintenance bronchodilator treatment for airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

1.2 Requested Listing Criteria

Requested Listing Criteria
For the long-term, twice-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, if the following clinical criteria are met: • Moderate to severe COPD • Inadequate response to a long-acting bronchodilator (i.e., a LABA or a LAMA).

1.3 Manufacturer's Rationale and Place in Therapy for the Combination

1.3.1 Rationale

Aclidinium/formoterol FDC is a new treatment option for COPD. Aclidinium/formoterol FDC is a fixed-dose combination (FDC) of the LAMA, aclidinium bromide (hereafter called aclidinium) (400 mcg), and the LABA, formoterol fumarate dihydrate (hereafter called formoterol) (12 mcg), delivered via a pre-loaded, multi-dose dry powder inhaler (Duaklir Genuair). Aclidinium (Tudorza Genuair) has been approved in Canada since July 2013 for the treatment of COPD and formoterol (Foradil) has been available in Canada for more than 17 years and is widely used in combination therapy for the management of COPD.[1] Genuair is an established inhaler technology currently used in COPD treatment as the delivery device for Tudorza. The choice of formoterol in the FDC with aclidinium in aclidinium/formoterol FDC was based on evidence of its efficacy, rapid onset of action, and safety in COPD in addition to its complementary safety profile and dosing regimen to aclidinium.[1]

One option for the delivery of combined LAMA and LABA therapy would be the concurrent use of the approved individual LAMA and LABA inhalers. There are extensive data to show that the use of a single inhaler device has significant advantages in terms of adherence and outcomes compared with use of multiple inhalers.[2, 3, 4, 5] In a retrospective analysis of 23,494 patients with COPD by Yu et al.,[3] multiple inhaler use was associated with significantly higher rates of discontinuation over the 12-month study period (adjusted hazard ratio [HR] 1.40; 95% confidence interval [CI], 1.35 to 1.46; $P < 0.001$) and significantly lower rates of 12-month adherence (mean [standard deviation (SD)] proportion of days covered: 0.51 [0.272] for multiple inhaler users versus 0.55 [0.279] for a single inhaler; $P < 0.0001$). As suboptimal adherence is associated with significant health and economic burdens in patients with COPD,[3,6] increasing adherence by administration of a LAMA and a LABA via a single inhaler may improve the health status of patients, as well as reduce the economic burden of COPD. These data, therefore, support the potential benefit of FDC LAMA/LABA therapies such as aclidinium/formoterol FDC over concurrent use of individual LAMA and LABA products for non-exacerbating patients with moderate to severe COPD who are still symptomatic with LAMA or LABA monotherapy.

1.3.2 Place in Therapy

a) Need for Effective, Safe and Easy-to-Use Options for Combined LAMA/LABA Therapy

Combined LAMA and LABA therapy is recommended in the Canadian[7] and Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines[7] as step-up therapy to improve symptom control in patients with moderate to severe COPD with infrequent exacerbations (average of < 1 per year), whose symptoms are not controlled on LAMA or LABA monotherapy. Aclidinium/formoterol FDC fits this category of LAMA/LABA combination therapy. In contradiction to the guidelines, the recent Ontario Drug Policy Research Network report on LAMAs for the treatment of COPD indicated < 10% use of combined LAMA and LABA monotherapies, and high use of LABA/ICS combination therapy (23%), and LABA/ICS/LAMA triple therapy combinations (23%) in this patient population.[8] Similar results were obtained in a study conducted in the US and Europe.[9] The significant underutilization of a combined long-acting bronchodilator therapy in this patient population in favour of ICS-containing regimens has major implications for both patient safety and health care costs. According to the guidelines, the addition of ICS is not warranted given that these patients are not exacerbating;[7] consequently, this unnecessarily exposes patients to the deleterious adverse effects of ICS (e.g., pneumonia, cataract, glaucoma, diabetes, and bone fractures). [10,11,12] Combined LAMA and LABA therapy, therefore, has an important role in the treatment of the moderate to severe, infrequently exacerbating patient who is still breathless on monotherapy as it facilitates compliance with Canadian COPD treatment guidelines, avoids harm to the patient from the serious adverse effects of ICS, and potentially results in cost savings to the health care system.

Key considerations in the choice of a combined LAMA and LABA therapy for the treatment of COPD include a quick onset of action combined with demonstrated 24-hour symptom control, to provide rapid relief of breathlessness and other symptoms and to maintain control throughout the day and night; a good safety profile given the high prevalence of significant comorbidities in COPD patients and therefore the need to avoid adverse outcomes due to worsening of pre-existing comorbidities or interactions with drugs used to treat pre-existing comorbidities; and a simple, easy-to-use inhaler that provides dose confirmation to help ensure proper delivery of medication in the clinical practice setting, given the overwhelming body of evidence showing the incorrect use of inhalers by patients, resulting in reduced efficacy outcomes.

Potential treatment advantages for aclidinium/formoterol FDC are that it may provide relief of daily symptoms of COPD, such as dyspnea, and rapid improvement in lung function and 24-hour symptom control. Based on its safety profile, aclidinium/formoterol FDC may offer benefits with respect to systemic anticholinergic effects and for patients with additional comorbidities, including renal impairment and cardiovascular disease. In addition, the delivery of the product via Genuair, a pre-loaded, multi-dose delivery device with a reduced level of resistance, and dose confirmation through visual, auditory, and tactile feedback features that communicate to the patient that the medication has been delivered correctly, offers a unique drug delivery solution. All of these features make aclidinium/formoterol FDC a potentially valuable treatment option in the stepwise management of COPD as recommended by the Canadian treatment guidelines in non-exacerbating patients with moderate to severe COPD whose symptoms are not controlled on single LAMA or LABA therapy.

Reflective of the Canadian Guidelines,[7] combined LAMA/LABA therapy with aclidinium/formoterol FDC would be beneficial for non-exacerbating patients with moderate to severe COPD who are not well controlled with LAMA or LABA monotherapy. Therefore, initiation of therapy should be with a LAMA or LABA monotherapy and not with a combination therapy such as aclidinium/formoterol FDC.

1.3.3 Dosing Considerations

Aclidinium/formoterol FDC contains the same Health Canada–approved dose of aclidinium bromide (400 mcg) as its available LAMA component, found in aclidinium bromide (Tudorza Genuair). Aclidinium/formoterol FDC also contains the same prescribed dose of formoterol fumarate (12 mcg) as its available LABA component found in formoterol (Foradil),[13] which is the only formoterol fumarate product indicated in the treatment of COPD in Canada. Formoterol fumarate dihydrate is also available as Oxeze Turbuhaler in 6 mcg and 12 mcg doses, but does not have a Health Canada–approved indication for the treatment of COPD. Formoterol fumarate dihydrate is indicated for the treatment of asthma only as add-on therapy to an ICS as long-term asthma control medication in patients aged six years and older with reversible obstructive airway disease, including patients with symptoms of nocturnal asthma.[14] However, formoterol fumarate dihydrate is reimbursed in the treatment of COPD by several CADTH Common Drug Review (CDR)–participating federal/territorial/provincial drug plans in a similar manner to formoterol (see Appendix 2). In addition, according to IMS Brogan claims data, the 12 mcg dose of formoterol fumarate dihydrate is the most commonly prescribed dose of this individual component. [15]

When combination therapy is initiated following a switch from monotherapy with aclidinium or formoterol, no titration is required, as aclidinium/formoterol FDC contains the same prescribed doses of aclidinium (400 mcg) and formoterol (12 mcg) contained in both of these products individually. The product monograph for formoterol fumarate dihydrate recommends that the dose should be individualized to the patient's needs and should be the lowest possible dose that keeps the patient symptom free or fulfills the therapeutic objective for non-COPD airway disease. [14] Most likely, if a patient were initiating combination therapy due to a lack of therapeutic response with formoterol fumarate dihydrate alone, the current dose would have previously been increased from 6 mcg to 12 mcg in an attempt to keep the patient symptom free or to fulfill the therapeutic objective.

Aclidinium/formoterol FDC is available in dosage strengths complimentary to its available monocomponents; therefore, there is full ability to titrate dosing to the combination product in the necessary dosage strengths from either of the individual monocomponents. Both components, aclidinium bromide and formoterol fumarate dihydrate, also have uncomplicated linear pharmacokinetic characteristics; [16] therefore, increasing the dose of one component should not result in an unnecessary dose increase of the other component.

2. CLINICAL EVIDENCE

2.1 Pivotal Clinical Studies

The phase 3 program (which included approximately 4,933 patients, of which 1,580 patients were treated with aclidinium/formoterol FDC) consisted of two identical, pivotal, six-month, double-blind, randomized, placebo- and active-controlled studies LAC 30 (ACLIFORM) and LAC 31 (AUGMENT), which compared the efficacy and safety of aclidinium/formoterol FDC versus placebo and its monotherapy components; two long-term (up to 52 weeks of treatment) safety studies, LAC 36 and LAC 32, which also provided data on long-term efficacy; and a six-month comparator study (LAC 39, AFFIRM) versus salmeterol/fluticasone propionate LABA/ICS FDC [17,18] (see Table 1). A pre-defined, pooled analysis was also conducted on the data from the pivotal six-month studies to increase the precision in determining treatment effects on key efficacy end points.[17] The pivotal trials are combined into one section below, because of their similar design.

TABLE 1: INCLUDED STUDIES

Study Name	Design	Objectives	Population
ACLIFORM (LAC 30) **Pivotal Trial**	Multi-centre, placebo- and active-controlled, randomized, double-blind, parallel-group, 24-week study	Assessment of long-term bronchodilator efficacy of aclidinium/formoterol FDC, and efficacy regarding COPD symptoms, disease-related health status, COPD exacerbations, and safety and tolerability	Patients with COPD with moderate to severe stable airflow limitation (post-bronchodilator $FEV_1 \geq 30\%$ predicted and < 80% predicted)
AUGMENT (LAC 31) **Pivotal Trial**	Multi-centre, placebo- and active-controlled, randomized, double-blind, parallel-group, 24-week study	Assessment of long-term bronchodilator efficacy of aclidinium/formoterol FDC, and efficacy regarding COPD symptoms, disease-related health status, COPD exacerbations, and safety and tolerability	Patients with COPD with moderate to severe stable airflow limitation (post-bronchodilator $FEV_1 \geq 30\%$ predicted and < 80% predicted)
AFFIRM (LAC 39)	Randomized, double-blind, double-dummy, active comparator–controlled, parallel-group, multinational, multi-centre, clinical, 24-week study	Randomized, double-blind, double-dummy, comparator study to compare the efficacy and safety of aclidinium/formoterol FDC vs. salmeterol/fluticasone	Patients with COPD with moderate to severe stable airflow limitation (post-bronchodilator $FEV_1 \geq 30\%$ predicted and < 80% predicted), and symptomatic patients with a CAT score ≥ 10 at Screening and Randomization Visit (visits 1 and 2)
LAC 36	Multi-centre, placebo- and active-controlled, randomized, double-blind, parallel-group, 28-week extension study of LAC 31	Assessment of long-term safety and efficacy of aclidinium/formoterol FDC	Patients with COPD with moderate to severe stable airflow limitation (post-bronchodilator $FEV_1 \geq 30\%$ predicted and < 80% predicted)
LAC 32	Long-term, multi-centre,	Long-term safety and	Patients with COPD with

Study Name	Design	Objectives	Population
	double-blind, active-controlled, randomized, 52-week study	tolerability of aclidinium/formoterol FDC	moderate to severe stable airflow limitation (post-bronchodilator $FEV_1 \geq 30\%$ predicted and < 80% predicted)

CAT = COPD assessment test; COPD = chronic obstructive pulmonary disease; FDC = fixed-dose combination; FEV1 = forced expiratory volume in one second; vs. = versus.

2.1.1 ACLIFORM (LAC 30)

A phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of aclidinium/formoterol FDCs compared with individual components and placebo for 24 weeks of treatment when administered to patients with moderate to severe, stable COPD.

2.1.2 AUGMENT (LAC 31)

A phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of aclidinium/formoterol FDCs compared with individual components and placebo for 24 weeks of treatment in patients with moderate to severe, stable COPD.

a) Study Characteristics

These pivotal studies were multi-centre, prospective, double-blind, randomized, parallel-group, active comparator- and placebo-controlled study of aclidinium/formoterol FDC (400 mcg/12 mcg) and aclidinium/formoterol (400 mcg/6 mcg) in patients with COPD with moderate to severe stable airflow limitation (post-bronchodilator forced expiratory volume in one second [FEV_1] ≥ 30% predicted and < 80% predicted) (see Table 2). Data for aclidinium/formoterol (400 mcg/6 mcg) will not be presented as this is not a Health Canada–approved dose.

TABLE 2: STUDY CHARACTERISTICS OF LAC 30 AND LAC 31

Characteristics		Details for LAC 30 (ACLIFORM) [19, 20] and LAC 31 (AUGMENT) [21, 22]
STUDY DESIGN	**Objective**	Pivotal efficacy and safety trials
	Blinding	Double-blind
	Study period LAC 30, LAC 31	October 2011 to January 2013 (LAC 30) September 2011 to February 2013 (LAC 31)
	Study centres LAC 30, LAC 31	193 centres across Europe, South Africa, and South Korea (LAC 30) 222 centres in the US, Canada, Australia, and New Zealand (LAC 31)
	Design	Prospective, double-blind, randomized, parallel-group, active comparator- and placebo-controlled studies
STUDY POPULATION	**Randomized (N) LAC 30, LAC 31**	1,729 (LAC 30) 1,692 (LAC 31)
	Inclusion criteria	• Patients were aged 40 years or older. • Patients had a clinical diagnosis of stable moderate to severe COPD, with COPD severity defined on the basis of airflow limitation as per the GOLD Global Strategy (2010). Eligible patients must have had a post-bronchodilator FEV1 < 80% predicted and ≥ 30% of predicted, and an FEV1/FVC of < 70%. • Patients were current or ex-smokers, with a smoking history of at least 10 pack-years.
	Exclusion criteria	• Patients had experienced a respiratory tract infection or COPD exacerbation in the 6 weeks (or 3 months if hospitalization for COPD exacerbation was required)

Characteristics		Details for LAC 30 (ACLIFORM) [19, 20] and LAC 31 (AUGMENT) [21, 22]
		prior to screening. • Patients in whom the use of anticholinergic drugs is contraindicated were excluded; i.e., those with a history of acute urinary retention or with known symptomatic prostatic hypertrophy, bladder neck obstruction, or narrow-angle glaucoma. • Clinically significant relevant cardiac and respiratory conditions (except COPD) and history or current diagnosis of asthma.
DRUGS	**Intervention**	Aclidinium/formoterol FDC (aclidinium 400 mcg/formoterol 12 mcg), via inhalation (Genuair), b.i.d.[a]
	Comparator(s)	Aclidinium (400 mcg) monotherapy, formoterol (12 mcg) monotherapy, placebo, all via inhalation (Genuair), b.i.d.
DURATION	**Run-in**	2 to 3 weeks
	Treatment	24 weeks
	Follow-up	2 weeks
OUTCOMES	**Primary end point(s)**	Change from baseline to week 24 in FEV_1 at 1 hour post-dose vs. aclidinium Change from baseline to week 24 in morning trough FEV_1 vs. formoterol
	Other End Points	Secondary endpoints: • Improvement in TDI focal score at week 24 • Change from baseline in SGRQ total score at week 24 • Safety and tolerability were evaluated by recording of AEs, clinical laboratory assessments, vital signs, 12-lead ECGs
NOTES	**Publications LAC 30, LAC 31**	• LAC 30 (Singh et al. 2014[20]) • LAC 30 NCT01462942 • LAC 31 (D'Urzo et al., 2014[22]) • LAC 31 NCT01437397

AE = adverse event; b.i.d. = twice daily; COPD = chronic obstructive pulmonary disease; ECG = electrocardiogram; FDC = fixed-dose combination; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease; TDI = Transition Dyspnea Index; SGRQ = St. George's Respiratory Questionnaire.
[a] Both studies included an aclidinium/formoterol (400 mcg/6 mcg) treatment group; however, data for this treatment group are not presented in this review because this dose is not Health Canada–approved for the treatment of patients with COPD.

Intervention and Comparators

Interventions employed in the trials: Patients in studies LAC 30 and LAC 31 were randomized to one of five treatments: aclidinium/formoterol FDC 400 mcg/12 mcg, aclidinium/formoterol FDC 400 mcg/6 mcg, aclidinium (400 mcg), formoterol (12 mcg), or placebo. All of the treatments were given twice daily via inhalation. Duration of treatment was 24 weeks.[20,22]

Allowed concomitant medication: During the run-in period and throughout the study, salbutamol or albuterol was allowed as rescue medication. In addition, patients enrolled in the pivotal studies were permitted during the study to continue treatment with stable doses of background medications for the treatment of COPD (i.e., ICS, systemic corticosteroids [up to a dose equivalent to 10 mg prednisone per day or 20 mg every other day], oral sustained-release theophylline, and oxygen [for less than 15 hours per day]), as long as the medication and dose had been stable for at least four weeks prior to study entry. The use of rescue medication and the continuation of the patients' background therapies during the studies were permitted to minimize the risk of COPD-related complications.[17]

Outcomes

Key outcomes included effects on lung function, dyspnea, HRQoL, exacerbations and safety, and tolerability. Lung function was assessed using standard spirometric measurements; e.g., FEV_1 and forced vital capacity (FVC). The key end points were the change from baseline in FEV_1 at one hour post-dose versus aclidinium, and in trough FEV_1 versus formoterol at week 24. Effects on dyspnea were assessed using the Transition Dyspnea Index (TDI) focal score. The TDI focal scores range from –9 to 9, with a positive increase in score indicating improvement from baseline.[23] The key efficacy measure was the improvement in the TDI focal score at 24 weeks. HRQoL was assessed using the St. George's Respiratory Questionnaire (SGRQ), a validated patient-reported outcome measure for the assessment of impaired health and perceived well-being (quality of life) in patients with respiratory diseases. [24] The SGRQ is a disease-specific measure of HRQoL consisting of 50 items and was specifically developed for patients with chronic airflow limitation. The SGRQ-COPD (SGRQ-C) is a well-established instrument for the assessment of health status in patients with COPD. The questionnaire is divided into three dimensions: Symptoms, Activity, and Impacts of the disease. The total score ranges from 0 to 100, where 0 indicates no impairment and 100 indicates the most severe impairment.[15-18] Exacerbations were assessed using two different methods, one based on health care resource utilization (HRU), [25] and the other on changes in COPD symptoms for at least two consecutive days.[26] For the HRU assessment, exacerbations were defined as mild if they required an increase in the patients' usual medication (short-acting bronchodilator or ICS), moderate if they required the use of antibiotics or systemic corticosteroids, or as severe if they resulted in hospitalization.[25] To increase the robustness of the exacerbation assessment, exacerbations were also assessed using the EXAcerbations of Chronic Obstructive Pulmonary Disease Tool (EXACT),[26] which assesses the frequency, severity, and duration of exacerbations of COPD. EXACT is a 14-item daily diary which is completed by the patient nightly before bedtime. The summed score from the EXACT ranges from 0 to 100, with higher scores indicating more severe symptoms of exacerbation. An exacerbation was defined as a persistent increase from baseline in total EXACT score of at least 9 points for at least three days, or at least 12 points for at least two days. Safety outcomes were assessed through adverse events (AEs) and serious adverse events (SAEs), clinical laboratory parameters, blood pressure, and 12-lead electrocardiogram (ECG) parameters.[17]

Statistical Analyses

The co-primary efficacy variables (change from baseline in FEV_1 at one hour post-dose and change from baseline in morning pre-dose [trough] FEV_1) were analyzed by means of a mixed model for repeated measures (MMRM).[17] Primary treatment comparisons were made between each aclidinium/formoterol dose and aclidinium 400 mcg for the change from baseline in FEV_1 at one hour post-dose and between each aclidinium/formoterol dose and formoterol 12 mcg for the change from baseline in trough FEV_1.[17] Treatment effects and treatment differences were estimated by least-square means (LS means) taking into consideration the corresponding treatment-by-visit interaction at week 24, along with standard errors (SEs), 95% CIs, and the *P* values corresponding to between-treatment group differences.[18]

The primary population for the analysis of efficacy variables for the phase 3 pivotal studies was the modified intention-to-treat (mITT) population. The mITT population (for all end points except COPD exacerbation end points) was defined as all randomized patients who took at least one dose of investigational medicine product (IMP) and who had a baseline FEV_1 assessment and at least one post-baseline FEV_1 assessment. For COPD exacerbation end points, the mITT-exacerbations population was defined as all randomized patients who took at least one dose of IMP. The per-protocol (PP) population was defined as a subset of the mITT population who met all eligibility criteria likely to affect efficacy assessments, who were sufficiently compliant with the treatment, and who did not present any serious protocol deviations that would affect efficacy evaluation.[17]

The secondary efficacy variables (i.e., improvement in TDI focal score and change from baseline in SGRQ total score) were also analyzed by means of MMRM. The main treatment comparisons were made between each aclidinium/formoterol dose and placebo. The rate of COPD exacerbations per patient per year was analyzed by means of a negative binomial regression model, and time-to-event variables were analyzed using the Cox proportional hazards model.[17]

The phase 3 pivotal studies were adequately powered (at least 90% nominal power) to detect a significant difference of 0.065 L between either aclidinium/formoterol FDC and aclidinium/formoterol (400 mcg/6 mcg) and formoterol 12 mcg in the change from baseline to week 24 in morning trough FEV_1, and to detect as significant a 0.1 L difference between either aclidinium/formoterol FDC or aclidinium/formoterol dose (400 mcg/6 mcg) and aclidinium 400 mcg in the change from baseline to week 24 in FEV_1 at one hour post-dose, using two-sided tests and adjusting for multiple treatment comparisons at the overall significance level of 0.05.[17] The assumptions used for the sample size calculation were based on data obtained from the phase 2b dose-finding studies of aclidinium/formoterol and from the phase 3 studies of aclidinium monotherapy.[17] Subsequent to commencement of the phase 3 pivotal studies of aclidinium/formoterol, data have become available from phase 3 clinical studies of recently approved LABA/ LAMA fixed combinations that support the selected delta for the phase 3 pivotal studies.[17]

For the TDI and the SGRQ, the main treatment comparisons for the individual phase 3 pivotal studies were made for each dose of aclidinium/formoterol compared with placebo. Treatment comparisons between each dose of aclidinium/formoterol and either monotherapy were supportive.[17] As only trends toward statistical superiority were expected for aclidinium/formoterol FDC compared with monotherapies for the individual studies, a more robust evaluation of the relative efficacy of aclidinium/formoterol FDC and the monotherapies on these assessments was conducted using the pooled population of the phase 3 pivotal studies.[17]

The aim was to increase the precision of effect estimates on selective clinically relevant efficacy end points (pulmonary function, quality of life, symptoms, and exacerbations), and to allow the assessment of the consistency of treatment effect in subpopulations (i.e., sex, race, age group, BMI group, COPD severity, smoking status, bronchodilator reversibility, and concomitant use of ICS).[17] The pooled analysis was also conducted to provide estimates of the treatment effect of each dose of aclidinium/formoterol FDC compared with component monotherapies on the key TDI and SGRQ end points and compared with placebo on exacerbation end points.

b) Results (LAC 30 and LAC 31)

Baseline Characteristics (LAC 30 and LAC 31)

Demographic characteristics of patients enrolled in phase 3 pivotal studies, LAC 30 and LAC 31, and in the pooled population of LAC 30 and LAC 31 populations, are presented in Table 3.[17]

TABLE 3: DEMOGRAPHIC CHARACTERISTICS

Variable (Unit) Statistic/Category		Study		Pooled Population[a]
		LAC 30	LAC 31	
		N = 1,726	N = 1,668	N = 3,394
Age (years)				
	Mean (SD)	63.2 (8.0)	63.9 (8.9)	63.5 (8.4)
	Range	40.0 to 85.0	40.0 to 93.0	40.0 to 93.0
Age group (years)				
≥ 40 to < 60	n (%)	566 (32.2)	521 (31.2)	1,077 (31.7)
≥ 60 to 0	n (%)	780 (45.2)	679 (40.7)	1,459 (43.0)
≥ 70	n (%)	390 (22.6)	468 (28.1)	858 (25.3)
Gender				
Male	n (%)	1,166 (67.6)	887 (53.2)	2,053 (60.5)
Race				
Caucasian	n (%)	1,638 (94.9)	1,555 (93.2)	3,193 (94.1)
Black/African American	n (%)	4 (0.2)	95 (5.7)	99 (2.9)
Other	n (%)	84 (4.9)	18 (1.1)	102 (3.0)
Geographical region				
US/Canada	n (%)	0	1,618 (7.0)	1,619 (47.7)
Europe	n (%)	1,535 (88.9)	0	1,535 (45.2)
Rest of world[b]	n (%)	191 (11.1)	50 (3.0)	240 (7.1)

SD = standard deviation.
[a] Pooled analysis of patient populations from LAC 30 and LAC 31.
[b] Rest of world in LAC 30 was South Africa and South Korea; in LAC 31 it was Australia and New Zealand.

Baseline COPD status and smoking history of patients enrolled in phase 3 pivotal studies, LAC 30 and LAC 31, and in the pooled population of LAC 30 and LAC 31: intention-to-treat (ITT) populations are presented in Table 4.[17]

TABLE 4: BASELINE CHRONIC OBSTRUCTIVE PULMONARY DISEASE STATUS AND SMOKING HISTORY

Variable (Unit) Statistic/Category		Study		Pooled Population[a]
		LAC 30	LAC 31	
		N = 1,726	N = 1,668	N = 3,394
COPD severity (based on degree of airway obstruction[b])				
Stage I (mild)	n (%)	1 (0.1)	4 (0.2)	5 (0.1)
Stage II (moderate)	n (%)	1,037 (60.1)	950 (57.0)	1987 (58.6)
Stage III (severe)	n (%)	685 (39.7)	697 (41.8)	1,382 (40.8)
Stage IV (very severe)	n (%)	2 (0.1)	12 (0.7)	14 (0.4)
Patients with exacerbations in the previous 12 months				
0	n (%)	1,088 (63.0)	1,318 (79.0)	2,406 (70.9)
1	n (%)	441 (25.6)	247 (14.8)	688 (20.3)
≥ 2	n (%)	197 (11.4)	103 (6.2)	300 (8.8)
SGRQ total score[c]				
	n Mean (SD)	1,702 46.2 (17.6)	1,622 46.0 (17.7)	3,324 46.1 (17.6)
BDI focal score[d]				
	n Mean (SD)	1,682 6.6 (2.1)	1,615 6.4 (2.3)	3,297 6.5 (2.1)
Smoking history				
Current smoker Smoking consumption (pack-years)	n (%) Mean (SD)	816 (47.3) 40.3 (20.6)	860 (51.6) 52.7 (26.3)	1,676 (49.4) 46.4 (26.4)

BDI = Baseline Dyspnea Index; COPD = chronic obstructive pulmonary disease; SD = standard deviation; SGRQ = St. George's Respiratory Questionnaire.

[a] Pooled analysis of patient populations from LAC 30 and LAC 31.

[b] Global Initiative for Chronic Obstructive Lung Disease classification of COPD severity based on airway limitation: Stage I — post-bronchodilator $FEV_1 \geq 80\%$ predicted; Stage II — post-bronchodilator $FEV_1 \geq 50\%$ and $< 80\%$ predicted; Stage III — post-bronchodilator $FEV_1 \geq 30\%$ and $< 50\%$ predicted; Stage IV — post-bronchodilator $FEV_1 < 30\%$ predicted.

[c] SGRQ total score ranges from 0 to 100; higher scores indicate worse health status.

[d] BDI focal score ranges from 0 to 12; lower scores indicate worse dyspnea.

The COPD severity distributions, Baseline Dyspnea Index (BDI) focal scores, and baseline SGRQ total scores of patients in LAC 30 and LAC 31 were similar. A higher proportion of patients in LAC 30 had experienced COPD exacerbations in the previous 12 months (37.0%) compared with LAC 31 (21.0%). While a similar proportion of patients in the two studies were current smokers, the smoking consumption of patients in LAC 31 (52.7 pack-years) was higher than in LAC 30 (40.3 pack-years).[17]

Analysis of the pooled population of LAC 30 and LAC 31 showed that nearly all (99.4%) of the enrolled patients had moderate or severe COPD, an observation that is consistent with the protocols' eligibility criteria (Module 2.7.3.1.5.1). A higher proportion of patients had moderate COPD (58.6%) than severe COPD (40.8%). The majority of patients had not experienced an exacerbation of their COPD within the previous 12 months. Mean smoking consumption was 46.4 pack-years, and approximately 50% of the population were current smokers.[17] Overall, lung function (as determined by pre- and post-bronchodilator FEV_1/percentage predicted FEV_1 and post-bronchodilator FEV_1/FVC ratio) at screening was very similar between the patients enrolled in the two studies. Bronchial reversibility to short-acting beta-2 agonists (SABAs) was higher in LAC 31 (percentage and absolute reversibility: 17.9% and 0.205 L, respectively) than in LAC 30 (12.7% and 0.152 L, respectively).[17]

Patient Disposition (LAC 30)

In LAC 30, a total of 2,443 patients were screened for the study, with 1,729 being randomized to study treatment. A slightly higher proportion of patients in the placebo group prematurely discontinued study treatment (17.5%) compared with the active treatment groups (range: 8.8% to 13.0%). Withdrawals due to AEs (WDAEs) were similar across the treatment groups (see Table 5).

TABLE 5: SUMMARY OF PATIENT DISPOSITION FOR ACLIFORM — LAC 30

Disposition	ACLIFORM			
	Aclidinium/Formoterol FDC	Aclidinium	Formoterol	Placebo
Screened, N (2,443)				
Randomized, N (1,729)	385	385	384	194
Discontinued, N (%)	34 (8.8)	50 (13.0)	45 (11.7)	34 (17.5)
WDAEs, N (%)	12 (3.1)	11 (2.9)	11 (2.9)	7 (3.6)
Withdrawal due to SAEs, N (%)	7 (1.8)	4 (1.0)	3 (0.8)	4 (2.1)
Lost to follow-up, N (%)	1 (0.3)	1 (0.3)	1 (0.3)	0 (0)
Modified intention-to-treat, N (%)[b]	385 (100)	383 (99.5)	383 (99.7)	194 (100)
Per-protocol, N (%)	363 (94.3)	365 (94.8)	358 (93.2)	179 (92.3)
Safety, N (%)[b]	385 (100)	385 (100)	384 (100)	194 (100)

FDC = fixed-dose combination; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
Data Sources: Patient disposition;[20] study populations, Module 2.7.3;[17] withdrawal due to SAE.[21]

Efficacy (LAC 30)

Primary end points: The increases from baseline to week 24 in FEV_1 at one hour post-dose were statistically significantly greater for aclidinium/formoterol FDC than for aclidinium (by 0.125 L [$P < 0.0001$] and 0.069 L [$P < 0.001$], respectively).[17,20] Similarly, the increases from baseline to week 24 in trough FEV_1 were statistically significantly greater for aclidinium/formoterol FDC than for formoterol (by 0.085 L [$P < 0.0001$] and 0.053 L [$P = 0.002$]), respectively.[17,20] However, compared with aclidinium, there was no statistically or clinically significant difference between aclidinium/formoterol FDC and aclidinium monotherapy in terms of changes from baseline of trough FEV_1 (0.026 L; 95% CI, –0.007 to 0.060; $P = 0.1274$)[10] (see Table 12).

Secondary end points: Statistically significant and clinically meaningful improvements in TDI focal score at week 24 were observed between aclidinium/formoterol FDC and placebo (1.29 units [$P < 0.001$]).[20] Trends toward greater improvements in TDI focal score at week 24 with aclidinium/formoterol FDC compared with either aclidinium or formoterol were also observed, but they were not statistically significant (0.40 units [$P = 0.084$] and 0.45 units [$P = 0.052$], respectively).[17] No statistically significant difference (–0.65 units, $P = 0.598$) was observed in SGRQ scores between aclidinium/formoterol FDC and placebo following 24 weeks of treatment. Treatment with aclidinium/formoterol FDC produced only a small decrease in SGRQ total score compared with placebo of –0.65 units ($P = 0.598$), at least in part due to a large placebo response[20] (see Table 13).

A statistically significant reduction in exacerbation rate of 29% was observed with aclidinium/formoterol FDC compared with placebo (RR 0.71, $P = 0.016$) when exacerbations were assessed according to EXACT, with a numerical reduction in exacerbation rate when assessed by HRU.[17]

Patient Disposition (LAC 31)

A higher proportion of patients in the placebo group prematurely discontinued study treatment (30.0%) compared with the proportions prematurely discontinuing in the active treatment groups (range: 18.3% to 21.2%) (see Table 6). No significant differences across treatment groups were observed in the reasons for premature discontinuation, with the exception of insufficient therapeutic response, which was reported for a higher proportion of patients in the placebo group (5.9%) compared with those reported for the active treatment groups (1.2% to 2.9%).

TABLE 6: SUMMARY OF PATIENT DISPOSITION FOR AUGMENT — LAC 31

Disposition	AUGMENT			
	Aclidinium/Formoterol FDC	Aclidinium	Formoterol	Placebo
Screened, N (3,260)				
Randomized, N (1,692)	338	340	339	337
Discontinued, N (%)	66 (20)	72 (21.2)	69 (20)	101 (30)
WDAEs, N (%)	21 (6.2)	16 (2.9)	14 (4.1)	22 (6.5)
Withdrawal due to SAEs, N (%)	8 (2.4)	7 (2.1)	9 (2.7)	7 (2.1)
Lost to follow-up, N (%)	9 (2.7)	2 (0.6)	4 (0.3)	5 (1.5)
Modified Intention-to-treat, N (%)	335 (99.1)	337 (99.1)	332 (97.9)	331 (98.2)
Per-protocol, N (%)	302 (89.3)	292 (85.9)	301 (88.8)	296 (87.8)
Safety, N (%)	335 (99.1)	337 (99.1)	332 (97.9)	332 (98.5)

FDC = fixed-dose combination; WDAE = withdrawal due to an adverse event.
Data Sources: Patient disposition;[22] study populations Module 2.7.3;[17] withdrawal due to SAE.[21]

Efficacy (LAC 31)

Primary end points: The increases from baseline to week 24 in FEV_1 at one hour post-dose were statistically and clinically significantly greater for aclidinium/formoterol FDC than for aclidinium (by 0.108 L, $P < 0.0001$).[22] Improvements in trough FEV_1 were statistically significantly greater in patients treated with aclidinium/formoterol FDC than with formoterol (by 0.045 L, $P = 0.01$).[22] Statistically significant increases from baseline to week 24 in both FEV_1 at one hour post-dose and in trough FEV_1 were also observed for both doses of aclidinium/formoterol FDC compared with placebo.[22] However, compared with aclidinium, there was no statistically significant difference between aclidinium/formoterol FDC and aclidinium monotherapy in terms of changes from baseline of trough FEV_1 (0.028 L; 95% CI, –0.0006 to 0.0627; $P = 0.1035$)[11] (see Table 12).

Secondary end points: At week 24, significant improvements in TDI focal scores were achieved with aclidinium/formoterol FDC compared with placebo ($P < 0.0001$), with the difference surpassing the minimal clinically important difference (MCID) of 1-unit improvement from baseline.[22] The magnitude of the improvements in TDI focal score were numerically, but not statistically significantly, greater with aclidinium/formoterol FDC than with either formoterol (by 0.49 units, $P = 0.084$) or with aclidinium (0.46 units, $P = 0.108$)[17] (Module 2.7.3-11). Statistically significant and clinically meaningful mean improvements from baseline in SGRQ total score were observed with aclidinium/formoterol FDC compared with placebo (–4.35 units, $P < 0.001$). The magnitude of the improvements from baseline to week 24 in SGRQ total score were numerically greater with aclidinium/formoterol FDC than with formoterol (by –1.87 units), and were of a similar magnitude to those observed with aclidinium (treatment differences of –0.13 units).[22] However, these differences were not statistically or clinically significant (see Table 13).

There were numerical reductions in the rate of exacerbations of any severity (according to HRU and EXACT definitions) and in the rate of moderate exacerbations compared with placebo.[17]

2.1.3 AFFIRM (LAC 39)

A randomized, double-blind, double-dummy, active-controlled study that evaluated the efficacy, safety, and tolerability of twice-daily aclidinium/formoterol FDC compared with twice-daily salmeterol/ fluticasone propionate for 24 weeks treatment in symptomatic patients with COPD (see Table 7).

TABLE 7: STUDY CHARACTERISTICS FOR AFFIRM — LAC 39

Characteristics		Details for AFFIRM — LAC 39 [18]
STUDY DESIGN	**Objectives**	• To assess the long-term bronchodilator efficacy of aclidinium/formoterol FDC administered b.i.d., compared with salmeterol/fluticasone (S/F) in symptomatic COPD patients • To compare the benefits of aclidinium/formoterol FDC vs. S/F in disease-related health status and COPD symptoms • To evaluate the long-term safety and tolerability of aclidinium/formoterol FDC vs. S/F.
	Blinding	Double-blind, double-dummy
	Study period	November 2013 to August 2014
	Study centres	Conducted at 140 sites in 14 countries, including Canada, Europe, and South Africa
	Design	Randomized, double-blind, double-dummy, comparator study
STUDY POPULATION	**Randomized (N)**	933
	Inclusion criteria	• Male and female patients aged ≥ 40 years • Clinical diagnosis of COPD according to 2013 GOLD guidelines, with a post-bronchodilator FEV_1 < 80%, and FEV_1/FVC < 70% at Screening Visit (visit 1) • Symptomatic patients with a CAT score ≥ 10 at Screening and Randomization Visit (visit 1 and 2) • Current or ex-smokers of ≥ 10 pack-years.
	Exclusion criteria	• No signs of respiratory tract infection or COPD exacerbation within 6 weeks (or 3 months if hospitalization was required) before the Screening Visit (visit 1) or during the run-in period • No evidence of clinically significant respiratory and/or cardiovascular conditions (myocardial infarction < 6 months, hospitalization for cardiac failure, New York Heart Association class III to IV or unstable arrhythmia < 12 months before Screening Visit) • No contraindication to use of anticholinergic drugs (symptomatic prostatic hypertrophy, symptomatic bladder neck obstruction, or known narrow-angle glaucoma) • Patients who were currently participating in, or had participated in, a pulmonary rehabilitation program within the previous 3 months were excluded • Patients treated on a daily basis with triple therapy (LAMA + LABA + ICS) within 4 weeks prior to the Screening Visit (visit 1).
DRUGS	**Intervention**	Aclidinium/formoterol FDC, (400 mcg/12 mcg) via inhalation (Genuair), b.i.d.
	Comparator	Salmeterol 50 mcg/fluticasone propionate 500 mcg, b.i.d.
DUR	**Run-in**	2 to 3 weeks

Characteristics		Details for AFFIRM — LAC 39 [18]
	Treatment	24 weeks
	Follow-up	2 weeks
OUTCOMES	**Primary end point**	Change from baseline in peak FEV_1 at week 24
OUTCOMES	**Other End Points**	**Key secondary endpoints** • Improvement from baseline to week 24 in the TDI focal score • Change from baseline to week 24 in the SGRQ total score • Percentage of patients with ≥ 1 COPD exacerbation: based on the health care resource utilization definition and EXACT-PRO • Safety: AEs and SAEs, clinical laboratory parameters, BP, 12-lead ECG
NOTES	**Publications**	LAC 39 CSR NCT01908140

AE = adverse event; b.i.d. = twice daily; BP = blood pressure; CAT = COPD assessment test; COPD = chronic obstructive pulmonary disease; CSR = Clinical Study Report; ECG = electrocardiogram; EXACT-PRO = EXAcerbations of Chronic Obstructive Pulmonary Disease Tool–Patient-Reported Outcomes; FDC = fixed-dose combination; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroid; LABA = long-acting beta2-agonist; LAMA = long-acting muscarinic antagonist; SAE = severe adverse event; S/F = salmeterol/fluticasone propionate; SGRQ = St. George's Respiratory Questionnaire; TDI = Transition Dyspnea Index.

a) Intervention and Comparators

Interventions in the trial were aclidinium/formoterol FDC (400 mcg/12 mcg) twice daily and salmeterol/fluticasone (50 mcg/500 mcg) oral inhalation by Accuhaler dry powder inhaler, twice daily.

b) Outcomes

Key efficacy outcomes were peak FEV_1, TDI focal score, and SGRQ total score at week 24. Safety outcomes were AEs, serious adverse events (SAEs), clinical laboratory parameters, BP, and 12-lead ECG (see Sections 2.1.1 and 2.1.2 for LAC 30 and LAC 31, respectively).

c) Statistical Analyses

The following is taken from the Clinical Study Report (CSR).[19] The analyses of the primary and secondary efficacy variables, peak FEV_1 and TDI at week 24, were performed for the mITT and PP populations. The analysis on the PP population was the primary analysis when assessing non-inferiority objectives, and the analyses on the ITT population was the primary analysis when assessing the switch to superiority. All other efficacy variables were performed on the ITT population. Safety outcomes were analyzed on the safety population.

Non-inferiority of aclidinium/formoterol FDC compared with salmeterol/fluticasone was assessed first for the primary efficacy variable. If non-inferiority was satisfied, then superiority was assessed for the primary efficacy variable. If superiority was satisfied for the primary efficacy variable, then non-inferiority was tested on the main secondary variable. The primary and main secondary efficacy variables, peak FEV_1 and TDI at week 24, were analyzed by means of a MMRM as well as for all continuous variables.

Except for data on the number of patients with one or more COPD exacerbations, which were analyzed using a logistic regression model, dichotomous variables were analyzed by means of logistic random

regression models. Preference variables were analyzed using a chi-square test. A Cox model was performed for time to exacerbation. Safety outcomes (AEs, laboratory parameters, blood pressure, and 12-lead ECG) were summarized by means of descriptive statistics. Additionally, potentially clinically significant changes in the last three safety outcomes were assessed.

Summary of Patient Disposition for LAC 39

A total of 1,125 patients were screened, of whom 933 patients were assessed as eligible and were randomized into the study. Overall, 788 (84.5%) of the randomized patients completed the study. A total of 145 (15.5%) patients discontinued from the study, mainly due to withdrawal of informed consent by the patient (23 [4.9%] patients in the aclidinium/formoterol FDC group and 24 [5.2%] patients in the salmeterol/fluticasone group, and AEs (22 [4.7%] patients in the aclidinium/formoterol FDC group and 23 [4.9%] patients in the salmeterol/fluticasone group) (see Table 8).

TABLE 8: PATIENT DISPOSITION FOR LAC 39

Disposition	AFFIRM — LAC 39	
	Aclidinium/Formoterol FDC	Salmeterol/Fluticasone FDC
Screened, N (1,125)		
Randomized, N (933)	468	465
Discontinued, N 145 (15.5%)	66 (14.1%)	79 (17.0%)
WDAEs, N = 45 (4.8%)	[redacted]	[redacted]
Lost to follow-up, N = 7 (0.8%)	[redacted]	[redacted]
Intention-to-treat, N = 931	468 (100%)	463 (99.6%)
Per-protocol, (N = 837)	423 (90.4%)	414 (89.0%)
Safety, (N = 933)	467 (99.8%)	466 (100.2%)

FDC = fixed-dose combination; WDAE = withdrawal due to an adverse event.
Note: Data are taken from the Clinical Study Report.[19]

Efficacy

Primary efficacy variable: Peak FEV_1 at week 24: After 24 weeks of treatment, non-inferiority of aclidinium/formoterol FDC compared with salmeterol/fluticasone was satisfied, as the lower bound of the two-sided 95% CI for the difference between aclidinium/formoterol FDC and salmeterol/fluticasone was 0.070 L in the PP population, exceeding the non-inferiority limit of –0.055 L. Following the pre-specified multiplicity approach, the switch from non-inferiority to superiority was tested. After 24 weeks of treatment, superiority was satisfied, as the aclidinium/formoterol FDC group showed a statistically significantly greater peak FEV_1 compared with the salmeterol/fluticasone group in the ITT population, with an adjusted mean difference compared with salmeterol/fluticasone of 0.093 L ($P < 0.0001$). This result was supported by the sensitivity analysis.

In terms of trough FEV_1, aclidinium/formoterol FDC showed no statistically significant difference compared with salmeterol/fluticasone, with adjusted mean differences of –0.014 L ($P > 0.05$).These differences were also not considered to be clinically meaningful[9] (see Table 12).

Main secondary efficacy variable: Improvement in TDI at week 24: Non-inferiority of aclidinium/formoterol FDC compared with salmeterol/fluticasone was satisfied, as the lower bound of the two-sided 95% CI for the difference between aclidinium/formoterol FDC and salmeterol/fluticasone was –0.46 units, exceeding the non-inferiority limit of –0.5 units. No difference between the treatment groups was observed ($P = 0.9951$) (see Table 13).

Secondary TDI focal, SGRQ, exacerbations end points: Clinically meaningful improvements (i.e., increases of ≥ 1.0 unit) in the TDI focal scores were observed for both treatment groups at all post-baseline visits. However, no statistically or clinically significant differences between the treatment groups in the adjusted means were observed for the TDI focal and dimension scores ([redacted] in all cases). Clinically meaningful improvements (i.e., decreases of ≥ 4.0 units) from baseline in the mean SGRQ-C total scores were observed for both treatment groups after 24 weeks of treatment. However, no statistically or clinically significant differences between the treatment groups in the adjusted means for the SGRQ-C total and the three dimension scores (data not presented for the three dimensions) were observed at any post-baseline visits ($P > 0.05$ in all cases). There were no significant differences between in the aclidinium/formoterol FDC and salmeterol/fluticasone groups in the percentage of patients with COPD exacerbations during the study (15.8% and 16.6%, respectively)(see Table 13).

Secondary safety end points: Overall, aclidinium/formoterol FDC was similar to salmeterol/fluticasone with respect to AEs. The most common TEAEs were COPD (exacerbation) (17.5% of patients overall), headache (6.4% of patients overall), and nasopharyngitis (5.8% of patients overall), all of which were reported at similar frequencies between the treatment groups. The majority of TEAEs were either mild or moderate in intensity, with severe TEAEs reported at a slightly higher frequency for the aclidinium/formoterol FDC group (9.4%) compared with the salmeterol/fluticasone group (7.5%). The frequency of TEAEs leading to discontinuation was higher in the salmeterol/fluticasone group (7.3% of patients) compared with the aclidinium/formoterol FDC group (5.4% of patients). Respiratory events were the most common type of steroid-related event, reported more frequently for the salmeterol/fluticasone group (4.5% of patients) compared with the aclidinium/formoterol FDC group (1.7% of patients).

2.1.4 LAC 36 (Extension Study)

A phase 3, long-term, randomized, double-blind extension study (to LAC 31) of the efficacy, safety and tolerability of two FDCs of aclidinium/formoterol, aclidinium, formoterol, and placebo during 28 weeks of treatment in patients with moderate to severe, stable COPD (Table 9).

TABLE 9: STUDY CHARACTERISTICS OF LAC 36

Characteristics		Details for LAC 36[27]
STUDY DESIGN	**Objective**	Long-term safety and tolerability of aclidinium/formoterol FDC, long-term efficacy, pharmacoeconomics, and HRQoL
	Blinding	Double-blind
	Study period	April 2012 to June 2013
	Study centres	US and Canada
	Design	Prospective, double-blind, randomized, parallel-group, active comparator- and placebo-controlled, 28-week study extension study from LAC 31
STUDY POPULATION	**Randomized (N)**	921 (randomized in a 1:1:1:1:1 ratio) in the lead-in LAC 31
	Inclusion criteria	Patients in the US and Canada with a diagnosis of stable moderate to severe COPD who completed the treatment phase of the lead-in study, LAC 31
	Exclusion criteria	NA
DRUGS	**Intervention**	Aclidinium/formoterol FDC (aclidinium 400 mcg/formoterol 12 mcg), via inhalation (Genuair), b.i.d.
	Comparator(s)	Aclidinium (400 mcg), formoterol (12 mcg), placebo, all via inhalation (Genuair), b.i.d.

Characteristics		Details for LAC 36[27]
DURATION	**Run-in**	NA
	Treatment	28 weeks
	Follow-up	2 weeks
OUTCOMES	**Primary End Point(s)**	None specified, as primary objective was safety
	Other End Points	Changes from baseline in FEV_1 at 1 hour post-dose and trough FEV_1 by visit over 52 weeks, improvements in TDI, and changes in SGRQ total score, rate of exacerbations/year (HRU and EXACT), change in rescue medication use, change in nighttime and early morning symptoms.
NOTES	**Publications**	• NCT01572792

b.i.d. = twice daily; COPD = chronic obstructive pulmonary disease; EXACT = EXAcerbations of Chronic Obstructive Pulmonary Disease Tool; FDC = fixed-dose combination; FEV_1 = forced expiratory volume in one second; HRQoL = health-related quality of life; HRU = health care resource utilization; NA = not applicable; SGRQ = St. George's Respiratory Questionnaire; TDI = Transition Dyspnea Index.

Statistical Analyses

The efficacy analysis populations for LAC 36 for all efficacy variables except for COPD exacerbation variables were the mITT population and combined ITT population, respectively. Analyses of COPD exacerbation variables were based on the combined ITT-exacerbation population (LAC 36). For LAC 36, the definition of the combined mITT population was the same as that of the mITT population of LAC 32, except that the required baseline and post-baseline assessments of FEV_1 were in lead-in study LAC 31. The combined ITT-exacerbation population was defined as all patients who took at least one dose of randomized treatment (which for LAC 36 was in lead-in study LAC 31).[17]

Summary of Patient Disposition for (LAC 36)

A lower proportion of patients in the placebo group completed LAC 31/36 (35.9%) compared with the proportions completing in the active treatment groups (45.9% to 53.0%). No significant differences across treatment groups were observed in the reasons for premature discontinuation during LAC 31/36, with the exception of insufficient therapeutic response, which was reported for a higher proportion of patients in the placebo group (6.5%) compared with those in the active treatment groups (2.1% to 3.5%). Patient disposition was similar between the groups, with similar discontinuation rates between the groups and similar rates of WDAEs (see Table 10).

TABLE 10: PATIENT DISPOSITION FOR LAC 36

Disposition	LAC 36			
	A/F FDC	Aclidinium	Formoterol	Placebo
Screened (NA)	Not available			
Enrolled in LAC 36[a] (N = 716)	184	194	192	146
Discontinued (LAC 36), N (%)	29 (15.8)	29 (14.9)	32 (16.7)	25 (17.1)
***WDAEs,* N (%)**	6 (3.3)	6 (3.1)	4 (2.1)	7 (4.8)
***Lost to follow-up,* N (%)**	2 (1.1)	3(1.5)	3 (1.6)	6 (4.1)
Combined LAC 31/LAC 36 Intention-to-treat population	335	337	332	331
Extension safety population (LAC 36)	182	194	192	146

A/F = aclidinium/formoterol; FDC = fixed-dose combination; WDAE = withdrawal due to an adverse event.
[a] Not all eligible patients chose to participate in the double-blind extension trial. Includes all patients from the lead-in study who signed informed consent at visit 1 of the extension study.
Note: The combined ITT population consisted of all patients in the combined safety population who had a baseline assessment in the lead-in study (visit 2 of LAC 31) and at least one post-baseline assessment of forced expiratory volume in one second (FEV_1) in the lead-in study, LAC 31. The extension safety population consisted of all patients in the enrolled population who took at least one dose of the double-blind investigational product in this extension study.
Source: Data are taken from the Clinical Study Report.[27]

Efficacy

Lung function: The improvements from baseline in FEV_1 at one hour post-dose observed with aclidinium/formoterol FDC compared with placebo at day 4 of dosing (in LAC 31) were sustained up to week 52. Over the 52-week treatment period, adjusted mean treatment differences between aclidinium/formoterol FDC and placebo ranged from 0.284 L to 0.299 L ($P < 0.0001$). Statistically significant improvements were also observed at all time points up to week 52 with aclidinium/formoterol FDC relative to formoterol or aclidinium monotherapies.[17] Treatment with aclidinium/formoterol FDC was associated with clinically significant improvements from baseline in trough FEV_1, which were maintained for the duration of the 52-week treatment period. Adjusted mean treatment differences between aclidinium/formoterol FDC and placebo ranged from 0.118 L to 0.152 L ($P < 0.0001$).[17] Numerically more increases from baseline in trough FEV_1 compared with formoterol or aclidinium were observed with aclidinium/formoterol FDC at all visits up to week 52.[17] However, at week 52, compared with aclidinium, there was no statistically or clinically significant difference between aclidinium/formoterol FDC and aclidinium monotherapy in terms of change from baseline of trough FEV_1 (0.0077 L; 95% CI –0.0345 to 0.00499; $P = 0.7211$)[11] (see Table 12).

Dyspnea: Clinically and statistically significant improvements in dyspnea status (TDI focal score) with aclidinium/formoterol FDC compared with placebo were maintained from week 4 to week 52 (adjusted mean treatment differences from 1.07 units to 1.49 units [$P < 0.005$ for all comparisons]).[17] Improvements in TDI focal score were not statistically significantly superior with aclidinium/formoterol FDC compared with either constituent monotherapy at all visits up to week 52.

HRQoL:[17] SGRQ total score was used to measure changes in HRQoL, but only descriptive statistical analyses were conducted. Adjusted mean treatment differences between aclidinium/formoterol FDC 400 mcg/12 mcg and placebo in the changes from baseline in SGRQ total score ranged from –1.19 units (week 4) to –4.35 units (week 24).

Exacerbations: Rates of moderate or severe exacerbations (HRU definition) were lower in the aclidinium/formoterol FDC arm ([redacted] per patient/year) than in the placebo arm ([redacted] per patient/year), while rates of exacerbations of any severity (HRU definition) were similar in the aclidinium/formoterol FDC and placebo arms ([redacted] per patient/year, respectively).[17] A non-statistically significant reduction ([redacted]) in EXACT exacerbation rate was observed with aclidinium/formoterol FDC compared with placebo (rate ratio (RR) [redacted]).[17]

2.1.5 LAC 32 (week 52)

LAC 32, a double-blind, randomized controlled trial, compared aclidinium/formoterol FDC (400 mcg/12 mcg) with formoterol (12 mcg) and was conducted at 135 centres in the US. The objective of LAC 32 was to assess the long-term safety and tolerability of aclidinium/formoterol FDC versus monotherapies; efficacy parameters were not classified as primary, secondary, and additionally, were analyzed for descriptive purposes. Most of the patients enrolled in LAC 32 also had Global Initiative for Chronic Obstructive Lung Disease (GOLD) Stage II COPD (52.4%, n = 309) and GOLD Stage III COPD (46.3%, n = 273), representing moderate to severe disease. The patient disposition is presented in Table 11. Efficacy results for trough FEV_1 and COPD exacerbations are presented in Table 12. TEAEs were reported in 71.4% of the aclidinium/formoterol FDC group and in 65.7% of the formoterol group. The most commonly reported TEAEs (> 5%) in both treatment groups were sinusitis (5.1% to 5.6%) and urinary tract infection (5.6% to 6.6%). TEAEs (in > 2% in either treatment group) were reported for nasopharyngitis (aclidinium/formoterol FDC versus formoterol: 6.4% versus 4.5%), anxiety (5.9% versus 2.5%), muscle spasms (3.8% versus 2.0%), back pain (4.8% versus 2.5%), and headache (2.8% versus 2.5%), which showed a greater frequency in the aclidinium/formoterol FDC than in formoterol group. The proportions of patients with exacerbation of any severity, or moderate or severe exacerbation, were similar for the aclidinium/formoterol FDC group (27.3% and [redacted] respectively) and for the formoterol group (29.8% and [redacted] respectively). No differences in rates of moderate to severe exacerbations between aclidinium/formoterol FDC and formoterol monotherapy arms were observed in LAC 32 ([redacted] per patient/year and [redacted] per patient/year, respectively). The percentage of patients who had an SAE was similar between treatment groups (aclidinium/formoterol FDC versus formoterol: 9.7% versus 10.6%). Most SAEs in both treatment groups were reported by one patient only. The most commonly reported SAE was pneumonia in four patients (1.0%) in the aclidinium/formoterol FDC group and one patient (0.5%) in the formoterol group. A total of six deaths (aclidinium/formoterol FDC versus formoterol: five versus one) occurred during the treatment period, and two deaths (in the aclidinium/formoterol FDC group) occurred more than 30 days after the last dose of study drug; none of the deaths was considered to be related to study drugs.[10,12,13] The withdrawal rate at week 52 was 32.4% in the aclidinium/formoterol FDC group and 32.87% in the formoterol group. WDAEs were similar (6.6%) in both groups.

At week 52, a statistically significantly greater improvement from baseline for trough FEV_1 was observed with aclidinium/formoterol FDC compared with formoterol (LS mean = 0.082 L; 95% CI, 0.01 L to 0.15 L; P = 0.02).[13] The clinical significance of this difference is uncertain.

TABLE 11: PATIENT POPULATIONS FOR LAC 32

Population	Aclidinium/Formoterol FDC 400 mcg/12 mcg	Formoterol 12 mcg	Total
	N (%)	N (%)	N (%)
Randomized	392	198	590
Discontinuations	127 (32.4)	65 (32.8)	192 (32.5)
Completed patients	265 (67.6)	133 (67.2)	398 (67.5)
Safety	392 (100)	198 (100)	590 (100)
mITT-exacerbations	392 (100)	198 (100)	590 (100)
mITT	385 (98.2)	196 (99.0)	581 (98.5)

FDC = fixed-dose combination; mITT = modified intention-to-treat.
Source: Health Canada review report, [13] European Medicines Agency report,[12] and Module 2.7.3.[10]

TABLE 12: SUMMARY OF FEV_1 IN INCLUDED STUDIES

Outcomes	LAC 30	LAC 31	LAC 39	LAC 32
	Between-Group Difference of LS Mean Change From Baseline (95% CI)			
Trough FEV_1 (L), week 24				
A/F vs. F	0.085 (0.051, 0.119) *P* < 0.0001	0.0448 (0.011, 0.079) *P* < 0.010	NA	0.082 (0.01, 0.15) *P* = 0.02
A/F vs. A	0.026 (–0.007, 0.060) *P* = 0.127	0.028 (–0.006, 0.063) *P* = 0.104	NA	NR
A/F vs. S/F	NA	NA	**Additional analysis (mITT)** –0.014 (–0.043, 0.016) *P* = 0.3635[a]	NA
A/F vs. placebo	0.143 (0.101, 0.185) *P* < 0.0001	0.130 (0.095, 0.165) *P* < 0.0001	NA	NA
Peak FEV_1 (L), week 24				
A/F vs. S/F	NA	NA	**NI analysis (PP)** 0.101 (0.070, 0.131)[b] *P* < 0.0001[c] **Superiority analysis (mITT)** 0.093 (0.063, 0.123) *P* < 0.001	NA
1 hour post-dose FEV_1 (L) week 24				
A/F vs. F	0.139 (0.104, 0.174) *P* < 0.0001	0.0825 (0.047, 0.118) *P* < 0.0001	NA	NR
A/F vs. A	0.125	0.108	NA	NR

Outcomes	LAC 30	LAC 31	LAC 39	LAC 32
	Between-Group Difference of LS Mean Change From Baseline (95% CI)			
	(0.090, 0.160) *P* < 0.0001	(0.073, 0.144) *P* < 0.0001		
A/F vs. placebo	0.299 (0.255, 0.343) *P* < 0.0001	0.284 (0.247, 0.320) *P* < 0.0001	NA	*NA*

A = aclidinium; A/F = aclidinium/formoterol FDC; CI = confidence interval; F = formoterol; FEV_1 = forced expiratory volume in one second; LS = least-squares; mITT = modified intention-to-treat; NA = not applicable; NI = non-inferiority; NR = not reported; PP = per-protocol; S/F = salmeterol/fluticasone FDC; vs = versus.

[a] Trough FEV_1 was classified as an "additional analysis" in this study. It was not an NI analysis. The *P* value was obtained from the LS means.

[b] Peak FEV_1 was a primary outcome; the primary analysis was NI analysis based on the PP analysis. The NI was satisfied because the lower limit of 95% CI (0.07) exceeded the NI margin of –0.055 L.

[c] The *P* value was obtained from the LS means.

Source: Clinical Study Reports,[6-9] additional data from manufacturer,[11] and Health Canada report.[13]

TABLE 13: TRANSITION DYSPNEA INDEX, ST. GEORGE'S RESPIRATORY QUESTIONNAIRE, AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE EXACERBATION IN INCLUDED STUDIES

Outcomes	Comparison	LAC 30	LAC 31	LAC 39	LAC 32
TDI	**Between-group difference of LS mean change from baseline (95% CI)**				
	A/F vs. F	0.45 (–0.00, 0.90) *P* = 0.52	0.49 (–0.07, 1.06) *P* = 0.084	NA	NA
	A/F vs. A	0.40 (–0.05, 0.85) *P* = 0.084	0.46 (–0.10, to 1.02) *P* = 0.108	NA	NA
	A/F vs. S/F	NA	NA	0.0 (–0.46, 0.46) *P* = 0.9951	NA
	A/F vs. placebo	**1.29** **(0.73, 1.86)** ***P* < 0.0001**	**1.44** **(0.85, 2.02)** ***P* < 0.0001**	NA	NA
SGRQ	**Between-group difference of LS mean change from baseline (95% CI)**				
	A/F vs. F	–1.59 (–3.52, 0.35) *P* = 0.169	–1.87 (–3.92, 0.19) *P* = 0.075	NA	NA
	A/F vs. A	–1.36 (–3.30, 0.58) *P* = 0.169	–0.13 (–2.18, 1.92) *P* = 0.901	NA	NA
	A/F vs. S/F	NA		[redacted]	NA
	A/F vs. placebo	-0.65 (–3.08, 1.78) *P* = 0.598	**–4.35** **(–6.64, –2.24)** ***P* < 0.0001**	NA	NA
Moderate to severe COPD exacerbation	**COPD exacerbation rate: No. of events/patient/year RR (95% CI), P value**				
	A/F vs. F	NR	NR	NA	0.52 vs. 0.49 *P* = NS
	A/F vs. A	NR	NR	NA	NA
	A/F vs. S/F	NA	NA	Number of patients with COPD 1.0 (0.69, 1.44) *P* = 0.9805	NA
	A/F vs. placebo	0.77 (0.44, 1.36) *P* = 0.37	0.69 (0.46, 1.02) *P* = 0.066		NA
	A/F vs. placebo	**Pooled: 0.71 (0.51, 0.98), *P* = 0.036**			
	F vs. placebo	1.08 (0.63, 1.86) *P* = 0.769	0.74 (0.50, 1.10) *P* = 0.14		
	A vs. placebo	0.78 (0.45, 1.37) *P* = 0.388	0.89 (0.61, 1.31) *P* = 0.565		

A = aclidinium; A/F = aclidinium/formoterol FDC; CI = confidence interval; COPD = chronic obstructive pulmonary disease; F = formoterol; LS = least-squares; NA = not applicable; NR = not reported; NS = not statistically significant; RR = rate ratio; S/F = salmeterol/fluticasone; SGRQ = St. George's Respiratory Questionnaire; TDI = Transition Dyspnea Index vs = versus.
Source: Clinical Study Reports,[6-9] additional data from manufacturer,[11] and submission package.[10]

2.2 Critical Appraisal of Pivotal Clinical Studies

2.2.1 Internal Validity

All included studies were randomized and double-blind. The blinding was maintained until the end of the study. Allocation concealment was well reported. Baseline characteristics of patients were generally similar across treatment groups within all included studies with respect to demographics, smoking history, COPD duration and severity, ICS use, and co-existing medical conditions. In the two pivotal studies (LAC 30 and LAC 31), the majority of patients had no COPD exacerbations (61% to 66% in LAC 30 and 77% to 80% in LAC 31). Key outcomes included effects on lung function, dyspnea, HRQoL, exacerbations, and safety. In both pivotal studies (LAC 30 and LAC 31), sample size was calculated to provide at least 90% nominal power to detect a significant difference of 0.065 L between aclidinium/formoterol FDC dose (FDC 400 mcg/12 mcg) and formoterol monotherapy (12 mcg) in change from baseline trough FEV1 at week 24, and 0.1 L between aclidinium/formoterol FDC and aclidinium monotherapy 400 mcg in change from baseline at morning one hour post-dose FEV1 at week 24. An SD of 3.4 units was used to detect at least a 1-unit difference in TDI focal score between aclidinium/formoterol FDC and placebo, and an SD of 12.8 units to detect at least a 4-unit difference in SGRQ total score between any aclidinium/formoterol FDC and placebo. The co-primary efficacy variables (change from baseline in FEV1 at one hour post-dose and change from baseline in trough FEV1) were analyzed by means of a MMRM for the ITT population. Results for the PP population were, in general, consistent with the ITT population. A sensitivity analysis using a pattern-mixture model based on non-future dependent missing value restrictions was performed to assess the robustness of the primary MMRM results to the possible violation of the missing-at-random assumption. Multiplicity of testing for secondary outcomes was performed to control for type 1 error in both trials.

The potential limitations of the included studies (with a focus on the two pivotal studies) are discussed below. First, in the two pivotal studies, the reversibility test was done in the screening phase, but was not used as an exclusion criterion to exclude potential patients with asthma. The reversibility (% of increased FEV1) was 12.7 % to 17%; the absolute reversibility (L) of FEV1 increase was 0.157 L to 0.204 L. The reversible rates (i.e., patients who meet the reversible criteria) were 33% to 45%. However, the study has shown that bronchodilator reversibility status varies temporally and does not distinguish between clinically relevant outcomes, making it an unreliable test. It is no longer recommended to use the reversibility test to exclude patients with asthma.[10,19] Considering the relatively lower reversibility, and the fact that the study drug (aclidinium/formoterol FDC) does not contain steroids, it is unlikely that potential patients with asthma were enrolled or that there was any bias in favour of the study drug in this regard. Second, co-primary outcomes in the two pivotal studies were the trough FEV1 of aclidinium/formoterol FDC versus formoterol, and one hour post-dose trough FEV1 of aclidinium/formoterol FDC versus aclidinium, while trough FEV1 of aclidinium/formoterol FDC versus aclidinium and morning one hour post-dose FEV1 of aclidinium/formoterol FDC versus formoterol were not analyzed as primary outcomes. In LAC 39, the primary outcome was peak FEV1 (the rationale for this was not provided) instead of change from baseline trough FEV1, which is more commonly accepted as a primary outcome in COPD clinical trials and is easier to interpret clinically, according to the clinical expert involved in the review. Based on input from the clinical expert involved in the review, there is no bias in favour of one drug over another by assessing peak FEV1 as the primary outcome. Third, although the discontinuation rates observed in the pivotal studies are similar to those in studies performed with other approved FDCs (umeclidinium/vilanterol and glycopyrronium/indacaterol), the discontinuation rate at week 24 tended to be high in LAC 31, ranging from 20% to 30% across the treatment groups. The discontinuation rates at week 24 were higher in the placebo arms (17.5% and 30% in LAC 30 and LAC 31,

respectively) than in the active treatment arms (9% to 13% in LAC 30 and 20% to 21% in LAC 31, respectively).

The discontinuation rates at one year were 32% in both the aclidinium/formoterol FDC and the formoterol arms in LAC 32. In LAC 36, the 28-week extension of study LAC 31, an extra 15% patients discontinued. Although the discontinuation rates were comparable among the active treatment arms, it is unclear whether the high rate of withdrawals influenced the validity of the reported outcomes. In addition, LAC 36 included only the patients from US and Canada (approximately 65% of the included patients for LAC 31); patients from Australia and New Zealand were not included. As a result, the findings of the extension study only partially (65%) represent the total population of LAC 31. In LAC 39, the proposed non-inferiority margin for trough FEV1 response was –0.055 L. The manufacturer stated that the non-inferiority margin was based on the margins used in recent non-inferiority studies comparing two COPD treatments that varied between 0.050 L and 0.1 L.[20-22] The manufacturer reported that for LAC 39, assuming that the MCID established for trough FEV1 improvement versus placebo is 0.1 L, the non-inferiority margin of 0.055 L was taken to be approximately half of this. Nonetheless, the manufacturer did not provide a clear rationale as to why the non-inferiority margin for LAC 39 was set to be more than half of the lower range of the MCID for change in FEV1. Based on the minimal information provided, it remains unclear whether the non-inferiority margin was appropriately derived and is clinically relevant. Due to the high discontinuation rate, using mITT analysis would potentially overestimate the treatment effects. However, the discontinuation rate in active treatment groups within the study was similar. Lastly, in LAC 32, the MMRM analysis was performed based on all post-baseline measurements using only the observed cases without imputing missing values. This approach could be biased in favour of the combination group. Sensitivity analyses using a pattern-mixture model or other suitable analyses should be provided.[12]

2.2.2 External Validity

The majority of patients were older than 60 years, which is consistent with the COPD population in Canada. However, this was a very well-controlled and stable population of patients, given they had to be free of COPD exacerbations, relatively stable, and not receiving any prohibited concomitant medications prior to the start of the study. Nevertheless, the potential concerns of the generalizability of the findings do exist. First, about 53% to 65% of patients were male. The clinical expert involved in this review pointed out that in North America due to the considerable increase in the proportion of current female smokers, it is anticipated that more females will be diagnosed with COPD in the near future. Second, almost all included patients were Caucasian (> 93%); whether the findings can be generalized to various ethnic populations needs to be further investigated. Third, the trial durations of the two pivotal studies and LAC 39 were 24 weeks; although the durations were comparable to those in many other COPD clinical trials, they may have been insufficient for a comprehensive assessment of the long-term efficacy and safety (including mortality) outcomes for COPD. Fourth, most of the patients enrolled in the studies had GOLD Stage II COPD (ranged from 52.4% in LAC 32[10] to 60.1% in LAC 30,[6]) or GOLD Stage III COPD (from 35.2% in LAC 39[9] to 46.3% in LAC 32).[10,12,13] The majority of patients (63% in LAC 30 and 79% in LAC 31) did not experience a COPD exacerbation in the year prior to the studies; therefore, the generalizability of these findings to patients with COPD exacerbations is uncertain, as no subgroup analysis findings were available for patients with a history of COPD exacerbation within one year. Fifth, according to Canadian clinical practice guidelines[4] and GOLD guidelines (2015),[3] the LAMA/LABA combination is recommended to be used for patients who responded inadequately to LABA or LAMA monotherapy. Due to the insufficient information on the history of treatment with a specific LAMA or LABA agent, it could not be determined whether aclidinium/formoterol FDC will benefit patients who

are still symptomatic after treatment with aclidinium or formoterol or any other LAMA or LABA agent. Sixth, in the two pivotal studies, about 40% to 50% of patients who had used ICS or systemic steroids prior to the study were allowed to continue to use them as concomitant medication during the study. Patients using LABA/ICS were switched to the same ICS as monotherapy during the study. Therefore, for those patients who kept using ICS or systemic steroids, adding aclidinium/formoterol FDC does not reflect clinical practice, as ICS are recommended for use only in combination with a LABA and in patients who are symptomatic after combined LAMA/LABA treatment and/or who are frequent exacerbators. Nonetheless, it has been common in more recent COPD trials for patients to continue their prior ICS or low doses of systemic corticosteroids to minimize the risk of effects associated with discontinuing ICS prior to trial randomization, as described elsewhere.[23] More importantly, the lack of an active comparator with currently available LAMA/LABA FDCs is a major concern in this review. Due to the lack of comparative head-to-head clinical data, the efficacy and safety profile of aclidinium/formoterol FDC relative to other existing LAMA/LABA FDCs (i.e., umeclidinium/vilanterol FDC or indacaterol/glycopyrronium FDC) is unknown. The clinical expert involved in this review pointed out that formoterol is not used very often to treat patients with COPD in Canada. Therefore, whether a patient who had inadequately responded to a LABA other than formoterol or a LAMA other than aclidinium is suitable to switch to aclidinium/formoterol FDC is uncertain. Finally, the Genuair device is claimed to be user-friendly. In particular, patients already on aclidinium would likely be moved to aclidinium/ formoterol FDC although there is no clear evidence to show an advantage for patients who were on a LAMA other than aclidinium.

2.3 Summary of Safety

2.3.1 Safety Evaluation Plan

The data summarized in the following sections are taken from the Summary of Clinical Safety, Module 2.7.4. [28]

The primary safety data for aclidinium/formoterol FDC are provided from the two pivotal studies, LAC 30 and LAC 31, and the two long-term supportive studies, LAC 32 and LAC 36. Data from these studies have been integrated and analyzed to provide data about patient populations of special interest (i.e., subgroups including age, gender, race, body weight, COPD severity, and smoking status).[28] Safety assessments included recording of AEs and SAEs, monitoring of hematology, blood biochemistry, and urinary parameters, as well as physical examination, blood pressure, and ECG assessments. In addition, at selected sites in LAC 30, LAC 31, and LAC 32, 24-hour Holter monitoring was performed.[28] ECG and Holter data were collected via a centralized cardiology vendor. Laboratory assessments were also centralized. Integrated summaries, including descriptive statistics, tabulations, and enumerations are provided for the extent of study medication exposure, demographics and baseline characteristics, and concomitant medication usage, as well as treatment-emergent AEs (TEAEs), SAEs and deaths, TEAEs leading to permanent treatment discontinuation, laboratory evaluations, vital signs, and ECGs. In addition, analysis of TEAEs of special interest was performed for cardiac and cerebrovascular events, potential anticholinergic and beta2 adrenergic events, and lower respiratory tract infections including pneumonia. Additionally, an analysis of major adverse cardiac events has been performed in phase 3 studies.

2.3.2 Safety Populations Evaluated

The placebo-controlled phase 3 study population is the primary population analyzed for assessment of the safety of aclidinium/formoterol FDC, and comprises data from completed LAC 30, LAC 31, and LAC 36. This safety assessment is supported by analysis of data from all phase 3, twice-daily treatment studies (i.e., all phase 3 study populations).

The COPD population included was the same in all studies. Only one study (M-40464-02[29]), a pharmacokinetic study, was conducted in healthy subjects. The principal characteristics of the inclusion and exclusion criteria for patient enrolment in all pivotal studies conducted in patients with COPD were as follows:

- Male and females aged 40 years or older
- Current or ex-smokers with a smoking history of more than or equal to 10 pack-years
- Clinical diagnosis of stable, moderate to severe COPD. Severity of airflow obstruction was classified on the basis of airflow limitation as measured by post-bronchodilator FEV_1. Eligible patients must have had a post-bronchodilator FEV_1 < 80% of predicted and ≥ 30% of predicted, and FEV_1/FVC < 0.7
- Absence of respiratory tract infection or COPD exacerbation in the six weeks (3 months if hospitalization was required) prior to the screening visit
- Those without known symptomatic prostatic hypertrophy, bladder neck obstruction, or narrow-angle glaucoma
- No clinically relevant respiratory conditions (except COPD)
- No clinically significant cardiovascular conditions (e.g., newly diagnosed arrhythmia [within the previous 3 months], myocardial infarction within the previous six months, unstable angina or unstable arrhythmia within the previous six months [LAC 31 and LAC 32] or 12 months [in LAC 30], heart failure [New York Heart Association functional classes III or IV] that required hospitalization in the previous 12 months], or a QTcB [QT interval corrected for heart rate using Bazett's formula] above 470 msec at screening or prior to randomization)
- No history or current diagnosis of asthma, allergic rhinitis, or atopy
- No other clinically relevant (in the investigator's opinion) medical conditions.

In the phase 3 studies, patients were permitted to continue treatment with stable doses of ICS, oral sustained-release theophylline, and/or oxygen, as required (≤ 15 hours per day). Stable doses of oral and/or parenteral corticosteroids (≤ 10 mg/day or ≤ 20 mg every other day) were also permitted. Patients were provided with a marketed salbutamol/albuterol metered dose inhaler, to be taken as needed.

Male or female healthy subjects aged between 18 and 45 years were recruited in M-40464-02.[29]

2.3.3 Overview of Safety

The number of patient-years of exposure was lower for placebo-treated patients (275.6 patient-years) than for patients in the active treatment groups (394.9 to 408.4 patient-years) due to the lower randomization ratio (2:1 each active and placebo) and number of patients in the placebo arm from LAC 30 and also due to the higher number of discontinuations in this treatment arm. The number of patients per 1,000 patient-years with at least one TEAE was similar for the aclidinium/formoterol FDC group and the aclidinium group, and lower than in the formoterol group. In all treatment groups, few patients experienced severe TEAEs (< 11% of patients in each group). The proportion of patients with TEAEs considered by the investigator to be related to study treatment was also low (< 12% of patients in any treatment group), but was slightly higher in the aclidinium/formoterol FDC group (11.8%) than in the placebo group (10.1%) or in the aclidinium or formoterol groups (9.8% and 9.6%, respectively).[29] The proportion of patients who died was low and similar across the treatment groups (0.3% to 0.6%), and the proportion of patients with treatment-emergent SAEs was similar for placebo (7.4%) and for aclidinium/formoterol FDC (8.1%). The proportion of patients who discontinued the study prematurely due to TEAEs was lower in the active treatment groups than in the placebo group.

Infections and infestations and respiratory, thoracic, and mediastinal disorders, reported by more than 20% of patients, were the most frequently reported TEAEs. Respiratory, thoracic, and mediastinal

disorders were reported for a higher proportion of patients in the placebo group than for either aclidinium/formoterol FDC group. Infections and infestations were reported by a higher proportion of patients in the aclidinium/formoterol FDC group than in the placebo, aclidinium, or formoterol groups. The small differences between treatments did not appear to be due to any specific TEAE, and ≤ 1.1% of patients in any group had infections and infestations that were considered to be treatment-related. The incidence of lower respiratory tract and lung infections was lower for aclidinium/formoterol FDC (2.1%) than for placebo (3.2%), and the incidence of upper respiratory tract infections was similar in the two groups (14.3% and 13.9%, respectively). There were no important differences in the incidence of gastrointestinal disorders, musculoskeletal and connective tissue disorders, and nervous system disorders for aclidinium/formoterol FDC compared with placebo or the individual monotherapies.

TEAEs in the investigations system organ class (SOC) were reported more commonly with aclidinium/formoterol FDC 400 mcg/12 mcg than with placebo. The incidence in the other active treatment groups was similar to that seen for placebo. The difference between aclidinium/formoterol FDC 400 mcg/12 mcg and placebo was not attributable to an important difference in any specific TEAE within the investigations SOC and only 1.1% of patients in the aclidinium/formoterol FDC 400 mcg/12 mcg group had investigations TEAEs that were considered to be treatment-related. For other SOCs, TEAEs were reported at a generally similar incidence across treatments.[29]

The most commonly reported TEAEs (incidence > 5%) in patients treated with aclidinium/formoterol FDC were exacerbations of COPD (preferred term: chronic obstructive pulmonary disease), nasopharyngitis, and headache. COPD exacerbations were reported more commonly for placebo than for either aclidinium/formoterol FDC group.

In general, nasopharyngitis and headache were reported at a similar incidence with aclidinium/ formoterol FDC 400 mcg/12 mcg as with placebo (rate ratio (RR) of events < 1.5;). The majority of these events were of mild or moderate severity.[10]For other TEAEs reported in at least 2% of patients treated with aclidinium/formoterol FDC, the number of events was similar to that seen for placebo (RR < 1.5 versus placebo) with the exception of muscle spasms (RR = 2.06) and urinary tract infection (RR = 1.52). Both these TEAEs were also reported more frequently for aclidinium/formoterol FDC than for aclidinium. Urinary tract infection was reported more frequently with aclidinium/formoterol FDC than with formoterol, but muscle spasms were reported at a similar incidence in these two treatment groups.[29]

Dry mouth occurred more frequently in patients treated with aclidinium/formoterol FDC (1.8%) than in the other active treatment groups (0.8% to 1.0%). None of the reports of dry mouth in the aclidinium/formoterol FDC group were of severe intensity (Table 5.1.1, Statistical Report for the SCS and RMP), and only one patient from this group was permanently discontinued from study treatment due to this TEAE.[29] Supraventricular extrasystoles were reported in all active groups at a similar frequency for aclidinium/formoterol FDC, aclidinium, and formoterol (0.4%, 0.4%, and 0.3%, respectively). All events were of mild intensity.[29] Tachycardia was reported for < 0.6 % of patients in the aclidinium/formoterol FDC group, which was lower than that seen in the aclidinium group (1.0%). Hypokalemia, a well-known potential side effect of beta2- agonist treatment, was reported more commonly in the formoterol group (1.0%) than in the other treatment groups (0.4%, 0.6%, and 0.3% for placebo, aclidinium/formoterol FDC, and aclidinium, respectively).

The proportion of patients reporting any cardiac event of interest (myocardial infarction, tachycardia, atrial fibrillation, angina, congestive heart failure, bradycardia, and conduction defects) was low (≤ 5% in any treatment group), and was lower for aclidinium/formoterol FDC than for placebo. No clinically significant effects of aclidinium/formoterol FDC 400 mcg/12 mcg on cardiac rhythm were observed on

24-hour Holter monitoring in a subset of 551 patients, of whom 114 received aclidinium/formoterol FDC twice daily. The number of patients with cerebrovascular events (combination of haemorrhagic cerebrovascular conditions and ischemic cerebrovascular conditions) was < 1% in all treatment groups, and there were no notable differences between treatments.

2.4 Bioequivalence

Please note that formal bioequivalence studies were not conducted for aclidinium/formoterol FDC. Instead, bioavailability studies were performed to evaluate the pharmacokinetics of aclidinium and formoterol when administered as aclidinium/formoterol FDC as compared to their administration as individual monotherapy. For Health Canada, the criteria for subsequent-entry oral inhalation products are still in draft form and are not well established. Therefore, a complete clinical program was undertaken for aclidinium/formoterol FDC and the Health Canada Comprehensive Summary of Bioequivalence template was not required as a component of a New Drug Submission (NDS) for this combination product. For these reasons, a minimum of two trials was required to demonstrate the clinical safety and efficacy of aclidinium/formoterol FDC, which were submitted to Health Canada as part of the NDS submission for the product. The two pivotal studies being reviewed by Health Canada as part of the NDS submission are LAC 30 (ACLIFORM) and LAC 31 (AUGMENT). These studies were designed to compare the efficacy and safety of aclidinium/formoterol FDC to its individual monocomponents.

Both components, aclidinium bromide and formoterol dihydrate, have uncomplicated linear pharmacokinetic characteristics.[16]

The following data are taken from the Clinical Study Report for M-4064-02.[29] The detail of bioequivalence information is presented in Table 14.

The rate and extent of absorption of aclidinium in terms of the maximum plasma concentration (C_{max}) and the area under the curve (AUC) parameters for aclidinium/formoterol FDC were similar to those with the individual aclidinium 400 mcg dose. Variability (CV%) was high for C_{max} and AUC parameters and ranged from 52% to 74%. The elimination half-life could be correctly estimated in only 10 out of 29 patients for aclidinium/formoterol FDC treatment, and in 9 out of 29 patients for the aclidinium 400 mcg treatment. This parameter was subject to a high degree of variability (CV% > 75%), and there was a considerable overlap between treatments, resulting in individual values ranging from 1.13 hours to 20.4 hours for aclidinium/formoterol FDC treatment and from 2.26 hours to 15 hours for the aclidinium 400 mcg treatment. Thus, despite the mean half-life ($t_{½}$) being slightly longer following aclidinium/formoterol FDC (8.9 hours) compared with the aclidinium 400 mcg dose (6.1 hours), no clear conclusions can be drawn about the trend of this parameter between treatments. Mean total clearance of the drug from plasma (CL/F) and apparent volume of distribution (Vz/F) were comparable between the two treatments.

The rate and extent of formoterol absorption in terms of C_{max} and AUC parameters for the aclidinium/formoterol FDC dose were similar to those for the formoterol 12 mcg dose. The CV% was moderate for the formoterol C_{max} and AUC parameters, and ranged from 25% to 43%. The mean $t_{½}$ was longer following aclidinium/formoterol FDC (7.1 hours) compared with the formoterol 12 mcg dose (5.4 hours). This parameter was subjected to a moderate to high degree of variability (CV% from 31.9% to 47.8%), and there was a considerable overlap between treatments, obtaining individual values ranging from 3.22 hours to 16.9 hours for aclidinium/formoterol FDC treatment and from 2.49 hours to 8.86 hours for the formoterol 12 mcg treatment. Mean CL/F and Vz/F were comparable between the two treatments.

The relative bioavailability for the aclidinium/formoterol FDC treatment was assessed by comparison of mean C_{max} and $AUC_{(0-t)}$ results obtained following administration of the FDC and aclidinium and formoterol as individual monotherapies. For aclidinium, the ratio of C_{max} was 126% and the relative bioavailability (F_{rel}) based on $AUC_{(0-t)}$ was 103% for aclidinium/formoterol FDC versus aclidinium 400 mcg. For formoterol, the ratio of C_{max} was 118% and F_{rel} $AUC_{(0-t)}$ was 111% for aclidinium/formoterol FDC versus formoterol 12 mcg.

TABLE 14: BIOAVAILABILITY PROFILE FOR ACLIDINIUM/FORMOTEROL FIXED-DOSE COMBINATION[29]

Parameter	Aclidinium Administered in Aclidinium/ Formoterol FDC	Aclidinium Administered as a Single Product	Formoterol Administered in Aclidinium/ Formoterol FDC	Formoterol Administered as a Single Product
$AUC_{(0-t)}$	N = 29	N = 29	N = 29	N = 30
• Mean	229	222	36	32.4
• SD	19	13.1	13.1	14
• Coefficient of variance	60.9	58.8	36.5	43.3
C_{max}	N = 29	N = 29	N = 29	N = 30
• Mean	270	215	11	9.3
• SD	198	143	3.49	3.91
• Coefficient of variance	73.5	66.7	31.8	42
T_{max}	N = 29	N = 29	N = 29	N = 30
• Median	0.08	0.08	0.08	0.08
• Minimum	0.07	0.07	0.07	0.08
• Maximum	0.12	0.1	1.52	2

$AUC_{(0-t)}$ = area under the curve; C_{max} = maximum plasma concentration; FDC = fixed-dose combination; SD = standard deviation; T_{max} = time to reach maximum plasma concentration.

3. PHARMACOECONOMIC EVALUATION

3.1 Manufacturer-Submitted Cost Information

TABLE 15: COST COMPARISON OF NEW COMBINATION PRODUCT AND INDIVIDUAL COMPONENTS

Drug/Comparator[a]	Strength	Dosage Form	Price ($)	Recommended Daily Use	Daily Drug Cost ($)
Aclidinium bromide/formoterol fumarate dihydrate (Aclidinium/formoterol FDC)	**400 mcg/ 12 mcg**	**Inhalation powder**	**74.1000[b]**	**b.i.d.**	**2.47000**
Individual component (A) Tudorza Genuair (aclidinium bromide)	400 mcg	Inhalation powder	53.1000[c]	b.i.d.	1.7700
Individual component (B) Formoterol (formoterol fumarate)	12 mcg	Inhalation powder	50.5300[c]	b.i.d.	1.6843
Total (A + B)					**3.4543**
Individual component (A) Tudorza Genuair (aclidinium bromide)	400 mcg	Inhalation powder	53.1000[c]	b.i.d.	1.7700
Individual component (B) Oxeze Turbuhaler (formoterol fumarate dihydrate)	12 mcg	Inhalation powder	44.8000[c]	b.i.d.	1.4933
Total (A + B)					**3.2633**

b.i.d. = twice daily; FDC = fixed-dose combination.
[a] Aclidinium bromide has one active patent, Patent #CA2381165, expiration date: July 7, 2020; formoterol fumarate dihydrate does not have any active patents.
[b] Source: Anticipated market price provided to the CADTH Common Drug Review by AstraZeneca Canada Inc.
[c] Source: Ontario Public Drug Programs Drug Benefit Formulary.

Use of aclidinium/formoterol FDC in place of combination use of the individual monocomponents represents a potential daily drug cost savings of $0.9843 per day, when the cost of formoterol is considered as the individual formoterol fumarate component of aclidinium/formoterol FDC. When the cost of formoterol fumarate dihydrate is considered as the individual formoterol fumarate dihydrate component of aclidinium/formoterol FDC Genuair, the use of aclidinium/formoterol FDC represents a potential daily drug cost savings of $0.7933 per day.

There are extensive data to show that use of a single inhaler device has significant advantages in terms of adherence and outcomes compared with use of multiple inhalers.[23,45] In the study by Yu et al.,[3] a retrospective analysis of 23,494 patients with COPD, multiple inhaler use was associated with significantly higher rates of discontinuation over the 12-month study period (hazard ratio [HR] 1.40, $P < 0.001$) and significantly lower rates of 12-month adherence (proportion of days covered: 0.51 versus 0.55 for a single inhaler, $P < 0.0001$). As suboptimal adherence is associated with a significant health and

economic burden in patients with COPD,[36] increasing adherence by administration of a LAMA and a long-acting beta2-agonist (LABA) via a single inhaler should improve the health status of patients as well as reduce the economic burden of COPD. These data support the advantage of FDC LAMA/LABA therapies such as aclidinium/formoterol FDC over concurrent use of individual LAMA and LABA products for non-exacerbating patients with moderate to severe COPD who have failed LAMA or LABA monotherapy.

3.1.1 Cost Comparison Table

TABLE 16: COST COMPARISON TABLE

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Daily Use	Average Daily Drug Cost ($)
Aclidinium/formoterol (Aclidinium/formoterol FDC)	**400 mcg/ 12 mcg**	**Inhalation powder**	**74.1000[a]**	**b.i.d.**	**2.4700**
Aclidinium bromide + Formoterol fumarate dihydrate (Tudorza Genuair + Formoterol)	400 mcg + 12 mcg	Inhalation powder	103.6300[b] (53.1000 + 50.5300)	b.i.d.	3.4543 (1.7700 + 1.6843)
Aclidinium bromide + Formoterol fumarate dihydrate (Tudorza Genuair + Oxeze Turbuhaler)	400 mcg + 12 mcg	Inhalation powder	97.9000[b] (53.1000 + 44.8000)	b.i.d.	3.2633 (1.7700 + 1.4933)
Glycopyrronium + formoterol (Seebri Breezhaler + Formoterol)	50 mcg + 12 mcg	Inhalation powder	103.6300[b] (53.1000 + 50.5300)	q.d./b.i.d	3. 4543 (1.7700 + 1.6843)
Glycopyrronium + formoterol (Seebri Breezhaler + Oxeze Turbuhaler)	50 mcg + 12 mcg	Inhalation powder	97.9000[b] (53.1000 + 44.8000)	q.d./b.i.d	3.2633 (1.7700 + 1.4933)
Glycopyrronium/ Indacaterol (Ultibro Breezhaler)	50 mcg/ 110 mcg	Inhalation powder	80.4000[c]	q.d.	2.6800
Umeclidinium Bromide/ Vilanterol trifenatate (Anoro Ellipta)	62.5 mcg/ 25 mcg	Inhalation powder	81.0000	q.d.	2.7000
Tiotropium + Formoterol (Spiriva + Formoterol)	18 mcg + 12 mcg	Inhalation powder	115.5310[b] (65.0010 + 50.5300)	q.d./b.i.d	3.8510 (2.1667 + 1.6843)
Tiotropium + Formoterol (Spiriva + Oxeze Turbuhaler)	18 mcg + 12 mcg	Inhalation powder	109.8010[b] (65.0010 + 44.8000)	q.d./b.i.d	3.6600 (2.1667 + 1.4933)

CDR = CADTH Common Drug Review; FDC = fixed-dose combination; b.i.d. = twice daily; q.d. = once daily.
[a] Source: Anticipated market price provided to CDR by AstraZeneca Canada Inc.
[b] Source: Ontario Drug Benefit Formulary.
[c] Source: CDR-submitted price.

3.1.2 Manufacturer-Submitted Pharmacoeconomic Analysis Report Summary

The data summarized in the following section are taken from the manufacturer-submitted *Economic Analysis of a Fixed-Dose Combination of Aclidinium and Formoterol (aclidinium/formoterol FDC) for the Treatment of Chronic Obstructive Pulmonary Disease* report.[30]

Aclidinium/formoterol FDC is a twice-daily FDC of aclidinium bromide 400 mcg (a LAMA) and formoterol 12 mcg (a LABA). The submitted market price per unit for aclidinium/formoterol FDC is $74.1000. There are two other fixed-dose LAMA/LABA combination products that have recently been approved in Canada. These products are umeclidinium/vilanterol 62.5 mcg/25 mcg (Anoro Ellipta) and indacaterol/glycopyrronium 110 mcg/50 mcg (Ultibro Breezhaler). Hence, there are now three LAMA/LABA FDCs as alternatives to the LAMA + LABA mono components (e.g., tiotropium bromide + formoterol) available for use in Canadian patients with COPD. To provide pharmacoeconomic data for aclidinium/formoterol FDC as an alternative to Anoro Ellipta, Ultibro Breezhaler, and the LAMA and LABA mono components, a cost-consequence analysis (CCA) and a subsequent cost-minimization analysis (CMA) were conducted from a Canadian health care system perspective.[30]

A cost-minimization approach was used over a cost-utility analysis (CUA) because the latter would require considerably more and unsubstantiated assumptions in building the economic model (e.g., long-term estimates for changes in trough/peak forced expiratory volume in one second (FEV_1), long-term safety and efficacy against the comparators, reductions in the risk of exacerbations, hospital admissions, and overall risk of death). Therefore, in the provided study, a CCA followed by a CMA, supported by an indirect comparison of safety, efficacy, and patient-reported outcomes between the four alternative therapies, were undertaken. A health care system perspective was used in the current analysis, with a one-year time horizon.

The primary requirement for a CMA evaluating active interventions is that all clinical outcomes between treatments be comparable.[30] Therefore, the first step in the analysis was to demonstrate that aclidinium/formoterol FDC has comparative safety and efficacy relative to Anoro Ellipta, Ultibro Breezhaler, and the LAMA + LABA monotherapy components. This supporting evidence would justify a CMA between the current treatments for COPD in Canada. There were no head-to-head randomized trials comparing aclidinium/formoterol FDC to the available alternatives. As a result, an indirect analysis of placebo-controlled trials using Bayesian mixed treatment comparison (MTC) models across multiple end points was undertaken to support the comparative effectiveness assumption required for a CMA. The base-case CMA considered costs for drug therapy, pharmacy fees, physician visits, laboratory and diagnostics tests, and functional studies. In addition, costs for secondary pharmacotherapy in cases where the primary drug had to be discontinued because of AEs were also included. Keeping in mind the caveats associated with comparisons across placebo-controlled clinical trials, the indirect MTC suggested that aclidinium/formoterol FDC was at least clinically comparable to Anoro Ellipta, Ultibro Breezhaler, and tiotropium bromide + formoterol for end points such as improvement in trough/peak FEV_1, clinically meaningful increases in the SGRQ total score and TDI, reductions in exacerbations, and WDAEs. Given the data supporting the assumption of comparative safety and effectiveness between the various treatments, a CMA was conducted. The CMA evaluated one year of therapy. Therefore, costs were not discounted because of the short time periods involved, but the base-case results were supported with a one-way sensitivity analysis on the key cost drivers. The data from the CCA were then used for the CMA. The analysis began with a comparison of the monthly drug acquisition cost only, for the six alternatives. As indicated in Table 17, aclidinium/formoterol FDC had the lowest monthly acquisition cost, followed by Ultibro Breezhaler.

TABLE 17: MONTHLY DRUG ACQUISITION COST FOR THE ALTERNATIVES

Product	Daily Dose	Cost per Day ($)	Monthly Cost[a] ($)
Aclidinium/Formoterol FDC	b.i.d.	2.47	75.58[b]
Alternatives			
Anoro Ellipta	q.d.	2.70	82.62[c]
Ultibro Breezhaler	q.d.	2.68	82.01[d]
Tiotropium bromide + formoterol (18/12)	q.d./b.i.d.	3.66	112.10[e]
Aclidinium + formoterol (400/12)	b.i.d.	3.26	99.86[e]
Glycopyrronium + formoterol (50/12)	q.d./b.i.d.	3.26	99.86[e]

b.i.d. = twice daily; CDR = CADTH Common Drug Review; FDC = fixed-dose combination; q.d. = once daily.
[a] Assuming an average of 30.6 days in one month.
[b] Anticipated market price provided to CDR by AstraZeneca Canada Inc.
[c] Manufacturer's list price.
[d] CDR-submitted price.
[e] Costs for the current products were those reimbursed by the Ontario Drug Benefit program.

Using the data from the cost-comparison table and the monthly prescription costs, a CMA was conducted for 12 months of therapy. In addition to the drug cost, the analysis considered physician visits, laboratory/diagnostic tests, and secondary pharmacotherapy costs where the initial LAMA/LABA had to be permanently discontinued in the first month because of adverse events.

Aclidinium/formoterol FDC was associated with an annual cost savings per patient relative to all of the alternatives, ranging from $69 to $563 per patient (Table 15). Hence, the use of aclidinium/formoterol FDC in place of high-cost treatments like tiotropium bromide + formoterol for patients with COPD will result in substantial cost savings to CDR-participating public drug plans. The savings were due to a lower drug acquisition cost and the avoidance of one pharmacy prescription in the case of tiotropium bromide + formoterol.

TABLE 18: COST PER PATIENT FOR 12 MONTHS OF THERAPY

Resource Item	Aclidinium/ Formoterol FDC ($)	Anoro Ellipta ($)	Ultibro Breezhaler ($)	Tiotropium Bromide + Formoterol ($)	Aclidinium + Formoterol ($)	Glycopyrronium + Formoterol ($)
Drug cost	980	1,071	1,063	1,453	1,294	1,294
Dispensing fee	100.80	100.80	100.80	201.60	201.60	201.60
Physician visits	624.40	624.40	624.40	624.40	624.40	624.40
Laboratory/diagnostics	286.31	286.31	286.31	286.31	286.31	286.31
Functional studies	76.46	76.46	76.46	76.46	76.46	76.46
Secondary therapy[a]	49.53	59.73	35.20	38.40	49.52	35.20
TOTAL COST	**2,117**	**2,218**	**2,186**	**2,680**	**2,532**	**2,518**
Aclidinium/ Formoterol FDC Cost Savings	**-**	**101**	**69**	**563**	**415**	**401**

FDC = fixed-dose combination.

[a] In cases of intolerable side effects developing during the first month of therapy, expert opinion indicated that ULTIBRO BREEZHALER would be used in cases of intolerance developed to aclidinium/formoterol FDC or to the aclidinium/formoterol monotherapy components. Aclidinium/formoterol FDC would be used in cases where Anoro Ellipta, Ultibro Breezhaler, tiotropium bromide/formoterol, and glycopyrronium/formoterol had to be stopped because of intolerable side effects.

3.2 Manufacturer-submitted Information Regarding Current Patent Status

Aclidinium bromide contains one active patent, Patent #CA2381165, with an expiration date of July 7, 2020.

Formoterol fumarate dihydrate does not have any active patents.

3.3 Critical Appraisal of Cost Information

CDR noted a number of issues for consideration.

3.3.1 Choice of comparators

The manufacturer's cost analysis considered available LAMA/LABA FDCs and monotherapies administered as separate inhalers. The relevance of separate LAMA + LABA monotherapies as comparators is questionable as FDCs may be chosen based on convenience, adherence, and persistence not observed with separately administered monotherapies,[24-26] as suggested by the CDR clinical expert. As such, the cost savings associated with aclidinium/formoterol FDC compared with LAMA + LABA separate monotherapies may be of questionable relevance.

The manufacturer did not consider the costs of aclidinium/formoterol FDC compared with LABA/ICS combinations, despite the appropriateness of LABA/ICS combinations as comparators for some patients as per COPD treatment guidelines.[3,25] Furthermore, the manufacturer states that the use of aclidinium/formoterol FDC would serve to reduce inappropriate use of LABA/ICS among non-exacerbating patients, thereby presumably reducing costs and harms associated with inappropriate use.[27,28] CDR notes that the manufacturer considered salmeterol/fluticasone as a comparator in the LAC 39 trial, highlighting the appropriateness of LABA/ICS as a potential comparator. At the submitted price of $2.47 per day, aclidinium/formoterol FDC is less expensive than available LABA/ICS combinations (range: $2.80 to $4.76 per day) (Table 30).

3.3.2 Comparative clinical information

The manufacturer states that aclidinium/formoterol FDC is "at least clinically comparable" to the assessed comparators based on an MTC. CDR identified concerns regarding this analysis as well as the individual trials that inform it, which introduce uncertainty into claims of similar comparative safety and efficacy:

1. Individual trials used spirometric measurements as primary outcomes, which are of questionable relevance. FEV_1 is known to be poorly correlated with patient-centred outcomes such as quality of life, exercise tolerance, and dyspnea.[29]
2. Individual trials in some cases failed to demonstrate clinically significant differences between aclidinium/formoterol FDC and individual components (e.g., the change in trough FEV_1 in LAC 31 between aclidinium/formoterol FDC and formoterol was less than the 0.1 L MCID[30]).
3. A higher proportion of aclidinium/formoterol FDC patients had TEAEs than with the individual components.
4. Several issues were noted with the manufacturer's MTC, including lack of detail on how clinical heterogeneity was accounted for, low number of trials per drug, and an absence of any data on tiotropium bromide. Furthermore, it was unclear how exacerbation data were derived from such a limited time of follow-up.

Further issues for consideration:

Given that inhaler continuity is associated with increased treatment adherence and persistence,[25] the use of the Genuair inhaler may be beneficial for patients who were initially on Tudorza Genuair. Aclidinium/formoterol FDC requires twice-daily dosing, while all other LAMA/LABA FDCs make use of once-daily dosing. While more frequent dosing is generally associated with poorer treatment adherence, this does not appear to be a concern for twice-daily aclidinium bromide[31] and, as per clinical expert input, is not expected to be a concern for aclidinium/formoterol FDC.

At the submitted price of $2.47 per day, aclidinium/formoterol FDC is less expensive than other LAMA/LABA FDCs (range: $2.67 to $2.70 daily) and separately administered LAMA + LABA monotherapies (range: $3.26 to $3.85 daily). The lack of comparative studies or a well-conducted indirect comparison for aclidinium/formoterol FDC limits comparison with other LAMA/LABA FDCs, and introduces uncertainty regarding its similar efficacy on patient-important outcomes.

4. DISCUSSION

4.1 Summary of Available Evidence

A total of five studies were included in this submission, including two pivotal studies (LAC 30 and LAC 31) and three supportive studies (LAC 39, LAC 36, and LAC 32). The two pivotal studies (LAC 30 and LAC 31) compared aclidinium/formoterol FDC with aclidinium and formoterol monotherapy as well as placebo. LAC 39 compared aclidinium/formoterol FDC with salmeterol/fluticasone FDC. LAC 36 was a 28-week extension study of LAC 31. LAC 32 compared aclidinium/formoterol FDC with formoterol monotherapy. All were randomized and double-blind studies, and were conducted in multiple countries. The studies evaluated the efficacy and safety (LAC 30, LAC 31, and LAC 39) of aclidinium/formoterol FDC at week 24, and the longer-term safety at week 52 (LAC 36 and LAC 32) of aclidinium/formoterol FDC and its components. The primary outcomes were the trough forced expiratory volume in one second (FEV1) and one hour post-dose FEV1 in two pivotal studies (LAC 30, LAC 31), and peak FEV1 in LAC 39. The objective of LAC 32 and LAC 36 was to evaluate the long-term (at week 52) safety profile of aclidinium/formoterol FDC, in which the primary outcome was not specified.

The key limitations of the studies included the relatively short duration (24 weeks) in the two pivotal studies and LAC 39, which is not likely a sufficient duration to assess clinical outcomes such as mortality, HRU, and exacerbations of COPD. The majority of patients (63% to 79%) did not experience COPD exacerbation in the year prior to the studies. The clinical expert involved in this review indicated that COPD is associated with both short- and long-term consequences on overall health. Therefore, assessing how aclidinium/formoterol FDC prevents or reduces the likelihood of acute exacerbations (especially moderate to severe exacerbations) is an important clinical issue. Furthermore, there was a substantial proportion of discontinuations (ranging as high as 20% to 30%) in studies LAC 30 and LAC 31 at week 24, and an extra 16% of patients discontinued during a 28-week extension period (at week 52) in LAC 36. The discontinuation rate at one year was 33%, reported in LAC 32. Although there was no clear discontinuation differential between groups within studies (except those on placebo discontinued more frequently), there is a concern regarding the validity of the findings once frequencies of discontinuations are this high. Finally, there were no head-to-head comparison studies comparing aclidinium/formoterol FDC with other long-acting beta2-agonist (LABA)/LAMA combinations. Therefore, there is no evidence to guide the clinical choice among the three available LAMA/LABA FDCs in the long-term maintenance treatment of patients with moderate to severe COPD. Although the manufacturer conducted and submitted a MTC that suggested that aclidinium/formoterol FDC is similar in terms of certain efficacy and WDAE rates compared with indacaterol/glycopyrronium FDC and umeclidinium bromide/vilanterol trifenatate FDC, the potential limitations of the MTC (i.e., relatively short duration of included trials, no head-to-head direct comparison, and the potential clinical heterogeneity of the included trials) mean there is a high degree of uncertainty with respect to the findings and conclusions derived from this MTC. Furthermore, the comparative effects of aclidinium/formoterol versus other LAMA/LABA combinations was not sufficiently powered to assess for key outcomes such as mortality, HRU, SAEs, and AEs of particular interest, including cardiovascular events, anticholinergic events, and pneumonia.

4.2 Interpretation of Results

4.2.1 Efficacy

As emphasized by the patient group and clinical expert involved in this submission, mortality, COPD exacerbation, hospitalization, quality of life, and symptom relief are key outcomes for patients with COPD; however, none of the included studies were adequately designed to assess these outcomes, except quality of life and symptoms. The overall rate of death at week 24 was < 0.5% in all studies

except LAC 32 (about 1% at one year). Only one death was reported in the placebo group of LAC 36. None of the reported deaths from any of the included studies was considered related to the study drug. As mentioned above, none of the studies were large enough or of sufficient duration to determine whether a difference in mortality exists between treatments.

Improving lung function, such as FEV1, measured by using pulmonary function tests, is not in and of itself an objective of COPD management,[3,32,33] but it is the primary end point most frequently used in trials on drugs to treat COPD, and is accepted by regulatory agencies in interpreting drug efficacy in COPD trials.[29] It was found that the increases from baseline to week 24 in FEV1 at one hour post-dose were statistically significantly greater for aclidinium/formoterol FDC than for aclidinium (by 0.108 L to 0.125 L; P < 0.0001) or formoterol (by 0.083 L to 0.139 L; P < 0.001), respectively.[10] The increases from baseline to week 24 in trough FEV1 were statistically significantly greater for aclidinium/formoterol FDC than for formoterol (by 0.045 L to 0.085 L; P < 0.0001), although the clinical significance of the between-group difference of change from baseline in trough FEV1 is uncertain given that the lower range of the MCID is 0.1 L. However, it may be unrealistic to expect the incremental improvement in trough FEV1 gained by adding a second drug to an existing drug would be as great as the difference between an active drug and placebo.[32] It is worth noting that, in terms of trough FEV1, no statistically significant difference was identified between aclidinium/formoterol FDC and aclidinium in LAC 30,[6] LAC 31,[11] or LAC 36.[11] However, the studies might not be sufficiently powered for comparison between aclidinium/formoterol FDC and aclidinium for change from baseline trough FEV1. In LAC 39, the aclidinium/formoterol FDC group showed not only non-inferior (the lower bound of the two-sided 95% CIs for the difference between aclidinium/formoterol FDC and salmeterol/fluticasone FDC was 0.070 L in the PP population, exceeding the non-inferiority limit of –0.055 L), but it also showed a statistically significantly greater peak FEV1 compared with salmeterol/fluticasone FDC in the modified intention-to-treat (mITT) population, with an adjusted mean difference of 0.093 L (P < 0.0001). In terms of trough FEV1, which is more commonly accepted as the primary outcome in studies on COPD, aclidinium/formoterol FDC showed no statistically or clinically significant difference in trough FEV1 compared with salmeterol/fluticasone FDC at week 24, with adjusted mean differences of –0.014 L (P > 0.05). However, the study may not have been sufficiently powered for comparison between aclidinium/formoterol FDC and aclidinium for change from baseline trough FEV1.

As mentioned by the COPD patient group input for this review, the most commonly experienced symptoms in patients with COPD are fatigue, shortness of breath, wheezing, frequent chest infections, and coughing. The findings from the included study showed that treatment with aclidinium/formoterol FDC resulted in statistically significant improvements in dyspnea as measured with TDI scores, and that more responders achieved the MCID of ≥ 1 unit improvement at week 24 compared with placebo in both pivotal studies. However, there were no statistically significant differences between aclidinium/formoterol FDC and aclidinium or formoterol monotherapy. No difference between the treatment groups was reported (P = 0.9951) between aclidinium/formoterol FDC and salmeterol/fluticasone FDC in terms of TDI at week 24. In terms of health-related quality of life measured with SGRQ total score and SGRQ 3-Domain scores, statistically significant differences between aclidinium/formoterol FDC and placebo were observed only in LAC 31, but not in LAC 30. In addition, no statistically significant difference was reported between aclidinium/formoterol FDC and aclidinium or formoterol monotherapy at 24 weeks in any included studies. This may be in part because of lack of power to detect the difference. The manufacturer conducted a pooled analysis of the two pivotal studies, which indicated statistically significantly greater improvements in TDI focal score with aclidinium/formoterol FDC compared with aclidinium 400 mcg (0.44 units; P < 0.05) and formoterol

12 mcg (0.47 units; P < 0.01) at week 24. In the pooled analysis of the two pivotal studies, aclidinium/formoterol FDC also showed greater improvements in SGRQ total score compared with formoterol fumarate (–1.7 units; 95% CI, –3.2 to –0.3; P = 0.018) or aclidinium bromide (–0.8 units; 95% CI, –2.2 to 0.6; P = 0.273). However, despite achieving statistical significance in the change from baseline in TDI and SGRQ with the pooled analysis, the clinical significance of these findings is uncertain. No difference between the treatment groups was reported (P = 0.9951) between aclidinium/formoterol FDC and salmeterol/fluticasone FDC in terms of SGRQ at week 24.

A potential advantage of aclidinium/formoterol FDC is the administration of a LAMA/LABA together once daily for patients requiring dual administration of a LABA and a LAMA. However, it is administered twice daily. A once-daily dosing regimen, such as umeclidinium bromide/vilanterol trifenatate (Anoro Ellipta) or indacaterol maleate/glycopyrronium bromide (Ultibro Breezhaler), might lead to improved adherence versus a twice-daily regimen. The reported patient adherence rates were greater than 95% in both pivotal studies, which simply reflects the number of doses actuated rather than whether the dose was delivered optimally. There are no direct comparison data on the adherence of aclidinium/formoterol FDC with other existing, once-daily LAMA/LABA FDCs; however, the clinical expert involved in this review indicated that adherence should not be a concern with aclidinium/formoterol FDC because patients are not likely to be less adherent with twice-daily dosing versus once-daily dosing.

The clinical expert pointed out that the current clinical practice has not abided well with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline[3] or the Canadian recommendations,[4] which suggest LAMA/LABA combinations for patients with COPD who inadequately responded to LABA or LAMA monotherapy. Due to the adverse effects associated with steroids, an ICS is recommended to be added for patients who have failed with LAMA/LABA combination therapy; i.e., triple therapy for patients with moderate to severe disease and persistent symptoms.[3,4] In the two pivotal studies, about 40% to 50% patients who had used ICS or systemic corticosteroids prior to the study were allowed to continue to use the ICS and systemic steroids as concomitant medication during the study. Patients using LABA/ICS were switched to the same ICS as monotherapy during the study. Therefore, for those patients who kept using the ICS or systemic steroids, adding aclidinium/formoterol FDC actually reflects triple therapy, not really dual therapy. While it reflects the real clinical practice scenario to prevent COPD exacerbation from withdrawing steroids, whether these findings of the two pivotal studies can be generalized to those subgroup patients who had not used ICS is uncertain, because no subgroup analysis was provided in the submission.

4.2.2 Harms

The primary safety data for aclidinium/formoterol FDC are provided from the two pivotal studies (LAC 30 and LAC 31), LAC 39, and the two long-term (52 weeks) supportive studies, LAC 32 and LAC 36. Across studies, the overall incidence of treatment-emergent adverse events (TEAEs) between treatment groups were generally similar at both week 24 [6,7,9] and week 52, [8,10] although numerically more TEAEs were reported in the aclidinium/formoterol FDC groups. The proportion of patients who died was low and similar across the treatment groups (0.3% to 0.6%), and the proportion of patients with treatment-emergent SAEs was similar for placebo (7.4%) and for aclidinium/formoterol FDC (8.1%). The reported discontinuation rates at week 24 were higher in placebo (17.5% to 30%) than in the active treatment arms (9% to 21%). The discontinuation rates at one year were as high as 33%. It is worth noting that in LAC 36, an extra 16% of patients discontinued from the study during the 28-week extension period of LAC 31. The discontinuation rates were similar among the active treatment arms.

The most commonly reported TEAEs (incidence > 5%) in patients treated with aclidinium/formoterol FDC were exacerbations of COPD (although it was evaluated as efficacy in LAC 31), nasopharyngitis, and headache. COPD exacerbations were reported more commonly for the placebo than for the aclidinium/formoterol FDC group. But the exacerbation frequency at week 24 was found to be similar between aclidinium/formoterol FDC and its monocomponent therapy, as well as between aclidinium/formoterol FDC and salmeterol/fluticasone FDC. Treatment group difference in terms of COPD exacerbation at week 52 was also not statistically significant between aclidinium/formoterol FDC and formoterol.[10,12,13]

Notable harms were considered based on the anticholinergic and beta-agonist components of aclidinium/formoterol FDC. AEs of anticholinergic syndrome (including dry mouth, dizziness, urinary retention, and worsening vision) were also low and with similarities across treatment arms. Dry mouth occurred more frequently in patients treated with aclidinium/formoterol FDC (1.8%) than in the other active treatment groups (0.8% to 1.0%). Events related to cardiovascular death and non-fatal myocardial infarction were rare and similar in patients who received active treatments. Pneumonia is another key safety issue associated with COPD and COPD management (such as using ICS). Patients with COPD are at high risk of pneumonia and this risk increases further with use of ICS. As it does not contain a corticosteroid, aclidinium/formoterol FDC might be expected to carry a lower risk of pneumonia than ICS/LABA combinations. The incidence of pneumonia was numerically higher in the salmeterol/fluticasone group FDC (1.9%) than in the aclidinium/formoterol FDC group (1%) reported in LAC 39, LAC 30, and LAC 31.

Conclusion

Supported by the findings from the five included studies, aclidinium/formoterol FDC appears superior to placebo in terms of improving lung function (FEV_1) at week 24 and week 52. Aclidinium/formoterol FDC also showed statistically significantly greater improvement in terms of trough FEV_1 than formoterol at both week 24 and week 52, but not when compared to aclidinium monotherapy. None of the studies were sufficiently powered to assess comparative efficacy for clinically important outcomes such as mortality, health care resource use (HRU), and COPD exacerbations. In terms of HRQoL measured with the SGRQ, aclidinium/formoterol FDC showed a statistically significant difference (in favour of aclidinium/formoterol FDC) compared with placebo in only one study, and did not show a statistically significant difference compared with aclidinium or formoterol monotherapy. Up to week 52, the overall safety profiles were similar between aclidinium/formoterol FDC and aclidinium or formoterol monotherapy. A key limitation of the included studies was the lack of a head-to-head comparison with another LAMA/LABA combination inhaler such as indacaterol/glycopyrronium FDC or umeclidinium/vilanterol FDC. The manufacturer's MTC suggested that aclidinium/formoterol FDC appears similar in terms of changes in FEV_1, TDI, HRQoL, and WDAEs when compared with indacaterol/glycopyrronium FDC and umeclidinium/vilanterol FDC. However, due to potential limitations (i.e., the relatively short duration and potential clinical heterogeneity of the included trials), the validity of the results of the MTC are considered to be highly uncertain.

At the submitted price of $2.47 per day, aclidinium/formoterol FDC is less expensive than other LAMA/LABA FDCs (range: $2.67 to $2.70 daily) and separately administered LAMA+LABA monotherapies (range: $3.26 to $3.85 daily). The lack of comparative studies or a well-conducted indirect comparison for aclidinium/formoterol FDC limits the relative assessment to other LAMA/LABA FDCs and introduces uncertainty regarding its comparative efficacy on patient-important outcomes.

APPENDIX 1: DRUG PLAN LISTING STATUS FOR INDIVIDUAL COMPONENTS

Abbreviation	Description
EX	Exception item for which coverage is determined on a case-by-case basis
FB	Full benefit
NAB	Not a benefit
RES	Restricted benefit with specified criteria (e.g., Special Authorizations, exception drug status, limited use benefit)
UR	Under review
–	Information not available

TABLE 19: LISTING STATUS FOR INDIVIDUAL COMPONENTS OF THE NEW COMBINATION PRODUCT FOR THE TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Components[a]	CDR-Participating Drug Plans													
	BC	AB	SK	MB	ON	NB	NS	PE	NL	YK	NT	NIHB	DND	VAC
Aclidinium bromide (Tudorza Genuair)	**RES**	**FB**	**RES**	**RES**	**FB**	**RES**	**RES**	**RES**	**RES**	**RES**	**RES**	**RES**	**RES**	**RES**
Formoterol fumarate (formoterol)	**NAB**	**FB**	**RES**	**FB**	**NAB**	**RES**	**RES**	**RES**	**RES**	**RES**	**RES**	**RES**	**RES**	**RES**
Formoterol fumarate dihydrate (Oxeze Turbuhaler)	**NAB**	**FB**	**RES**	**FB**	**NAB**	**RES**	**RES**	**RES**	**RES**	**RES**	**NAB**	**NAB**	**NAB**	**NAB**

AB = Alberta, BC = British Columbia, CDR = CADTH Common Drug Review; DND = Department of National Defence; FB = full benefit; MN = Manitoba; NAB = not a benefit; NB = New Brunswick; NIHB = Non-Insured Health Benefits Program; NL = Newfoundland and Labrador; NS = Nova Scotia; NT = Northwest Territories; ON = Ontario; PE = Prince Edward Island; RES = restricted benefit; SK = Saskatchewan; VAC = Veterans Affairs Canada; YK = Yukon.

[a] Add non-proprietary name for each component.

TABLE 20: RESTRICTED BENEFIT CRITERIA FOR ACLIDINIUM BROMIDE (TUDORZA GENUAIR) FOR THE TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Drug Plan	Criteria for Restricted Benefit
BC Pharmacare	Diagnosis of COPD where spirometry measures are: • FEV_1 as a percentage of predicted value (less than or equal to 65%) **AND** • Ratio of actual FEV_1/FVC (less than 0.7) **AND** • Inadequate response after a 3-month trial of either: o ipratropium at a dose of 12 puffs daily **OR** o ipratropium and salbutamol combination inhaler (Combivent Respimat) at a dose of 6 puffs daily. Note: 12 puffs of ipratropium via metered dose inhaler is equivalent to 6 puffs of ipratropium via Combivent Respimat inhaler.
SK Drug Plan	a) COPD in patients unresponsive to short-acting beta-agonists or short-acting anticholinergic bronchodilators, **OR** b) Moderate to severe COPD (i.e., MRC Dyspnea Scale[a] score 3 to 5), in conjunction with spirometry demonstrating moderate to severe airflow obstruction (i.e., FEV_1 < 60 % and low FEV_1/FVC < 0.7), without a trial of short-acting agents.
MB Pharmacare Program	For patients with moderate to severe COPD who remain symptomatic despite an adequate trial (3 months) of ipratropium.
NB Prescription Drug Program	• For the treatment of COPD if symptoms persist after 2 to 3 months of short-acting bronchodilator therapy (i.e., salbutamol at a maximum dose of 8 puffs/day or ipratropium at maximum dose of 12 puffs/day). • Coverage can be provided without a trial of short-acting agent if there is spirometric evidence of at least moderate to severe airflow obstruction (FEV_1 < 60% and FEV_1/FVC ratio < 0.7) and significant symptoms (i.e., MRC Dyspnea Scale[a] score of 3 to 5). • Combination therapy with tiotropium **AND** a LABA/ICS will be considered only if: o there is spirometric evidence of at least moderate to severe airflow obstruction (FEV_1 < 60% and FEV_1/FVC ratio < 0.7), and significant symptoms (i.e., MRC Dyspnea Scale score of 3 to 5) AND o there is evidence of one or more moderate to severe exacerbations per year, on average, for 2 consecutive years requiring antibiotics and/or systemic (oral or intravenous) corticosteroids. **Clinical Note:** If spirometry cannot be obtained, reasons must be clearly explained and other evidence regarding severity of condition must be provided for consideration (i.e., MRC scale). Spirometry reports from any point in time will be accepted.
NS Pharmacare	• For the treatment of COPD, if symptoms persist after 2 to 3 months of short-acting bronchodilator therapy (i.e., salbutamol at a maximum dose of 8 puffs/day or ipratropium at maximum dose of 12 puffs/day) • Coverage can be provided without a trial of short-acting agent if: o there is spirometric evidence of at least moderate to severe airflow obstruction (i.e., post-bronchodilator values FEV_1 < 60% and FEV_1/FVC ratio < 0.7), and significant symptoms (i.e., MRC Dyspnea Scale score of 3 to 5[b]) • Combination therapy with aclidinium bromide and LABA/ICS will be considered only if: o there is spirometric evidence of at least moderate to severe airflow obstruction (post-bronchodilator values FEV_1 < 60% and FEV_1/FVC ratio < 0.7), and significant symptoms (i.e., MRC Dyspnea Scale score of 3 to 5[b]); AND o there is evidence of one or more moderate to severe exacerbations per year, on average, for 2 consecutive years requiring antibiotics and/or systemic (oral or intravenous) corticosteroids.

Drug Plan	Criteria for Restricted Benefit
PEI Drug Cost Assistance Programs	a) For the treatment of mild, moderate, and severe COPD (i.e., MRC Dyspnea Scale score ≥2[a]) in patients who continue to be symptomatic after a 3-month trial of ipratropium at a dose of 12 puffs/day and appropriate use of SABAs. b) For the treatment of moderate to severe COPD (i.e., MRC Dyspnea Scale score 3 to 5) without a trial of short-acting agents (e.g., ipratropium and beta2-agonists) where spirometry shows moderate to severe airflow obstruction (i.e., FEV_1 < 60% predicted **AND** low FEV_1/FVC < 0.7). A copy of the spirometry report must accompany the Special Authorization. **Note:** The drug programs will not pay for concurrent use of tiotropium bromide and ipratropium. **Note:** Concurrent use of tiotropium bromide and LABAs or LABA/ICSs will be considered only in patients where FEV_1 < 60% predicted **AND** FEV_1/FVC < 0.7. A copy of the spirometry report must accompany the Special Authorization.
NL Pharmaceutical Services	• For the treatment of COPD, if symptoms persist after 2 to 3 months of short-acting bronchodilator therapy (i.e., salbutamol at maximum dose of 8 puffs/day or ipratropium at maximum dose of 12 puffs/day). • Coverage can be approved without a trial of a short-acting agent if there is spirometric evidence of at least moderate to severe airflow obstruction — i.e., FEV_1 < 60% AND FEV_1/FVC ratio < 0.7 — and significant symptoms — i.e., MRC Dyspnea Scale score 3 to 5.[b] Combination therapy with aclidinium bromide and a LABA/corticosteroid (i.e., Tudorza plus Advair or Symbicort) will be considered only if: • there is spirometric evidence of a least moderate to severe airflow obstruction (FEV_1 < 60% AND FEV_1/FVC ratio < 0.7), and significant symptoms, i.e., MRC Dyspnea Scale score of 3 to 5[b] **AND** • there is evidence of one or more moderate to severe exacerbations per year on average, for 2 years (24 consecutive months) requiring antibiotics and/or systemic (oral or intravenous) corticosteroids. **Note:** • Coverage of combination therapy with aclidinium bromide and a LABA (without an ICS) will not be considered due to insufficient evidence to support substantial benefit. • If spirometry cannot be obtained, reasons must be clearly explained and other evidence regarding severity of condition must be provided for consideration (i.e., MRC Dyspnea Scale).
YK Health and Social Services	For patients diagnosed with COPD where spirometry measures are: • FEV_1 as a percentage of predicted value ≤ 65% **AND** • ratio of actual FEV_1/FVC < 0.7 **AND** • inadequate response after 3-month trial of ipratropium at maximum dosage.
NT Health Care Plan	For patients with COPD and who: • did not respond to a trial of ipratropium (Atrovent); **OR** • did not have a previous trial of ipratropium, but who have moderate to severe COPD, defined as < 60% FEV_1, FEV_1/FVC < 0.7 and MRC Dyspnea Scale 3 to 5.
NIHB Drug Program	For patients with COPD and who: • did not respond to a trial of ipratropium (Atrovent); **OR** • did not have a previous trial of ipratropium, but who have moderate to severe COPD, defined as < 60% FEV_1, FEV_1/FVC < 0.7 and MRC Dyspnea Scale 3 to 5.

Drug Plan	Criteria for Restricted Benefit
DND Drug Program	For patients with COPD and who: • did not respond to a trial of ipratropium (Atrovent); **OR** • did not have a previous trial of ipratropium, but who have moderate to severe COPD, defined as < 60% FEV_1, FEV_1/FVC < 0.7 and MRC Dyspnea Scale 3 to 5.
VAC Drug Program	For patients with COPD and who: • did not respond to a trial of ipratropium (Atrovent); **OR** • did not have a previous trial of ipratropium, but who have moderate to severe COPD, defined as < 60% FEV_1, FEV_1/FVC < 0.7 and MRC Dyspnea Scale score 3 to 5.

AB = Alberta, BC = British Columbia, COPD = chronic obstructive pulmonary disease; DND = Department of National Defence; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; ICS = inhaled corticosteroid; LABA = long-acting beta2-agonist; MN = Manitoba; MRC = Medical Research Council; NIHB = Non-Insured Health Benefits Program; NL = Newfoundland and Labrador; NS = Nova Scotia; NT = Northwest Territories; ON = Ontario; PE = Prince Edward Island; SABA = short-acting beta2-agonist; SK = Saskatchewan; VAC = Veterans Affairs Canada; YK = Yukon.

[a] MRC Dyspnea Scale

COPD Stage	Symptoms
Mild – 2	Shortness of breath from COPD when hurrying on the level or walking up a slight hill.
Moderate – MRC 3 to 4	Shortness of breath from COPD causing the patient to stop after walking about 100 m (or after a few minutes) on the level.
Severe – MRC 5	Shortness of breath from COPD resulting in the patient being too breathless to leave the house or breathless after undressing, or the presence of chronic respiratory failure or clinical signs of right heart failure.

[b] Canadian Thoracic Society COPD Classification By Symptoms and Disability

Moderate: (MRC 3 to 4) Shortness of breath from COPD causing the patient to stop after walking about 100 m (or after a few minutes) on the level.

Severe: (MRC 5) Shortness of breath from COPD resulting in the patient being too breathless to leave the house or breathless after undressing, or the presence of chronic respiratory failure or clinical signs of right heart failure.

TABLE 21: RESTRICTED BENEFIT CRITERIA FOR FORMOTEROL FUMARATE (FORMOTEROL) FOR THE TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Drug Plan	Criteria for Restricted Benefit
SK Drug Plan	COPD unresponsive to short-acting beta-agonists or short-acting anticholinergic bronchodilators.
NB Prescription Drug Program	• For the treatment of COPD if symptoms persist after 2 to 3 months of short-acting bronchodilator therapy (i.e., salbutamol at a maximum dose of 8 puffs/day or ipratropium at maximum dose of 12 puffs/day). • Coverage can be provided without a trial of short-acting agent if there is spirometric evidence of at least moderate to severe airflow obstruction (FEV_1 < 60% and FEV_1/FVC ratio < 0.7) and significant symptoms (i.e., MRC Dyspnea Scale score of 3 to 5). • Combination therapy with tiotropium **AND** a LABA/ICS will be considered only if: o there is spirometric evidence of at least moderate to severe airflow obstruction (FEV_1 < 60% and FEV_1/FVC ratio < 0.7), and significant symptoms; i.e., MRC Dyspnea Scale score of 3 to 5) **AND** o there is evidence of one or more moderate to severe exacerbations per year, on average, for 2 consecutive years requiring antibiotics and/or systemic (oral or intravenous) corticosteroids. **Clinical Note:** If spirometry cannot be obtained, reasons must be clearly explained and other evidence regarding severity of condition must be provided for consideration (i.e., MRC Dyspnea Scale scale)[a]. Spirometry reports from any point in time will be accepted.
NS Pharmacare	• For the treatment of COPD, if symptoms persist after 2 to 3 months of short-acting bronchodilator therapy (i.e., salbutamol at a maximum dose of 8 puffs/day or ipratropium at maximum dose of 12 puffs/day) • Coverage can be provided without a trial of short-acting agent if: o there is spirometric evidence of at least moderate to severe airflow obstruction, (i.e., post-bronchodilator values FEV_1 < 60% and FEV_1/FVC ratio < 0.7), and significant symptoms (i.e., MRC Dyspnea Scale score of 3 to 5[b]) • Combination therapy with tiotropium and LABA/ICS will be considered only if: o there is spirometric evidence of at least moderate to severe airflow obstruction (post-bronchodilator values FEV_1 < 60% and FEV_1/FVC ratio < 0.7), and significant symptoms (i.e., MRC Dyspnea Scale score of 3 to 5[b]) *and* o there is evidence of one or more moderate to severe exacerbations per year, on average, for 2 consecutive years requiring antibiotics and/or systemic (oral or intravenous) corticosteroids **Note:** • Coverage of combination therapy with tiotropium and a LABA (without an ICS) will not be considered due to insufficient evidence to support substantial benefit. • If spirometry cannot be obtained, reasons must be clearly explained and other evidence regarding severity of condition must be provided for consideration (i.e., MRC Dyspnea Scale scale).
PEI Drug Cost Assistance Programs	For the treatment of COPD, see Chronic Obstructive Pulmonary Disease. **Note:** Patients using these products must also have access to a SABA bronchodilator for the relief of acute symptoms.
NL Pharmaceutical Services	• For the treatment of COPD, if symptoms persists after 2 to 3 months of short-acting bronchodilator therapy (i.e., salbutamol at maximum dose of 8 puffs/day or ipratropium at maximum dose of 12 puffs/day). • Coverage can be approved without a trial of a short-acting agent if there is spirometric evidence of at least moderate to severe

Drug Plan	Criteria for Restricted Benefit
	airflow obstruction — i.e., FEV_1 < 60% AND FEV_1/FVC ratio < 0.7 — and significant symptoms — i.e., MRC Dyspnea Scale score 3 to 5.[b] **Note:** • Coverage of combination therapy with tiotropium, glycopyrronium bromide, or aclidinium bromide and a LABA (without an ICS) will not be considered due to insufficient evidence to support substantial benefit. • If spirometry cannot be obtained, reasons must be clearly explained and other evidence regarding severity of condition must be provided for consideration (i.e., MRC Dyspnea Scale).
YK Health and Social Services	For moderate to severe COPD (MRC Dyspnea Scale score 3 to 5 and spirometric results FEV_1 < 60% and FEV_1/FVC < 0.7).
NT Health Care Plan	For the treatment of COPD in patients not adequately controlled with either ipratropium, tiotropium, or a SABA.
NIHB Drug Program	For the treatment of COPD in patients not adequately controlled with either ipratropium, tiotropium, or a SABA.
DND Drug Program	For the treatment of COPD in patients not adequately controlled with either ipratropium, tiotropium, or a SABA.
VAC Drug Program	For the treatment of COPD in patients not adequately controlled with either ipratropium, tiotropium, or a SABA.

AB = Alberta, BC = British Columbia, COPD = chronic obstructive pulmonary disease; DND = Department of National Defence; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; ICS = inhaled corticosteroid; LABA = long-acting beta2-agonist; MN = Manitoba; MRC = Medical Research Council; NIHB = Non-Insured Health Benefits Program; NL = Newfoundland and Labrador; NS = Nova Scotia; NT = Northwest Territories; ON = Ontario; PE = Prince Edward Island; SABA = short-acting beta-agonist; SK = Saskatchewan; VAC = Veterans Affairs Canada; YK = Yukon.
Note: Add non-proprietary name for each component.

[a] MRC Dyspnea Scale

COPD Stage	**Symptoms**
Mild: 2	Shortness of breath from COPD when hurrying on the level or walking up a slight hill.
Moderate: MRC 3 to 4	Shortness of breath from COPD causing the patient to stop after walking about 100 metres (or after a few minutes) on the level.
Severe: MRC 5	Shortness of breath from COPD resulting in the patient being too breathless to leave the house or breathless after undressing, or the presence of chronic respiratory failure or clinical signs of right heart failure.

[b] Canadian Thoracic Society COPD Classification By Symptoms and Disability
Moderate: (MRC 3 to 4) Shortness of breath from COPD causing the patient to stop after walking about 100 metres (or after a few minutes) on the level.
Severe: (MRC 5) Shortness of breath from COPD resulting in the patient being too breathless to leave the house or breathless after undressing, or the presence of chronic respiratory failure or clinical signs of right heart failure.

TABLE 22: RESTRICTED BENEFIT CRITERIA FOR FORMOTEROL FUMARATE DIHYDRATE (OXEZE TURBUHALER) FOR THE TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Drug Plan	Criteria for Restricted Benefit
SK Drug Plan	COPD in patients where there has been concurrent or past use of a LAMA or LABA
NB Prescription Drug Program	• For the treatment of COPD if symptoms persist after 2 to 3 months of short-acting bronchodilator therapy (i.e., salbutamol at a maximum dose of 8 puffs/day or ipratropium at maximum dose of 12 puffs/day). • Coverage can be provided without a trial of short-acting agent if there is spirometric evidence of at least moderate to severe airflow obstruction (FEV_1 < 60% and FEV_1/FVC ratio < 0.7) and significant symptoms (i.e., MRC Dyspnea Scale score of 3 to 5[a]). • Combination therapy with tiotropium AND a LABA/ICS will be considered only if: ○ there is spirometric evidence of at least moderate to severe airflow obstruction (FEV_1 < 60% and FEV_1/FVC ratio < 0.7), and significant symptoms; i.e., MRC Dyspnea Scale score of 3 to 5 **AND** ○ there is evidence of one or more moderate to severe exacerbations per year, on average, for 2 consecutive years requiring antibiotics and/or systemic (oral or intravenous) corticosteroids. **Clinical Note:** If spirometry cannot be obtained, reasons must be clearly explained and other evidence regarding severity of condition must be provided for consideration (i.e., MRC Dyspnea Scale score). Spirometry reports from any point in time will be accepted.
NS Pharmacare	• For the treatment of COPD, if symptoms persist after 2 to 3 months of short-acting bronchodilator therapy (i.e., salbutamol at a maximum dose of 8 puffs/day or ipratropium at maximum dose of 12 puffs/day) • Coverage can be provided without a trial of short-acting agent if: ○ there is spirometric evidence of at least moderate to severe airflow obstruction (i.e., post-bronchodilator values FEV_1 < 60% and FEV_1/FVC ratio < 0.7), and significant symptoms (i.e., MRC Dyspnea Scale score of 3 to 5[b]). • Combination therapy with tiotropium bromide and a LABA/ICS will be considered only if: ○ there is spirometric evidence of at least moderate to severe airflow obstruction (post-bronchodilator values FEV_1 < 60% and FEV_1/FVC ratio < 0.7), and significant symptoms (i.e., MRC Dyspnea Scale score of 3 to 5[b]) **AND** ○ there is evidence of one or more moderate to severe exacerbations per year, on average, for 2 consecutive years requiring antibiotics and/or systemic (oral or intravenous) corticosteroids **Note:** • Coverage of combination therapy with tiotropium bromide and a LABA (without an ICS) will not be considered due to insufficient evidence to support substantial benefit. • If spirometry cannot be obtained, reasons must be clearly explained and other evidence regarding severity of condition must be provided for consideration (i.e., MRC Dyspnea Scale). Spirometry reports from any point in time will be accepted.
PEI Drug Cost Assistance Programs	For the treatment of COPD, see Chronic Obstructive Pulmonary Disease. **Note:** Patients using these products must also have access to a SABA bronchodilator for the relief of acute symptoms.
NL Pharmaceutical Services	• For the treatment of COPD, if symptoms persists after 2 to 3 months of short-acting bronchodilator therapy (i.e., salbutamol at maximum dose of 8 puffs/day or ipratropium at maximum dose of 12 puffs/day).

Drug Plan	Criteria for Restricted Benefit
	• Coverage can be approved without a trial of a short-acting agent if there is spirometric evidence of at least moderate to severe airflow obstruction (i.e., FEV_1 < 60% AND FEV_1/FVC ratio < 0.7) and significant symptoms (i.e., MRC Dyspnea Scale score 3 to 5[b]). **Note:** • Coverage of combination therapy with tiotropium bromide, glycopyrronium bromide, or aclidinium bromide and a LABA (without an ICS) will not be considered due to insufficient evidence to support substantial benefit. • If spirometry cannot be obtained, reasons must be clearly explained and other evidence regarding severity of condition must be provided for consideration (i.e., MRC Dyspnea Scale).
YK Health and Social Services	For moderate to severe COPD (MRC Dyspnea Scale score 3 to 5[a]) and spirometric results FEV_1 < 60% and FEV_1/FVC < 0.7)

AB = Alberta, BC = British Columbia, COPD = chronic obstructive pulmonary disease; DND = Department of National Defence; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; LABA = long-acting beta2-agonist; LAMA = long-acting muscarinic receptor antagonist; MN = Manitoba; MRC = Medical Research Council; NIHB = Non-Insured Health Benefits Program; NL = Newfoundland and Labrador; NS = Nova Scotia; NT = Northwest Territories; ON = Ontario; PE = Prince Edward Island; SABA = short-acting beta2-agonist; SK = Saskatchewan; VAC = Veterans Affairs Canada; YK = Yukon.

[a] MRC Dyspnea Scale

COPD Stage	Symptoms
Mild: 2	Shortness of breath from COPD when hurrying on the level or walking up a slight hill.
Moderate: MRC 3 to 4	Shortness of breath from COPD causing the patient to stop after walking about 100 metres (or after a few minutes) on the level.
Severe: MRC 5	Shortness of breath from COPD resulting in the patient being too breathless to leave the house or breathless after undressing, or the presence of chronic respiratory failure or clinical signs of right heart failure.

[b] Canadian Thoracic Society COPD Classification By Symptoms and Disability

Moderate: (MRC 3 to 4) Shortness of breath from COPD causing the patient to stop after walking about 100 metres (or after a few minutes) on the level.

Severe: (MRC 5) Shortness of breath from COPD resulting in the patient being too breathless to leave the house or breathless after undressing, or the presence of chronic respiratory failure or clinical signs of right heart failure.

TABLE 23: LISTING STATUS FOR ACLIDINIUM BROMIDE/FORMOTEROL FUMARATE DIHYDRATE COMPARATORS FOR THE TREATMENT OF COPD

Components[a]	CDR-Participating Drug Plans													
	BC	AB	SK	MB	ON	NB	NS	PE	NL	YK	NT	NIHB	DND	VAC
Glycopyrronium/Indacaterol (Ultibro Breezhaler)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Umeclidinium bromide/Vilanterol trifenatate (Anoro Ellipta)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Tiotropium bromide (Spiriva)	RES	FB	RES	RES	FB	RES	RES	RES	RES	RES	RES	RES	RES	RES
Glycopyrronium (Seebri Breezhaler)	RES	FB	RES	RES	FB	RES	RES	RES	RES	RES	-	-	-	-
Budesonide/Formoterol fumarate dihydrate (Symbicort Turbuhaler)	NAB	FB	RES	FB	NAB	RES	RES	RES	RES	RES	RES	RES	RES	RES

AB = Alberta; BC = British Columbia, CDR = CADTH Common Drug Review; COPD = chronic obstructive pulmonary disease; DND = Department of National Defence; FB = full benefit; MN = Manitoba; NAB = not a benefit; NB = New Brunswick; NIHB = Non-Insured Health Benefits Program; NL = Newfoundland and Labrador; NS = Nova Scotia; NT = Northwest Territories; ON = Ontario; PE = Prince Edward Island; RES = restricted benefit; SK = Saskatchewan; VAC = Veterans Affairs Canada; YK = Yukon.

[a] Add non-proprietary name for each component.

TABLE 24: RESTRICTED BENEFIT CRITERIA FOR TIOTROPIUM BROMIDE (SPIRIVA) FOR THE TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Drug Plan	Criteria for Restricted Benefit
BC Pharmacare	Diagnosis of COPD where spirometry measures are: • FEV_1 as a percentage of predicted value (≤ 65%) **AND** • Ratio of actual FEV_1/FVC (< 0.7) **AND** • Inadequate response after 3 month trial of either: ○ ipratropium at a dose of 12 puffs daily **OR** ○ ipratropium and salbutamol combination inhaler (Combivent Respimat) at a dose of 6 puffs daily. **Note:** 12 puffs of ipratropium via metered dose inhaler is equivalent to 6 puffs of ipratropium via Combivent Respimat inhaler.
SK Drug Plan	a) COPD in patients unresponsive to short-acting beta-agonists or short-acting anticholinergic bronchodilators, **OR** b) b) Moderate to severe COPD (i.e., MRC Dyspnea Scale score 3 to 5), in conjunction with spirometry demonstrating moderate to severe airflow obstruction (i.e., FEV_1 < 60 % and low FEV_1/FVC < 0.7), without a trial of short-acting agents.
MB Pharmacare Program	For patients with moderate to severe COPD who remain symptomatic despite an adequate trial (3 months) of ipratropium.
NB Prescription Drug Program	• For the treatment of COPD if symptoms persist after 2 to 3 months of short-acting bronchodilator therapy (i.e., salbutamol at a maximum dose of 8 puffs/day or ipratropium at maximum dose of 12 puffs/day). • Coverage can be provided without a trial of short-acting agent if there is spirometric evidence of at least moderate to severe airflow obstruction (FEV_1 < 60% and FEV_1/FVC ratio < 0.7) and significant symptoms (i.e., MRC Dyspnea Scale score of 3 to 5[a]). • Combination therapy with tiotropium bromide **AND** a LABA/ICS will only be considered if: ○ there is spirometric evidence of at least moderate to severe airflow obstruction (FEV_1 < 60% and FEV_1/FVC ratio < 0.7), and significant symptoms (i.e., MRC score of 3 to 5[a]) **AND** ○ there is evidence of one or more moderate to severe exacerbations per year, on average, for 2 consecutive years requiring antibiotics and/or systemic (oral or intravenous) corticosteroids. **Clinical Note:** If spirometry cannot be obtained, reasons must be clearly explained and other evidence regarding severity of condition must be provided for consideration (i.e., MRC Dyspnea Scale). Spirometry reports from any point in time will be accepted.
NS Pharmacare	• For the treatment of COPD, if symptoms persist after 2 to 3 months of short-acting bronchodilator therapy (i.e., salbutamol at a maximum dose of 8 puffs/day or ipratropium at maximum dose of 12 puffs/day) • Coverage can be provided without a trial of short-acting agent if: ○ there is spirometric evidence of at least moderate to severe airflow obstruction (i.e., post-bronchodilator values FEV_1 < 60% and FEV_1/FVC ratio < 0.7), and significant symptoms (i.e., MRC Dyspnea Scale score of 3 to 5[b]) • Combination therapy with tiotropium bromide and a LABA/ICS will be considered only if: ○ there is spirometric evidence of at least moderate to severe airflow obstruction (post-bronchodilator values FEV_1 < 60% and FEV_1/FVC ratio < 0.7), and significant symptoms (i.e., MRC Dyspnea Scale score of 3 to 5[b]); **AND** ○ there is evidence of one or more moderate to severe exacerbations per year, on average, for 2 consecutive years requiring antibiotics and/or systemic (oral or

Drug Plan	Criteria for Restricted Benefit
	intravenous) corticosteroids. **Note:** • Coverage of combination therapy with tiotropium bromide and a LABA (without an ICS) will not be considered due to insufficient evidence to support substantial benefit. • If spirometry cannot be obtained, reasons must be clearly explained and other evidence regarding severity of condition must be provided for consideration (i.e., MRC scale). Spirometry reports from any point in time will be accepted.
PEI Drug Cost Assistance Programs	a) For the treatment of mild, moderate, and severe COPD (i.e., MRC Dyspnea Scale score ≥ 2) in patients who continue to be symptomatic after a 3-month trial of ipratropium at a dose of 12 puffs/day and appropriate use of SABAs. b) For the treatment of moderate to severe COPD (i.e., MRC Dyspnea Scale score 3 to 5) without a trial of short-acting agents (e.g., ipratropium and beta2-agonists) where spirometry shows moderate to severe airflow obstruction (i.e., FEV_1 < 60% predicted **AND** low FEV_1/FVC < 0.7). A copy of the spirometry report must accompany the Special Authorization. **Note:** The drug programs will not pay for concurrent use of tiotropium and ipratropium. **Note:** Concurrent use of tiotropium bromide and LABAs or LABA/ICSs will be considered only in patients where FEV_1 < 60% predicted **AND** FEV_1/FVC < 0.7. A copy of the spirometry report must accompany the Special Authorization.
NL Pharmaceutical Services	• For the treatment of COPD, if symptoms persist after 2 to 3 months of short-acting bronchodilator therapy (i.e., salbutamol at maximum dose of 8 puffs/day or ipratropium at maximum dose of 12 puffs/day). • Coverage can be approved without a trial of a short-acting agent if there is spirometric evidence of at least moderate to severe airflow obstruction (i.e., FEV_1 < 60% AND FEV_1/FVC ratio < 0.7) and significant symptoms (i.e., MRC Dyspnea Scale score 3 to 5[b]). • Combination therapy with tiotropium bromide and a LABA/corticosteroid (i.e., Spiriva plus Advair or Symbicort) will be considered only if: ○ there is spirometric evidence of a least moderate to severe airflow obstruction (FEV_1 < 60% AND FEV_1/FVC ratio < 0.7) and significant symptoms (i.e., MRC score of 3 to 5[b]) **AND** ○ there is evidence of one or more moderate to severe exacerbations per year on average, for 2 years (24 consecutive months) requiring antibiotics and/or systemic (oral or intravenous) corticosteroids. **Note:** • Coverage of combination therapy with aclidinium bromide and a LABA (without an ICS) will not be considered due to insufficient evidence to support substantial benefit. • If spirometry cannot be obtained, reasons must be clearly explained and other evidence regarding severity of condition must be provided for consideration (i.e., MRC Dyspnea Scale).
YK Health and Social Services	For patients diagnosed with COPD where spirometry measures are: • FEV_1 as a percentage of predicted value ≤ 65% **AND** • ratio of actual FEV_1/FVC < 0.7 **AND** • inadequate response after 3-month trial of ipratropium at maximum dosage.
NT Health Care Plan	For patients with COPD and who: • did not respond to a trial of ipratropium (Atrovent); **OR** • did not have a previous trial of ipratropium, but who have moderate to severe COPD, defined as < 60% FEV_1, FEV_1/FVC < 0.7 and MRC Dyspnea Scale score 3 to 5.
NIHB Drug Program	For patients with COPD and who: • did not respond to a trial of ipratropium (Atrovent); **OR**

Drug Plan	Criteria for Restricted Benefit
	• did not have a previous trial of ipratropium, but who have moderate to severe COPD, defined as < 60% FEV_1, FEV_1/FVC< 0.7 and MRC Dyspnea Scale score 3 to 5.
DND Drug Program	For patients with COPD and who: • did not respond to a trial of ipratropium (Atrovent); **OR** • did not have a previous trial of ipratropium, but who have moderate to severe COPD, defined as < 60% FEV_1, FEV_1/FVC< 0.7 and MRC Dyspnea Scale score 3 to 5.
VAC Drug Program	For patients with COPD and who: • did not respond to a trial of ipratropium (Atrovent); **OR** • did not have a previous trial of ipratropium, but who have moderate to severe COPD, defined as < 60% FEV_1, FEV_1/FVC < 0.7 and MRC Dyspnea Scale score 3 to 5.

AB = Alberta, BC = British Columbia, COPD = chronic obstructive pulmonary disease; DND = Department of National Defence; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; ICS = inhaled corticosteroid; LABA = long-acting beta2-agonist; MN = Manitoba; MRC = Medical Research Council; NIHB = Non-Insured Health Benefits Program; NL = Newfoundland and Labrador; NS = Nova Scotia; NT = Northwest Territories; ON = Ontario; PE = Prince Edward Island; SABA = short-acting beta2-agonist; SK = Saskatchewan; VAC = Veterans Affairs Canada; YK = Yukon.

[a] MRC Dyspnea Scale

COPD Stage	Symptoms
Mild: 2	Shortness of breath from COPD when hurrying on the level or walking up a slight hill
Moderate: MRC 3 to 4	Shortness of breath from COPD causing the patient to stop after walking about 100 m (or after a few minutes) on the level.
Severe: MRC 5 5	Shortness of breath from COPD resulting in the patient being too breathless to leave the house or breathless after undressing, or the presence of chronic respiratory failure or clinical signs of right heart failure.

[b] Canadian Thoracic Society COPD Classification By Symptoms and Disability

Moderate: (MRC 3 to 4) Shortness of breath from COPD causing the patient to stop after walking about 100 m (or after a few minutes) on the level.

Severe: (MRC 5) Shortness of breath from COPD resulting in the patient being too breathless to leave the house or breathless after undressing, or the presence of chronic respiratory failure or clinical signs of right heart failure.

TABLE 25: RESTRICTED BENEFIT CRITERIA FOR GLYCOPYRRONIUM (SEEBRI BREEZHALER) FOR THE TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Drug Plan	Criteria for Restricted Benefit

BC Pharmacare	Diagnosis of COPD where spirometry measures are:
	• FEV_1 as a percentage of predicted value (≤ 65%) **AND**
	• ratio of actual FEV_1/FVC (< 0.7) **AND**
	• inadequate response after 3-month trial of either:
	  ○ ipratropium at a dose of 12 puffs daily **OR**
	  ○ ipratropium and salbutamol combination inhaler (Combivent Respimat) at a dose of 6 puffs daily.
	Notes: 12 puffs of ipratropium via metered dose inhaler is equivalent to 6 puffs of ipratropium via Combivent Respimat inhaler.

SK Drug Plan	a) COPD in patients unresponsive to short-acting beta-agonists or short-acting anticholinergic bronchodilators, **OR** b) b) Moderate to severe COPD (i.e., MRC Dyspnea Scale score 3 to 5), in conjunction with spirometry demonstrating moderate to severe airflow obstruction (i.e., FEV_1 < 60 % and low FEV_1/FVC < 0.7), without a trial of short-acting agents.
MB Pharmacare Program	For patients with moderate to severe COPD who remain symptomatic despite an adequate trial (3 months) of ipratropium.

NB Prescription Drug Program	• For the treatment of COPD if symptoms persist after 2 to 3 months of short-acting bronchodilator therapy (i.e., salbutamol at a maximum dose of 8 puffs/day or ipratropium at maximum dose of 12 puffs/day).
	• Coverage can be provided without a trial of short-acting agent if there is spirometric evidence of at least moderate to severe airflow obstruction (FEV_1 < 60% and FEV_1/FVC ratio < 0.7) and significant symptoms (i.e., MRC Dyspnea Scale score 3 to 5[a]).
	• Combination therapy with glycopyrronium AND a LABA/ICS will be considered only if:
	  ○ there is spirometric evidence of at least moderate to severe airflow obstruction (FEV_1 < 60% and FEV_1/FVC ratio < 0.7), and significant symptoms (i.e., MRC Dyspnea Scale score 3 to 5[a]) **AND**
	  ○ there is evidence of one or more moderate to severe exacerbations per year, on average, for 2 consecutive years requiring antibiotics and/or systemic (oral or intravenous) corticosteroids.
	Clinical Note: If spirometry cannot be obtained, reasons must be clearly explained and other evidence regarding severity of condition must be provided for consideration (i.e., MRC Dyspnea Scale). Spirometry reports from any point in time will be accepted.

NS Pharmacare	• For the treatment of COPD, if symptoms persist after 2 to 3 months of short-acting bronchodilator therapy (i.e., salbutamol at a maximum dose of 8 puffs/day or ipratropium at maximum dose of 12 puffs/day)
	• Coverage can be provided without a trial of short-acting agent if:
	  ○ there is spirometric evidence of at least moderate to severe airflow obstruction (i.e., post-bronchodilator values FEV_1 < 60% and FEV_1/FVC ratio < 0.7), and significant symptoms (i.e., MRC Dyspnea Scale score 3 to 5[b])
	• Combination therapy with glycopyrronium and a LABA/ICS will be considered only if:
	  ○ there is spirometric evidence of at least moderate to severe airflow obstruction (post-bronchodilator values FEV_1 < 60% and FEV_1/FVC ratio < 0.7), and significant symptoms (i.e., MRC Dyspnea Scale score 3 to 5[b]); **AND**
	  ○ there is evidence of one or more moderate to severe exacerbations per year, on average, for 2 consecutive years requiring antibiotics and/or systemic (oral or intravenous) corticosteroids.

PEI Drug Cost	a) For the treatment of mild, moderate, and severe COPD (i.e., MRC Dyspnea Scale score

Drug Plan	Criteria for Restricted Benefit
Assistance Programs	≥ 2) in patients who continue to be symptomatic after a 3-month trial of ipratropium at a dose of 12 puffs/day and appropriate use of SABAs. b) For the treatment of moderate to severe COPD (i.e., MRC score 3 to 5) without a trial of short-acting agents (e.g., ipratropium and beta2-agonists) where spirometry shows moderate to severe airflow obstruction (i.e., FEV_1 < 60% predicted **AND** low FEV_1/FVC < 0.7). A copy of the spirometry report must accompany the Special Authorization. **Note:** • The drug programs will not pay for concurrent use of tiotropium bromide and ipratropium. • Concurrent use of tiotropium bromide and LABAs or LABA/ICSs will be considered only in patients where FEV_1 < 60% predicted **AND** FEV_1/FVC < 0.7. A copy of the spirometry report must accompany the Special Authorization.
NL Pharmaceutical Services	• For the treatment of COPD, if symptoms persist after 2 to 3 months of short-acting bronchodilator therapy (i.e., salbutamol at maximum dose of 8 puffs/day or ipratropium at maximum dose of 12 puffs/day). • Coverage can be approved without a trial of a short-acting agent if there is spirometric evidence of at least moderate to severe airflow obstruction (i.e., FEV_1 < 60% AND FEV_1/FVC ratio < 0.7, and significant symptoms (i.e., MRC score 3 to 5[b]). • Combination therapy with aclidinium bromide and a LABA/corticosteroid (i.e., Tudorza plus Advair or Symbicort) will be considered only if: ○ there is spirometric evidence of a least moderate to severe airflow obstruction (FEV_1 < 60% AND FEV_1/FVC ratio < 0.7) and significant symptoms (i.e., MRC Dyspnea Scale score 3 to 5[b]) **AND** ○ there is evidence of one or more moderate to severe exacerbations per year on average, for 2 years (24 consecutive months) requiring antibiotics and/or systemic (oral or intravenous) corticosteroids. **Note:** • Coverage of combination therapy with aclidinium bromide and a LABA (without an ICS) will not be considered due to insufficient evidence to support substantial benefit. • If spirometry cannot be obtained, reasons must be clearly explained and other evidence regarding severity of condition must be provided for consideration (i.e., MRC Dyspnea Scale).
YK Health and Social Services	1) For COPD, if symptoms persist after 2 to 3 months of short-acting bronchodilator therapy (salbutamol or ipratropium at optimal doses). 2) Please provide post-bronchodilator spirometric evidence of at least moderate to severe airflow obstruction. 3) If spirometry cannot be obtained, other evidence regarding severity of condition must be provided for consideration of moderate to severe airflow obstruction (i.e., FEV_1 < 65% and FEV_1/FVC ratio < 0.7) and significant symptoms (i.e., MRC Dyspnea Scale score 3 to 5[b]). **Note:** Coverage of combination therapy with glycopyrronium or tiotropium bromide + LABA/ICS considered for moderate to severe COPD.
NT Health Care Plan	For patients with COPD and who: • did not respond to a trial of ipratropium (Atrovent); **OR** • did not have a previous trial of ipratropium, but who have moderate to severe COPD, defined as < 60% FEV_1, FEV_1/FVC < 0.7 and MRC Dyspnea Scale score 3 to 5.
NIHB Drug Program	For patients with COPD and who: • did not respond to a trial of ipratropium (Atrovent); **OR** • did not have a previous trial of ipratropium, but who have moderate to severe COPD, defined as < 60% FEV_1, FEV_1/FVC < 0.7 and MRC Dyspnea Scale score 3 to 5.

Drug Plan	Criteria for Restricted Benefit
DND Drug Program	For patients with COPD and who: • did not respond to a trial of ipratropium (Atrovent); **OR** • did not have a previous trial of ipratropium, but who have moderate to severe COPD, defined as < 60% FEV_1, FEV_1/FVC < 0.7 and MRC Dyspnea Scale score 3 to 5.
VAC Drug Program	For patients with COPD and who: • did not respond to a trial of ipratropium (Atrovent); **OR** • did not have a previous trial of ipratropium, but who have moderate to severe COPD, defined as < 60% FEV_1, FEV_1/FVC < 0.7 and MRC Dyspnea Scale score 3 to 5.

AB = Alberta, BC = British Columbia, COPD = chronic obstructive pulmonary disease; DND = Department of National Defence; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; MN = Manitoba; MRC = Medical Research Council; NIHB = Non-Insured Health Benefits Program; NL = Newfoundland and Labrador; NS = Nova Scotia; NT = Northwest Territories; ON = Ontario; PE = Prince Edward Island; SABA = short-acting beta2-agonist; SK = Saskatchewan; VAC = Veterans Affairs Canada; YK = Yukon.

[a] MRC Dyspnea Scale

COPD Stage	Symptoms
Mild: 2	Shortness of breath from COPD when hurrying on the level or walking up a slight hill.
Moderate: MRC 3 to 4	Shortness of breath from COPD causing the patient to stop after walking about 100 m (or after a few minutes) on the level.
Severe: MRC 5	Shortness of breath from COPD resulting in the patient being too breathless to leave the house or breathless after undressing, or the presence of chronic respiratory failure or clinical signs of right heart failure.

[b] Canadian Thoracic Society COPD Classification By Symptoms and Disability

Moderate: (MRC 3 to 4) Shortness of breath from COPD causing the patient to stop after walking about 100 m (or after a few minutes) on the level.

Severe: (MRC 5) Shortness of breath from COPD resulting in the patient being too breathless to leave the house or breathless after undressing, or the presence of chronic respiratory failure or clinical signs of right heart failure.

TABLE 26: RESTRICTED BENEFIT CRITERIA FOR BUDESONIDE/FORMOTEROL FUMARATE DIHYDRATE (SYMBICORT TURBUHALER) FOR THE TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Drug Plan	Criteria for Restricted Benefit
SK Drug Plan	COPD in patients where there has been concurrent or past use of a LAMA or a LABA**.**
NB Prescription Drug Program	• For the treatment of COPD if symptoms persist after 2 to 3 months of short-acting bronchodilator therapy (i.e., salbutamol at a maximum dose of 8 puffs/day or ipratropium at maximum dose of 12 puffs/day). • Coverage can be provided without a trial of short-acting agent if there is spirometric evidence of at least moderate to severe airflow obstruction (FEV_1 < 60% and FEV_1/FVC ratio < 0.7) and significant symptoms (i.e., MRC Dyspnea Scale score 3 to 5[a]). • Combination therapy with tiotropium bromide AND a LABA/ICS will be considered only if: ○ there is spirometric evidence of at least moderate to severe airflow obstruction (FEV_1 < 60% and FEV_1/FVC ratio < 0.7) and significant symptoms (i.e., MRC score 3 to 5[a]) **AND** ○ there is evidence of one or more moderate to severe exacerbations per year, on average, for 2 consecutive years requiring antibiotics and/or systemic (oral or intravenous) corticosteroids. **Clinical Note:** If spirometry cannot be obtained, reasons must be clearly explained and other evidence regarding severity of condition must be provided for consideration (i.e., MRC Dyspnea Scale). Spirometry reports from any point in time will be accepted.
NS Pharmacare	• For the treatment of COPD, if symptoms persist after 2 to 3 months of short-acting bronchodilator therapy (i.e., salbutamol at a maximum dose of 8 puffs/day or ipratropium at maximum dose of 12 puffs/day) • coverage can be provided without a trial of short-acting agent if: ○ there is spirometric evidence of at least moderate to severe airflow obstruction (i.e., post-bronchodilator values FEV_1 < 60% and FEV_1/FVC ratio < 0.7), and significant symptoms (i.e., MRC Dyspnea Scale score 3 to 5[b]) • Combination therapy with tiotropium bromide and a LABA/ICS will be considered only if: ○ there is spirometric evidence of at least moderate to severe airflow obstruction (post-bronchodilator values FEV_1 < 60% and FEV_1/FVC ratio < 0.7), and significant symptoms (i.e., MRC Dyspnea Scale score 3 to 5[b]); **AND** ○ there is evidence of one or more moderate to severe exacerbations per year, on average, for 2 consecutive years requiring antibiotics and/or systemic (oral or intravenous) corticosteroids.
PEI Drug Cost Assistance Programs	a) For the treatment of mild, moderate, and severe COPD (i.e., MRC Dyspnea Scale score ≥ 2) in patients who continue to be symptomatic after a 3-month trial of ipratropium at a dose of 12 puffs/day and appropriate use of SABAs. b) For the treatment of moderate to severe COPD (i.e., MRC Dyspnea Scale score 3 to 5) without a trial of short-acting agents (e.g., ipratropium and beta2-agonists) where spirometry shows moderate to severe airflow obstruction (i.e., FEV_1 < 60% predicted **AND** low FEV_1/FVC < 0.7). A copy of the spirometry report must accompany the Special Authorization. **Note:** • The drug programs will not pay for concurrent use of tiotropium bromide and ipratropium. • Concurrent use of tiotropium bromide and LABAs or LABA/ICSs will be considered only in patients where FEV_1 < 60% predicted **AND** FEV_1/FVC < 0.7. A copy of the spirometry report must accompany the Special Authorization.
NL Pharmaceutical Services	• For the treatment of COPD, if symptoms persist after 2 to 3 months of short-acting bronchodilator therapy (i.e., salbutamol at maximum dose of 8 puffs/day or ipratropium at maximum dose of 12 puffs/day). • Coverage can be approved without a trial of a short-acting agent if there is spirometric evidence of at least moderate to severe airflow obstruction (i.e., FEV_1 < 60% AND FEV_1/FVC ratio < 0.7) and significant symptoms (i.e., MRC Dyspnea Scale score 3 to 5[b]). • Combination therapy with aclidinium bromide and a LABA/corticosteroid (i.e., Tudorza plus

Drug Plan	Criteria for Restricted Benefit
	Advair or Symbicort) will be considered only if: ○ there is spirometric evidence of a least moderate to severe airflow obstruction (FEV_1 < 60% AND FEV_1/FVC ratio < 0.7) and significant symptoms (i.e., MRC Dyspnea Scale score of 3 to 5[b]) **AND** ○ there is evidence of one or more moderate to severe exacerbations per year on average, for 2 years (24 consecutive months) requiring antibiotics and/or systemic (oral or intravenous) corticosteroids. **Note:** • Coverage of combination therapy with aclidinium bromide and a LABA (without an ICS) will not be considered due to insufficient evidence to support substantial benefit. • If spirometry cannot be obtained, reasons must be clearly explained and other evidence regarding severity of condition must be provided for consideration (i.e., MRC Dyspnea Scale).
YK Health and Social Services	For the treatment of moderate to severe COPD (MRC Dyspnea Scale score 3 to 5 and spirometric results of FEV_1 < 60% and FEV_1/FVC < 0.7).
NT Health Care Plan	• For the treatment of moderate COPD, if a patient continues to be symptomatic after an adequate trial of a long-acting anticholinergic **AND** a LABA. • For the treatment of severe COPD, if a patient continues to be symptomatic after an adequate trial of a long-acting anticholinergic OR a LABA.
NIHB Drug Program	• For the treatment of moderate COPD, if a patient continues to be symptomatic after an adequate trial of a long-acting anticholinergic **AND** a LABA. • For the treatment of severe COPD, if a patient continues to be symptomatic after an adequate trial of a long-acting anticholinergic OR a LABA.
DND Drug Program	• For the treatment of moderate COPD, if a patient continues to be symptomatic after an adequate trial of a long-acting anticholinergic **AND** a LABA. • For the treatment of severe COPD, if a patient continues to be symptomatic after an adequate trial of a long-acting anticholinergic OR a LABA.
VAC Drug Program	• For the treatment of moderate COPD, if a patient continues to be symptomatic after an adequate trial of a long-acting anticholinergic **AND** a LABA. • For the treatment of severe COPD, if a patient continues to be symptomatic after an adequate trial of a long-acting anticholinergic OR a LABA.

AB = Alberta, BC = British Columbia, COPD = chronic obstructive pulmonary disease; DND = Department of National Defence; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; ICS = inhaled corticosteroid; LABA = long-acting beta2-agonist; LAMA = long-acting muscarinic receptor antagonist; MN = Manitoba; MRC = Medical Research Council; NIHB = Non-Insured Health Benefits Program; NL = Newfoundland and Labrador; NS = Nova Scotia; NT = Northwest Territories; ON = Ontario; PE = Prince Edward Island; SABA = short-acting beta2-agonist; SK = Saskatchewan; VAC = Veterans Affairs Canada; YK = Yukon.

[a] MRC Dyspnea Scale

COPD Stage	Symptoms
Mild: 2	Shortness of breath from COPD when hurrying on the level or walking up a slight hill.
Moderate: MRC 3 to 4	Shortness of breath from COPD causing the patient to stop after walking about 100 m (or after a few minutes) on the level.
Severe: MRC 5	Shortness of breath from COPD resulting in the patient being too breathless to leave the house or breathless after undressing, or the presence of chronic respiratory failure or clinical signs of right heart failure.

[b] Canadian Thoracic Society COPD Classification By Symptoms and Disability

Moderate: (MRC 3 to 4) Shortness of breath from COPD causing the patient to stop after walking about 100 m (or after a few minutes) on the level.

Severe: (MRC 5) Shortness of breath from COPD resulting in the patient being too breathless to leave the house or breathless after undressing, or the presence of chronic respiratory failure or clinical signs of right heart failure.

APPENDIX 2: SUMMARY OF PATIENT INPUT

This section was summarized by CADTH Common Drug Review (CDR) staff based on the input provided by patient groups. It has not been systematically reviewed.

1. Brief Description of Patient Group(s) Supplying Input

Two patient groups, the Ontario Lung Association (OLA) and COPD Canada, submitted their inputs for this review. OLA is a charity that supports patients with lung disease and their caregivers, provides resources to health care providers, and invests in lung research. It also advocates for the prevention of respiratory illness, tobacco cessation, and air quality. OLA has received funding from Pfizer, GlaxoSmithKline (GSK), Boehringer Ingelheim, AstraZeneca, Merck, Novartis, Nycomed/Takeda, InterMune, Grifols, Actelion, Astellas, Bayer, Johnson & Johnson, Roche, Rx&D, Valent Pharmaceuticals, Eli Lilly, and Ontario Home Respiratory Services Association.

COPD Canada is an independent, non-profit patient advocacy association with the primary mandate to assist Canadians who suffer from chronic obstructive pulmonary disease (COPD). The association is involved in providing patient education materials and services, in a variety of formats, and using different delivery methodologies. COPD Canada also develops, sponsors, and produces quality-of-life seminars for patients and their families. COPD Canada strives to heighten visibility and awareness of COPD to the Canadian public. Membership in COPD Canada is free of charge, but is restricted to COPD patients and their caregivers. Members are invited to participate in all COPD events and receive complimentary copies of its newsletter, "Living with COPD." COPD Canada reported the conflict of interest in respect of corporate and joint working, sponsorship, or funding arrangements with Almirall Canada, AstraZeneca Canada, GlaxoSmithKline Canada, Novartis Pharmaceuticals, Nycomed/Takeda Canada, and ProResp Canada.

No conflicts of interests were declared by either of the above two organizations with regard to this submission.

2. Condition and Current Therapy-Related Information

The two patient groups gathered information from COPD patients, family members, and caregivers via online or email surveys, phone interviews, and direct one-on-one conversations. Information from the scientific literature was also included. One of the respirologists involved in the clinical trial for aclidinium/formoterol fixed-dose combination (FDC) was also interviewed for his comments and observations.

The patient groups believe that COPD — a progressively debilitating disease with treatment but no cure — affects almost all aspects of daily living, including physical and leisure activities, as well as relationships with family and friends. It affects basic activities like breathing, working, socializing, talking, sleeping, dressing, cooking, hygiene care, taking stairs, and travelling. The most commonly experienced symptoms are fatigue and shortness of breath (which may occur even at rest in severe cases), followed by mucus, wheezing, frequent chest infections, and coughing. Inability to perform daily activities results in depression, hopelessness, frustration, and loss of self-worth for some. In addition to the social stigma and isolation that COPD causes, patients have been forced to adapt their lifestyles dramatically. A typical week for a COPD patient consists of reading, spending most of their time indoors, with infrequent outings to attend pulmonary rehabilitation classes. One patient commented, "It affects every aspect of my everyday life; I am virtually housebound; prednisone taken for exacerbations contributed

significantly to my now-severe osteoporosis; it affects all my activities of daily living." Patients may feel they are burdening their families. Many patients have to leave the work force, which can affect them financially. Patients reported constantly needing medications, and as the condition worsens, they may take multiple medications and potentially be on supplementary oxygen therapy. As COPD symptoms worsen, patients are usually forced to take early retirement. As the disease progresses, it has an increasingly profound effect on all aspects of patients' lives, severely impeding the ability to do even the most basic daily tasks, limiting social interactions, and causing depression.

Caregivers experience similar negative impacts. Caring for a COPD patient affects caregivers' work, social relationships, physical and leisure activities, independence, and ability to travel and socialize. They have to take time off work to run errands and to make frequent medical appointments. Caregivers also face financial challenges related to purchasing medicines (depending on the level of reimbursement), and to expenses incurred by purchasing assistive devices and home modifications for the patient. They feel exhausted, socially isolated, depressed, and have limited ability to manage their own physical and mental well-being.

Interviewed patients had had treatment experience with Spiriva, Advair, Symbicort, Daxas, prednisone, Ventolin, Atrovent, Serevent, Seebri, Onbrez, and Breo Ellipta. Current treatments provide some relief for fatigue, shortness of breath, cough, appetite loss, low energy, and the inability to fight infection. The effectiveness of existing medications diminishes over time. One of the two patient groups reported the experience of adverse effects such as extremely hoarse voice associated with Advair; very dry mouth with Spiriva; and stomach upset, general swelling, an increase in the symptoms of osteoporosis, and ophthalmic problems with prednisone.

3. Related Information About the Drug Being Reviewed

No patients from OLA and COPD Canada reported treatment experience with aclidinium/formoterol FDC.

Although there are similar medications for COPD, both groups believe there is a need for more alternative medicines, such as aclidinium/formoterol FDC, that can improve lung function and quality of life, reduce exacerbations, delay disease progression, and improve survival over the long-term. No patients from the two groups had had experience with aclidinium/formoterol FDC; however, based on their knowledge of aclidinium/formoterol FDC, one group pointed out that the combination appears to have a number of key advantages over existing COPD medicines: the aclidinium component has fewer adverse effects (dry mouth, urinary tract retention) than other LAMAs that are currently available. It has also been noted that the twice-daily dosage helps relieve morning symptoms; also, the fast-acting nature of formoterol is very helpful for those still working who need to get moving at the start of the day; as a nonsteroidal agent, aclidinium/formoterol FDC should have fewer adverse effects than inhaled corticosteroid (ICS) therapies. The group also believes that aclidinium/formoterol FDC is delivered via a pre-loaded Genuair inhaler that is easy to use, and in some instances (i.e., users of aclidinium) will be familiar to the patient, obviating the need for training on how to use the inhaler. Incorrect use of inhalers is a constant challenge in COPD. The potential improved ease of use of the Genuair inhaler may assist in issues of compliance while at the same time ensuring that patients receive the prescribed amount, with little to no chance of wastage. Patients also indicated that some adverse effects are acceptable as long as there is nothing irreversible or worse than what they are currently experiencing. One patient commented, "Most side effects would be bearable if I could just breathe a bit better and could wake up with enough energy to get through the day." In addition, patients would like there to be a lower or no cost burden associated with new treatments.

In summary, two patients groups (OLA, COPD Canada) submitted their input for this review. Both groups expressed that the current therapies for COPD still do not meet all patients' needs. Although no patients had had experience with aclidinium/formoterol FDC, both patient groups expect to have access to the new drug, and hope that it may improve the overall management of their COPD.

APPENDIX 3: SUMMARY AND APPRAISAL OF MIXED TREATMENT COMPARISON

Objective

To summarize and critically appraise the manufacturer-conducted, mixed treatment comparison (MTC)[34] on the comparative clinical efficacy and safety of aclidinium/formoterol fixed-dose combination (FDC) (Duaklir Genuair) with other long-acting beta2-agonist (LABA)/ long-acting muscarinic antagonist (LAMA) FDCs, including umeclidinium/vilanterol (Anoro Ellipta) and indacaterol/glycopyrronium (Ultibro Breezhaler) in the treatment of patients with chronic obstructive pulmonary disease (COPD). No head-to-head randomized controlled trials (RCTs) between aclidinium/formoterol FDC with other LAMA/LABA FDCs were identified in a literature search.

Findings of MTC

Methods

PubMed, Embase, and the Cochrane Database were searched from January 1992 to January 2015 for RCTs evaluating aclidinium/formoterol FDC, umeclidinium/vilanterol FDC, indacaterol/glycopyrronium FDC, and the two monotherapy components combinations including tiotropium bromide + formoterol, or glycopyrronium + formoterol in the treatment of COPD. Studies were eligible for inclusion into the systematic review and meta-analyses if they were published in English between 1992 and January 2015, consisted of at least 25 patients in each treatment group, and had a trial duration greater than 12 weeks. Studies also had to include at least one treatment group who received a regulator-approved dose regimen of aclidinium/formoterol FDC (400 mcg/12 mcg twice daily), umeclidinium/vilanterol (62.5 mcg/25 mcg once daily), or glycopyrronium/indacaterol (110 mcg/50 mcg once daily).

Outcomes of interest for the MTC were change from baseline in peak forced expiratory volume in one second (peak FEV_1) and trough forced expiratory volume in one second (trough FEV_1), as well as health-related quality of life (HRQoL) as measured by the St. George's Respiratory Questionnaire (SGRQ) total score (proportion of patients with ≥ 4-unit decrease in SGRQ), degree of dyspnea as measured by Transition Dyspnea Index (TDI) (proportion of patients with ≥ 1-unit increase in TDI), the proportion of patients with one or more acute exacerbation(s), and the proportion of patients who withdrew due to an adverse event (WDAE).

A Bayesian MTC model was fitted for each of the efficacy and safety outcomes using WinBUGs and R statistical software. The estimates were mean differences compared with placebo for the continuous variables, odds ratios (ORs) for SGRQ and TDI response, and rate ratios (RR) for exacerbations and WDAEs.

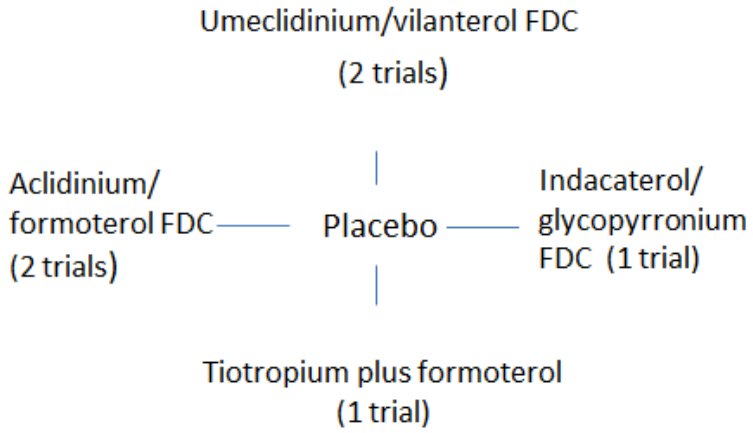
Results

Study and Patient Characteristics

The network diagram for the treatments evaluated in the analysis is presented in Figure 1. A total of six placebo-controlled trials met the inclusion criteria for the MTC. Among them, two were for aclidinium/formoterol FDC,[24,35] one for umeclidinium/vilanterol,[36] two for indacaterol/glycopyrronium,[37,38] and one for tiotropium bromide/formoterol dual therapy.[39] All included studies were double-blinded except one,[39] which was partially blinded. The sample sizes per study arm ranged from 113 to 483 patients. The trough FEV_1 for inclusion varied from less than 70% to 80% of predicted, indicating that patients had moderate to severe COPD. Treatment duration was 24 weeks in

four studies,[24,35,36,39] and 26 weeks and 52 weeks for the two remaining studies, respectively[37,38] (see Table 27).

FIGURE 1: CADTH COMMON DRUG REVIEW REPRESENTATION OF THE NETWORK FOR MIXED TREATMENT COMPARISON ANALYSIS



FDC = fixed-drug combination.

TABLE 27: BASELINE CHARACTERISTICS OF INCLUDED STUDIES

Author, Year, Country	Design	Treatment Groups	Sample Size (ITT)	FEV_1 Inclusion Criterion	Duration (Weeks)
Bateman et al., 2013, [37] Global	DB RCT	I/G 110 mcg/50 mcg q.d. IND 150 mcg q.d. GLY 50 mcg q.d. TIO 18 mcg q.d. Placebo q.d.	475 477 475 483 234	< 80% of predicted	26
Dahl et al., 2013, [38] Europe, Canada, Asia, South Africa	DB RCT	I/G, 110 mcg/50 mcg Placebo	225 113	< 80% of predicted	52
Donohue et al., 2013 [36] Global	DB RCT	U/V 62.5 mcg/25 mcg q.d. UME 62.5 mcg VIL 25 mcg Placebo	413 421 421 280	< 80% of predicted	24
Singh et al., 2014 [24] Europe and Asia	DB RCT	A/F 400 mcg/12 mcg b.i.d. A/F 400 mcg/6 mcg b.i.d. ACL 400 mcg b.i.d. FOR 12 mcg b.i.d. Placebo	385 381 385 384 194	< 80% of predicted	24
D'Urzo, et al., 2014 [35] USA, Canada, Australia, and New Zealand	DB RCT	A/F 400 mcg/12 mcg b.i.d. A/F 400 mcg/6 mcg b.i.d. ACL 400 mcg b.i.d. FOR 12 mcg b.i.d. Placebo	338 338 340 339 337	< 70% of predicted	24

Author, Year, Country	Design	Treatment Groups	Sample Size (ITT)	FEV_1 Inclusion Criterion	Duration (Weeks)
Vogelmeier et al., 2008,[39] Europe	PB	TIO 18 mcg q.d. + FOR 10 mcg b.i.d. FOR 10 mcg b.i.d. TIO 18 mcg q.d. + placebo b.i.d. Placebo	207 210 221 209	< 70% of predicted	24

ACL = aclidinium; A/F = aclidinium/formoterol FDC (400 mcg/12 mcg, Duaklir Genuair); b.i.d. = twice daily; FEV_1 = forced expiratory volume in one second; DB = double-blind; FOR = formoterol; GLY = glycopyrronium; I/G = indacaterol/glycopyrronium FDC (110 mcg/50 mcg; Ultibro Breezhaler); IND = indacaterol; q.d. = once daily; RCT = randomized controlled trial; PB = partial blind; TIO = tiotropium; UME = umeclidinium; U/V = umeclidinium/vilanterol FDC (62.5 mcg/25 mcg, Anoro Ellipta); VIL = vilanterol.

Outcomes

The focus of this summary is the comparative efficacy of aclidinium/formoterol FDC versus other LAMA/LABA combinations. Therefore, only results of the MTC related to comparisons between LAMA/LABA combinations are described; evidence for individual combinations versus placebo are not presented.

Change from Baseline in Trough FEV_1 and Peak FEV_1: No statistically or clinically significant differences were found between LAMA/LABA combinations for both pulmonary function outcomes. The between-group difference in mean change from baseline in trough FEV_1 for the comparison of aclidinium/formoterol FDC and umeclidinium/vilanterol was –0.031 L (95% credible intervals [CrI]: –0.079 to 0.016), and 0.0485 L (95% CrI, –0.008 to 0.0974) for peak FEV_1. For aclidinium/formoterol FDC versus glycopyrronium/indacaterol, the between-group difference in mean change from baseline in trough FEV_1 was –0.0547 L (95% CrI, –0.0958 to 0.0138), and –0.0273 L (95% CrI, –0.070 to 0.0149) for peak FEV_1 (Table 28).

St. George's Respiratory Questionnaire: The MTC results also suggested no statistically significant difference in improvement on SGRQ between aclidinium/formoterol FDC compared with umeclidinium/vilanterol (OR 0.9; 95% CrI, 0.6 to 1.3) and glycopyrronium/indacaterol (OR 1.2; 95% CrI, 0.8 to 1.8) in terms of the number of patients who achieved a clinical meaningful improvement in SGRQ total score (≥ 4 unit increase) (Table 28).

Transition Dyspnea Index: No statistically significant difference in the proportion of patients with a clinically significant improvement in breathlessness (≥ 1 unit change in TDI total score) was detected between aclidinium/formoterol FDC and umeclidinium/vilanterol (OR 1.16; 95% CrI, 0.79 to 1.71) or between aclidinium/formoterol FDC and glycopyrronium/indacaterol (OR 1.46; 95% CrI, 0.98 to 2.19), based on the MTC analysis (Table 28).

Chronic Obstructive Pulmonary Disease Exacerbations: COPD exacerbation as an outcome was not reported in studies for umeclidinium/vilanterol. The MTC analysis indicated no statistically significant difference between aclidinium/formoterol FDC and glycopyrronium/indacaterol with respect to COPD exacerbations (RR 1.08; 95% CrI, 0.76, to 1.53).

Withdrawals Due to Adverse Events: WDAEs were the only safety parameter evaluated in the MTC. The MTC analysis indicated that the rate of WDAEs appeared similar in aclidinium/formoterol FDC compared with umeclidinium/vilanterol or glycopyrronium/indacaterol (see Table 28).

TABLE 28: SUMMARY OF INDIRECT STATISTICAL COMPARISON USING BAYESIAN MIXED TREATMENT METHODS FOR LAMA/LABA COMBINATIONS

Outcomes	Between-Group Difference
Change from baseline in peak FEV_1	Mean (95% CrI), L
A/F vs. U/V	0.0485 (–0.0008 to 0.0974)
A/F vs. I/G	–0.0273 (–0.070 to 0.0149)
Change from baseline in trough FEV_1[1]	Mean (95% CrI), mL
A/F vs. U/V	–0.0315 (–0.079 to 0.016)
A/F vs. I/G	–0.0547 (–0.0958 to 0.0138)
Patients with ≥ 4 unit improvement on the SGRQ	OR (95% CrI)
A/F vs. U/V	0.86 (0.58 to 1.27)
A/F vs. I/G	1.21 (0.82 to 1.80)
Patients with ≥ 1 unit improvement on the TDI	**OR (95% CrI)**
A/F vs. U/V	1.16 (0.79 to 1.71)
A/F vs. I/G	1.46 (0.98 to 2.19)
Patients with ≥ 1 COPD exacerbation	**RR (95% CrI)**
A/F vs. I/G	1.06 (0.76 to 1.53)
A/F vs. U/V	NR
A/F vs. TIO + FOR	1.89 (0.97 to 3.85)
WDAE	**RR (95% CrI)**
A/F vs. U/V	0.56 (0.22 to 1.32)
A/F vs. I/G	1.77 (0.80 to 3.91)
A/F vs. TIO + FOR	1.00 (0.34 to 2.97)

A/F = aclidinium/formoterol FDC (400 mcg/12 mcg); COPD = chronic obstructive pulmonary disease; CrI = credible interval; FEV_1 = forced expiratory volume in one second; I/G = indacaterol/glycopyrronium FDC (110 mcg/50 mcg); LABA = long-acting beta2-agonist; LAMA = long-acting muscarinic receptor antagonist; NR = not reported; OR = odds ratio; RR = relative risk; SGRQ = St. George's Respiratory Questionnaire; TDI = Transition Dyspnea Index; U/V = umeclidinium/vilanterol FDC (62.5 mcg/25 mcg); vs. = versus; WDAE = withdrawal due to an adverse event.

Critical Appraisal of Network Meta-Analysis

The quality of the manufacturer-submitted network meta-analysis (NMA) was assessed according to recommendations provided by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.[40] The commentary for each of the relevant items identified by ISPOR for both MTCs are provided in Table 29.

Strengths

The manufacturer-submitted MTC satisfied some of the ISPOR criteria. It was based on a systematic review to identify all relevant studies. The literature search appeared comprehensive. The baseline characteristics and key findings in each included study were presented. The methodological quality of all individual studies was assessed with the National Institute of Health and Care Excellence (NICE) checklist for RCTs,[41] and the quality assessment of each individual study was presented. The MTC analysis was conducted using an appropriate and well-reported methodology (i.e., Bayesian analysis models). The outcome measures assessed in the MTC were appropriate and generally consistent with the key efficacy assessments included in the review by the CADTH Common Drug Review (CDR) of aclidinium/formoterol FDC.

Limitations

There are several potential limitations of this MTC. First, methodologically, the detail of the study selection and data extraction process was not clearly provided; it is not clear whether these were conducted in a duplicate process, so the potential selection bias is unknown. Second, the clinical heterogeneity (such as patient age, trial duration, baseline severity of COPD, concomitant medications, use of rescue medication, baseline FEV_1, and current smoking status) of the trials included in the analysis might have affected the estimates of treatment effects; however, how these potential sources of clinical heterogeneity were assessed and accounted for (i.e., subgroup, sensitivity, or meta-regression analyses) was not reported. Third, although the methodological quality of the included studies was assessed and reported, it is uncertain whether this was taken into account in the MTC (i.e., were studies of poor quality removed from the base-case analysis?). Fourth, whether the analysis was based on a random-effects model or fixed-effects model was not specified. Fifth, no information on deviance information criterion (DIC) was provided; therefore the goodness of fit of the reported MTC model is uncertain. Sixth, there is potential that the analysis suffered from insufficient power to detect differences between LAMA/LABA combinations for less frequently occurring outcomes (i.e., COPD exacerbations and WDAEs) given the small number of trials (n = 6) included in the MTC (all of which shared only placebo as the connector) and the potential for publication bias, may affect the estimated results. Finally, there were no head-to-head trials, so the inconsistency of the MTC result could not be checked.

Summary

The MTC revealed that aclidinium/formoterol FDC appears similar in terms of efficacy compared with umeclidinium/vilanterol and glycopyrronium/indacaterol. However, due to the potential limitations discussed above — including the relatively short duration of included trials, no head-to-head direct comparison, and the potential clinical heterogeneity of the included trials — there is a high degree of uncertainty with respect to the findings and conclusions derived from the MTC. Furthermore, the comparative effects of aclidinium/formoterol FDC versus other LAMA/LABA combinations were not assessed for key outcomes such as mortality, health care resource use (HRU), serious adverse events (SAEs), and adverse events (AEs) of particular interest including cardiovascular events, anticholinergic events, and pneumonia.

TABLE 29: APPRAISAL OF NETWORK META-ANALYSIS USING ISPOR CRITERIA

ISPOR Checklist Item		Details and Comments
1	Are the rationale for the study and the objectives stated clearly?	The rationale for conducting a network meta-analysis and the study objectives were clearly stated.
2	Does the methods section include the following? • Eligibility criteria • Information sources • Search strategy • Study selection process • Data extraction • Validity of individual studies	• The eligibility criteria for individual RCTs were clearly stated. • No list of excluded studies and reasons for exclusion was provided in the systematic review • Information sources and search strategy were well reported. • Methods for selection process, data extraction were provided; however, whether the study selection, data extraction were done by two reviewers (in a duplicate process) was not reported. • Validity of individual studies was assessed using the NICE checklist.[41] The quality assessment results were presented.
3	Are the outcome measures described?	• Outcomes assessed in the network meta-analysis were clearly stated. • Justification of the outcome measures was provided.

	ISPOR Checklist Item	Details and Comments
4	Is there a description of methods for analysis/synthesis of evidence? • Description of analyses methods/models • Handling of potential bias/inconsistency • Analysis framework	• Analysis framework was provided. • A description of the statistical model (Bayesian MTC) was briefly provided. • However, whether the analysis was based on random-effect model or fixed-effect model was not specified. No information on DIC was provided. • No information on how heterogeneity was handled. • Inconsistency is not applicable because there was no head-to-head direct pairwise comparison.
5	Are sensitivity analyses presented?	NR
6	Do the results include a summary of the studies included in the network of evidence? • Individual study data? • Network of studies?	• Individual study and patient characteristics were provided. • A figure showing the network of studies was provided. • The key findings on efficacy and safety in each individual study were presented.
7	Does the study describe an assessment of model fit?	NR
8	Are the results of the evidence synthesis presented clearly?	The results of the analysis were clearly reported for each outcome measure including point estimates and 95% credible intervals as a measure of uncertainty.
9	Sensitivity/scenario analyses	NR

DIC = deviance information criterion; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; MTC = mixed treatment comparison; NICE = National Institute for Health and Care Excellence; NR = not reported; RCT = randomized controlled trial.

APPENDIX 4: CADTH COMMON DRUG REVIEW COST COMPARISON TABLE

Clinical experts have deemed the comparator treatments presented in Table 30 to be appropriate. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified.

TABLE 30: CADTH COMMON DRUG REVIEW COST COMPARISON TABLE FOR LAMAS, LABAS, AND COMBINATIONS FOR COPD

Drug/Comparator	Strength	Dosage Form	Price ($)	Price/ Dose ($)	Recommended Daily Use	Daily Drug Cost ($)	Average Annual Cost ($)
Aclidinium bromide/formoterol fumarate dihydrate (Duaklir Genuair)	**400 mcg/ 12 mcg**	**Inhalant pwd (60 doses)**	**74.1000[a]**	**1.2350**	**400 mcg/ 12 mcg twice daily**	**2.47**	**902**
LABA/LAMA combinations							
Indacaterol/ glycopyrronium (Ultibro Breezhaler)	110 mcg/ 50 mcg	Inhalant pwd capsule	2.6800[b]	2.6800	110 mcg/ 50 mcg daily	2.68	978
Umeclidinium/ vilanterol (Anoro Ellipta)	62.5 mcg/ 25 mcg	Inhalant pwd (30 doses)	81.0000[c]	2.7000	62.5 mcg/ 25 mcg daily	N/A	N/A
Other LAMAs							
Aclidinium bromide (Tudorza Genuair)	400 mcg	Inhalant pwd (60 doses)	53.1000	0.8850	400 mcg twice daily	1.77	646
Glycopyrronium bromide (Seebri)	50 mcg	Inhalant pwd capsule	1.7700	1.7700	50 mcg daily	1.77	646
Tiotropium bromide (Spiriva HandiHaler)	18 mcg	Inhalant pwd capsule	2.1667	2.1667	18 mcg daily	2.17	791
LABAs							
Formoterol (Foradil)	12 mcg	Inhalant pwd capsule	0.8181	0.8181	12 mcg to 24 mcg twice daily	1.64 to 3.27	597 to 1,194
Indacaterol maleate (Onbrez)	75 mcg	Inhalant pwd capsule	1.5500	1.5500	75 mcg daily	1.55	566
Salmeterol (SereVent)	50 mcg	Inhalant pwd Dose	0.9350	0.9350	50 mcg twice daily	1.87	683

Drug/Comparator	Strength	Dosage Form	Price ($)	Price/ Dose ($)	Recommended Daily Use	Daily Drug Cost ($)	Average Annual Cost ($)
LABA/ICS combinations							
Budesonide/ Formoterol (Symbicort Turbuhaler)	100 mcg/ 6 mcg 200 mcg/ 6 mcg	Inhalant pwd (120 doses)	64.5600 83.8800	0.5380 0.6990	400 mcg/ 12 mcg twice daily	2.80	1,021
Fluticasone furoate/ Vilanterol trifenatate (Breo Ellipta)	100 mcg/ 25 mcg	Inhalant pwd (30 doses)	120.0000	4.0000	100 mcg/ 25 mcg once daily	4.000	1,460
Fluticasone propionate/ salmeterol (Advair Diskus)	100 mcg/ 50 mcg 250 mcg/ 50 mcg 500 mcg/ 50 mcg	Inhalant pwd (60 doses)	81.3900 97.4280 138.3120	1.3565 1.6238 2.3052	250 mcg/ 50 mcg or 500 mcg/ 50 mcg twice daily	3.25 to 4.61	1,186 to 1,684

CDR = CADTH Common Drug Review; COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid; LABA = long-acting beta2-agonist; LAMA = long-acting muscarinic antagonist; pwd = powder.
Source: Alberta Health Drug Benefit List (April 2015) unless otherwise stated.
[a] Source: Manufacturer's submitted price.
[b] Source: Canadian Drug Expert Committee Final Recommendation for Ultibro Breezhaler: http://www.cadth.ca/media/cdr/complete/cdr_complete_SR0369_Ultibro%20Breezhaler_Jan30_2015.pdf
[c] Source: Ontario Drug Benefit Formulary.
Note: Alternatives currently under review by CDR are umeclidinium bromide (Incruse Ellipta) and tiotropium bromide (Spiriva Respimat).

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